

9.01

Azepines and their Fused-ring Derivatives

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9.01.1 INTRODUCTION

What may be regarded as simple insertion of an extra carbon atom into a pyridine ring system, or an ethylidene group into a pyrrole ring system, has a profound effect upon the chemistry of the new ring system. All remnants of aromaticity have been lost and the azepine ring system is now a cyclic polyene system. The ramifications of this have been thoroughly discussed by Smalley <84CHEC-1(7)491> particularly with respect to the detailed structure of various azepine ring systems, and the reader is referred to that chapter in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) for background studies. Thus 1*H*-azepine is unstable and rapidly tautomerizes into the 3*H*-tautomer. Only *N*-substituted derivatives exist in the 1*H*-tautomeric form. The reason put forward for this is that the existence of a planar system would need the formation of an antiaromatic

8π electron system. Theoretical calculations have confirmed the extensive conjugation of the polyene system and the nonplanar geometry of the ring, although it has been suggested that the geometry owes more to steric influences than to electronic effects. Further calculations suggest that only the azepinium ion assumes full aromatic character. The polyene nature of the ring system is very evident in the chemistry of azepines, which is characterized by cycloaddition reactions and metal complex chemistry normally associated with homocyclic and acyclic polyene systems.

The chemistry of azepines has been well served by a number of excellent reviews. The chemistry of dibenzazepines and other tricyclic azepines and of azepine ring systems containing two heterocyclic rings has been discussed $\langle 84\text{HC}(43)1, 84\text{HC}(43)637 \rangle$, and azepines feature largely in reviews of medium ring nitrogen heterocycles $\langle 91\text{T9131} \rangle$ and azepine alkaloids $\langle 89\text{MI } 901-01 \rangle$. The use of diazabicycloundecene (DBU) as a base in synthetic chemistry as well as a number of related pyrimidinoazepines has been reviewed $\langle 87\text{AHC}(42)83 \rangle$. In addition to immediate reviews on azepine systems, reviews of areas which have impact on azepine chemistry have appeared. Most pertinent are on the chemistry of aryl azides and nitrenes $\langle \text{B-}84\text{MI } 901-01 \rangle$ and the photochemistry of phthalimide and its derivatives $\langle \text{B-}84\text{MI } 901-02 \rangle$. Current awareness is assisted by annual issues of *Progress in Heterocyclic Chemistry* published under the auspices of the International Society of Heterocyclic Chemistry.

The present chapter is not intended to be a catalogue of all aspects of azepine chemistry which have been published since CHEC-I. Thus, for example, many established areas such as the Beckmann and Schmidt reactions for the preparation of reduced azepines are discussed only in respect to newer developments. The Beckmann rearrangement has been reviewed $\langle 87\text{OR}(35)1 \rangle$. The emphasis is to take forward the knowledge of azepine chemistry, to describe new chemistry and to develop earlier aspects which were just emerging when CHEC-I was being prepared. Such aspects include the synthesis and properties of azepine-3(2*H*)-ones, the formation of bicyclic and tricyclic azepines by the cyclization of diene-conjugated nitrile ylides and those results since 1984, theoretical and experimental, on the mechanism and synthetic applications of aryl azide chemistry.

9.01.2 THEORETICAL ASPECTS

A current working hypothesis for the formation of substituted azepines from monocyclic azides suggests the formation of a singlet nitrene which rearranges into didehydroazepine, a process which is followed by addition of a suitable nucleophile. In the absence of such a nucleophile the didehydroazepine reverts to singlet nitrene which then undergoes intersystem crossing to produce triplet nitrene. MNDO/2 calculations reveal a possible alternative mechanism for the production of triplet nitrene $\langle 88\text{JA}8092 \rangle$. These calculations have revealed that triplet 2-azacycloheptatrienylidene has an energy only 3 kcal mol⁻¹ above didehydroazepine. Hence it is quite feasible that the conversion to triplet nitrene is via this carbene. This is supported by the isolation of a carbene-derived product from the photolysis of *o*-azidobiphenyl in the presence of TCNE $\langle 84\text{JCS}(P1)1198 \rangle$ (see Section 9.01.10.04).

Restricted Hartree-Fock (HF) calculations have been carried out on 1*H*-azepine and the results compared with those obtained by semiempirical MNDO results to test whether the latter were sufficiently rigorous to apply to larger cyclopolyenes for which *ab initio* calculations may be prohibitive $\langle 84\text{JST}(19)277 \rangle$. According to these results, 1-*H*-azepine possesses a boat configuration with 22% chair character. This permits π -delocalization of the cyclic double bond system to a level comparable to that of a linear polyene. The data further suggest that the ring puckering is a consequence of ring strain rather than a destabilizing antiaromatic 8π -interaction. Overall ring shape is better predicted by the HF calculation; alternating bond distances are more accurately represented, however, by MNDO calculations.

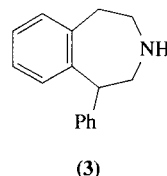
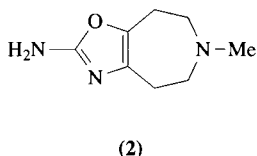
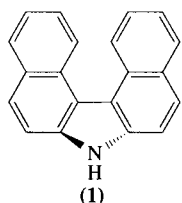
MOMM calculations, have been carried out on 1*H*- and 3*H*-azepine $\langle 88\text{MI } 901-01 \rangle$. The geometries of 1*H*-azepine are similar to those obtained by *ab initio* calculations, but with a better defined boat conformation. The MOMM calculations also show that the π -electrons of 3*H*-azepine are highly localized and that the molecule prefers to exist in a boat conformation, which is predicted to be 4.7 kcal mol⁻¹ more stable than the planar form and 17 kcal mol⁻¹ more stable than 1*H*-azepine. Semiempirical MNDO calculations on a number of methoxy 2,6-alkyl-1*H*-azepine-1-carboxylates predict that increasing the bulkiness of the alkyl substituent exaggerates the boat conformation $\langle 90\text{H}(31)163 \rangle$. The angles formed by C₇-N-C₂ and C₃-C₄-C₅-C₆ to the plane of the "hull" are comparable to those obtained by x-ray spectroscopy $\langle 81\text{AG}(E)699 \rangle$.

Ab initio calculations at HF, MP2, and CASSCF levels $\langle 93\text{JOC}6 \rangle$ predict that the singlet nitrenium

ion derived from 1*H*-azepine is planar and the empty p_z atomic orbital is fully conjugated with the orbitals around the ring, thus producing a fully conjugated, planar system with six π electrons and C_{2v} symmetry, i.e., an aromatic system. The N_1-C_2 and C_7-N_1 bonds show significant double bond character, and the bond angles average $128.57^\circ \pm 1.12^\circ$. The triplet azepinium ion is also planar but lacks the symmetry of the singlet state. The bond lengths are now intermediate between single and double bonds, and the bond angles vary from 119.32° for $C_1-C_2-C_3$ to 143.76° for $C_7-N_1-C_2$.

The dipole moments of 5- and 6-azaazulene have been calculated by semiempirical and *ab initio* methods (89JCS(P2)103). The compounds have lower ground state dipole moments than azulene itself, as the electron transfer from the seven-membered ring to the five-membered ring is counteracted by the inductive effect of the nitrogen atom, resulting in a partial reversal of charge transfer in the ground state.

Allinger's MM2 force field has been employed to model the differing stereochemical effects observed in the thermal and anionic Michael addition of compound (1) to acrylates (88JOC3879). Conformational studies have been carried out on 2-amino-6-methyl-4,5,7,8-tetrahydro-6*H*-oxazolo[5,4-*d*]azepine (2) and 2,3,4,5-tetrahydro-1-phenyl-1*H*-3-benzazepine (3) using the QCFF/PI method (87JST(37)137).



The recyclization of the aza-analogues of benzylium and naphthylmethylium ions to azatropylium ions and their benzylated analogues has been described by a variant of perturbation theory (PPP method) with bond orders on nonbonded atoms used as reactivity indices and the results correlated with the data obtained from mass spectrometry measurements (82KGS1673).

9.01.3 EXPERIMENTAL STRUCTURAL METHODS

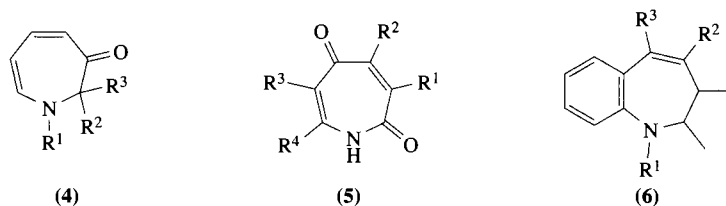
9.01.3.1 NMR Studies

The ^1H and ^{13}C NMR spectra of a number of new 1-substituted, 1,2-disubstituted, and 1,2,2-trisubstituted 1*H*-azepin-3(2*H*)-ones (4) have been fully assigned (90JCS(P1)3159). The data include carbon-proton coupling constants and long-range couplings in addition to proton and carbon chemical shifts. NMR studies of deuterium exchange in $[\text{D}_2]\text{trifluoroacetic acid}$ solution show immediate changes in the signal of the 5-position and a slower change in that of the 7-position, indicating deuterium exchange at, and hence loss of coupling to, the 4- and 6-positions (90JCS(P1)3163). Similarly, thorough characterization has been carried out on a number of 2-diethylamino-5-phenyl-3-substituted-3*H*-azepines (84RTC225).

The unequivocal assignment of structures to a number of chloroazepine-2,5-diones (5) by normal spectroscopic techniques was found not to be possible (84JHC801). However, very marked differences in the magnitudes of the concentration-dependent shifts of methyl substituents induced by $\text{Eu}(\text{fod})_3$ were observed which has made it possible to evaluate the regiochemistry of these compounds. The magnitude of shifts of the signals for the methyl group hydrogens was in the order 3-Me > 4-Me > 6-Me > 7-Me. The observed shifts have been rationalized in part by considering the dipole-dipole interaction of the azepindione-europium system.

The ^{13}C NMR spectra of a number of diastereoisomeric 2,3-dihydro-2,3-dimethyl-1*H*-benz[*b*]azepines (6) have allowed the relative configurations of the diastereoisomers to be assigned (83OMR(21)487). The chemical shifts of the asymmetric C_2 - and C_3 -carbon atoms of the R^*, R^* -diastereoisomers are approximately 1 ppm lower than those for the R^*, S^* -diastereoisomers. A second method, employing the chemical shifts of the Me-group at C_3 (δ_3), showed that when these

values were compared with the mean shift δ_m of the corresponding compounds with no C₂-substituent, the $\delta_3 - \delta_m$ difference was always negative for (*R*^{*},*R*^{*}), and always positive for (*R*^{*},*S*^{*}).

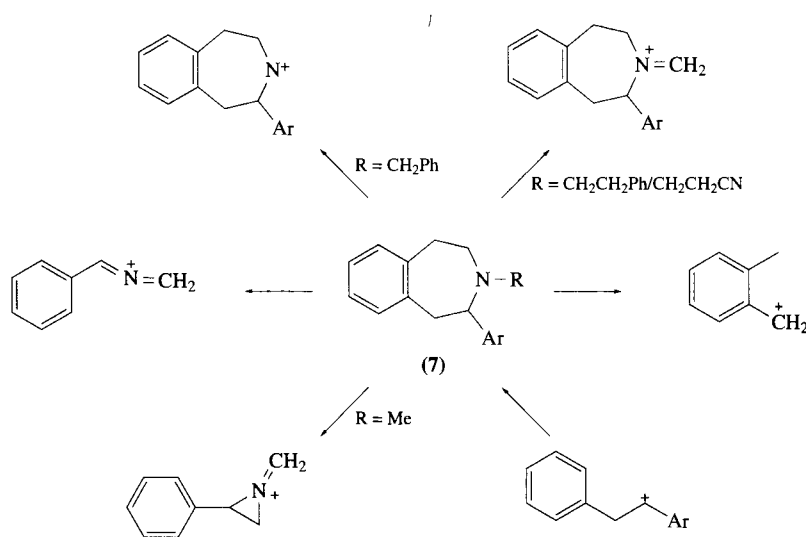


Selected ¹H and ¹³C NMR data of a number of azepines published in the 1980s and 1990s are reproduced in Tables 1 and 2, respectively. In many instances the spectrum selected is the simplest of a series of structurally related compounds. Unless otherwise stated, the spectra were measured in deuteriochloroform solution.

9.01.3.2 Mass Spectrometry

A comparative analysis of the EI breakdown of arylsulfonyl-1*H*-azepines and *N*-carboxymethylazepines carried out by Kulkarni *et al.* <88OMS(23)240> indicates the primary breakdown is one of, respectively, N—S and N—C cleavage. In the latter case there is little indication of a competitive hydrogen capture by the azepine ring, a process preferred in the fragmentation of the isomeric aniline derivatives, nor could a correlation between mass spectral behavior and thermal and photochemical reactions be established.

A detailed study <81MI 901-01> of the fragmentation of 2-aryl-2,3,4,5-tetrahydro-1*H*-benz[*d*]azepines (7) shows a number of common ions together with others which exhibit a marked dependency upon the nature of the *N*-substituent (Scheme 1). The major components from the fragmentation of 7-aryl-7,8-dihydro-6*H*-isoxazolo[4,5-*b*]azepines are arylcyclopropenium and isoxazoloazetine ions formed by α -cleavage and hydrogen migration <82OMS(17)348>.



Scheme 1

The mass spectral fragmentation patterns of 5*H*-dibenz[*b,f*]azepines have been reinvestigated employing 5*H*-dibenz[*b,f*]azepine and 10,11-dihydro-5*H*-dibenz[*b,f*]azepine, and the underlying fragmentation pathways have been elucidated by examination of the fragmentation of their deuterated derivatives and metastable ions <86JHC731>. In agreement with earlier studies <73JCS(P2)648>, the fragmentation pathways of both series of compounds are characterized by a series of complex skeletal rearrangements accompanied by hydrogen (or deuterium) exchanges. The methyl radical expelled in formation of M-15 in both the dihydro-derivative and its 5-methyl derivative is derived from the benzylic carbon. The fragmentation pattern for dibenz[*b,f*]azepine is shown in Scheme 2.

Table 1 Proton NMR chemical shifts for typical azepines.

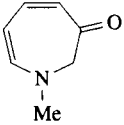
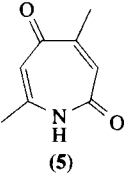
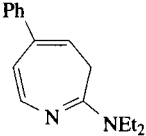
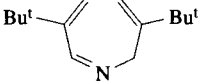
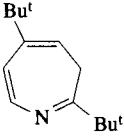
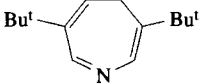
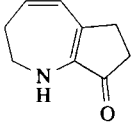
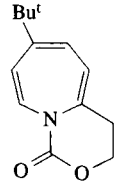
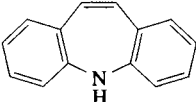
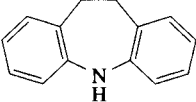
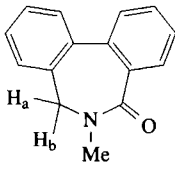
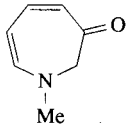
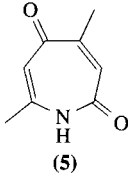
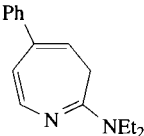
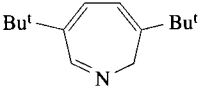
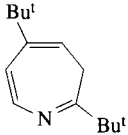
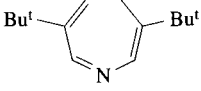
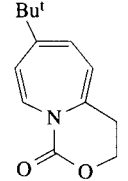
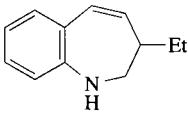
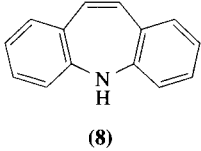
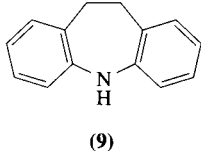
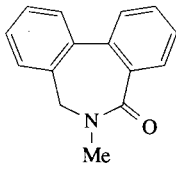
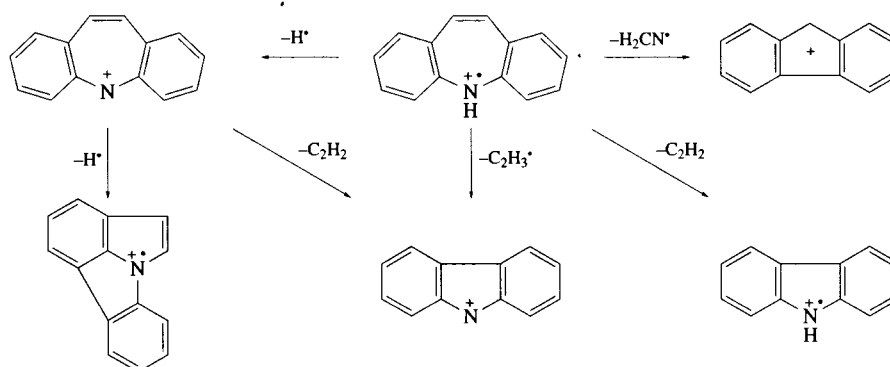
Azepine	Ring protons (ppm)							Other protons [J values] (Hz)	Ref.
	H-2	H-3	H-4	H-5	H-6	H-7	H-10(11)		
 (4)	3.57		6.17	5.68	5.17	6.72		[$J_{4,5}$ 11.0, $J_{3,6}$ 9.1, $J_{6,7}$ 7.2]	90JCS(P1)3159
 (5)		6.81			5.80			(Me 2.16, 2.19 H 8.63)	84JHC801
		2.77	5.33		5.97	7.30		[$J_{3,4}$ 7.5, $J_{6,7}$ 8.1]	84RTC225
	3.5		6.09	6.60		7.91		[$J_{4,5}$ 6.2, $J_{5,7}$ 1.9]	94JCS(P1)1753
		1.1 3.6	5.03		6.28	7.28		[$J_{3,4}$ 7.0, $J_{6,7}$ 8.5]	94JCS(P1)1753
	6.73		2.05	5.54		8.55		[$J_{4,5}$ 7.3, $J_{5,7}$ 2.1]	94JCS(P1)1753
	3.29	2.63	6.03	6.03					85MI 901-01
	5.94	5.53		5.63	5.15				84MI 901-03
							6.32	(NH 4.92)	84JHC197
							3.06	(NH 5.94)	84JHC197
						3.88 4.45		[$J_{a,b}$ 14.6]	91CZ193

Table 2 Carbon-13 NMR chemical shifts for typical azepines.

Azepine	Ring carbons (ppm)							Ref.
	C-2	C-3	C-4	C-5	C-6	C-7	C-10(11)	
 (3)	62.5	180.2	123.33	142.01	99.41	147.19		90JCS(P1)3159
 (5)	164.7	130.8	145.9	183.6	111.2	150.2		84JHC801 ^a
	146.4	31.3	108.4	141.2	110.1	142.1		84RTC225
	52.2	150.6	119.1	128.6	158.7			94JCS(P1)1753
	164.0	32.4	110.0	147.3	139.7			94JCS(P1)1753
	130.7	140.9	26.4	125.6	160.1			94JCS(P1)1753
	129	119.0	150.7	121.5	113.0	138.5		84MI 901-03
	48.5	45.4	134.2	128.8				83OMR(21)487
 (8)							132.12 132.10	84JHC197 83JHC109 ^a
 (9)							34.94	84JHC197
				168.34		53.07		91CZ193

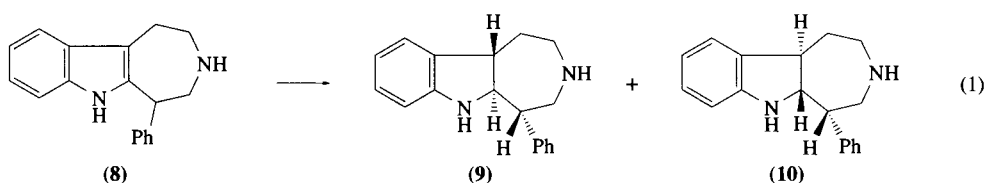
^aDMSO-d₆



Scheme 2

9.01.3.3 X-ray Studies

Trans reduction of 5-phenyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (**8**) gives two isomeric products, (**9**) and (**10**) (Equation (1)), the structures of which were established by x-ray crystallography (83JCS(P2)1599). In the solid state the conformations of the two products are associated by N—H···N and N—H···phenyl hydrogen bonds.

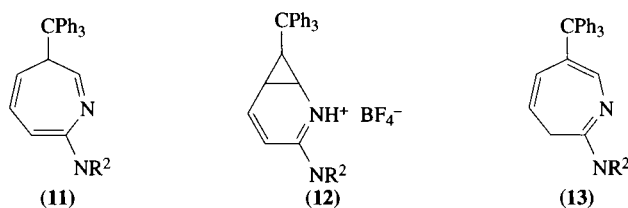


The molecular dimensions have been determined by x-ray crystallography for a considerable number of complex molecules. Of the more simple and representative structures, data have been reported for a number of oxazolo- and oxazinoazepine derivatives (84MI 901-03), 2,2-dimethyl-1-phenyl-1*H*-azepin-3(2*H*)-one (89JCS(P1)425), 3-methyl-3,5-diphenyl-5*H*-benz[*c*]azepine (92JCS(P1)1709), 2-diethylamino-3-isopropyl-5-phenyl-3*H*-azepine (84RTC225), 3,4,6,7-tetraphenyl-3*H*-azepine (87H(25)387), and a number of tetrahydroazepines (86AX(B)478).

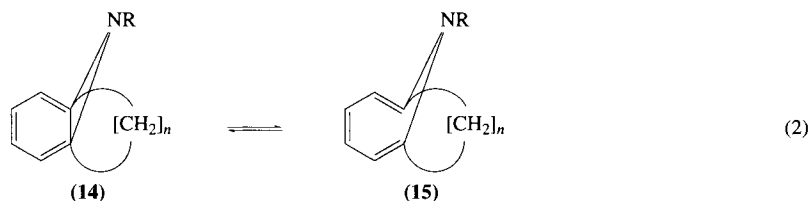
9.01.4 THERMODYNAMIC ASPECTS

Demethoxycarbonylation of methyl 3,6-di-*t*-butyl-3*H*-azepine-1-carboxylate by DBU in xylene gives a mixture of not only the corresponding 3,6-di-*t*-butyl-3*H*-azepine, but also the 2*H*-azepine and 4*H*-azepine isomers (94JCS(P1)1753). When heated in toluene at 125°C the 2*H*- and 3*H*-azepines are each converted quantitatively into azepine mixtures consisting of 2*H*-, 3*H*-, and 4*H*-azepines in the ratios 12:51:1 (from the 2*H*-isomer) and 12:56:1 (from the 3*H*-isomer). The distribution of the azepine isomers is proportional to their relative thermal stabilities as they interconvert via an allowed 1,5-hydrogen shift. Under similar conditions, methyl 2,5-di-*t*-butyl-3*H*-azepine-1-carboxylate gives only the 3*H*-tautomer. Similar thermal tautomerizations of 3-phenyl-3*H*-azepine to 7-phenyl-3*H*-azepine (89H(29)253) and ethyl 4-oxo-4*H*,10*H*-pyrimido[1,2-*a*]azepine-3-carboxylate (84H(22)2285) to the 4*H*,6*H*-tautomer have been observed.

Tetrafluoroboric acid treatment of 7-amino-3-trityl-3*H*-azepines (**11**) converts them into the azanorcaradiene salts (**12**) which revert back to (**11**) on treatment with potassium carbonate in acetone (88T3309). Warming compounds (**11**) converts them into 2-amino-6-trityl-3*H*-azepines (**13**).

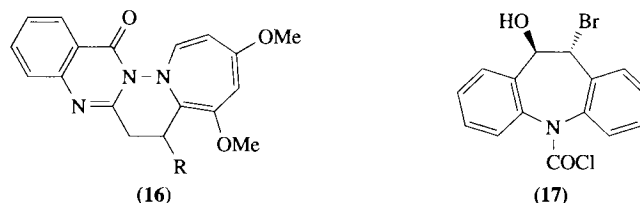


The valence tautomeric isomerism of oligomethylene clamped 1*H*-azepines, illustrated in Equation (2), shows a marked dependence upon the *N*-substituent and the value of *n*. For example, where *n* = 3 and R = COOMe, the closed tautomer (14) is preferred whereas, in contrast, for the next homologue the open tautomer (15) is preferred. In the case of R = H, when, *n* = 3 the closed tautomer predominates, which is reversed when *n* = 5. When *n* = 4, the two tautomers exist in a 3 : 7 equilibrium <89CB1765>.



The temperature-dependent NMR spectra of a number of methyl and ethyl 1*H*-azepine-1-carboxylate derivatives have been measured and the results interpreted as a function of hindered rotation around the amide bond, not in terms of nitrogen inversion <90BCJ3162>. The free energies of activation around the amide bonds calculated from the ¹H and ¹³C NMR spectra are reported.

The barrier for boat-to-boat inversion is considered to be below 5 kcal mol⁻¹ in 1*H*-azepines, but in the compounds (16; R = H, Me) the barrier is estimated to be much higher, with a minimum free energy barrier of 30 kcal mol⁻¹ <85JCS(P1)335>. A possible reason is the high barrier to inversion of the azepine ring nitrogen by eclipsing of nitrogen lone pairs of electrons. Variable-temperature studies of *trans*-10-bromo-10,11-dihydro-5*H*-dibenz[*b,f*]azepine-5-carbonyl chloride (17) show the presence of two conformationally restricted conformers which are interconverted through ring inversion about the C_{4a}—N₅—C_{5a} bonds <88T4863>. The free energy of activation for this ring inversion obtained in the 21–38°C range is 16.5 ± 0.2 kcal mol⁻¹.

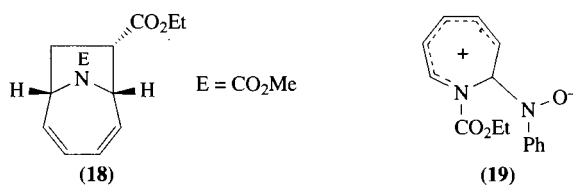


9.01.5 REACTIVITY OF MAXIMALLY CONJUGATED AZEPINES

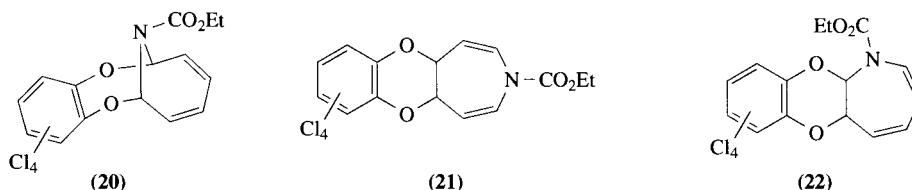
Fully conjugated azepines exhibit the character of cyclic polyenes, which is illustrated by their ability to undergo a number of electrocyclic cycloaddition reactions in which they participate as 2π, 4π, and 6π components <84CHEC-I(7)491>. Alkyl 1*H*-azepine-1-carboxylates successfully undergo Diels–Alder [4 + 2]π cycloadditions with most dienophiles at the C₂–C₅ positions, but, with increasing substitution at C₃ and C₆ steric constraints force the system towards competing kinetically favored [6 + 2]π cycloaddition, when the azepine functions as a triene. This triene character also predominates in Diels–Alder cycloaddition reactions, even for unsubstituted azepines, when the reaction is carried out in the presence of chromium(0). For example, methyl 1*H*-azepine-1-carboxylate reacts with excess ethyl acrylate in the presence of (η⁶-naphthalene)tricarbonylchromium(0) to form the homotropene (18) as a single diastereoisomer in 77% yield <92JOC5290>.

Ethyl 1*H*-azepine-1-carboxylate is known to react with nitrosobenzene in benzene to form a [6 + 2]π adduct together with a small yield (17%) of the [4 + 2]π adduct <80TL319>. If the reaction is carried out in refluxing chloroform, the yield ratio is reversed, the [4 + 2]π adduct now being formed in the higher yield (41%) and the [6 + 2]π adduct in 22% yield <92H(34)497>. The improved yields are attributed to stabilization of ionic intermediate (19) by solvation by chloroform.

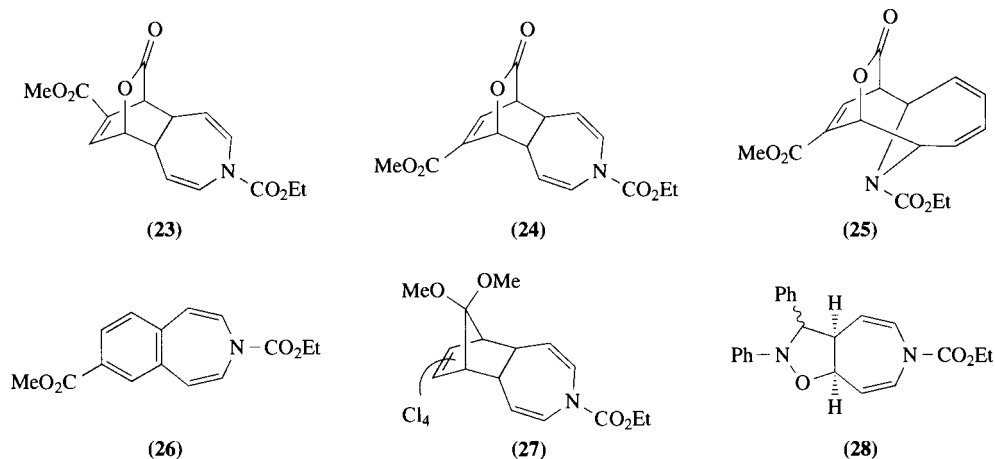
In addition to functioning as the polyene component in Diels–Alder reactions of 1*H*-azepines, a dienophilic character is demonstrated by the ease with which they also function as the dienophile in inverse cycloaddition reactions. In the reaction of ethoxy 1*H*-azepine-1-carboxylate with 3,4,5,6-tetrachloro-1,2-benzoquinone, both [2 + 4]π and [6 + 4]π adducts are formed in a hetero Diels–



Alder reaction <86BCJ2485>. The two adducts **(21)** and **(22)** are stable, remaining unchanged after heating at 180°C in benzene. On the other hand, the [6 + 4] π adduct **(20)**, the major product of the reaction, is converted into **(22)** in 63% yield at 90°C.



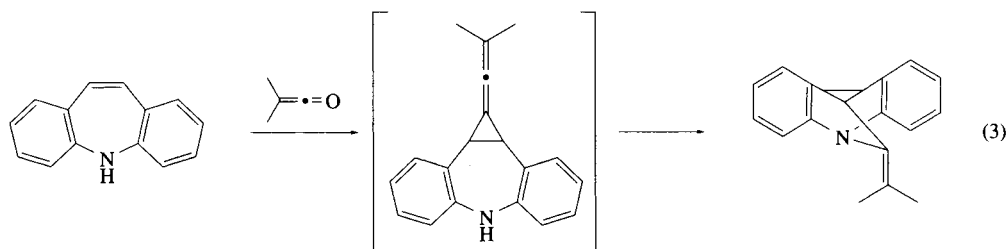
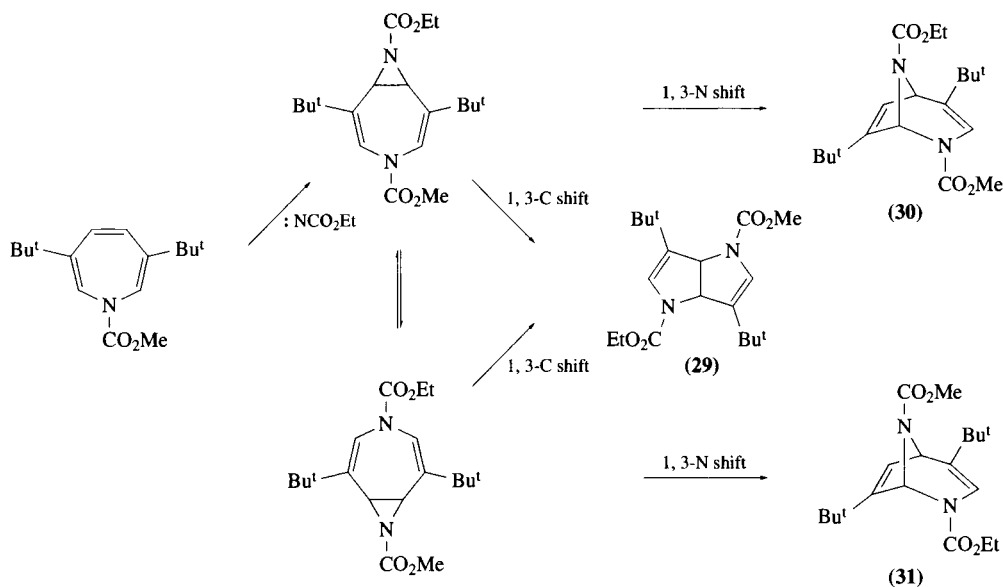
This ability of ethyl and methyl 1*H*-azepine-1-carboxylate to participate as an enophile and a dienophile is demonstrated in a further report describing their reactions with methyl pyrone-3-carboxylate and its 5-isomer <84BCJ3483>. On heating at 80°C for 68 hours, methyl 1*H*-azepine-1-carboxylate and the pyrone-3-isomer yielded the [2 + 4] π adduct **(23)** and the azepine [6 + 4] π dimer. Under similar conditions ethyl 1*H*-azepine-1-carboxylate and the corresponding pyrone-5-isomer gave a mixture of the [2 + 4] π and [6 + 4] π adducts **(24)** and **(25)** in yields of 25% and 20%, respectively. At 110°C the products consisted of the azepine [6 + 6] π dimer and a small amount of 3-ethyl 7-methyl 3*H*-3-benzazepine-3,7-dicarboxylate **(26)**, arising from **(24)** by extrusion of carbon dioxide. In a further reaction the same authors have demonstrated the formation of **(27)** by reaction with tetrachlorocyclopentadienone dimethyl acetal.



The reaction of methyl 1*H*-azepine-1-carboxylate with *N*, α -diphenylnitrone yields [2 + 3] dipolar cycloaddition products **(28)** as a mixture of *exo*- and *endo*-isomers <92H(34)497>, the structures of which were assigned with the aid of LAOCOON III simulated NMR spectra. The almost equal distribution of isomers at C₅ and the absence of any *trans*-product favors a concerted 1,3-dipolar addition rather than the involvement of a stepwise ionic mechanism, since in a stepwise reaction the conformational flexibility of the azepine ring would allow the second bond to be formed on either face of the azepine ring.

Methyl 3,6-di-*t*-butyl-1*H*-azepine-1-carboxylate reacts with ethyl azidoformate to give a mixture of the 2,6-diazabicyclo[3.3.0]octa-3,7-diene **(29)** in 30% yield, together with a smaller amount of the 2,8-diazabicyclo[3.2.1]octa-3,6-dienes **(30)** and **(31)** (Scheme 3) <83TL2275>. The initial step is assumed to be nitrene addition to the 4,5-double bond of the azepine (Scheme 3), although it is possible that **(30)** may also arise by direct 1,4-addition. If the reaction is carried out with *N*-toluenesulfonyloxyurethane as nitrene source, **(30)** is the main product. Similar studies showed that

the 3,6-trimethylsilyl derivative undergoes the same rearrangement, whereas the 4,7-trimethylsilyl isomer does not, suggesting that large C_3 - and C_6 -bulky substituents are necessary for the reaction to proceed $\langle 84TL5669 \rangle$. The base-catalyzed reaction of 5*H*-dibenzo[*b,f*]azepine with 2-chloro-2-methyl-3-butyne under phase-transfer conditions gives 11-isopropylidene-1a,10b-dihydro-1*H*-1,6-methanodibenz[*b,f*]cyclopropa[*d*]azepine, the structure of which was confirmed by x-ray analysis $\langle 89M797 \rangle$. The reaction proceeds by the initial formation of a cyclopropane derivative as illustrated in Equation (3).

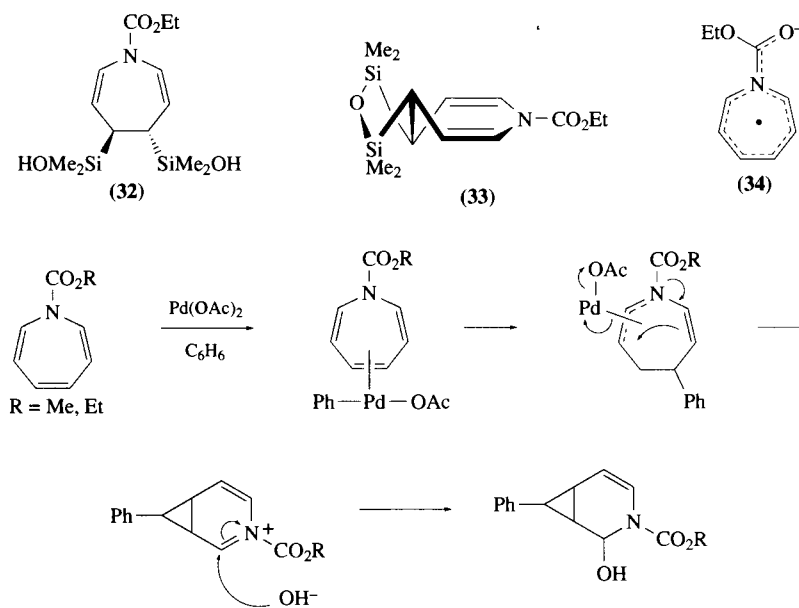


The ability of 5*H*-dibenzo[*b,f*]azepine to undergo triplet-sensitized photodimerization has been recorded $\langle 84CHEC-1(7)491 \rangle$. This property has been investigated in photopolymer systems containing terminal dibenzazepine groups in, for example, the production of block $\langle 92MAC1551 \rangle$, cross-linked thin films $\langle 87JPS(C)223 \rangle$, and photolithographic applications $\langle 88ZC65 \rangle$. A study of the photodimerization of 5-acyl derivatives using nanosecond laser photolysis $\langle 87MI 901-01 \rangle$ has revealed that the triplet intermediate has a lifetime of 17 ms at room temperature and the quantum yield of dimerization is 0.15 at a concentration of $2.0 \times 10^{-3} \text{ mol}^{-1}$.

Chlorosilane derivatives in the presence of magnesium undergo *trans*-addition to the 4,5-double bonds of ethyl 1*H*-azepine-1-carboxylate $\langle 83BCJ175 \rangle$. For example, the reaction with dimethyldichlorosilane, after treatment with water during workup, gives (32), which loses water to form the cyclic derivative (33). The reaction is considered to proceed by way of the radical anion (34) formed by one-electron transfer from magnesium.

The reaction of 1*H*-azepine derivatives with palladium acetate is highly solvent dependent. Ethyl and methyl 1*H*-azepine-1-carboxylates react in benzene in the presence of palladium acetate to give the bicyclo[4.1.0]-3-azahepta-4-ene (35) (Scheme 4) $\langle 89JOM(363)231 \rangle$. When the reaction is carried out on the ethoxy derivative in chloroform or acetonitrile, *trans-trans*-mucondialdehyde is formed, whereas in acetic acid, the product is ethyl 2,3-diacetoxy-2,3-dihydro-1*H*-azepine-1-carboxylate $\langle 90H(31)1491 \rangle$.

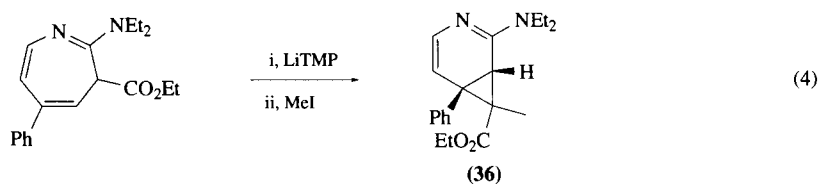
Tricarbonyl(2-5- η -1*H*-azepine)iron reacts with tropylium tetrafluoroborate to give a derivative which after decomplexation with trimethylamine oxide, yields 3-(2,4,6-cycloheptatrienyl)-3*H*-azep-



Scheme 4

ine <89H(29)253>. The 1-ethyl carboxylate tricarbonyliron derivative is known to form a $[4 + 2]\pi$ cycloadduct with tetracyanoethene, which undergoes rearrangement to the more usual $[6 + 2]\pi$ cycloadduct <84JOM(214)C36>. The effect of solvent upon the rate of reaction and a comparison of the rates of reaction with tetracyanoethene and tricyanoethene support the view that the cycloaddition reaction is concerted <87JCS(D)2927>, which is in contrast to the conclusions of investigations on a related ruthenium complex <77JCS(D)204>.

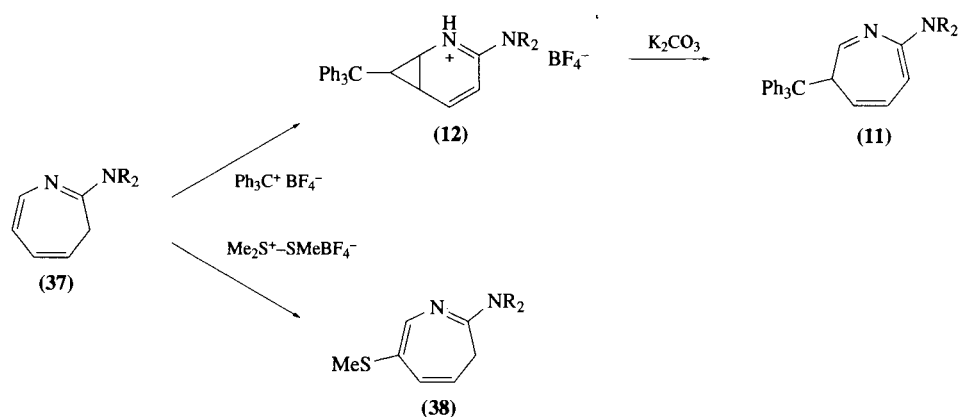
The azepinium anions from 2-methoxy-3*H*-azepine <90JHC107> and 2-dimethylamino-5-phenyl-3*H*-azepine <84RTC225> react with electrophiles to give a number of 3-alkyl-, 3-thioalkyl-, and 3-acyl-3*H*-azepines. Further alkylation studies reveal that C_5 is the next position of attack <85RTC166>. Under similar conditions, the anion from ethyl 2-dimethylamino-5-phenyl-3*H*-azepine-3-carboxylate undergoes rearrangement with methyl iodide to give the azanorcaradiene, ethyl 2-diethylamino-7-methyl-3,4-dihydro-3,4-methano-4-phenylpyridine-7-carboxylate (36) (Equation (4)) <87H(26)685>.



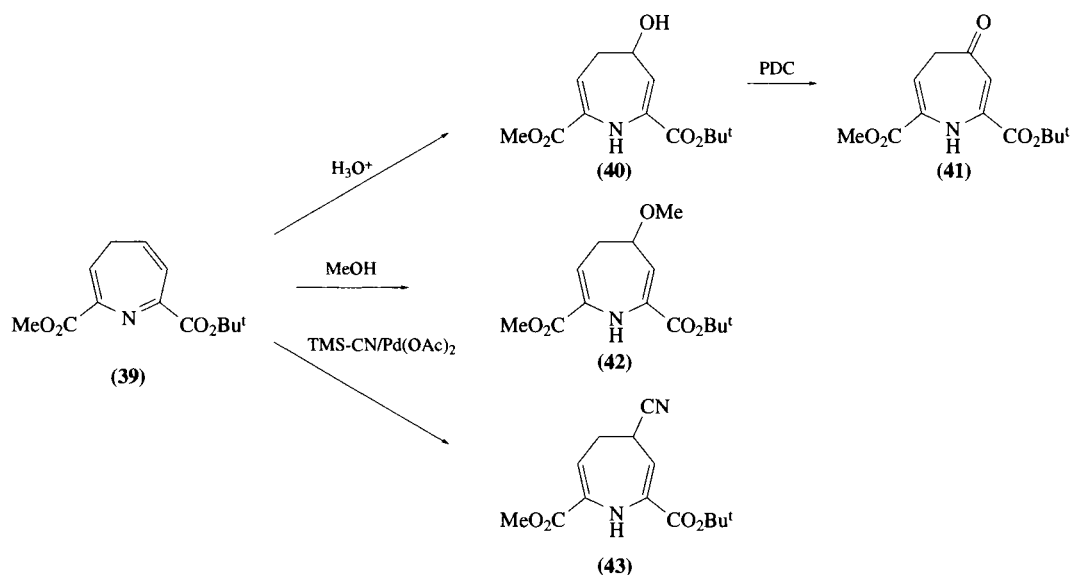
Treatment of 2-amino-3*H*-azepines (37) with trityltetrafluoroborate delivers the salts of the 2-azanorcaradienes (12) <88T3309> which on treatment with K_2CO_3 in acetone form the 7-amino-3-trityl-3*H*-azepines (11), the valence tautomerization of which has been described (see Section 9.01.4). In a similar fashion, 2-amino-6-trityl-3*H*-azepines (38) are obtained by reaction of (37) with dimethylmethylsulfonium tetrafluoroborate (Scheme 5). In this latter case no intermediate norcaradiene is isolated.

4*H*-Azepine esters (39) undergo a number of 1,4-additions of nucleophiles as shown in Scheme 6 <90JHC107>. With citric acid the hydroxy derivative (40) is obtained which can be converted to the ketone (41) on oxidation with PDC, and on gel chromatography with methanol the adduct (42) was formed in quantitative yield. Addition of TMS-CN to (39) in the presence of palladium(II) acetate yielded the nitrile (43).

The reaction of *N*-alkyl-5*H*-dibenz[*b,f*]azepines with MCPBA <84CHEC-1(7)491> has been extended to *N*-benzyl-10-substituted and 10,11-disubstituted derivatives <84CPB3857>. The products are 9-acyl-9*H*,10*H*-acridones, probably formed by acid-catalyzed rearrangement of the initially formed



Scheme 5



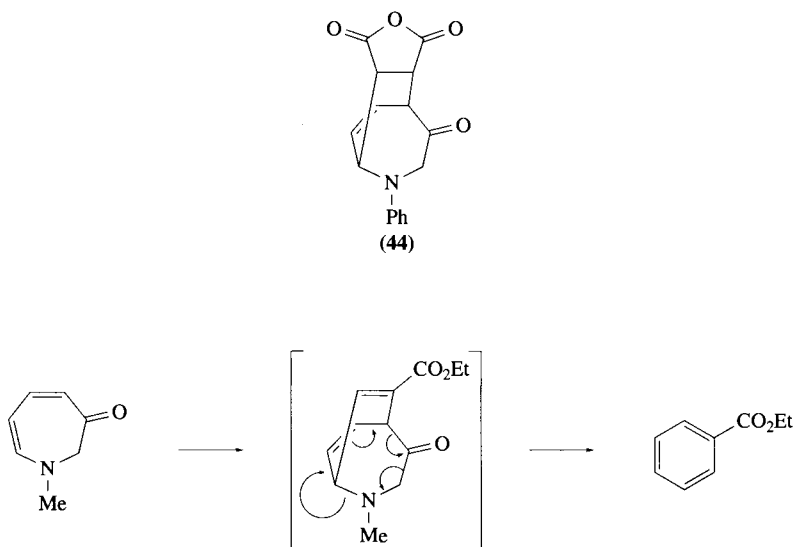
Scheme 6

10,11-epoxide. 5*H*-dibenz[*b,f*]azepine itself is oxidized to 9-formyl-9*H*,10*H*-acridine by *t*-butyl hypochlorite [88JHC863] and to acridine by silver salts [88JOC1112]. The involvement of a resonance-stabilized nitrenium ion has been invoked to rationalize the latter reaction.

9.01.6 REACTIVITY OF REDUCED AZEPINE SYSTEMS

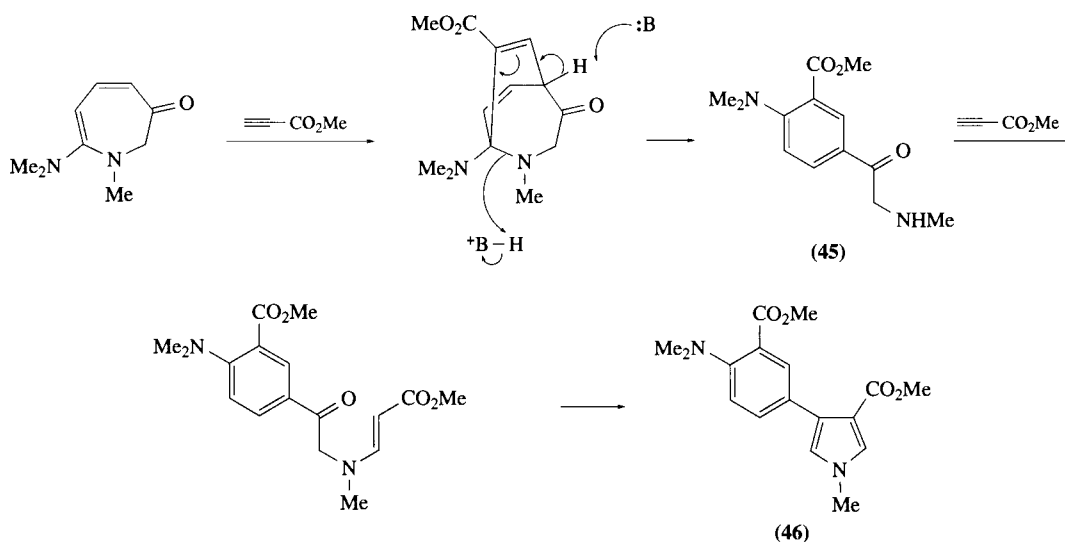
1*H*-azepin-3(2*H*)-ones react with dienophiles to give [4 + 2] π adducts, many of which are intermediates to ring transformation products. 1-Phenyl-1*H*-azepin-3(2*H*)-one reacts with maleic anhydride over 48 h at room temperature to give the adduct (44) as a stable solid in 64% yield [90JCS(P1)3169]. The *N*-methyl analogue reacts even more rapidly but the product is unstable. With (44) a retro-Diels-Alder reaction occurs by flash pyrolysis, giving the two starting materials, a behavior reflected in the mass spectrum. In the reaction of 1-methyl-1*H*-azepine-3(2*H*)-one with ethyl propiolate, the initial adduct undergoes rearrangement to give ethyl benzoate as shown in Scheme 7. A similar reaction also takes place with DMAD, and the product is dimethyl phthalate.

The regiochemistry of the cycloaddition step has been elucidated with deuterated 1-methyl-1*H*-azepin-3(2*H*)-one.



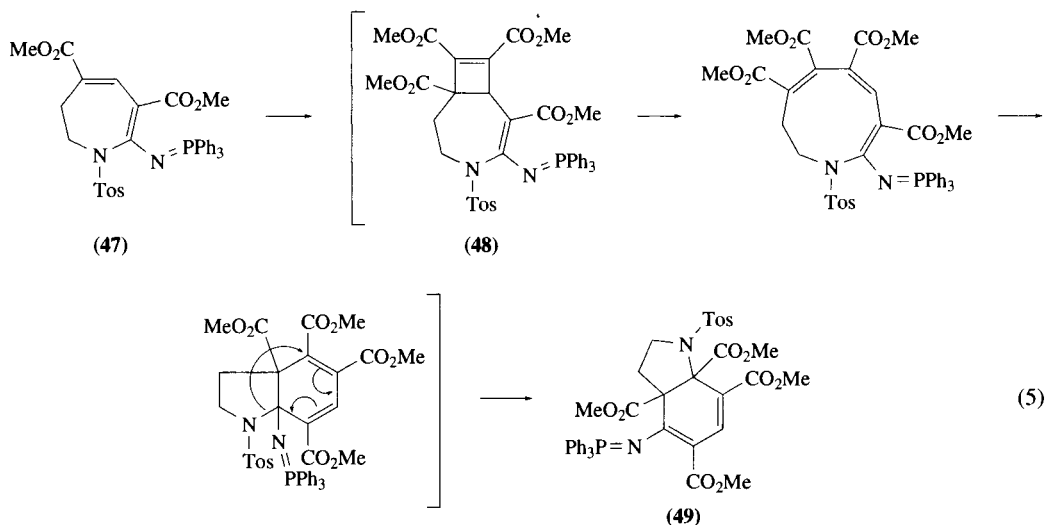
Scheme 7

The related cycloaddition of the more reactive 7-dimethylamino-1-methyl-1*H*-azepin-3(2*H*)-one with 2 mol of methyl propiolate <93CC1417> gives the trisubstituted pyrrole derivative (46). In this example, the initially formed phenyl derivative (45) reacts with a further molecule of ester which is then followed by a cyclocondensation reaction to give (46) (Scheme 8).

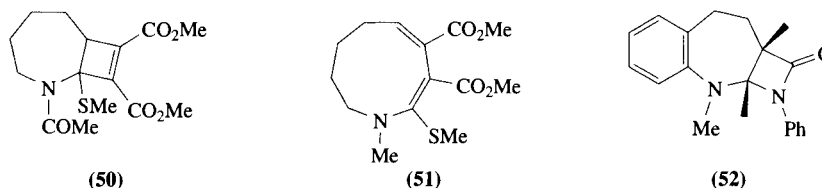


Scheme 8

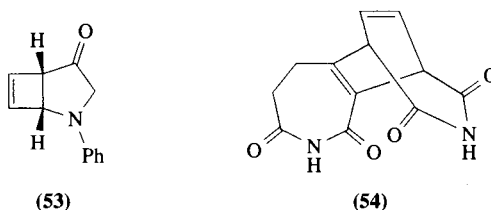
1-Methyl-2-(methylthio)-2,3,6,7-tetrahydroazepine reacts with 1,2,4,5-tetrazines to yield 1-methyl-2,3,4,5-tetrahydropyridazino[4,5-*b*]azepines <87JHC545>. Reaction of the 6,7-dihydro-1*H*-azepine (47) with DMAD gives the tetrahydroindole derivative (49) <86CB2114>. The initial reaction step is the formation of a cycloadduct, in this case a [2 + 2] π adduct (48), which undergoes ring expansion and subsequent recyclization (Equation (5)). Diethyl acetylenedicarboxylate undergoes a similar reaction. A ring expansion similar to that proposed above has also been observed in the reaction of 6,7-dihydro-1*H*-benz[*b*]azepines with methyl propiolate and DMAD <89JHC1719>.



1-Acetyl-2-thiomethyl-4,5,6,7-tetrahydro-1*H*-azepine reacts with DMAD in acetonitrile to give the stable $[2 + 2]\pi$ adduct (50) <82CPB3959>. In the case of the 1-methyl analogue the adduct cannot be isolated, the ring expanded product (51) being isolated. 4,5-Dihydro-1,3-dimethyl-1*H*-benz[*b*]azepine also gives a $[2 + 2]\pi$ adduct (52) with phenylisocyanate <91JCR(S)204>.



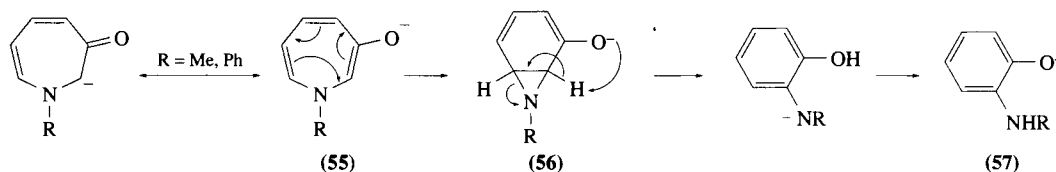
Photolysis of 1-phenyl-1*H*-azepin-3(2*H*)-one yields the bicyclic compound (53) upon irradiation <90JCS(P1)3169>, whereas 1*H*-azepine-2,7-dione gives a dimer, to which the structure (54) has been attributed <94JHC215>.



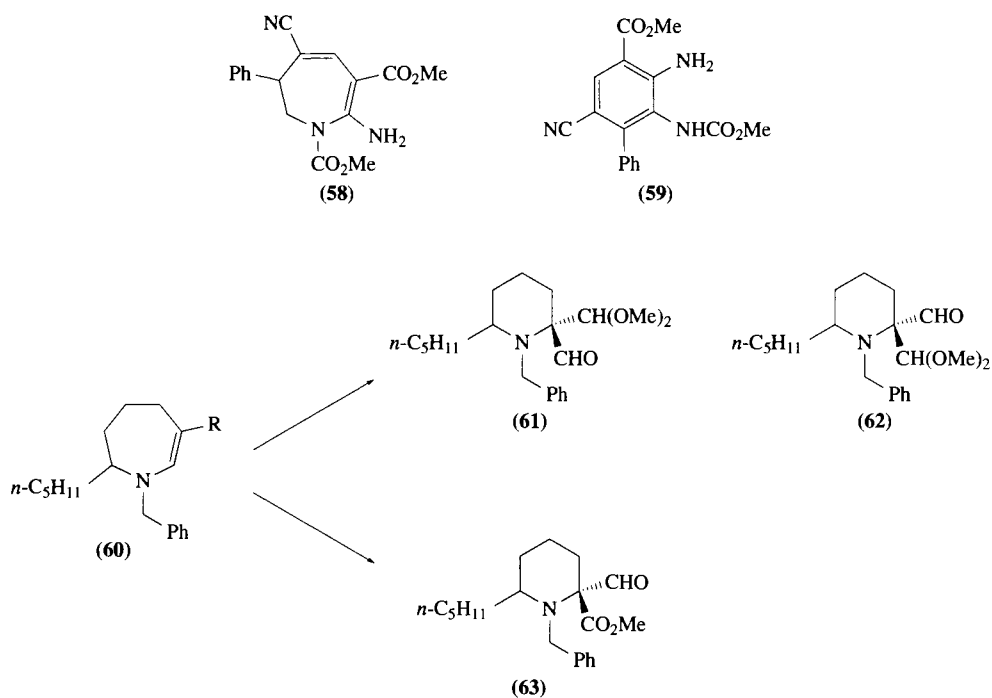
Dihydro- and tetrahydroazepines undergo a number of rearrangement reactions which range from simple bond shifts to complete change in structure. For example, substituted 2,5-dihydro-1*H*-benz[*b*]azepines undergo base-catalyzed rearrangement in a regiospecific and stereospecific manner to give 2,3-dihydro-1*H*-benz[*b*]azepines <84JCR(S)142>. Most rearrangements reported, however, involve ring contractions. When preparation of equilibrium concentrations of the enolates (55) from 1-methyl- and 1-phenyl-1*H*-azepin-3(2*H*)-ones is attempted, a smooth ring contraction to the aminophenol (57) occurs <90JCR(S)336>. The mechanism shown in Scheme 9 involves formation of the aziridine (56) which then undergoes ring opening to form (57). A similar ring contraction is involved <84CPB2596> when the 6,7-dihydro-1*H*-azepine (58) is oxidized with DDQ, the product being the urethane (59).

The aldehyde (60; R = CHO) undergoes ring contraction in the presence of bromine in methanol (Scheme 10) to give the two diastereoisomeric ketals (61) and (62) in the ratio 95:5 <89JOC4419>. If the aldehyde is first converted into the dimethyl ketal (60; R = (OMe)₂), the same two products are isolated in the ratio 20:80. Similar treatment of the ester (60; R = CO₂Me) gives the single diastereoisomer (63). No detectable amount of the other diastereoisomer is observed.

Photolysis of 10*H*-azepino[1,2-*a*]indole (64) in methanol or ethanol <82JCS(P1)1871> gives respec-



Scheme 9



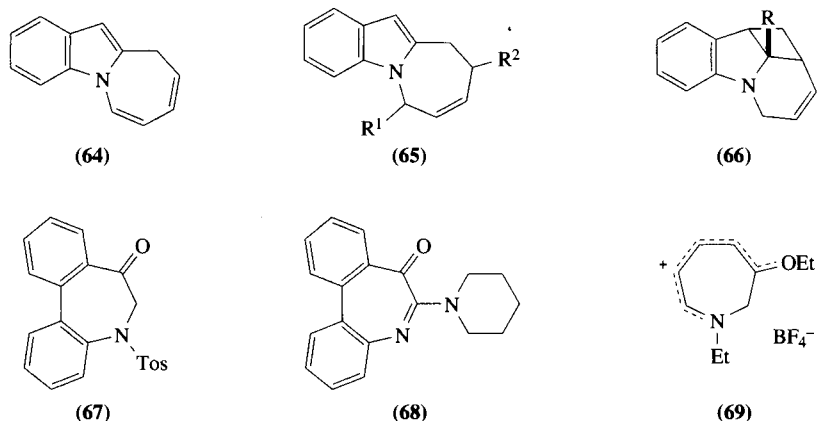
Scheme 10

tively the 6- and 9-alkoxy-6,9-dihydro-10*H*-azepino[1,2-*a*]indoles (**65**; $R^1 = \text{OMe}$ or OEt , $R^2 = \text{H}$) and (**65**; $R^1 = \text{H}$, $R^2 = \text{OMe}$ or OEt) together with substantial amounts of the rearrangement product, 1*a*,4,9*b*-tetrahydro-10-methoxybenzo[*b*]cyclobuta[*h*,*l*]indolizine (**66**; $R = \text{OMe}$, OEt). Reaction of 6,7-dihydro-1-tosyl-5*H*-dibenz[*b*,*d*]azepin-7-one (**67**) with piperidine results in ring contraction to phenanthridin-6-carboxaldehyde <85S612>. If the reaction is carried out in the presence of ethyl 3-(triphenylphosphonium)propionate perbromide the compound (**68**) is formed.

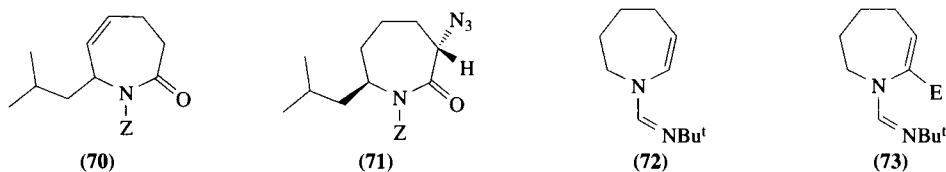
1-Methyl-1*H*-azepin-3(2*H*)-one gives the *O*-ethyl derivative (**69**) on treatment with triethyloxonium tetrafluoroborate <90JCS(P1)3163>. Observation of the rates of deuterium incorporation in [^2H]trifluoroacetic acid solution showed sequential deuterium exchange at the 4-, 6-, and 2-positions. Since (**69**) is unaffected under these conditions over a period of several weeks, it must be assumed that the exchange takes place via the free base. Chlorination of 1-methyl-1*H*-azepin-3(2*H*)-one with one or two equivalents of NCS affords respectively 4-chloro-1-methyl-1*H*-azepin-3(2*H*)-one and 4,6-dichloro-1-methyl-1*H*-azepin-3(2*H*)-one.

A number of interesting reactions have been carried out on ring systems of which the azepine ring is just one example of a number of cyclic amines. For example, treatment of (**70**) with potassium hexamethyldisilazide in THF at -78°C followed by trisyl azide gives a 65% yield of the *trans*-azide (**71**) <92TL6859>. A phenylseleno derivative is formed in 78% yield when trisyl azide is replaced by phenylselenenylchloride.

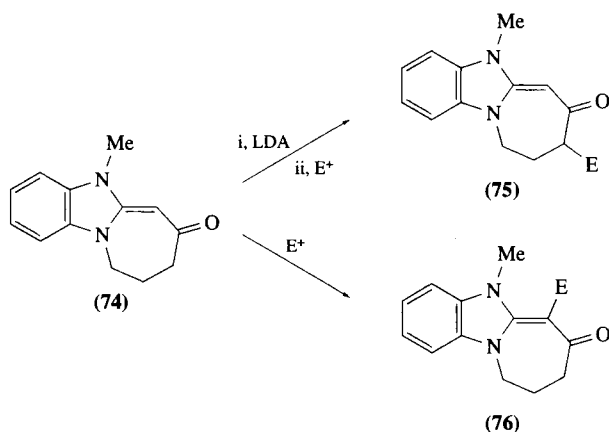
Treatment of the *t*-butyl formamidine (**72**) with *t*-butyllithium followed by an electrophile produces the tetrahydroazepine derivatives (**73**) <85JOC1019>. Typical electrophiles are *n*-propyl iodide, trimethylsilyl chloride, and benzyl bromide. 2,3,4,6-tetrahydro-1*H*-benz[*b*]azepines <93JOC6538> afford the corresponding 2-alkyl-dihydro derivatives together with the product from *o*-alkylation in the aromatic ring. *N*-Boc derivatives give an even better yield of the 2-alkyl derivative, which is in marked contrast to the five- and six-membered compounds, where the sole product from the *N*-Boc



derivative arises from *o*-substitution of the phenyl ring. Chiral formamidines have been used in the asymmetric synthesis of a wide variety of isoquinoline alkaloids <92T2589>, and the methodology has been extended to the synthesis of chiral 1-alkyl-2,3,4,5-tetrahydro-1*H*-benz[*c*]azepines <93T1807>. After removal of the chiral auxiliary the products are obtained in high yield in 84–96% *ee*.



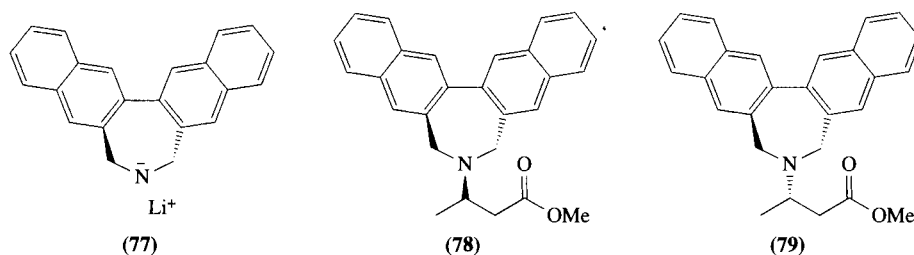
Treatment of the lithium enolate of 5-methyl-9,10-dihydro-5*H*-azepino[1,2-*a*]benzimidazol-7(8*H*)-one (**74**) with electrophiles <91CPB2787> gives the 8-substituted derivatives (**75**), whereas the enaminoketone alone affords the 6-substituted derivatives (**76**) (Scheme 11). Treatment of the lithium salt of racemic (*S*)-3,5-dihydro-4*H*-dinaphth[2,1-*c*:1'2'-*e*]azepine (**77**) with methyl crotonate gives the Michael adduct (**78**) in, respectively, 98% and 97% *de* <86JOC2820>. Treatment of methyl crotonate with racemic (**77**) as the free base gives the isomer (**79**), albeit in only 55% *de*.



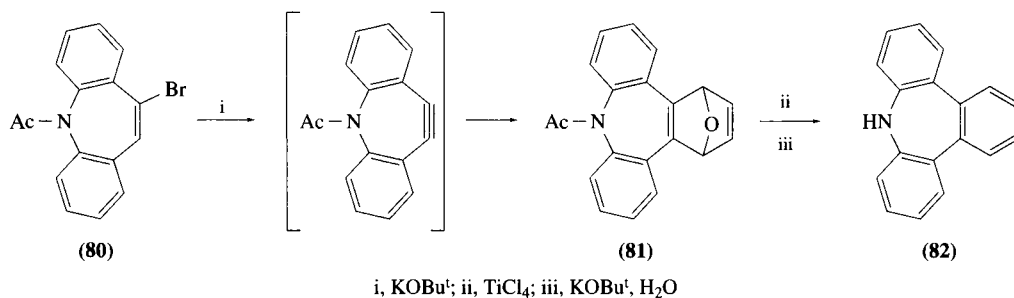
Scheme 11

9.01.7 REACTIVITY OF SUBSTITUENTS ON CARBON

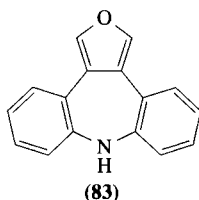
5-Fluoro- and 5-chloro-2-(dimethylamino)-3*H*-azepine react with *t*-butyllithium to give a mixture of 4- and 5-*t*-butyl-2-(dimethylamino)-3*H*-azepines in high yield <85H(23)2715>. The ratio of the two products is of the order of 2.5–3.0:1 and is independent of the halogen substituent, an observation supporting the intermediacy of 2-(dimethylamino)-3*H*-4,5-didehydroazepine in the reaction. A



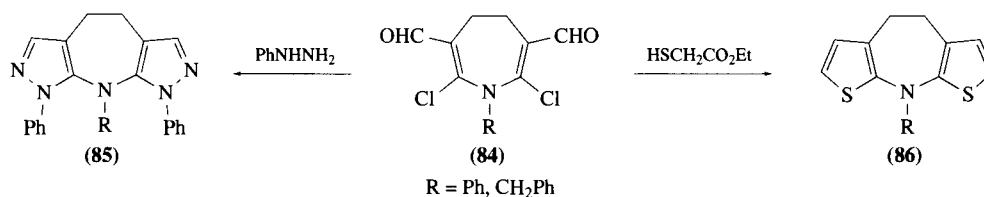
didehydro-species is also involved in the reaction of 1-acetyl-10-bromo-5*H*-dibenz[*b,f*]azepine (**80**) with furan in the presence of potassium *t*-butoxide <91JOC3906>. Deoxygenation of the adduct (**81**) with titanium tetrachloride, followed by base hydrolysis, affords 9*H*-tribenz[*b,d,f*]azepine (**82**) in a new and convenient synthesis (Scheme 12). The same product is also obtained by reaction of (**80**) with potassium *t*-butoxide and 1,3-cyclohexadiene in diglyme, whereas reaction of (**81**) with tetraphenylcyclopentadienone affords 8*H*-furo[3,4-*d*]dibenz[*b,f*]azepine (**83**) <90JHC1839>. Both of these latter reactions involve a retro-Diels-Alder reaction of the intermediate adduct. The mechanism for the electrochemical reduction of 5-carbamoyl-10,11-dibromo-5*H*-dibenz[*b,f*]azepine to 5-carbamoyl-5*H*-dibenz[*b,f*]azepine at a mercury cathode in (C₂H₅)₄NClO₄/DMF is considered also to involve the transient formation of the corresponding didehydro-species <92PHA426>.



Scheme 12

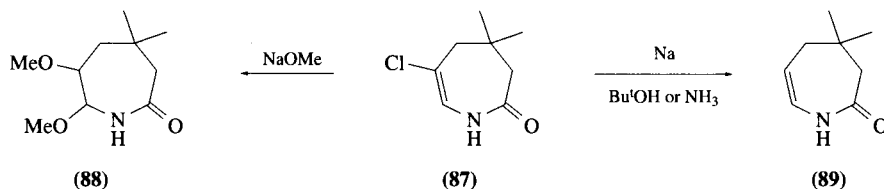


Reduction of 3,3-dichloro-4,5-dihydro-1*H*-benz[*b*]azepin-2(3*H*)-one over 5% Pd/BaSO₄ modified with cinchonine in THF with tri-*n*-butylamine as HCl acceptor gives an excellent yield of the monochloro derivative in 50% *ee* <91TA721>. The reaction occurs with excellent chemoselectivity with the dibromo analogue and with the corresponding dihalohexahydro-1*H*-azepin-2-ones, but without any trace of enantioselectivity. Condensation of 2,7-dichloro-3,6-diformyl-4,5-dihydro-1*H*-azepines (**84**) with phenyl hydrazine and ethyl 2-thiolacetate and triethylamine in pyridine yield, respectively, the pyrazolo and thieno analogues (**85**) and (**86**) of the dibenz[*b,f*]azepines (Scheme 13) <89JCS(P1)2095>.



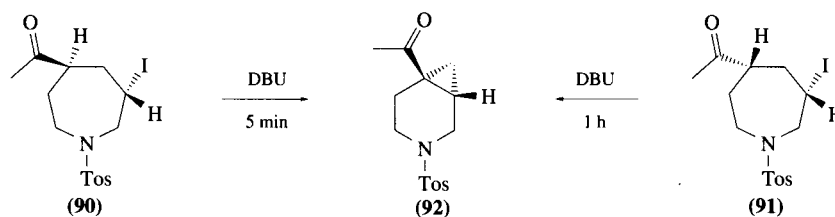
Scheme 13

When 6-chloro-4,4-dimethyl-1,3,4,5-tetrahydro-2*H*-azepin-2-one (**87**) is treated with methoxide the addition/elimination product (**88**) is obtained (Scheme 14) <93AJC135>. Sodium in either *t*-butyl alcohol or ammonia reduces (**87**) to give 4,4-dimethyl-1,3,4,5-tetrahydro-2*H*-azepin-2-one (**89**) in good yield.

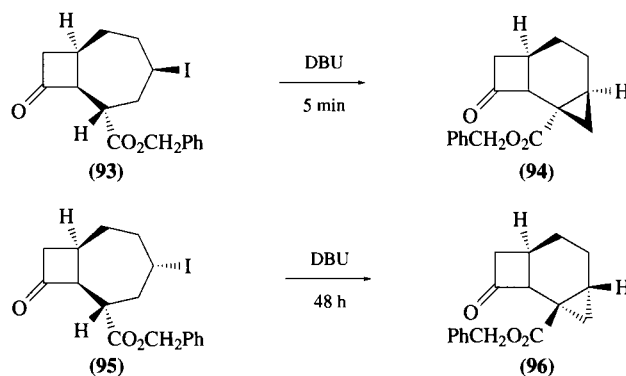


Scheme 14

1,3-Elimination of the iodoketones (**90**) and (**91**) with DBU in benzene, shown in Scheme 15, affords the piperidine (**92**) <88CC12>. The rates of reaction are markedly different in that (**90**) reacts within 5 min whereas the epimer (**91**) required 1 h. This observed difference in activity is probably due to the need for (**91**) to epimerize before the W-shaped geometry required for elimination can be adopted. Similar differences in rates of reaction are observed when the carbahomocephams (**93**) and (**94**) are similarly treated to afford, respectively, (**95**) and (**96**) (Scheme 16).



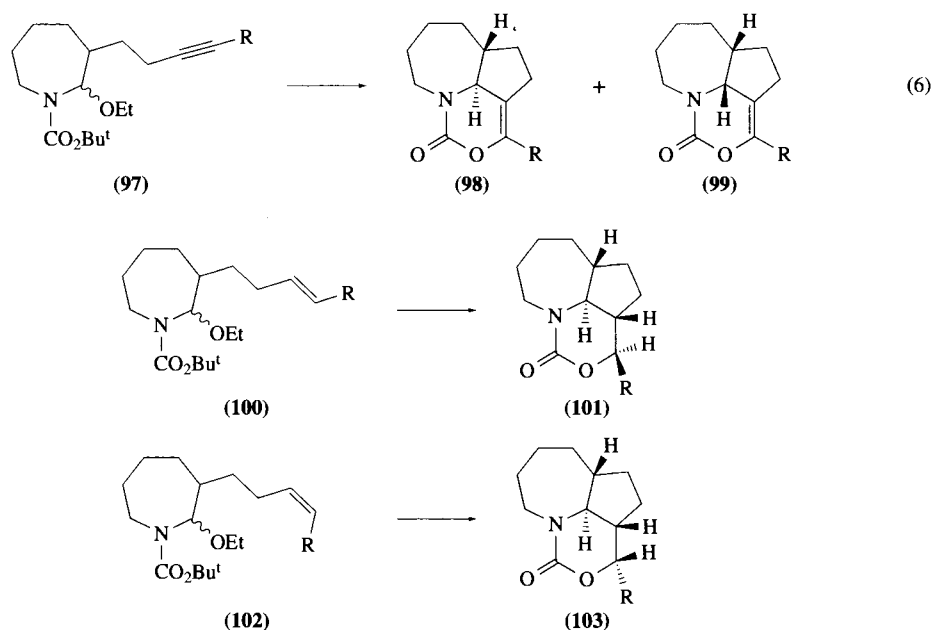
Scheme 15



Scheme 16

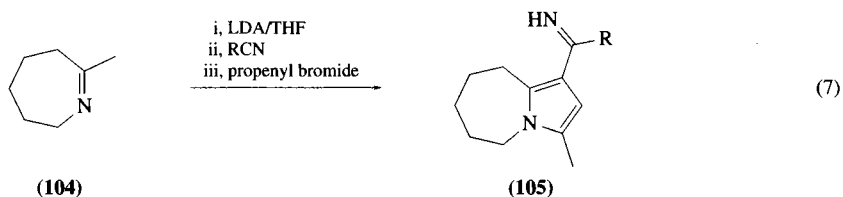
1,5-Dimethyl-1*H*-benz[*b*]azepin-2(3*H*)-ones may be converted into 2-chloro-1,5-dimethyl-1*H*-benz[*b*]azepines upon treatment with phosphorus oxychloride in pyridine <86AJC529>. The compounds are relatively stable in pyridine solution, but are rapidly hydrolyzed in the presence of moisture.

Intramolecular condensation of the propargyl compounds (**97**; R = Me, TMS, TMS-CH₂) with SnCl₄ in CH₂Cl₂ at -23°C gives the cyclization products (**98**) and (**99**) <90JOC1447>. The greatest selectivity is given with the trimethylsilylmethylene derivative (30:1). The phenyl derivative (**97**; R = Ph) gives (**98**; R = Ph) stereoselectively (Equation (6)). The (*E*)-alkenes (**100**; R = Me, Ph) also cyclize in a stereoselective manner affording the single isomer (**101**; R¹ = Me, Ph, R² = H), whereas the (*Z*)-alkene gives the enantiomer (**102**; R¹ = H, R² = Me, Ph) (Scheme 17).

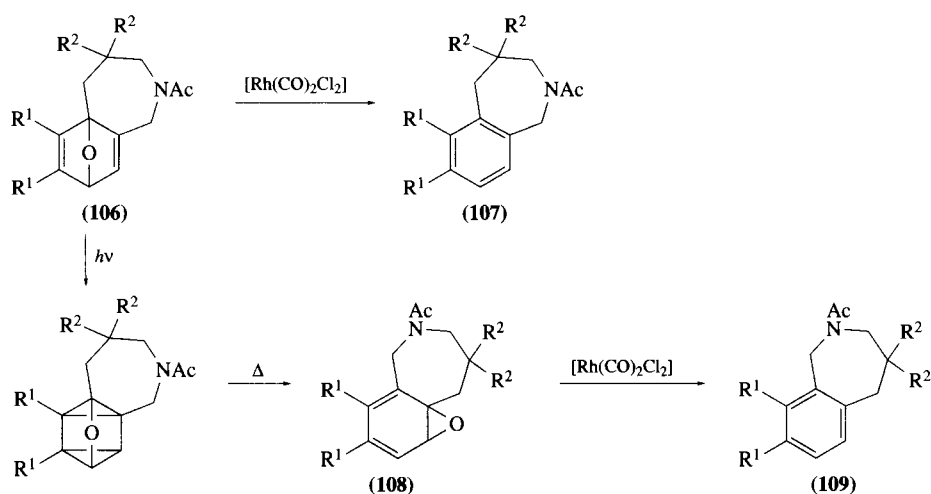


Scheme 17

Metalation of the imine (**104**) with LDA and treatment with a nitrile and regioselective trapping of the resulting diazapentadienyl anion with prop-2-ynyl bromide affords the 4-azaazulene (**105**) in high yield (Equation (7)) <92CC1419>.

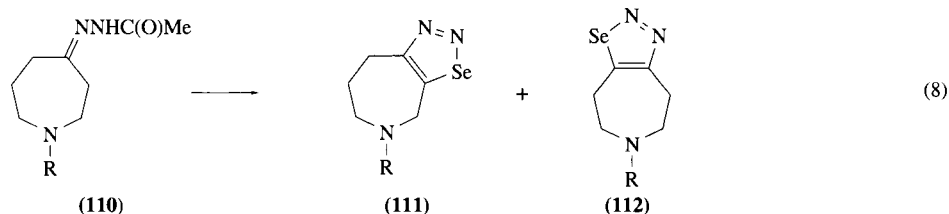


Deoxygenation of the readily available oxanorbornadienes (**106**; $R^1 = \text{CO}_2\text{Me}$, $R^2 = \text{H}$, Me) with $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ yields the benzazepines (**107**) in modest yields <82CB2125>. Light-induced valence tautomerization of (**106**) followed by thermal rearrangement affords the arene oxide (**108**), which leads to the benzazepine (**109**) on deoxygenation, a process which may be regarded as a 1–3 transposition of the nitrogen atom (Scheme 18).



Scheme 18

Many reactions of substituted diazepines and their fused derivatives frequently relate to a study of the functionality rather than being dependent on the presence of the azepine ring system, most particularly with reduced derivatives. Reaction of the unsymmetrical semicarbazones (**110**) <91JOC5203> gives the two selenodiazoles (**111**) and (**112**), the ratios of which show a solvent dependency (Equation (8)).

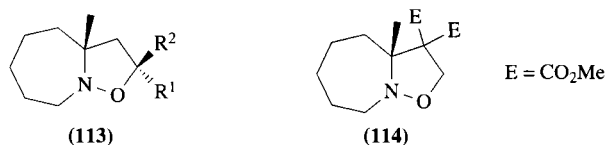


Lactim ethers and thioethers are reported to react with imides <93H(35)1055>, amino ketones and acetals <82JHC193>, amino acids <90JHC1973>, active methylene compounds <82JHC193, 82JHC431, 88T3309>, and diethyl ethoxymethylenemalonate <84H(22)2285>. 7,8,9,10-Tetrahydro-6*H*-1,3,5-triazino[1,2-*a*]azepine-2,4(3*H*)-dione has been prepared from 7-amino-3,4,5,6-tetrahydro-2(*H*)-azepine and diphenyl imidodicarboxylate <93JHC551>, and caprolactam acetals are reported to react with amino heterocycles <93S521> and ureas and urethanes <82KGS1553>. Most of these reactions lead to fused azepines either directly or after subsequent treatment of the isolated intermediate.

7-Methoxy-5*H*-pyrido[3,2-*c*]azepine readily undergoes displacement of the methoxy group by primary and secondary amines <82JCS(P1)431>. In contrast, however, both 5-methoxy-9*H*-pyrido[3,2-*c*]azepine and 9-methoxy-5*H*-pyrido[2,3-*c*]azepine are unaffected by a number of amines in a range of solvents <85JCS(P1)1911>. The lack of reactivity of the former compound can be attributed to unfavourable *peri*-interactions, but no such explanation is possible for the 9-methoxy-derivative. This result is all the more surprising since the 6,9-dimethoxy derivative readily undergoes replacement at the 9-position.

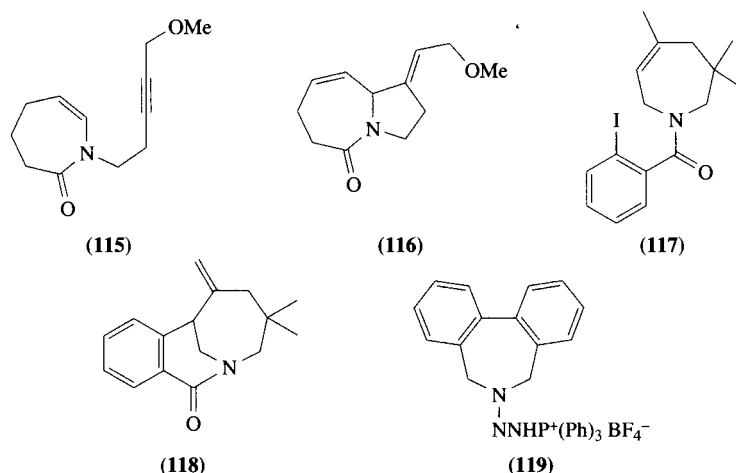
9.01.8 REACTIVITY OF SUBSTITUENTS ON NITROGEN

The 1,3-dipolar addition of alkenes to 3,4,5,6-tetrahydro-2*H*-azepine 1-oxide proceeds in a regioselective manner <90T7207, 92JCR(S)62>. Thus reaction with methyl methacrylate gives the two isomers (**113**; R¹ = CO₂Me, R² = Me) and (**113**; R¹ = Me, R² = CO₂Me) in the ratio 94:6, and dimethyl itaconate yields (**113**; R¹ = CO₂Me, R² = CH₂CO₂Me). The alternative regioisomers are not observed. This regioselective behavior is found with a number of different alkenes, with varying degrees of stereoselectivity. One exception is the behavior of dimethyl methylmalonate which forms (**113**; R¹ = R² = CO₂Me) and the regioisomer (**114**) in approximately equal amounts. A similar lack of regiospecificity is also noted with methyl cinnamate.



The above-mentioned ring system may also be obtained by reaction of 1-hydroxy-hexahydroazepine with alkenes in the presence of palladium black <83TL1049>. The 4,5-dihydro-1*H*-azepin-2(3*H*)-one (**115**) cyclizes in the presence of palladium to afford the azepinopyrrole (**116**) <92JA7292>, and the benzoyltetrahydroazepine (**117**) undergoes palladium-catalyzed ring closure to yield (**118**) <91T9703>.

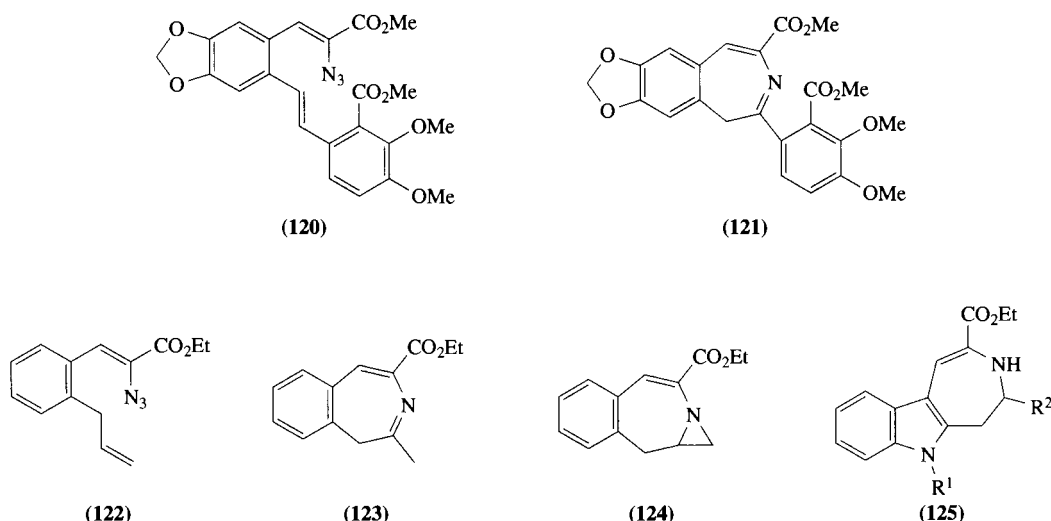
The azepino[3,2,1-*h*,*i*]indole skeleton has been formed by intramolecular Friedel-Crafts cyclization of 1-(2-methylthioethanoyl)-4,5-dihydro-benz[*b*]azepine with NCS <88JHC937>. Treatment of the hydrazinophosphonium tetrafluoroborate (**119**) with nitrosonium hexafluorophosphate in acetonitrile brings about ring contraction to phenanthridine together with a smaller amount of 5*H*-dibenz[*c,e*]azepine <82ZN(B)881>.



9.01.9 SYNTHESIS BY ATOM NUMBER

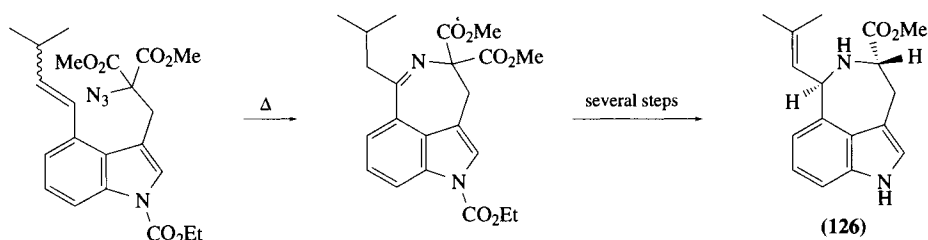
9.01.9.1 Type a (N—C—C—C—C—C—C)

The insertion of nitrenes derived by thermolysis of azides has been developed into an effective method for the synthesis of azepines. Thermolysis of azidocinnamates bearing an *o*-styryl substituent yields 2-aryl-3-benzazepines <86JCS(P1)1113>. Thus the vinylazidocinnamate (**120**) yields the 3-benzazepine (**121**), a key intermediate in the synthesis of the indoloazepine alkaloid lennoxamine <90JCS(P1)2929>. It is interesting to note that in the reaction of these *o*-styryl derivatives, it is the (*E*)-isomers which favor azepine formation. In the case of (*Z*)-isomers, isoquinolines form the major products. The *o*-allylcinnamate (**122**) gives a mixture of products from which, *inter alia*, the 3-benzazepine (**123**; R = Me) and the tricyclic product (**124**) may be isolated <86JCS(P1)1113>. In this reaction the pathway involves not a nitrene insertion, but a competing dipolar cycloaddition reaction of the azide across the double bond. In a further development of this reaction, the decomposition of azidoacrylates derived from 2-substituted indole-3-carboxaldehydes affords azepino[4,5-*b*]indoles (**125**) in a facile reaction <84JCS(P1)2895>.



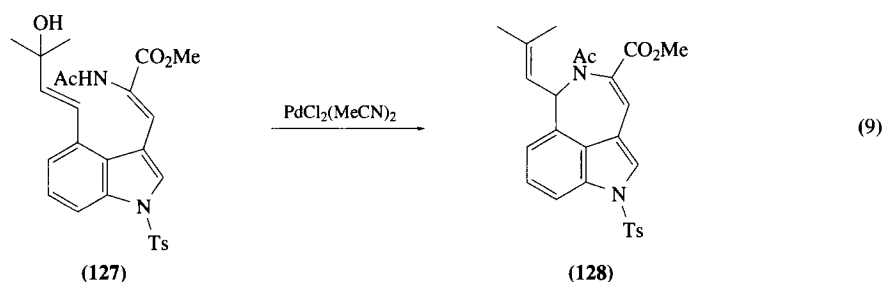
The formation of an azepine ring by means of an intramolecular azide cyclization has often provided the key step in the synthesis of clavicipitic acid (**126**) <84JOC2310> (Scheme 19).

Several other syntheses of the 1*H*-azepino[5,4,3-*c,d*]indole ring system have been reported, including the Mitsunobo reaction <85TL4043>, an intramolecular, acid-catalyzed aminoalkylation <88JOC5128> and intramolecular imine formation <87H(26)1197> leading to total synthesis of clavicipitic acid. Palladium-catalyzed ring closure of (**127**) afforded the cyclized derivative (**128**) (Equa-

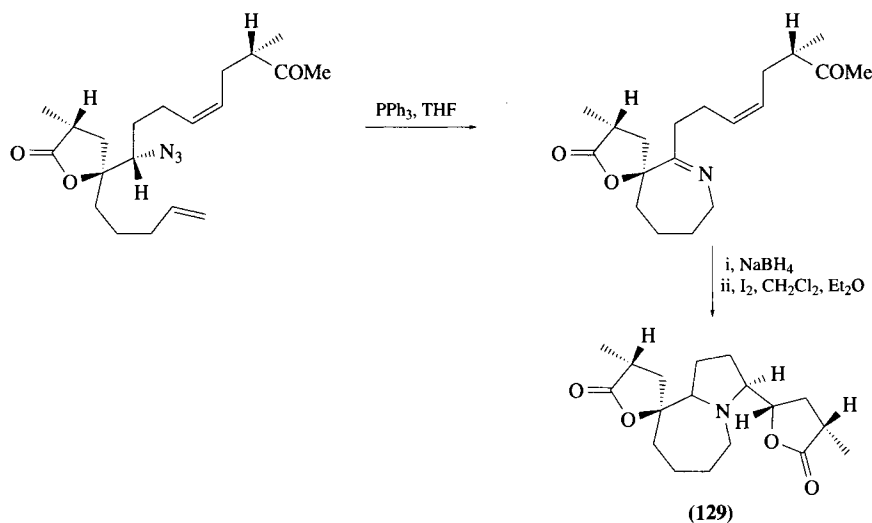


Scheme 19

tion (9)), a critical step in the synthesis of the *N*-acetyl methyl ester of ($\pm$)-clavicipitic acid <87JA4335>.



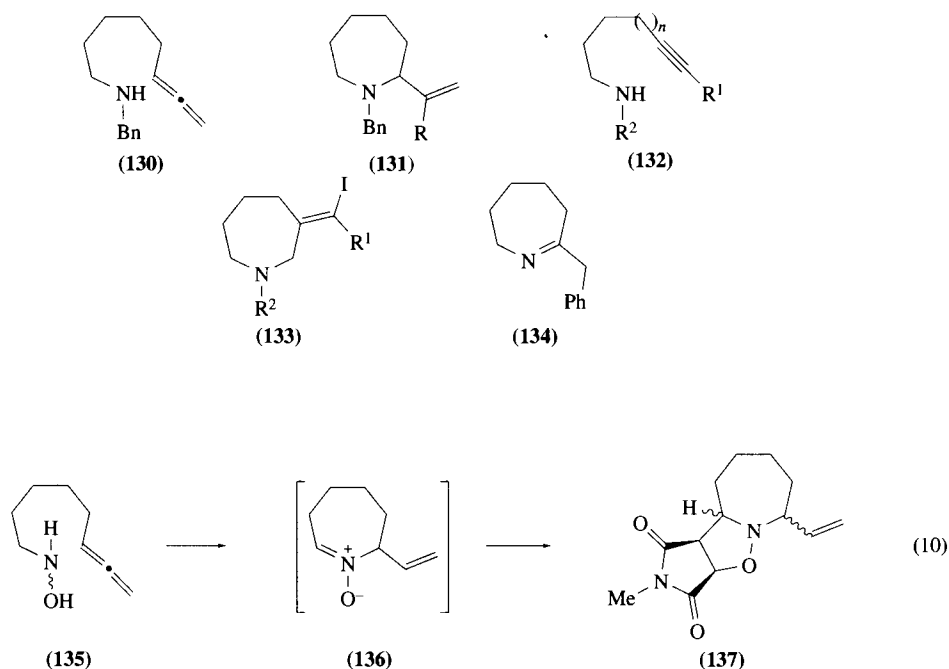
The application of the Staudinger reaction to ω -azidoketones is an efficient route to cyclic imines <82CC1224>, a reaction which has been applied to the synthesis of (+)-croomine (**129**) <89JA1923>, shown in Scheme 20.



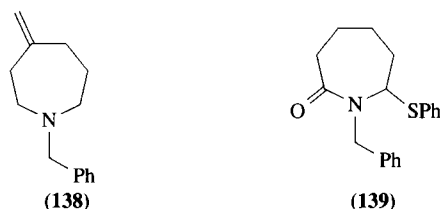
Scheme 20

Cyclization of the allene (**130**) with iodine <90SL584> or $\text{Pd}(\text{PhCN})_2\text{Cl}_2$ and carbon monoxide <92JCS(P1)433> affords the hexahydroazepines (**131**; $\text{R} = \text{I}$) and (**131**; $\text{R} = \text{CO}_2\text{Me}$), respectively, although yields are low. Iodine-promoted Mannich cyclizations of 5-alkynylamines (**132**; $\text{R}^1 = \text{Me}$, Et , $\text{R}^2 = \text{Bn}$, $n = 1$) give access to 3-alkylideneazepines (**133**; $\text{R}^1 = \text{Me}$, Et , $\text{R}^2 = \text{Bn}$) in good yields <92SL995>, whereas the primary amine (**132**; $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$, $n = 2$) undergoes an organolanthanide-catalyzed regiospecific hydroamination/cyclization reaction to yield the tetrahydroazepine (**134**) <94OM439>.

The allenic oxime (**135**) undergoes a silver-catalyzed cyclization to form the nitrone (**136**) (Equation (10)) which may be trapped as the dipolar adduct (**137**) with *N*-methylmaleimide <91JCS(P1)659>. Azepinonitrones have also been prepared by the spontaneous intramolecular cyclization of alkynylhydroxylamines, prepared by the reduction of the corresponding oximes <92TL7421, 92TL7425>.



5-Benzylamino-2-(trimethylsilylmethyl)-but-1-ene cyclizes in the presence of acid to afford the azepine (138) <86TL5067>, and *N*-benzyl-6-(phenylsulfinyl)-hexanamide reacts with *O*-methyl-*O*-*t*-butyldimethylsilyl ketene acetal to afford the lactam (139) <90CPB1473>. Direct irradiation of *ortho*-(*N*-methylaminoethyl)stilbene in acetonitrile affords *N*-methyl-2-phenyl-2,3,4,5-tetrahydro-benz[*d*]-1(*H*)-azepine whereas the *N*-methylaminopropyl homologue yields *N*-methyl-1-benzyl-2,3,4,5-tetrahydrobenz[*c*]-1(*H*)-azepine as the primary product but which undergoes demethylation upon further irradiation <92TL4249>. The demethylated product may also be obtained by irradiation of *o*-(3-amino-*n*-propyl)stilbene in the presence of *m*-dicyanobenzene as electron transfer agent.

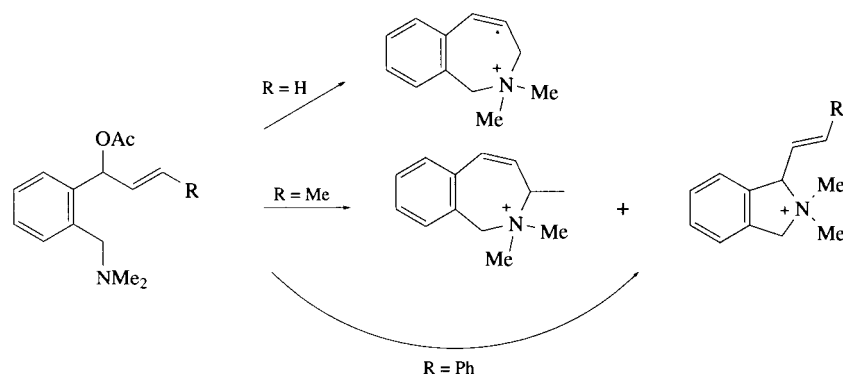


Dimethyl-2,3-dihydro-1(*H*)-benz[*c*]azepinium salts may be obtained by the palladium-catalyzed cyclization of 3-acetoxy-3-(2-dimethylaminomethylphenyl)-prop-1-enes <94TL2877>. However, if the alkene chain is extended there is an increasing tendency towards the formation of dihydro-isindolinium salts (Scheme 21).

Hexahydro-1(*H*)-azepine may be prepared by the Cu/Al₂O₃-catalyzed cyclization of 6-amino-1-hexanol <89AC107>, and hexamethylene diamine is converted to the cyclic imine by pea seedling diamine oxidase <90TL6907>.

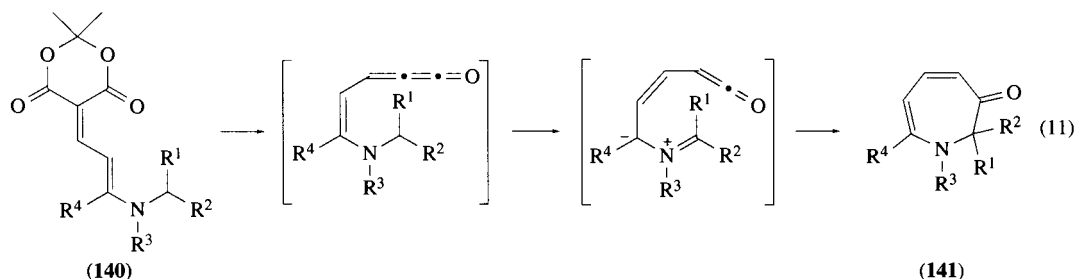
9.01.9.2 Type b (C—N—C—C—C—C—C)

Flash vacuum pyrolysis of vinylogous aminomethylene derivatives of Meldrum's acid (140) offers a new route to 1-, 1,2-, and 1,2,2-substituted-1(*H*)-azepin-3-(2*H*)-ones (141; R⁴ = H) in a novel cyclization reaction <89JCS(P1)425, 93CC1417>. The key intermediate would appear to be a dipolar ketene which undergoes an electrocyclization reaction as shown in Equation (11) <87CC140>. The coalescence temperature for ring inversion of the derivative (141; R¹ = R² = Me) is −96°C, corresponding to a Δ*G*[‡] of 36.4 kJ mol^{−1}. In an extension of this reaction, the synthesis of 4-dimethylamino-1-methyl-1*H*-azepin-3(2*H*)-one (141; R¹ = R² = H, R³ = Me, R⁴ = NMe₂) is reported <93CC1417>. The effect of the dimethylamino group is to raise the coalescence energy to 52

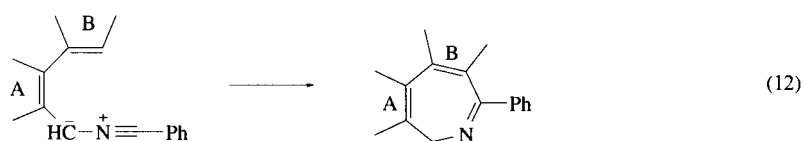


Scheme 21

kJ mol^{-1} and there is also restricted rotation about the C—N bond, evidence that it has significant double bond character.



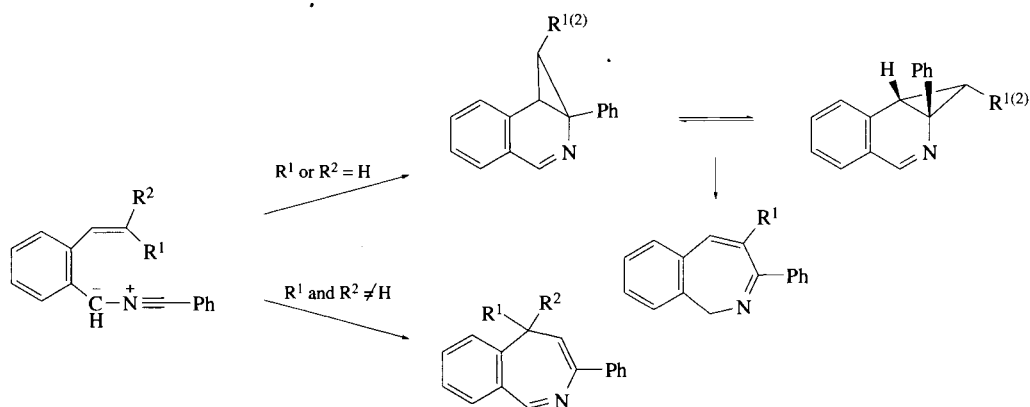
An efficient route to fused azepines is offered by the cyclization of diene-conjugated nitrile ylides, prepared by base-catalyzed dehalogenation of the corresponding imidoyl chloride (Equation (12)). Examples are quoted where A and B are both benzene rings <93JCS(P1)2961> and where one of A or B is a heterocyclic ring <94JCS(P1)1193>. In the former case a substitution effect has been observed in that cyclization is aided by a substituent *ortho* to the position of cyclization, irrespective of the polar effect of that substituent <92T7951>.



In an example where ring B is replaced by an ethenyl group the reaction follows the course shown in Scheme 22. Where one of R^1 or R^2 is hydrogen the initial product is a cyclopropa[*c*]isoquinoline whereby either the *endo*- or *exo*-isomer is formed depending upon whether the geometry about the double bond is (*Z*) or (*E*). Upon thermolysis, these isomers equilibrate rapidly and then undergo rearrangement in a slower step to give the 1*H*-benz[*c*]azepine. On the other hand, where neither R^1 nor R^2 is hydrogen, the 5*H*-benzazepine is formed exclusively <92JCS(P1)1709>.

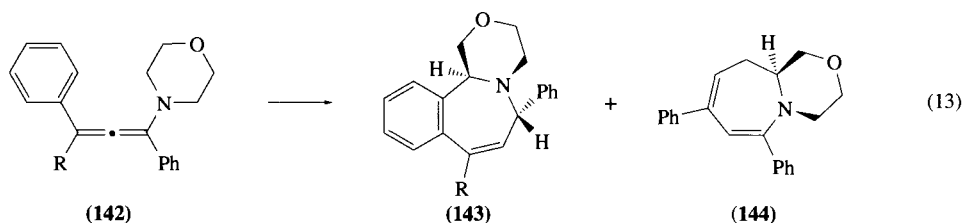
In a series of competitive cyclization experiments it has been shown that the rate of reaction is in the order alkenyl > thienyl > phenyl <91CC658>. The difference in rate between the alkenyl and phenyl groups is to be expected in that cyclization onto a phenyl ring would have the higher activation energy as it involves loss of aromatic stabilization effects. Thienyl occupies an intermediate position because of the lower aromatic stabilization energy and the higher double bond character of the 2,3 bond.

Condensation of *o*-aminophenylacetaldehyde dimethylacetyl with β -diketones followed by treatment of the intermediate enamino ketones with acetic acid affords 1*H*-benz[*b*]azepines in high yields <93BSF143>. Cyclization of the allene (142; $\text{R} = -\text{CH}=\text{CH}_2$) by heating in toluene affords the azepines (143; $\text{R} = -\text{CH}=\text{CH}_2$) and (144) in a stereoselective manner (Equation (13)). Where,

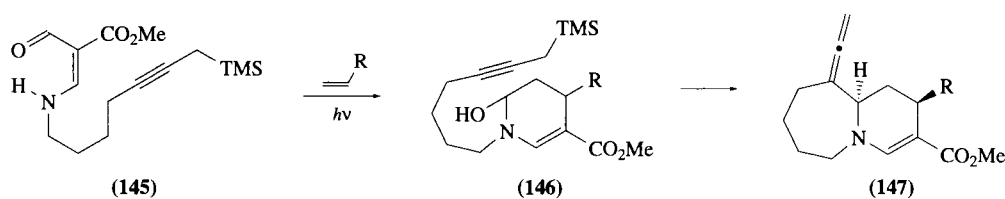


Scheme 22

however, the substituent $R = \text{Ph}$, *t*-butyl or SiPh_2 -*t*-butyl, there is no competition from a second double bond system and only (**143**; $R = \text{Ph}$, *t*-butyl, SiPh_2 -*t*-butyl) is isolated (92TL205).

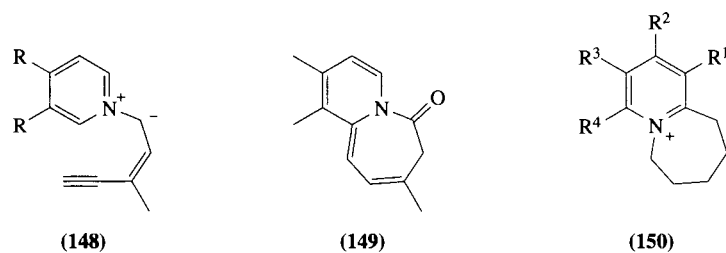


Irradiation of the alkynylaminoester (**145**) (Scheme 23) in the presence of an alkene ($R = \text{CO}_2\text{Me}$, CO_2Bu^t , CN) yields the tetrahydropyridine (**146**) which undergoes acid-catalyzed cyclization to afford the pyrido[1,2-*a*]azepine (**147**) together with just a small amount of the C_{10a} epimer (92T2081).



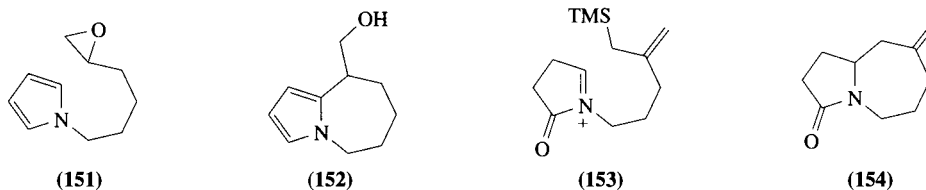
Scheme 23

The ylide (**148**) cyclizes in the presence of 30% aqueous hydrogen peroxide to afford the pyrido[1,2-*a*]azepines (**149**) (91HCA1095), and the pyrido[1,2-*a*]azepinium system (**150**) is also obtainable by intramolecular free radical cyclization of 5-(1-pyridinium)-pentyl iodide (91T4077).

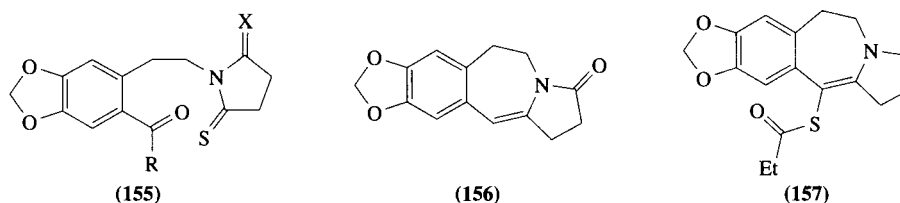


The pyrrolo[1,2-*a*]azepine system occurs in a number of natural products and compounds of biological interest, and a number of new syntheses have been reported. The pyrroloalkylepoide (**151**) cyclizes to the alcohol (**152**) in the presence of a number of Lewis acids, the highest yield

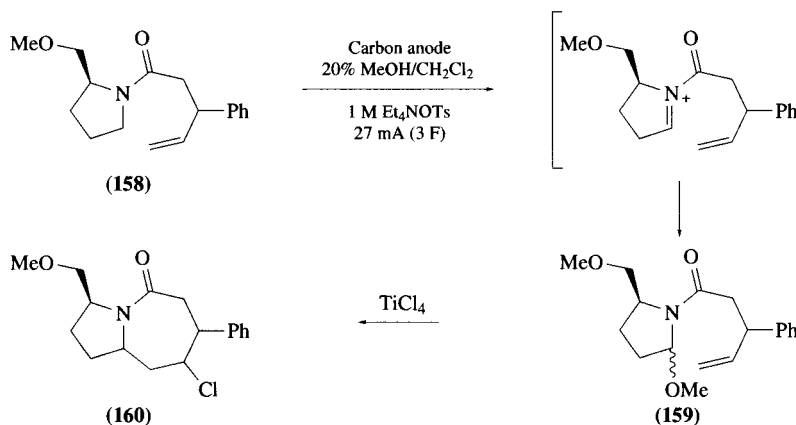
(85%) being recorded with $\text{Ti}(\text{OPr}^i)_3\text{Cl}$ <87JOC819>, and in a similar manner the allylsilyl substituted *N*-acyliminium salts (**153**) cyclize to (**154**) under the influence of a Lewis acid <92H(34)37>.



Treatment of the monothioimide (**155**; $\text{R} = \text{H}$, $\text{X} = \text{O}$) with metal reagents represents a convenient route to the pyrrolobenzazepine system (**156**). Reaction with tungsten hexacarbonyl affords (**156**) in 55% yield, probably by means of an intermediate tungsten carbene species which adds across the carbon-sulfur bond to be followed by sulfur extrusion. Prior conversion of the aldehyde into a hydrazone with 1-amino-*trans*-2,3-diphenylaziridine followed by treatment with rhodium(II) acetate furnishes the same compound in a yield of over 80% <90JOC831>. In further elaboration of this work, the diketone (**155**; $\text{R} = \text{COC}_2\text{H}_5$, $\text{X} = \text{H}_2$) is converted into (**157**) by treatment with trimethyl phosphite. These general procedures have been applied to the synthesis of the alkaloid chilene <89TL2747>.



The pyrroloazepine (**160**) is an important intermediate in the synthesis of conformationally constrained thyroliberin analogues and has been prepared by what is in effect the cyclization of the *n*-acyltetrahydropyrrole (**158**) <92TL2913>. The key step in this procedure is the anodic oxidation of (**158**) at a carbon anode in an undivided cell in the presence of methanol to trap the intermediate *n*-acyliminium ion to furnish (**159**) which is transformed into (**160**) by reaction with titanium tetrachloride (Scheme 24).

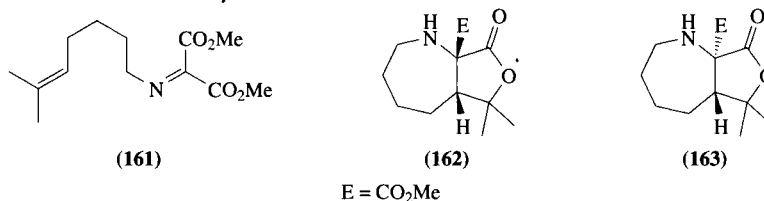


Scheme 24

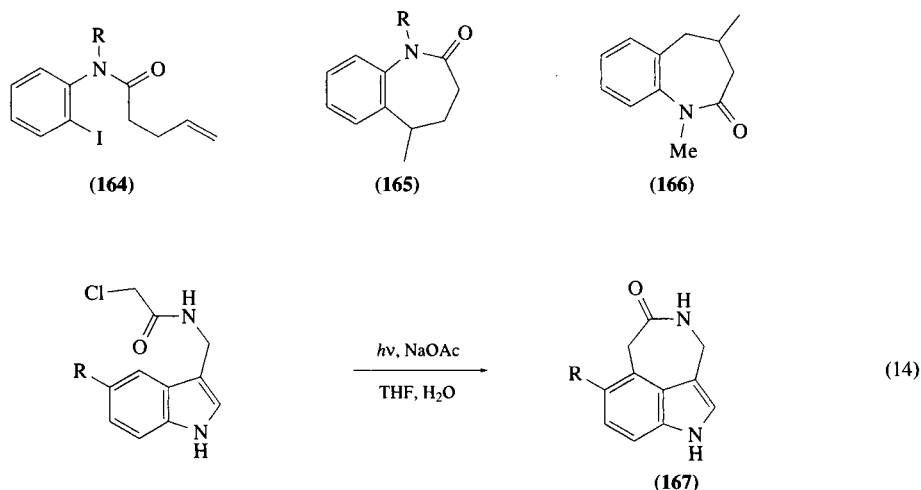
Cyclization of the heptenylimines (**161**) with TMS-OTf, FeCl₃ or GaCl₃, affords the *cis*- and *trans*-fused aminolactones (**162**) and (**163**) <89LA559>. The highest preference for the *trans*-isomer is shown by TMS-OTf in CH₂Cl₂, whereas the *cis*-isomer predominates with GaCl₃.

9.01.9.3 Type c (C—C—N—C—C—C—C)

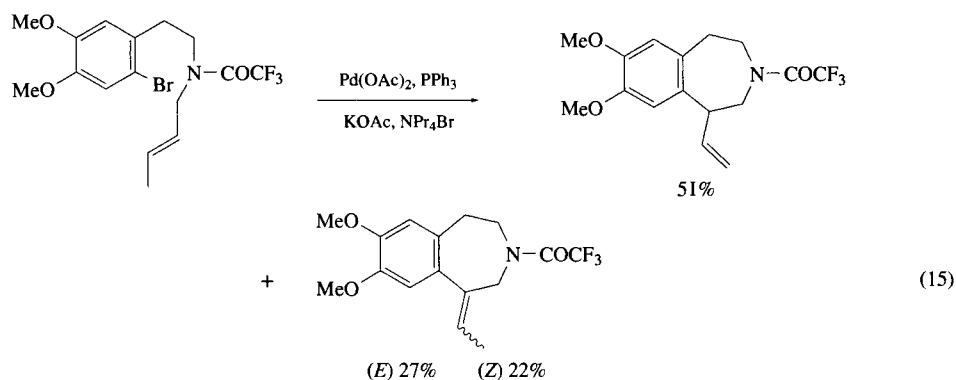
Radical- and metal-catalyzed cyclizations play an important role in the synthesis of benzazepines. Although the product radical has no stabilizing features, treatment of the pentenylamides (**164**;



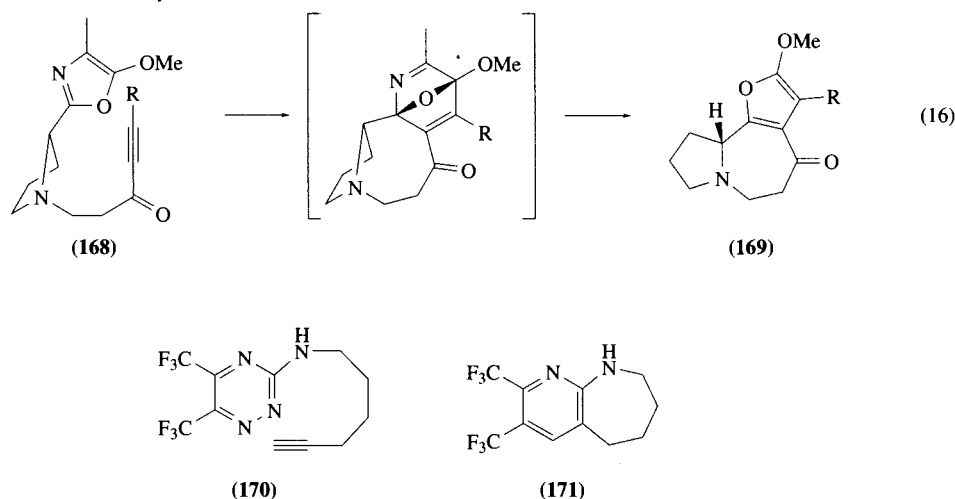
R = Me, CH₂Ph) with tri-*n*-butyl tin hydride followed by NaBH₃CN reduction affords the 7-*exo* cyclization products (**165**; R = Me, CH₂Ph), even if in only poor to moderate yield <91TL2829>. In a similar reaction, 2,2-dichloro-*N*-methyl-*N*-(*o*-allylphenyl)-acetamide furnishes the 7-*exo* product, 4-methyl-2,3,4,5-tetrahydro-1*H*-benz[*b*]azepine (**166**) in 49% yield <91JCS(P1)353>. The established photo-induced cyclization of chloracetamides has been applied to a synthesis of the azepino[3,4,5-*c,d*]indole system (**167**; R = H, OMe) (Equation (14)), a ring system isomeric to that of the clavicipitic acids <88SC671>.



Tietze and Schimpf have demonstrated that palladium-catalyzed Heck-type cyclization offers a viable route to 2,3,4,5-tetrahydro-1*H*-benz[*d*]azepines <93S876, 94AG(E)1089>. In the example shown in Equation (15), the product is a mixture of isomers.

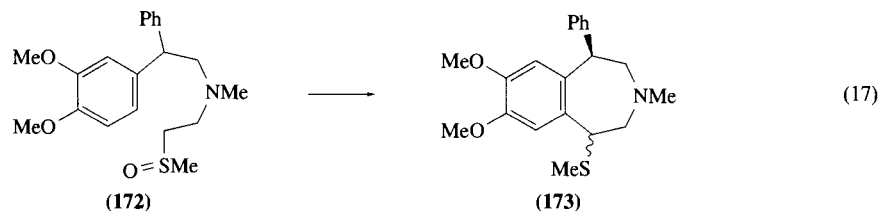


[4 + 2] π Cycloaddition reactions too have found a place in azepine synthesis. In studies related to the enantiomeric synthesis of norsecurine <91JA5384>, intramolecular cycloaddition of the alkyne group in (**168**) to the oxazole ring, followed by loss of acetonitrile from the adduct, furnishes the tricyclic azepine (**169**), as shown in Equation (16), and 2,3,4,5-tetrahydro-7,8-bis(trifluoromethyl)-1*H*-pyrido[2,3-*b*]azepine (**171**) is obtained by intramolecular [4 + 2] π cycloaddition of (**170**) followed by elimination of nitrogen <90CB133>.



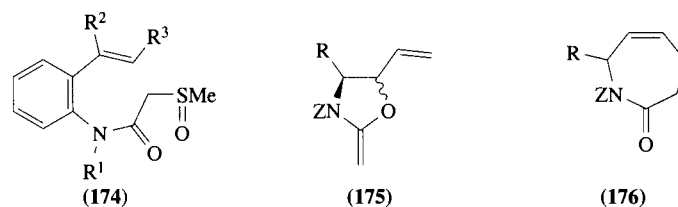
The acid-catalyzed cyclization of *N*-phenethyl-2-phenyl-2-hydroxyethylamines is an established method for the preparation of benz[*d*]azepines <84CHEC-I(7)491>, but none of the methods permit the direct synthesis of chiral products. If, however, the starting material is converted into the chiral chromium tricarbonyl complex prior to cyclization, the ring closure proceeds in a stereospecific manner <89TL3581>.

The synthesis of benzazepines by the acid-catalyzed cyclization of *N*-(2-arylethyl)-*N*-methyl-2-sulfinylacetamides is a convenient alternative to this acid-catalyzed cyclization. Thus treatment of the amide (172) (Equation (17)) with trifluoroacetic anhydride affords the benz[*d*]azepine (173) as the *trans*- and *cis*-isomer in over 90% yield and in the ratio of 3 : 1 <89CPB939>. This method has been used in a first synthesis of the benzopyranobenzazepine alkaloid (±)-clavizipine <94SL49>.



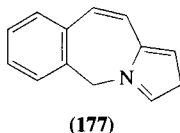
With a variant of this procedure it is possible to prepare benz[*b*]azepines by the acid treatment of *o*-allyl methylsulfinylacetanilides (174; R¹ = Me or Ts) <90CPB3331>. When R² stands for methyl or phenyl and R³ for hydrogen, the products of the cyclization are the 7-*endo* products, benz[*b*]azepines. If, however, this substitution pattern is reversed, quinolines are isolated from 6-*exo* cyclization. The unsubstituted allyl derivatives fail to cyclize, which is attributed to the reduced nucleophilicity of the alkenyl group.

Claisen rearrangement of the vinyl ketene aminal (175) offers a new route to 7-substituted caprolactams (176) <92TL6857>.



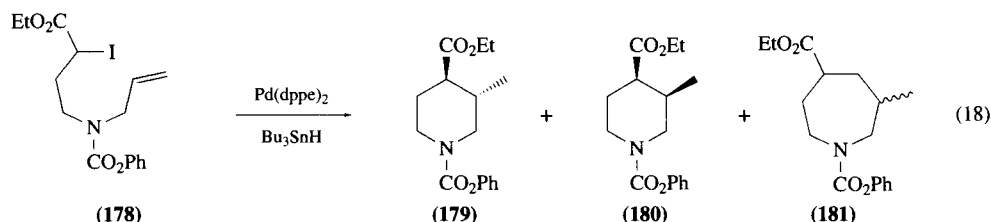
Dieckmann-type cyclizations have been used in the preparation of 5*H*-pyrrolo[1,2-*a*]azepine and 7*H*-pyrrolo[1,2-*a*]azepine <82JCS(P1)1123>, 5,6,7,8-tetrahydro-9*H*-pyrrolo[1,2-*a*]azepine-9-carboxylic acid <82CJC2295>, and 5-methyl-7,8,9,10-tetrahydro-5*H*-azepino[1,2-*a*]benzimidazol-7-one and

related compounds <90CPB301>. Intramolecular Wittig–Horner reactions have been applied to the synthesis of 5*H*-pyrrolo[1,2-*b*][2]benzazepine (**177**) and derivatives <90SC973> and the basic skeleton of the ribasine alkaloids <86TL3539>.

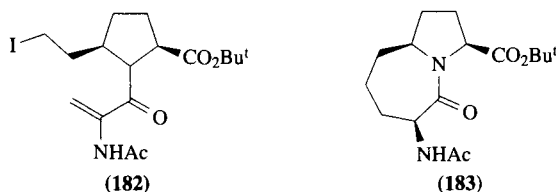


9.01.9.4 Type d (C—C—C—N—C—C—C)

The reaction of the iodoalkene (**178**) with Pd(dppe)₂ in HMPA followed by reduction with tributyltin hydride gave a mixture of the 6-*exo trans* product (**179**), the 6-*exo cis* product (**180**), and the 7-*endo* product (**181**) in a ratio of 1 : 1 : 2 in combined yield of 76% (Equation (18)), identical to the result of using hexalkylditin in benzene <90TL933>. This has led Curran and Chang to propose that the low valent palladium “ene-halogenocyclization” should be classed as a radical chain reaction that proceeds by way of an atom transfer mechanism and that palladium(0) may be a useful substitute for ditiin in other iodine atom transfer reactions.



Radical cyclization of (**182**) furnishes the pyrroloazepine (**183**) in moderate yield and good stereoselectivity. The best results (42% yield, >95% *de*) are obtained using (TMS)₃SiH as radical initiator in the presence of catalytic amounts of AIBN <94TL4031>.



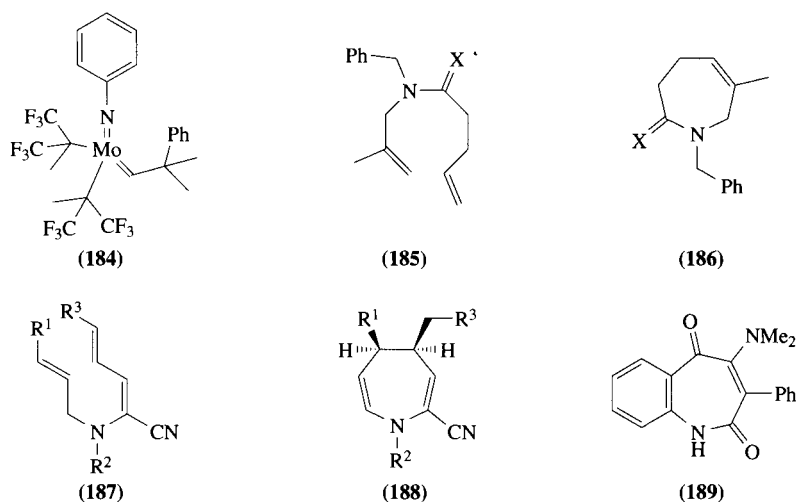
The molybdenum complex (**184**) is an effective catalyst for the transformation of the dienes (**185**; X = H₂, O) into the tetrahydroazepines (**186**; X = H₂, O) with concomitant loss of ethylene <92JA7324>. Dihydroazepines (**188**) are prepared from the α -allylamino dienenitriles (**187**) in a stereospecific conrotatory electrocyclic reaction <89JOC481>.

Subjecting acetanilides to the conditions of the Vilsmeier–Haack reactions is an effective method for the preparation of quinolines <81JCS(P1)1537>. On the other hand, if the phenacetanilide of anthranilic acid is subjected to the identical reaction conditions, 4-dimethylamino-3-phenyl-5*H*-benz[*b*]azepine-2,5-dione (**189**) is formed in high yield <84S349>. The phenyl group of anthranilic acid may be replaced by thienyl and pyridyl without loss in the efficiency of cyclization.

The synthesis of 6-chloro-1,2,3,7-tetrahydro-*N*-tosylazepin-4-one from 3-[*N*-(2-chloroprop-2-enyl)-*N*-tosylamino]-propionic acid has been reported <92JCS(P1)445>.

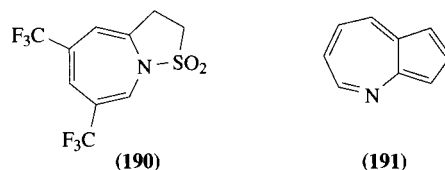
9.01.9.5 Reaction Involving the Formation of Two Bonds

Several methods have been described for the formation of azepines from C₆-fragments. 1-Substituted hexahydroazepines and 3-hydroxy-1-substituted azepines may be prepared by the ruthenium-catalyzed reaction of 6-hydroxy-1-hexylamine with alcohols or the reaction of 1,6-diols with amines <82TL229, 90JMOCL11, 93JMOC39>. Alternative cyclization systems employ NaHCO₃ in

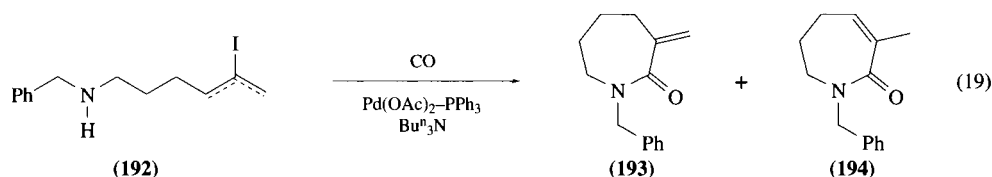


HMPA $\langle 89T629 \rangle$ or K_2CO_3 in dioxan for the cyclization of hexane-1,6-ditosylates $\langle 91JOC2936 \rangle$, and Al_2O_3 -catalyzed reaction of hexane-1,6-diol or tetrahydropyran with amines in the gas phase $\langle 85T101 \rangle$. Amines react with adipaldehyde in the presence of ethanolic tetracarbonylhydroferrate and CO also to yield 1-substituted hexahydroazepines $\langle 88JOC1383 \rangle$, and azepine and benz[d]azepine derivatives may also be obtained by the condensation of adipoyl chloride and 1,2-benzenediacyl dichloride, respectively, with iminophosphoranes $\langle 90S149 \rangle$. 1,7-Dihydro-1*H*-azepines are obtained by the reaction of substituted (*Z,Z*)-1,6-dibromohexa-2,4-dienes with amines $\langle 94CC67 \rangle$. A novel variation of these systems is the reaction of bis-epoxides with ammonia and amines to give polyhydroxylated hexahydroazepines $\langle 94TL3293 \rangle$; the diketene silyl acetal, 1,6-bis(trimethylsilyloxy)-1,6-diethoxy-1,6-hexadiene, reacts with bistihiomethyltrimethylamine in the presence of trimethylsilyl triflate to give diethyl 2,3,4,5,6,7-hexahydro-1-methyl-1*H*-azepinedicarboxylate $\langle 84CL785 \rangle$.

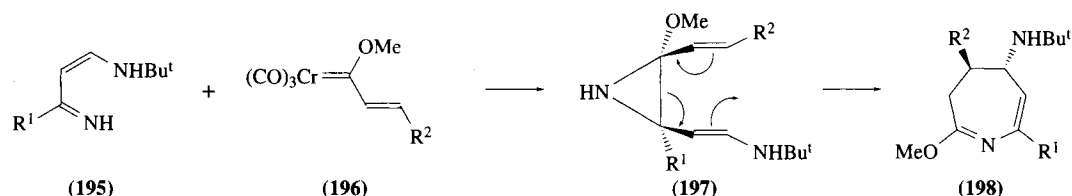
Flash vacuum pyrolysis of β -(3,5-trifluoromethylphenyl)-ethanesulfonyl azide at $300^\circ C$ furnishes the fused azepine (190) $\langle 84JOC5124 \rangle$, and spray pyrolysis of 2-bromoindan-1-yl azidoformate yields 4-azaazulene (191) $\langle 85JCS(P1)1793 \rangle$. The kinetics of the thermal decomposition of 2-azidodiphenylmethanes to yield 10*H*-indoloazepines has been studied $\langle 92JCS(P2)903 \rangle$. The initial step is the evolution of nitrogen and the formation of a nitrene, and a comparison of the rate constant of this step with that for product formation showed that nitrene formation was rate determining. Electron-donating substituents *para* to the azide group stabilize the incipient nitrene by resonance interactions, leading to higher proportions of amine products at the expense of azepine formation. It has been shown that yields of azepines from the decomposition of arylsulfonyl azides in aromatic solvents are improved by using a one-pot phase-transfer system $\langle 92S499 \rangle$.



(*Z*)-3-(Tributylstannyl)-allylamine reacts with *o*-functionalized bromobenzenes in the presence of $Pd(PPh_3)_4$ to yield benz[c]azepines in good yields $\langle 93JOC1443 \rangle$. Thus *o*-bromobenzaldehyde furnishes 3*H*-benz[c]azepine, and *o*-bromoacetophenone the corresponding 1-methyl analogue. The iodoamine (192) undergoes carbonylation under palladium catalysis to afford the two isomeric azepines (193) and (194) (Equation (19)) $\langle 83JOC4058 \rangle$.

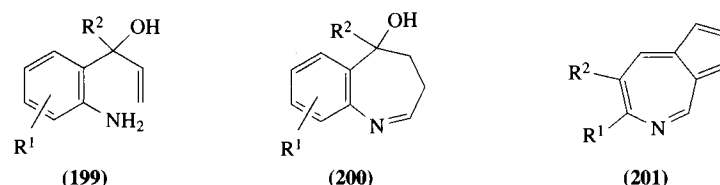


The [4 + 3] annulation of Fischer chromium carbene complexes with azadienes offers a facile synthesis of azepines <94CC321>. Thus, 3-iminoprop-1-enylamines (**195**) react with the α,β -unsaturated Fischer complexes (**196**) to furnish the azepines (**198**) as sole stereoisomers. The mechanism is considered to involve the formation of the aziridine (**197**) which undergoes an aza-Cope rearrangement followed by a 1,3 proton shift (Scheme 25).



Scheme 25

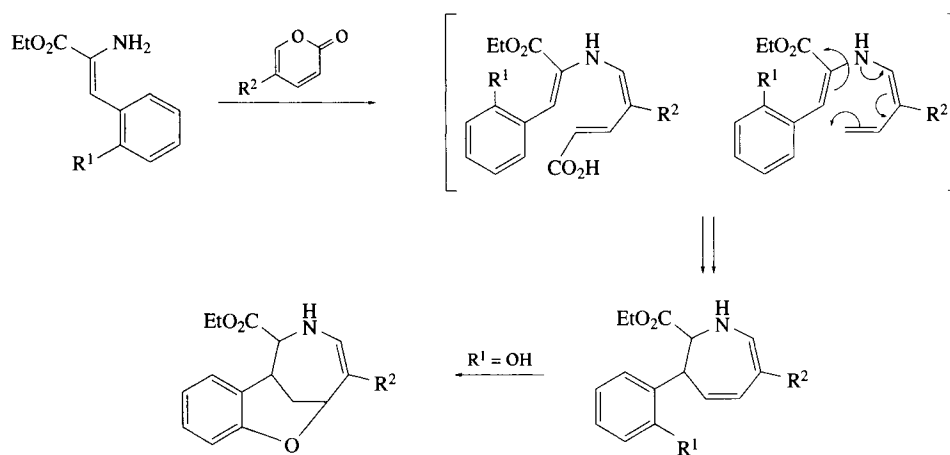
3,4-Dihydro-5-hydroxy-5*H*-benz[*b*]azepines (**200**) are formed in high yields by rhodium-catalyzed, kinetically controlled hydroformylation of the aminoalkenes (**199**) at high pressures <92AJC21>. The reactions were carried out using the substrate, rhodium acetate dimer, and triphenyl phosphine in the ratio 200:1:4 at 2760 kPa at 60°C. A small amount of 3-alkyl-isoquinoline is formed in all cases.



It has been shown that the 1,3-dipolar cycloaddition of *C,N*-diphenylnitrone to allenes containing electron-withdrawing groups affords 2,3,4,5-tetrahydrobenz[*b*]azepin-3(1*H*)-ones <89JOC810>. In this reaction, the transient 5-iminoisoxazoline undergoes N—C bond cleavage, and the resulting diradical cyclizes onto the *ortho*-position of the *N*-phenyl ring to form the benzazepine. Dichloroketene is reported to react with *N*-phenyl-2(2-phenylvinyl)-aziridine to furnish 3,3-dichloro-1,4-diphenyl-2,3,4,7-tetrahydro-1*H*-azepine in 39% yield <89S562>.

The intramolecular aza-Wittig reaction has been described previously as a convenient route for the synthesis of azepines, and, in a bimolecular equivalent, the reaction of 2-formyl-6-dimethylaminofulvene with phenyl-substituted vinyliminophosphoranes in a one-pot reaction offers a facile synthesis of phenyl-substituted 5-azaazulene (**201**) <91TL6727>.

In a new synthesis of azepines, it has been shown that 2*H*-pyrones react with 2-aminocinnamates to form 2,3-dihydro-1*H*-azepine derivatives <89HCA457> in a reaction which has potential for the synthesis of a number of polycyclic azepines (Scheme 26).

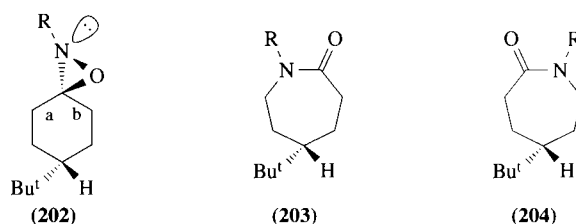


Scheme 26

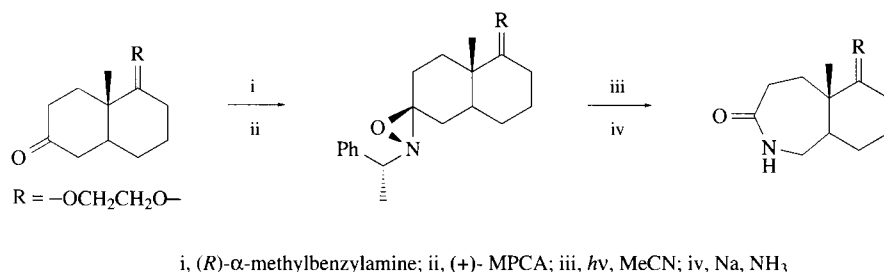
9.01.10 SYNTHESIS BY RING TRANSFORMATION

9.01.10.1 Transformation of a Three-membered Ring

The rearrangements of spirooxaziridines as a route to azepinones $\langle 84\text{CHEC-I}(7)491 \rangle$ has come under scrutiny, especially with respect to the degree of stereoelectronic control in the rearrangement. Lattes *et al.* $\langle 82\text{JA}3929 \rangle$ have shown that photolysis of the pure isomer (**202**), obtained by oxidation of the imine prepared from the prochiral 4-*t*-butylcyclohexanone and (–)-*S*- α -phenylethylamine, gave only one product in 80% yield after isolation and purification, identified as the azepinone (**203**; R = (–)-(*S*)- α -phenylethyl). It is thus clear that of the two possible cleavage pathways, only bond “a” in (**202**; R = (–)-(*S*)- α -phenylethyl), i.e., the bond *anti* with respect to the lone pair on nitrogen, is cleaved, which is contrary to the theory of stereoelectronic control of ring expansion. The alternative (“normal”) isomer (**204**; R = (–)-(*S*)- α -phenylethyl), formed by cleavage of bond “b”, is not observed.



This work has been significantly supplemented by the studies of Aubé *et al.* $\langle 90\text{JA}4879 \rangle$ starting from a range of prochiral cyclohexanones, and in all cases examined it is the relative stereochemistry of the oxaziridine which dictates the formation of a particular lactam. This work has been extended to the synthesis of the benzomorphinan ring system and to the Wieland–Miescher ketone $\langle 90\text{TL}2963 \rangle$ which has possible utility in the synthesis of ring A azahomosteroid derivatives (Scheme 27). The alternative regioisomer may be obtained by using (*S*)- α -methylbenzylamine to prepare the imine in the first reaction stage.



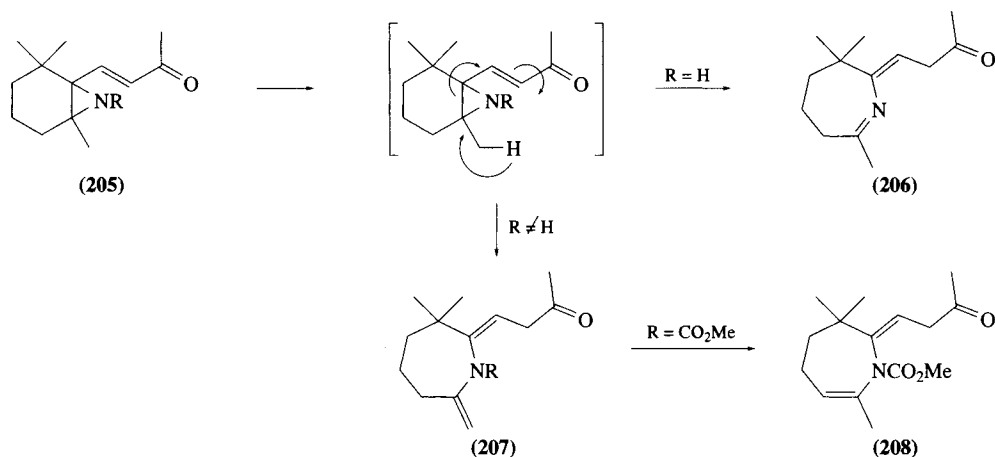
Scheme 27

A feature of this photochemical rearrangement is the high regioselectivity which may be attributed to a lack of nitrogen inversion during the photochemical process. In contrast, thermal rearrangement is substrate dependent and inferior to the photochemical process, both in efficiency and, particularly, selectivity. This has been overcome, however, with the aid of metalloporphyrin catalysis $\langle 94\text{CC}949 \rangle$. It has been demonstrated that trivalent iron, cobalt and, particularly, manganese tetraphenylporphyrin complexes with chloride as an axial substituent are highly effective in catalyzing the rearrangement under very mild conditions. However, the important result is that the high stereoselectivity is the reverse of that observed with the photochemical and non-catalyzed thermal rearrangements, i.e., it is the group orientated *cis* to the nitrogen lone pair which migrates. It is also notable that the method also gives access to *N*-phenyl caprolactams which are not accessible via the photochemical route.

The rearrangement of spirooxaziridines has focused on cyclohexanones, with little information on the influence of a phenyl ring. Johnson and Marples $\langle 88\text{JCS}(P1)3399 \rangle$ have investigated the photo-rearrangement of a number of oxaziridines prepared from α -tetralone and have shown that the rearrangement of spirooxaziridines with the *N*-substituent *anti*- to the aromatic ring is regioselective,

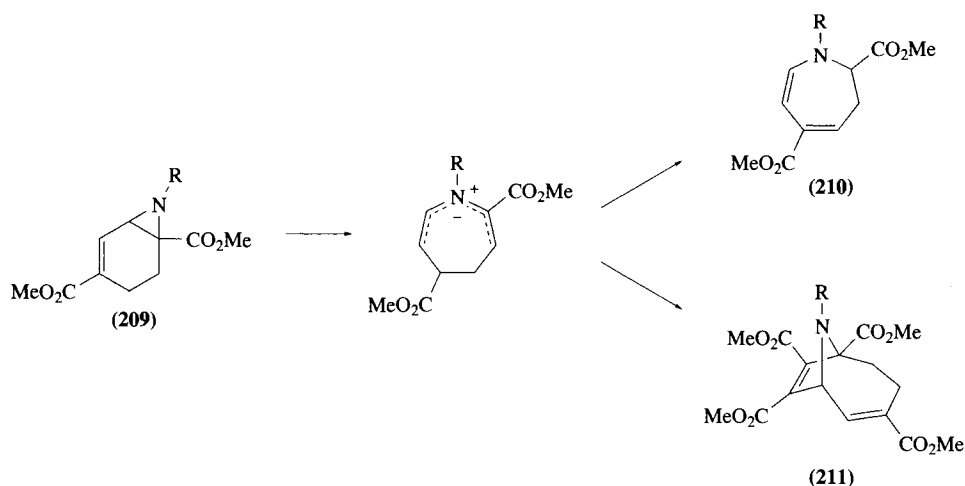
with the aromatic ring exerting no influence upon the course of the reaction. The *syn*-spiro-oxaziridines do not exhibit the same regioselectivity, suggesting that the processes of bond cleavage and re-cyclization are not synchronous, but allow sufficient time for bond rotation to the more stable *anti* conformation.

Bicyclic vinylaziridines fused at C₂ and C₃ yield thermolytic products which arise either from disrotatory ring opening to afford cyclic azomethine ylides or from a [1,5]-*H* shift. The thermolysis of 5,6-epimino-5,6-dihydro- β -ionine (**205**; R = H) and its *N*-methyl and *N*-carbomethoxy derivatives undergo [1,5] shifts as shown in Scheme 28 to yield the azepines (**206**; R = H) and (**207**; R = Me, CO₂Me) <85HCA1107>. Further treatment of (**207**; R = CO₂Me) affords the more stable isomer (**208**; R = CO₂Me).



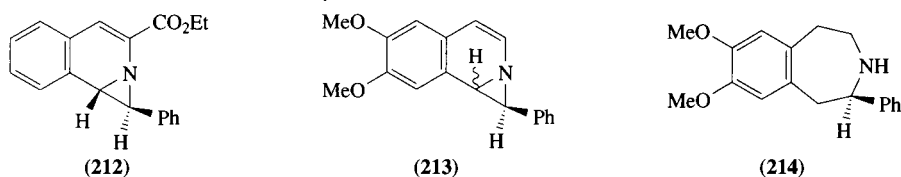
Scheme 28

From the results of deuterium labelling studies, a 1,5-proton shift has been rejected, however, for transformations of the 3,4-epiminocyclohexanes (**209**; R = phenyl or benzyl) to the corresponding 2,3-dihydro-1*H*-azepines (**210**) <83CB563>. The preferred mechanism is that of the formation of an azomethine ylide intermediate as described in Scheme 29, a mechanism supported by isolation of cycloaddition products (**211**) with DMAD.



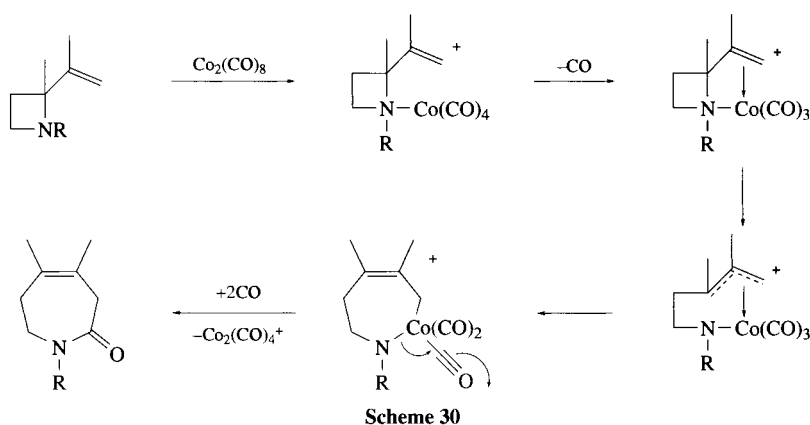
Scheme 29

The aziridine (**212**) is converted into the ethyl 2-phenyl-1*H*-benz[*d*]azepine-4-carboxylate on heating in toluene <86JCS(P1)1113>, and hydrogenolysis of the aziridine (**213**) affords the tetrahydrobenz[*d*]azepine (**214**) <86H(24)2099>.

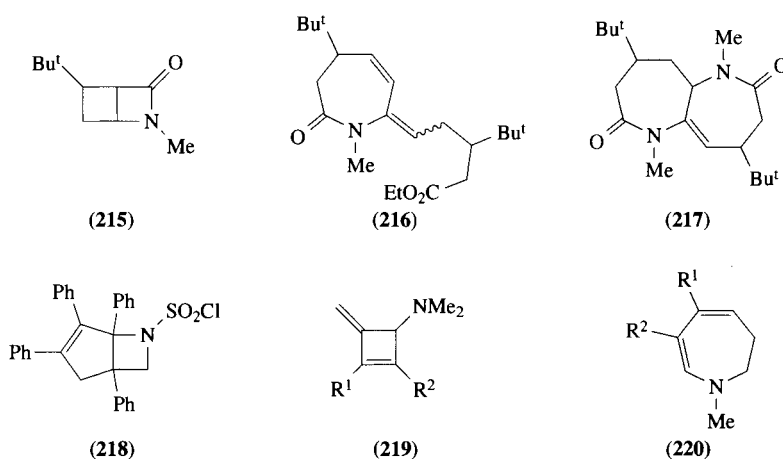


9.01.10.2 Transformation of a Four-membered Ring

2-Vinylazetidines undergo a combination of ring expansion and carbonylation when heated under pressure with carbon monoxide in benzene in the presence of $\text{Co}_2(\text{CO})_8$ to generate 1,2,6,7-tetrahydroazepin-2[3*H*]-ones in good yield <89JA7359>. The mechanism (Scheme 30) is considered to involve complexation of the cobalt with the ring nitrogen followed by π -complexation with the vinyl group.

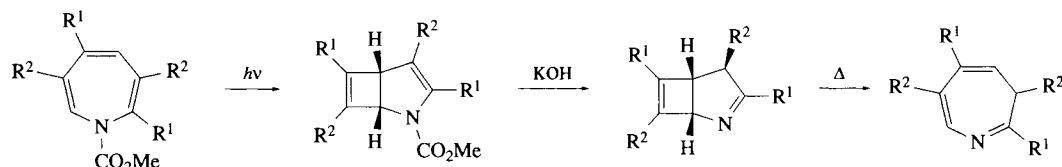


The azabicyclooctane (**215**) undergoes a ring cleavage/dimerization reaction to furnish the azepines (**216**) and (**217**) <87H(26)1611>. Tetraphenylcyclopentadiene is reported to react with chlorosulfonyl isocyanate to form the $[2 + 2]\pi$ adduct (**218**) which, after esterification and base treatment, yields 3,5,6,7-tetraphenyl-azepin-2[2*H*]-one <84H(22)2751>. If, following esterification, the carbonyl group is reduced, base treatment affords 3,5,6,7-tetraphenyl-2*H*-azepine, an assignment which is based upon a two-proton singlet at δ 4.02. Cyclobutanes (**219**) wherein R^1 is hydrogen or alkyl and R^2 is an electron-withdrawing group undergo rearrangement to form the 2,3-dihydro-1*H*-azepines (**220**) on heating <83CC988>. The rearrangement is dependent upon the presence of the electron-withdrawing group as, when it is replaced by a hydroxymethylene, the process does not occur.



9.01.10.3 Transformation of a Five-membered Ring

The reversible valence tautomerism of azepines and azabicyclo[3.2.0]heptadienes and the opportunity to use this as a synthetic method is described in <84CHEC-I(7)491>. This is nowhere better demonstrated than in the conversion of methyl 2,5- and 3,6-di-*t*-butyl-1*H*-azepine-1-carboxylate into 2,5- and 3,6-di-*t*-butyl-3*H*-azepine <88CC1121>, in which the 1*H*-azepine is tautomerized (Scheme 31) by irradiation. Subsequent hydrolysis and thermal tautomerism affords the corresponding 3*H*-azepines.

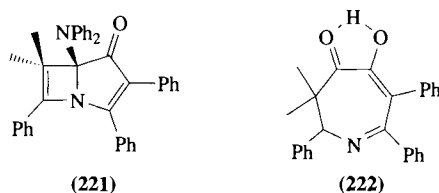


Scheme 31

The application of $[2 + 2]\pi$ cycloaddition reactions to form the azabicycloheptane ring system has led to a number of applications of this route to the synthesis of the azepine derivatives. There are fundamentally two approaches to this synthetic route. One is the cycloaddition of alkenes or alkynes to dihydropyrrolone or dihydropyrrolindiones, followed by thermal or base-catalyzed ring transformation. This method has been employed successfully by Sano and co-workers to prepare a number of azatropone and azatropolone derivatives <85CPB5197, 90CPB3283>. Also reported are the cycloaddition of DMAD to cyclic ketene acetals <82CPB3959>, alkenes to ethyl 2,3-dioxopyrrolidine-4-carboxylates <83TL1949>, alkynic esters to 2-amino-3-cyano-4,5-dihydropyrroles <84CPB2596> and alkyl 2-amino-4,5-dihydro-3-carboxylates <85CB863>, DMAD to 4,5-dimethyl-pyrrol-3(2*H*)one <85S612>, and the addition of ethyne to maleimide <90JHC107>; the extension to indoles is further exemplified in a number of examples <82JCS(P1)741, 83JHC1263, 90JHC655>. In contrast to azanorbornadienes, 1,4-dihydronaphthalen-1,4-imines carrying electron-withdrawing groups may be converted into 1*H*-azepines via their azaquadricyclane valence tautomers <86CB616>.

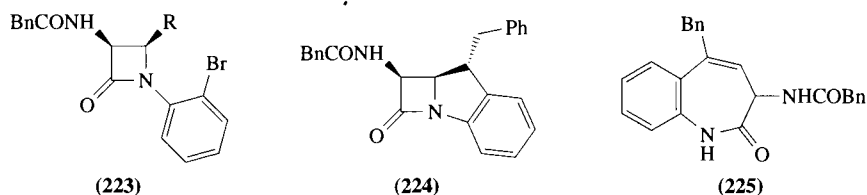
5-Chloro-1,4-dihydro-9-methylnaphthalen-1,4-imine is converted into isomeric dihydrocyclobut[*b*]indoles by direct photolysis, which are in turn converted into 6- and 9-chloro-1-methyl-1*H*-benz[*b*]azepines upon heating in toluene. The azepines are converted back into the dihydrocyclobut[*b*]indoles by light, from which it has been postulated that the azepines may be the primary products in the reaction <85TL2827>. The isomerization of a number of 1,4-dimethyl-9-halogeno-1,2,3,4-tetrahydro-1,4-iminonaphthalenes to 2,3,4,5-tetrahydro-1*H*-benz[*b*]azepines by AgBF_4 in benzene/methanol mixtures has been reported <86TL4071>. Under similar conditions, the 1,4-dihydro-derivatives are converted into quinolines.

The alternative approach is the preparation of an azabicyclopentadiene derivative by dipolar addition of a cyclobutene to oxazolium 5-oxides <84CHEC-I(7)491> and also to nitrile ylides <83M1145>. An extension to this method is the addition of cyclopropenones to azetines <83HCA1366>. Thus (221), formed by addition of diphenylcyclopropenone to 2-diphenylamino-3,3-dimethyl-4-phenyl-1-azetine, is hydrolyzed in HCl/EtOH at room temperature to (222) in 86% yield.



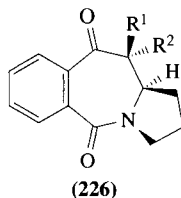
Free radical cyclization of the azetidinone (223; $\text{R} = -\text{CH}=\text{CHPh}$) gives a mixture of the debrominated starting material together with the carbapenem (224) and the benz[*b*]azepin-2(3*H*)-one (225) <87CJC104>. The carbapenem is unstable and is converted into (225) on standing. A similar result is obtained with the alkyne analogue (223; $\text{R} = -\text{C}\equiv\text{CPh}$).

The intra- and interphotoaddition of alkenes to phthalimides to yield 3,4-dihydrobenz[*c*]azepine-1,5-diones is considered to proceed by way of an initial concerted $[2 + 2]\pi$ cycloaddition. This proposal has been reinvestigated by Mazzocchi and co-workers who have shown that the addition of *cis*- and *trans*-2-butene to *N*-methylphthalimide to afford the respective *cis*- and *trans*-2,3,4-



trimethylbenzazepinediones occurs at greater than 95% stereoselectivity <83JOC2981>. This is in accord with a concerted mechanism, but does not totally exclude the possible involvement of a stepwise biradical process, in which the second bond is formed faster than rotation of the alkane C—C bond, which, in turn, would lead to loss of stereochemistry. These workers have shown further, however, that substitution effects are in total agreement with the concerted mechanism. The same level of stereoselectivity is achieved in intramolecular reactions of *cis*- and *trans*-*N*-hex-4-enylphthalimides in acetonitrile which affords, respectively, (226; $R^1 = \text{Me}$, $R^2 = \text{H}$) and (226; $R^1 = \text{H}$, $R^2 = \text{Me}$) <85JCS(P1)2025>.

In what may be regarded as a related reaction, 1-phenyl-2-pyrrolidinone undergoes a photochemical Fries rearrangement to furnish 1,2,3,4-tetrahydro-5*H*-benz[*b*]azepin-5-one <93H(36)743> together with 1-phenyl-pyrrole. The highest yields of the azepine are obtained in methanol containing 5% v/v of the singlet state photosensitizer piperylene, whereby only a trace of the pyrrole is formed.

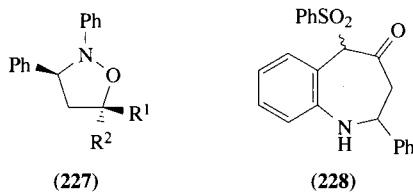


In extending this reaction to naphthalene analogues, Kubo *et al.* have demonstrated that benzazepine formation is the predominant reaction for *N*-methyl-1,2-naphthalenedicarboximide, but the 2,3- and 1,8-isomers are characterized by oxetane formation, an observation which has been attributed to the differing natures of the respective $S_1\pi\pi^*$ singlet states <86BCJ191>.

Imides prepared from α -amino acid esters with an extractable γ -proton (with respect to the phthalimide nitrogen as α) have been reported to furnish benz[*c*]diazepine-2,5-diones in a Norrish Type II process with retention of stereochemistry of the amino acid asymmetric centre <92CB2467, 94T3627>. Similar results are reported in the intramolecular cyclization of *N*-alkyl succinimides, in contrast to the reaction of such compounds with alkenes in an intermolecular reaction, when the usual product is an oxetane <84CPB950, 85MI 901-02>.

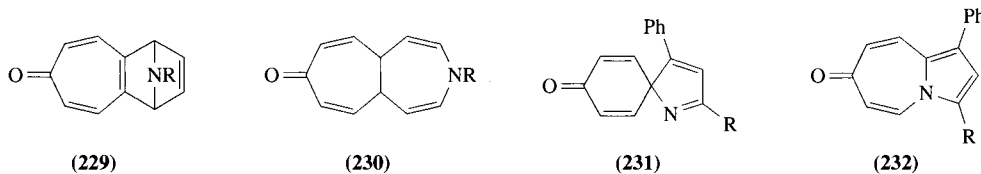
Cycloaddition of *C,N*-diphenyl nitron with 2,3-(diphenylsulfonyl)-1-propene at 80°C affords the isoxazolidine (227; $R^1 = \text{CH}_2\text{SO}_2\text{Ph}$, $R^2 = \text{SO}_2\text{Ph}$) in 80% yield. If the reaction is carried out under pressure the diastereoisomer (227; $R^1 = \text{SO}_2\text{Ph}$, $R^2 = \text{CH}_2\text{SO}_2\text{Ph}$) was formed. Both isomers give the same diastereoisomeric mixture of 2,3-dihydro-5-phenylsulfonyl-1*H*-benz[*b*]azepin-4(5*H*)-one (228) on treatment with DBU <88TL265>. 4,5-dihydroisoxazole-5-spirocyclobutanes prepared from nitrile oxides and methylenecyclobutane are reported to rearrange under flash pyrolysis conditions to afford dihydroazepin-4-one derivatives in modest yield <92T5283>.

Irradiation of benzofuroxan in acetonitrile containing 5% water using a high-pressure mercury lamp with a Pyrex filter furnishes 1*H*-azepin-2,7-dione <91JHC1079>, and treatment of 4,7-disulfonylbenzofurazan-1-oxides with azide yield tetrazolo[1,5-*a*]azepine derivatives <88JCS(P1)145>.

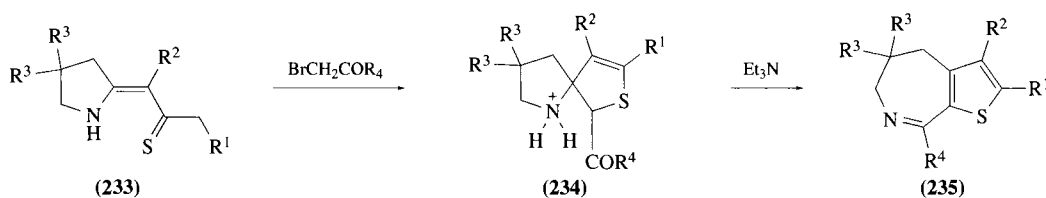


Treatment of 1-amino-1*H*-cycloheptatriazol-6-one with lead tetraacetate in dichloromethane in the presence of 1-acyl- or 1-sulfonyl-pyrroles affords the addition products (229; $R = \text{acyl or sulfonyl}$)

which undergo photolytic rearrangement to the 3-acyl- or 3-sulfonyl-8*H*-azaheptalen-8-ones (**230**; R = acyl or sulfonyl) <90CL91>; thermal rearrangement of 1-azaspiro[4,5]deca-1,3,6,9-tetraen-8-ones (**231**), where R is an alkoxy- or, preferably, secondary amino group, affords the 7*H*-pyrrolo[1,2-*a*]azepin-7-ones (**232**) <87S262>.

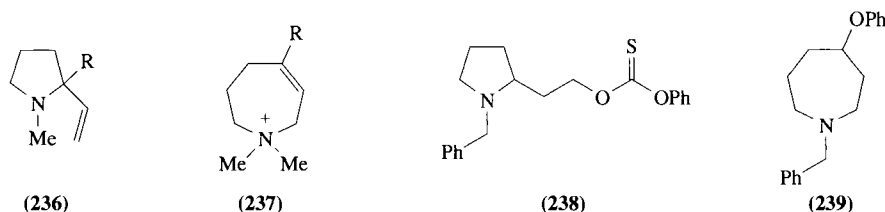


Pyrrolidine enaminothiones (**233**) react with bromomethylcarbonyl derivatives to form the thiaazaspiroene salts (**234**) which undergo a Smiles type rearrangement when treated with base to afford the dihydro-6*H*-thieno[2,3-*c*]azepines (**235**) as shown in Scheme 32 <87AP(320)582>. The reaction may also be carried out with 3,3-dimethyl-indolin-2-one to afford the corresponding benz[*b*]azepine derivatives.



Scheme 32

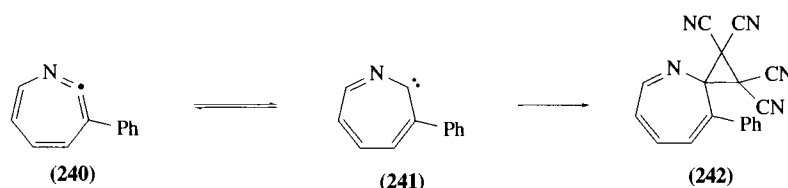
Examples of the ring expansion of pyrrolidine derivatives to azepine derivatives include the attempted alkylation of vinylpyrrolidine (**236**; R = aryl) with methyl iodide to afford the tetrahydroazepinium salt (**237**; R = aryl) <82AP(315)749> and thermal rearrangement of the thionocarbonate (**238**) to furnish the hexahydroazepine (**239**) <90CPB2981>.



9.01.10.4 Transformation of a Six-membered Ring

The nature of the intermediate species in the ring expansion of nitrenes to produce azepines has evoked considerable interest <84CHEC-I(7)491, B-84MI 901-01>, and a current conception is that in the photolysis of monocyclic azides the active intermediate is a didehydroazepine species formed directly from singlet nitrene and that the originally proposed aziridine intermediate may be of little significance in the reaction at normal temperatures. A number of investigators have demonstrated that a didehydroazepine species is involved in the reaction, often by using substituted azide precursors to modify the reactivity of the nitrene intermediate. In the mid-1980s, Dunkin and co-workers <85JCS(P2)307> investigated the photolysis of phenyl azide and a number of 3- and 4-substituted azides in nitrogen and argon matrices at 12 K and have been able to demonstrate that the major reaction pathway involves the formation of didehydroazepines as primary products with characteristic infrared absorptions at ca. 1890 cm⁻¹. Substituents have little effect upon the characteristic group frequency. No evidence for an azirine intermediate is forthcoming from this work; it has been supported by the observations of Schuster and co-workers <88JA8092>, who have found that, when irradiating cyclohexane solutions of substituted phenylazides in the presence of diethylamine or diisopropylamine, electron-donating substituents *para* to the azide group lead to a fall in the yield of azepine while electron-withdrawing substituents have the opposite effect. Except in the example of a 4-dimethylamino-substituent where no azepine was formed, didehydroazepine intermediates

were detected using time-resolved spectroscopy. In further studies by Dunkin and co-workers, didehydroazepinones have been observed during the irradiation of 2,6-dichloro- and 2,6-dibromo-4-azidophenol <94CC1695>. In contrast to these data, the results from the photolysis of 3-acetamido-4-trifluoroacetamidophenyl azide in THF have furnished evidence which has been interpreted as supporting the formation of an azirine intermediate <92CC1359>. At low temperatures or in the presence of a large excess of aniline the primary product is 3-acetamido-2-diethylamino-4-trifluoroacetamidylaniline. Only at temperature of 30°C and above are azepines formed in any appreciable yield. Kinetic data have lead the authors to conclude that an azirine is formed in equilibrium with the initial singlet nitrene which rearranges irreversibly to form the didehydroazepine at higher temperatures. The formation of a seven-membered species is further supported by the isolation of the spiroazepine derivative (**242**) from the photolysis of *o*-azidobiphenyl in the presence of TCNE <84CC1198>. It is assumed (Scheme 33) that the product is formed from the carbene (**241**) which is in equilibrium with the didehydroazepine (**240**). In this respect it is of interest to note that such a carbene species has been postulated as a possible intermediate in the formation of triplet nitrenes from the singlet species (see Section 9.01.2.).

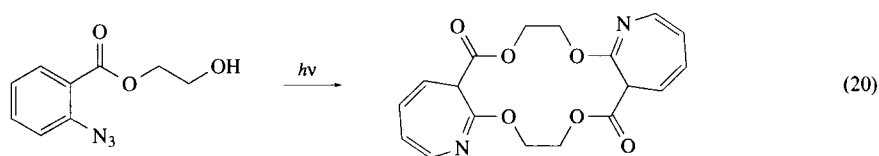


Scheme 33

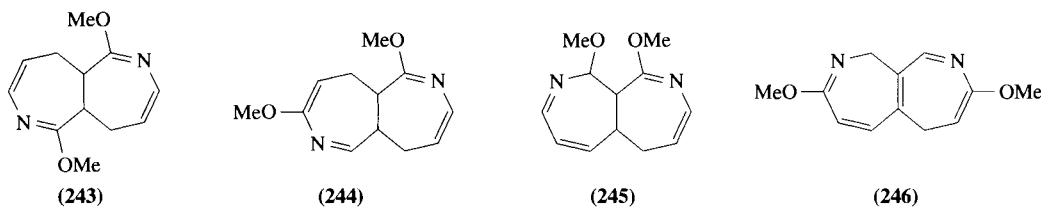
The preparative aspects of nitrene-induced ring expansion have continued to be explored. Photolysis and thermolysis of phenyl azide in acetic acid has furnished 1*H*-azepin-2(3*H*)-one and 2-phenoxy-3*H*-azepine on photolysis in ethanol in the presence of phenol <82JCS(P1)1269>. Methyl 2,4-dimethoxy-3*H*-azepine-5-carboxylate has been formed from dimethyl *p*-azidosalicylate by photolysis in methanol <83JOC5041>. Photolysis of a number of *para*-substituted phenyl azides with electron-withdrawing substituents in aqueous tetrahydrofuran affords 5-substituted 3*H*-azepin-2-ones, and photolysis of 2-azidobenzoic acid gives a mixture of products comprising 3*H*-azepin-2-one-3-carboxylate and its decarboxylated derivative together with 6*H*-azepino[2,1-*b*]quinazolin-12-one <91T2277>. *Ortho*-azidobenzonitriles yield a mixture of 3- and 7-cyano-3*H*-azepin-2-ones under similar conditions <94T5515>.

Thermolysis of *p*-azidoacetophenone, *p*-azidobenzophenone and methyl *p*-azido benzoate in methanol in sealed tubes yields the corresponding 5-substituted 2-methoxy-3*H*-azepine <86BCJ2317>. The 4-nitro analogue gives only tars. The *meta*-isomers, including the nitro-derivative, give mixtures of 4-substituted and 6-substituted derivatives. When *p*-azidoacetophenone is heated in piperidine 5-acetyl-2-piperidino-3*H*-azepine and, unexpectedly, 6-acetyl-2-piperidino-3*H*-azepinone are formed together with triplet nitrene-derived products. Similar results are observed in the presence of morpholine and also with *p*-azidobenzophenone. The 5-acyl derivatives are converted into the 6-acyl isomers in high yield on heating with the relevant amine but no isomerization is observed if the reaction is attempted in xylene. The results are explained by a mechanism involving a dipolar transition state or intermediate. Treatment of 4-substituted *N*-acetyl-*O*-methylsulfonylphenylhydroxylamines with *n*-butylamine afford 2-*n*-butyl-3*H*-azepines via nitrene formation <88TL1781>. A 4-carbomethoxy substituent affords the highest conversion, whilst a 4-nitro-substituent gives only triplet-derived products. 4-Cyano- and 4-acetyl-substituted hydroxylamines give mixtures of singlet and triplet nitrene-derived products, with azepine formation being favored at higher temperatures.

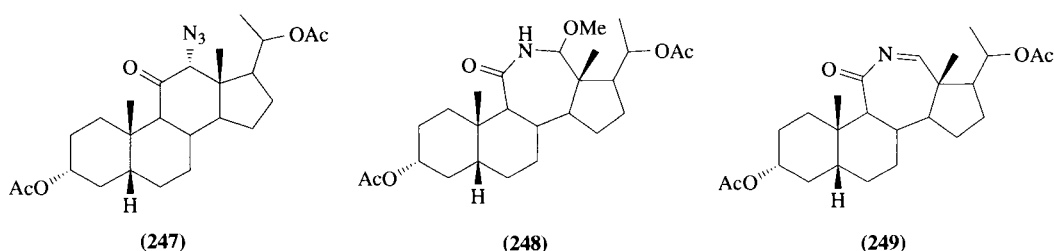
A number of novel pyridoazepine and thienoazepine derivatives have been prepared by the photolysis of the appropriate azidoquinoline or azidobenzothiophene <83JCS(P1)2495, 85JCS(P1)1911, 87JCR(S)164, 88JCR(S)14, 88JCS(P1)1933>. Irradiation of β -hydroxyethyl *o*-azidobenzoate in THF furnishes a diazepino-14-crown-4 analogue (Equation (20)) <85JCS(P1)1121>.



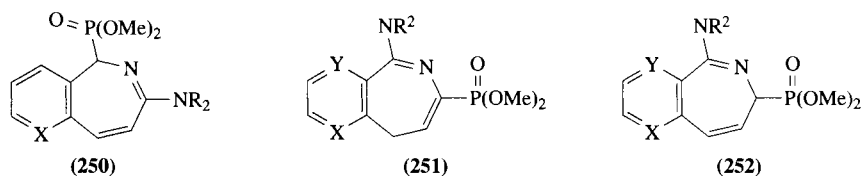
Photolytic ring expansion of 1,5-, 1,6-, 1,8-, and 2,7-diazidonaphthalenes result in the expansion of both rings to furnish the respective azepinoazepines (**243**) to (**246**) in addition to intermediate azidobenzazepines <90CC628>.



Photolytic or thermal treatment of α -azidoketones offers a route to azahomosteroids. Thus, for example, photolysis of the azide (**247**) in methanol affords the lactone (**248**), whilst irradiation in methylene chloride or heat forms the iminolactone (**249**) <92CJC2405>.



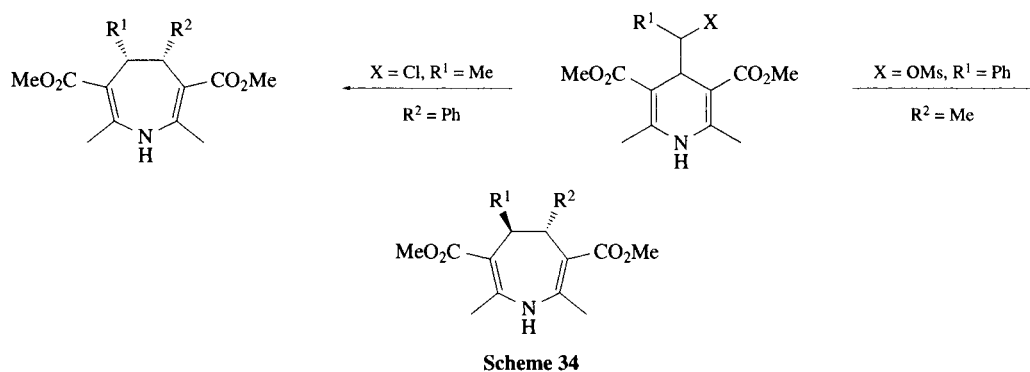
An alternative method for the preparation of benz[c]azepines and their pyrido analogues is the treatment of nitronaphthalenes and nitroquinolines with dimethyl phosphate under basic conditions <85CC1792, 91JOC1283>. Thus, treatment of 2-nitronaphthalene or 6-nitroquinoline with secondary amines and sodium methoxide affords the phosphonates (**250**; X = CH or N) whereas 1-nitronaphthalene and 5-nitro- or 8-nitroquinoline form a mixture of the tautomers (**251**; X and Y = CH or N) and (**252**; X and Y = CH or N).



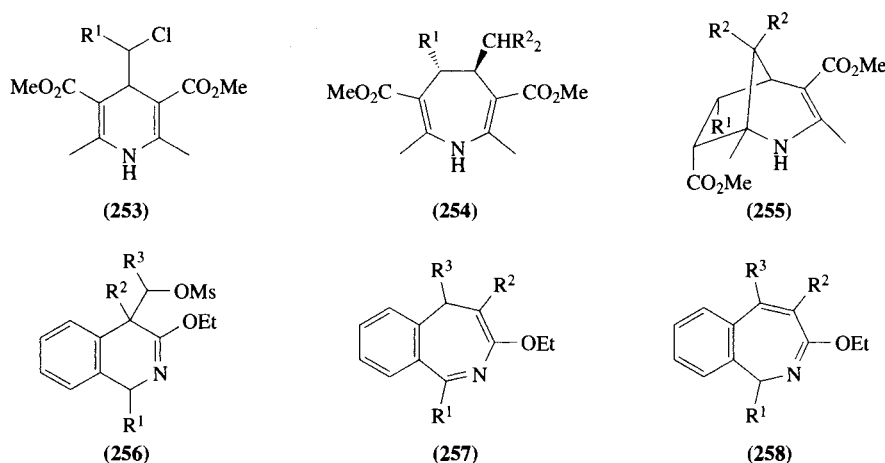
Thin films of poly-1,2-azepines formed by the photopolymerization of phenyl azides exhibit electric conductivities of up to 0.01 S cm⁻¹ upon oxidative doping with iodine or arsenic pentafluoride <88JA7209>.

The ring expansion of 1,4-dihydropyridines substituted at position 4 by a chloromethyl or a functionalized hydroxymethyl group by nucleophilic bases has been extended to reaction with Grignard reagents, particularly in respect to azepine analogues of the 1,4-dihydropyridine calcium channel blockers <84JOC3871>. The stereochemistry of 4,5-disubstituted 4,5-dihydro-1*H*-azepines prepared from these symmetrically substituted dihydropyridines can be selected, as aryl Grignard reagents give *cis* products with good stereoselectivity ($\geq 10:1$) and alkyl Grignard reagents give *trans* products ($\geq 15:1$) (Scheme 34).

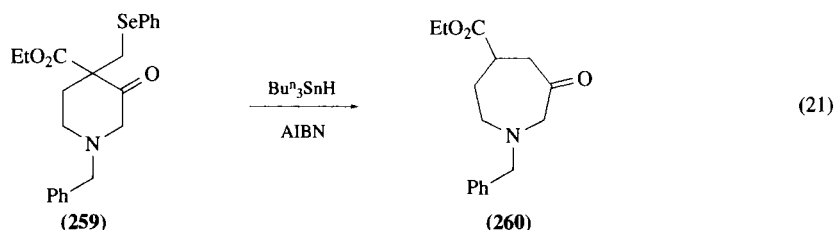
The dihydropyridines (**253**; R¹ = H or Me) react at room temperature with the sodium salts of ethyl acetoacetate or buta-1,3-dione to form the 4,5-dihydro-1*H*-azepines (**254**) <85CJC843>. Under more vigorous conditions, (**254**; R² = COCH₃) reacts further to give the 2-azabicyclo[3.2.1]oct-3-enes (**255**; R² = COCH₃). In contrast, the diesters (**254**; R² = CO₂Me) fail to cyclize. The work has been extended to the preparation of spiro compounds by reaction with the sodium salts of cyclic 1,3-diones and the sodium salt of cyclopentadiene, and also to the rearrangement of 1,4-dihydroisquinolines <92LA1179>. In the example of (**256**; R¹ = R³ = H, R² = Me) both possible isomers, (**258**; R¹ = R² = H, R³ = Me) and (**258**; R¹ = R³ = H, R² = Me), are isolable. In the example of (**256**; R¹ = Ph, R² = Me, R³ = H), the two respective isomers (**257**) and (**258**) are obtained. The 4*H*-isomer (**257**) is converted smoothly into the 1*H*-isomer (**258**) in a [1s,5s] sigmatropic hydrogen shift by



heating at 150°C. These ring expansion reactions have been applied to the synthesis of a number of dibenz[*b,f*]azepines <92LA199, 82EJM371>.



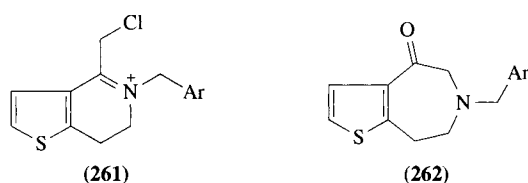
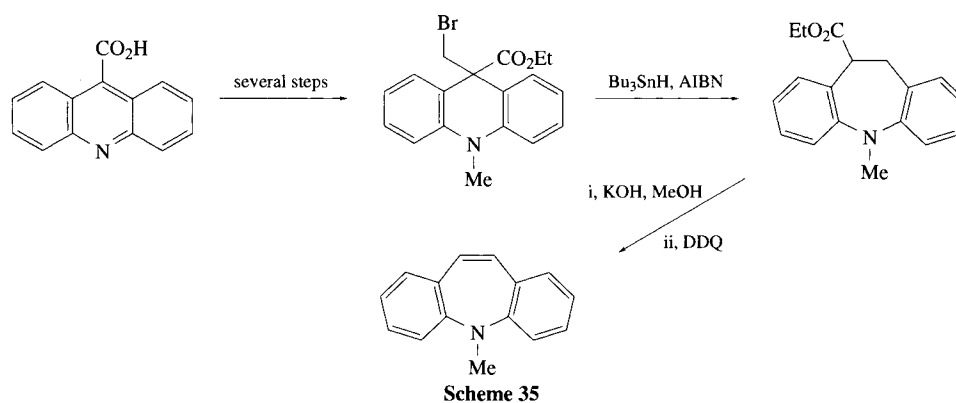
The ring expansion of substituted piperidines by means of free-radical-induced rearrangements has been used to prepare fully saturated azepines <91T4847>. Ethyl 1-benzyl-3-oxo-4-phenylselenomethylpiperidine-4-carboxylate (**259**) is converted into the azepinone (**260**) by tri-*n*-butyl tin hydride in benzene under reflux in the presence of AIBN (Equation (21)). The reaction works also with ethyl 3-phenylselenomethyl-4-oxo-piperidine-3-carboxylate, preferably with the benzyl group replaced by a trityl group.



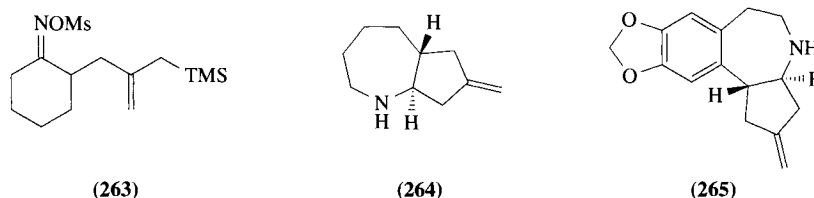
Ethyl 2,3-dihydro-1*H*-benz[*b*]azepin-5(4*H*)-one-3-carboxylate has been prepared in a similar manner from ethyl 3-bromomethyl-2,3-dihydroquinolin-4-one-3-carboxylate and 5-methyl-benz[*b,f*]azepine may be prepared from acridine-9-carboxylate as shown in Scheme 35 <93TL7709>.

Treatment of the thienopyridinium salt (**261**) with aqueous sodium acetate brings about a ring expansion to the thienozazepine (**262**) <85JHC1011>. The reaction almost certainly involves ring cleavage of the pseudobase followed by recyclization by an intramolecular S_N2 reaction.

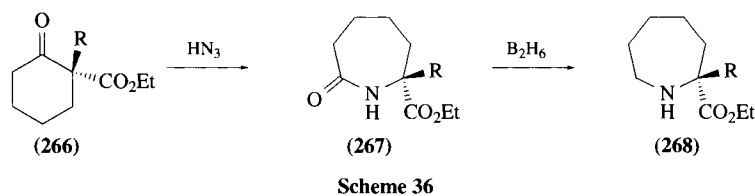
The Beckmann rearrangement of cyclohexanone oximes produces caprolactams in high yield if the reaction is carried out in the presence of tetrabutylammonium perhenate <93CL489>, and enamminolactams are obtained by the photolytic rearrangement of α,β-unsaturated ketone oximes <88JCS(P1)321>. The treatment of acylated or sulfonylated oximes with trimethylsilyl iodide or



diethylaluminum iodide forms imidoil iodides. In this manner, treatment of cyclohexanone oxime mesylate with diethylaluminum iodide forms the imidoil iodide which may be reacted *in situ* with phenyl magnesium bromide and dibal-H to furnish 2-phenyl-hexahydroazepine <83TL3255>. The Beckmann rearrangement has also been used to prepare a potentially useful resolving agent, (–)-(2*S*,*trans*)-hexahydro-2-isopropyl-5-methyl-azepineamine, from (–)-(E)-menthone oxime <87H(26)2411>. A number of cyclohexane oximes functionalized with allyl silanes have been converted into fused azepine derivatives by a useful tandem Beckmann rearrangement. Thus, reaction of (263) with dibal-H affords the bicycle (264) <91AG(E)687>. This reaction sequence has been used in a synthesis of (265), a partial structure of cephalotoxin <94SL375>.



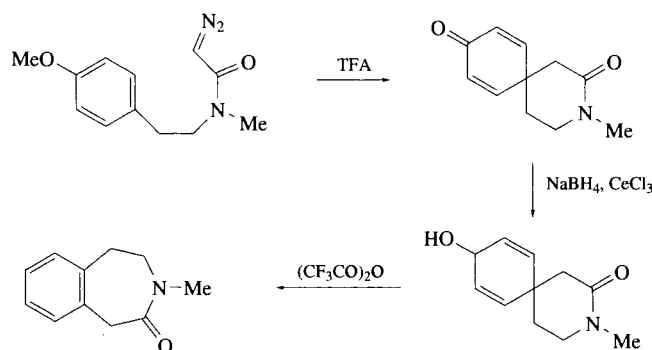
A new application of the Schmidt rearrangement is to give unnatural aminoacids <91BMC125>. Treatment of the optically active cyclic β -ketoester (266) with hydrazoic acid gives the optically active azepinone (267) which upon selective reduction with diborane furnishes the novel cyclic amino acid ester (268) (Scheme 36).



The ylide produced by the base treatment of 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate rearranges upon heating to give 3*H*-2,4,6,7-tetraphenylazepine <87H(25)387>. 1-Phenyl-2-methyl-2-trimethylsilylmethyl-tetrahydroisoquinolinium salts rearrange in the presence of fluoride ion to form 3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-benz[*d*]azepines in good yield <92JOC6711>. The reaction is limited to the 1-phenyl derivatives as 1-unsubstituted and 1-alkyl tetrahydroisoquinolinium salts follow different reaction pathways yielding isoquinoline and/or ring cleavage products. The ring expansion has also been observed with piperidinium salts, but the yields are low <89JOC836>. The 2-

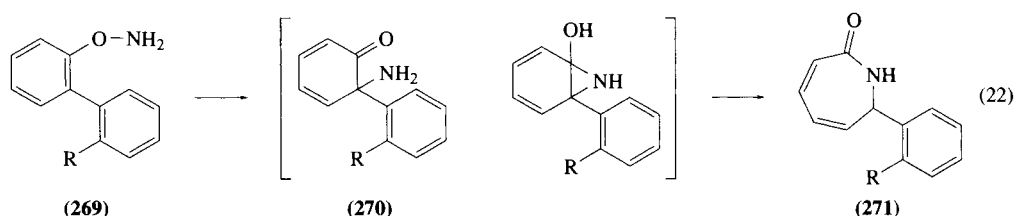
phenyl-tetrahydro-benz[*d*]azepines are obtained by the base-catalyzed rearrangement of *N*-benzyl-*N*-methyl-tetrahydroisoquinolinium salts <84JOC581>, and 4,5-dihydro-3-methyl-2-phenyl-3*H*-benz[*d*]azepines are formed by the reaction of 3,4-dihydro-*N*-methyl isoquinolinium salts with α -bromo- α -trimethylsilyltoluene in the presence of fluoride <91JOC3908>.

Further ring expansion reactions of isoquinoline derivatives which lead to benz[*d*]azepines include the reaction of acylenamides derived from 1-methyl and 1-ethyl-3,4-dihydroisoquinoline with lead tetraacetate to afford 3-acyl-1,2,4,5-tetrahydro-3*H*-benz[*d*]azepin-2-ones <88JOC5791>, the reaction of *N*-acyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids with trifluoroacetic anhydride to give 3-acyl-1,2,4,5-tetrahydro-2-trifluoromethyl-3*H*-benz[*d*]azepin-1-ones <92CC1076> and the rearrangement of methoxy-substituted 1-hydroxybenzyl-2-methyl-1,2,3,4-tetrahydroisoquinolines with formic acid to 1-benzyl-2,3,4,5-1*H*-benz[*d*]azepines <82JCS(P1)2163>. 4,5-Dihydro-benz[*d*]azepin-2(1*H*)-ones have been prepared by the rearrangement of spirodiones prepared by the acid cyclization of *N*-(2-(4-methoxyphenyl)ethyl)diazoacetamide (Scheme 37) <88TL2643>.

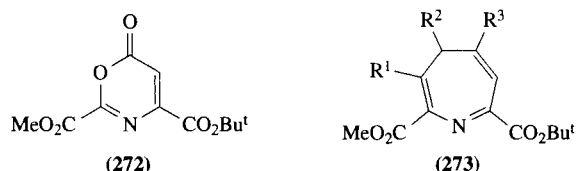


Scheme 37

N-cyclohexylhydroxylamines are converted into 4,5,6,7-tetrahydro-3*H*-azepines by treatment with *p*-nitrobenzenesulfonyl chloride under basic conditions <88JOC3316>. Heating the *O*-(2-arylphenyl)hydroxylamines (**269**; R = H, Me, NO₂) with acid brings about a rearrangement to 7-aryl-1*H*-benzazepin-2(3*H*)-one (**271**; R = H, Me, NO₂) <92TL3339>. The intermediate (**270**) may be trapped as its trifluoroacetamide if the reaction is carried out in the presence of trifluoroacetic anhydride (Equation (22)).

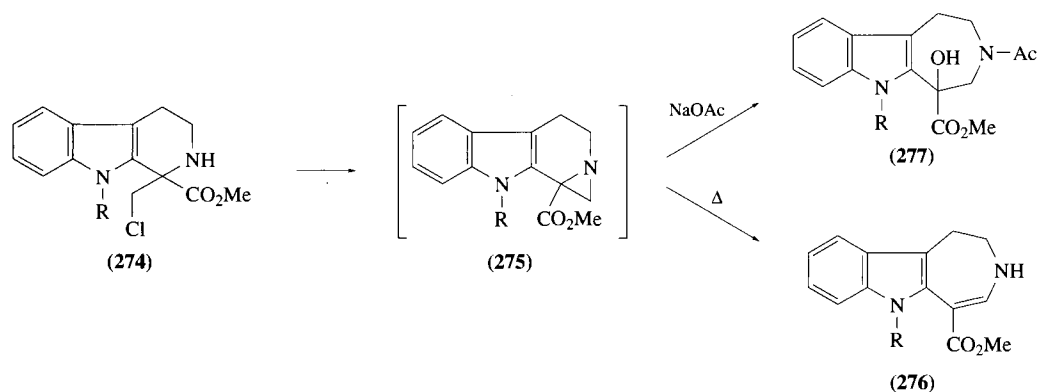


Cycloaddition of cyclopropenes to dialkyl 6*H*-1,3-oxazin-6-one-2,4-dicarboxylates (**272**) followed by loss of carbon dioxide furnishes the dialkyl 4*H*-azepine-2,6-dicarboxylates (**273**) <90H107>. Cyclopropene and 3-methyl-cyclopropene give, respectively, the azepines (**273**; R¹ = R² = R³ = H) and (**273**; R¹ = R³ = H, R² = Me). The reaction is not regiospecific, in that 1-methylcyclopropene gives a mixture of isomers (**273**; R¹ = Me, R² = R³ = H) and (**273**; R¹ = R² = H, R³ = Me).



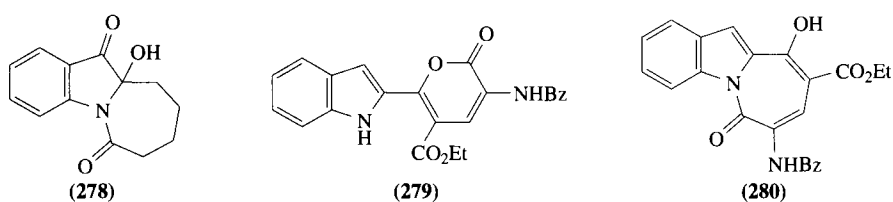
A number of azepinoindole syntheses have been described. Reaction of tryptamine or *N*^a-methyl-tryptamine with methyl chloropyruvate affords the β -carboline (**274**; R = H, Me) which on heating or treatment with sodium acetate in acetic acid rearrange to respectively, (**276**; R = H, Me) and

(**277**; R = H, Me) via the intermediate aziridine (**275**) as shown in Scheme 38 <85JOC919>. The same ring system in the form of 4-methyl-1,2,3,4,5,6-hexahydroazepine[3,4-*a*]indole is obtained in high yield by subjecting the phenylhydrazone of 1-methylpiperidine-3-carboxaldehyde to the Fischer indole synthesis using 20% aqueous H₂SO₄ at 95°C <87JHC623>.



Scheme 38

Oxidation of 7-methyl-1,2,3,4-tetrahydro-9(10*H*)-acridone with sodium dichloroisocyanurate furnishes the azepino[1,2-*a*]indole (**278**) <88JOC5287> although the reaction does not proceed if the 5-position is also substituted. This suggests that the 10-nitrogen plays a part in the reaction, possibly involving the formation of an N-Cl intermediate, and the substituent in the 5-position sterically hinders this step <90JOC1969>; 6-(indol-2-yl)pyran-2-ones, for example (**279**), rearrange in the presence of base to the more fully unsaturated azepino[1,2-*a*]indole system (**280**) <93JCS(P1)969>.



9.02

Oxepanes and Oxepines

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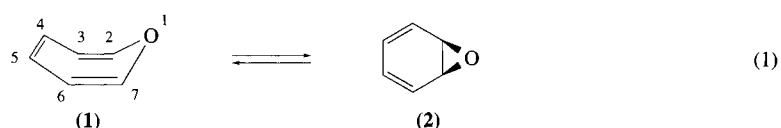
9.02.1 INTRODUCTION

This chapter follows on from the review by Boyd in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I), which dealt with oxepanes and oxepines <84CHEC-I(7)547>. The literature published from 1982 until 1993 (taken from *Chemical Abstracts*) is reviewed, as well as citations from some important earlier publications. This chapter does not contain a section devoted to

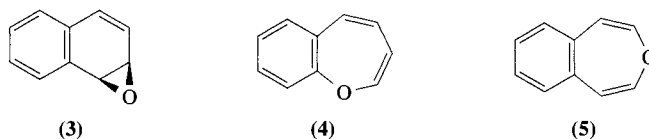
reactivity of substituents. Data of this kind are considered in Sections 9.02.5–9.02.9, since they are of little importance in the sections associated with other reactions and syntheses of oxepines and oxepanes. Syntheses of ϵ -caprolactone are omitted, its reactivity is included only to demonstrate transformations leading to other oxepanes and hydrooxepines.

9.02.2 THEORETICAL METHODS

Several quantum chemical calculations using both semiempirical and *ab initio* methods concerning the oxepin (1), benzene oxide (2), and their equilibrium should be noted (Equation (1)) <83MI 902-01, 84MI 902-01, 90MI 902-01>. The fully optimized geometry data <90MI 902-01> agree with experimentally found geometry of several substituted oxepines (see Section 9.02.3). According to calculations, the carbon skeleton of benzene oxide is practically planar while the angle between the epoxide ring and adjacent plane is ca. 106° ; whereas the oxepin molecule is boat-shaped with folding angles along the two lines between C_2 — C_7 (1) and C_3 — C_6 ca. 137 and 159° , respectively.



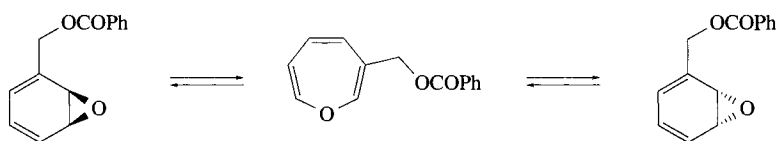
Semiempirical (AM1) and *ab initio* (6-31G) calculations of naphthalene oxides (3)–(5) show that the benzene nucleus retains benzenoid character while in both benzene oxide and oxepin a polyenic nature is found <91MI 902-01>. Molecular mechanics calculations were used in conformational studies of some complicated oxepanes, i.e. 3,3,6,6-tetramethyloxepan-4,5-dione <83JCS(P2)1351> and a 14β -steroid possessing an oxepan ring as a 17β -substituent <86ZN(C)297>.



9.02.3 EXPERIMENTAL STRUCTURAL METHODS

The first x-ray crystal structure analysis data for a monocyclic oxepin appeared in 1982 when the structure of 3,7-di-*t*-butyl-5-phenyl-2-(*p*-tolyl)oxepin was published <82CB385>. The data shows that the substituted oxepin exists in a boat conformation with dihedral angles between C_2OC_7 and $C_2C_3C_6C_7$ planes 117.6° , and that between $C_2C_3C_6C_7$ and $C_3C_4C_5C_6$ planes 150.7° (cf. the above data from quantum chemical calculations for the unsubstituted oxepin). Double and single bonds in the molecule show some degree of equalizing: O— C_2 1.424, C_2 — C_3 , 1.393, C_3 — C_4 1.426, C_4 — C_5 1.367, C_5 — C_6 1.441, C_6 — C_7 1.323, and C_7 —O 1.404 Å. Similar geometry has also been demonstrated for 2,7-diphenyloxepin <86JOC2784> and 7-*t*-butoxycarbonyloxepin <86CC970>. The x-ray data for fused dibenzoxepin is also available <82AX(B)200>.

Low-temperature NMR studies of 2-cyano- and 2-ethoxycarbonyl-7-ethyloxepines provided evidence for a nonplanar geometry with a ring inversion barrier of $6.5 \text{ kcal mol}^{-1}$ besides rotational isomerism involving 2-ethoxycarbonyl substituent <86CC970>. The geminal methylene protons in α -benzoyloxytoluene-2,3-oxide appeared as a singlet at ambient temperature and split into an AB system at -135°C , which supports the existence of two enantiomers, also in the equilibrium (Scheme 1) ca. 5% of the oxepin isomer was present <88T7551>. Analogous equilibrium was shown in the case of 3-ethylnaphthalene-1,2-oxide <88T7551>. The ^{13}C NMR spectra of partially hydrogenated oxepines, namely 2,3,4,5-tetrahydrooxepin <85JOC5583> as well as its anions and 2,3-dihydrooxepin <82JOC3094> were investigated.



Scheme 1

9.02.4 THERMODYNAMIC ASPECTS

Thermodynamic parameters of oxepines and oxepanes are considered, calculated, or measured in many publications. Among them, those which dealt with enthalpies of formation of oxepan and oxepin <92MI 902-01> and energetics of the arene oxide–oxepine valence isomerization <83JCS(P2)1351, 83MI 902-01, 84JA7696, 88T7551, 90MI 902-01, 91MI 902-01> are cited. The MNDO calculations <83MI 902-01> show that, in the gas phase, oxepin is more stable than benzene oxide, while in polar media the inverse is true. Dynamic NMR study <88T7551> gave the following activation parameters for the valence isomerization/degenerate racemization process: $\Delta G^\ddagger = 7.6 \text{ kcal mol}^{-1}$, $\Delta H^\ddagger = 8.6 \text{ kcal mol}^{-1}$, and $\Delta S^\ddagger = 5.8 \text{ eu}$.

A dynamic NMR study <83JCS(P2)1351> of a saturated compound, 3,3,6,6-tetramethyloxepan-4,5-dione, gave evidence for two conformations, a distorted chair and a twist-boat, the latter being less favorable (by $1.91 \text{ kcal mol}^{-1}$). Both conformations have similar CO—CO dihedral angles, 87.2° and 88.6° , respectively. An inversion barrier as high as $8.6 \text{ kcal mol}^{-1}$ (at 171K in CHCl_2F) was obtained.

Oxepin and benzo[c]oxepin as well as numerous other unsaturated cyclic systems were treated in terms of the concept of absolute and relative hardness (HOMO–LUMO gap) as a measure of aromaticity <89JA7371>. Both of these systems were shown to be nonaromatic; however, it should be noted that, according to <89JA7371>, the latter belongs to the same category as such *O*-heterocyclic systems, for example furan.

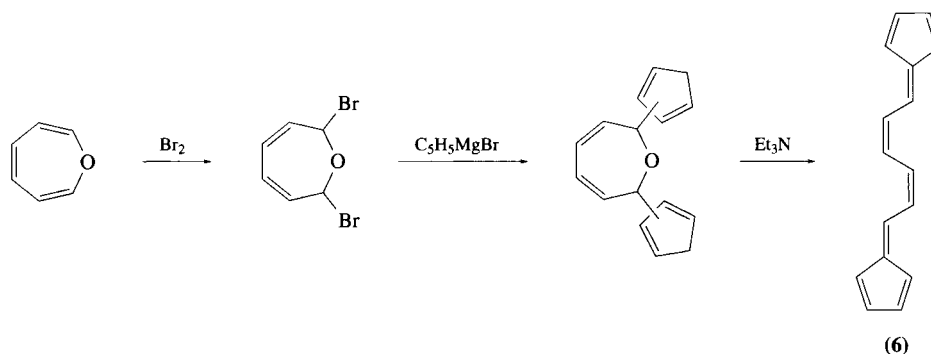
9.02.5 REACTIVITY OF FULLY CONJUGATED RINGS

The survey of reactivity of oxepines given in CHEC-I <84CHEC-I(7)547> is still noteworthy. The survey in CHEC-I covers such topics as (i) thermal and photochemical reactions, (ii) electrophilic attack on the ring oxygen atom, (iii) nucleophilic attack on carbon atoms, and (iv) reactions involving cyclic transition states. Considering other reactions of oxepines, the existence of oxepin–arene oxide equilibrium should be taken into account since some of the reactions can involve the latter form. Specific properties of the arene oxide system make it possible to interpret why electrophilic attack at carbon, and nucleophilic attack at the hydrogen atom, are not characteristic of oxepines. There is a lack of information devoted to reactions of oxepines with, for example, radicals and carbenes.

Considered below are two groups of oxepin reactions: (i) addition and cycloaddition reactions peculiar to their conjugated carbon chain, and (ii) those characteristic of vinyl ethers, particularly, beginning from an attack on ring oxygen. Both reaction types have been discussed in detail in CHEC-I; thus, only several important new examples are given here.

9.02.5.1 Addition and Cycloaddition Reactions

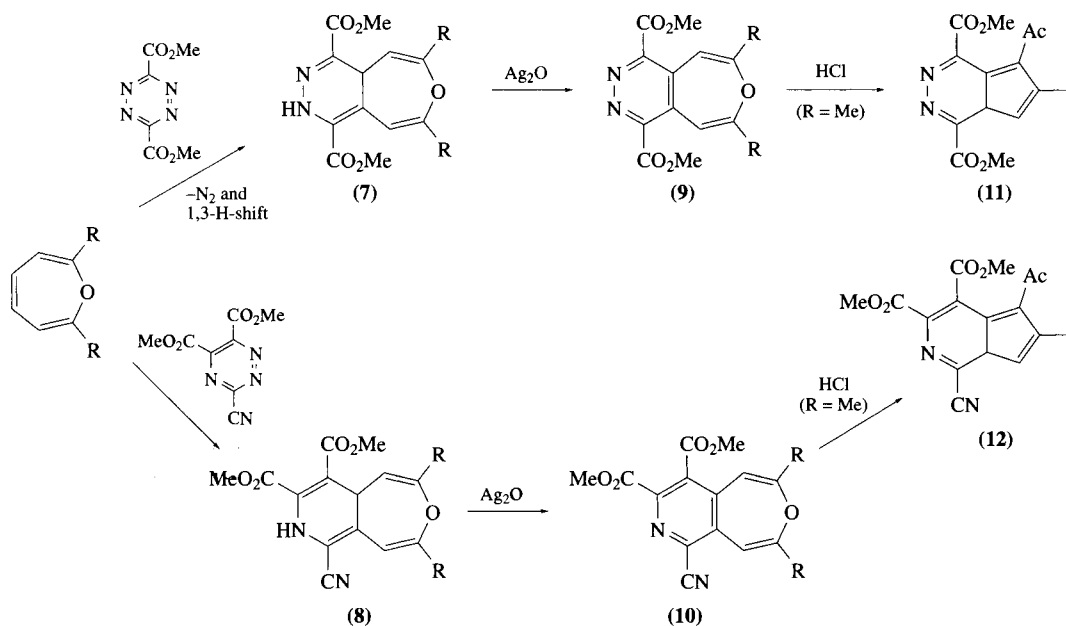
Successive addition of bromine to oxepin and the action of cyclopentadienylmagnesium bromide, followed by the treatment with triethylamine was used for the synthesis (albeit in a low yield) of a higher vinylogous fulvalene (6) (Scheme 2) <84CB2006>.



Scheme 2

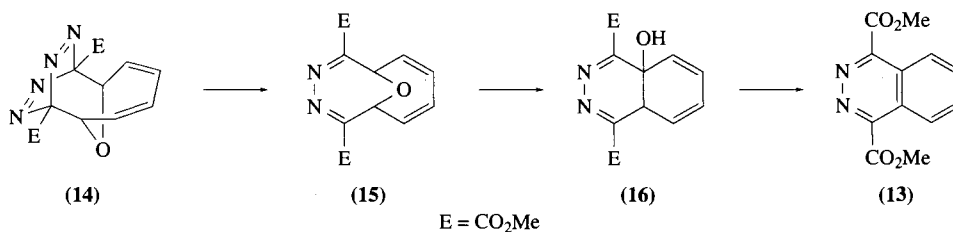
A study of Diels–Alder reactions of three oxepines differing in the positions of oxepin–benzene oxide equilibria, namely unsubstituted oxepin (considerable amounts of both valence isomers), 2,7-dimethyloxepin (principally in the oxepin form), and indene oxide (predominantly benzene oxide form), has shown that all three compounds act exclusively in [4 + 2] cycloaddition reactions as benzene oxides, giving *endo*-adducts with *anti*-configuration relative to the bridge oxygen atom <91CJC1337>.

An interesting and important reaction of oxepines is their participation as dienophiles in [2 + 4] cycloaddition with inverse electron demand. Using 1,2,4,5-tetrazines or 1,2,4-triazines bearing electron-withdrawing substituents as dienes, this reaction leads to dihydrooxepino[4,5-*d*]pyridazines (7) or dihydrooxepino[4,5-*c*]pyridines (8), each of which can be oxidized to corresponding oxepino[4,5-*d*]pyridazines (9) or oxepino[4,5-*c*]pyridines (10); the latter are converted by the treatment with an acid to cyclopenta[*d*]pyridazines (11) or cyclopenta[*c*]pyridines (12), respectively (Scheme 3) <83CB97>.



Scheme 3

In the case of unsubstituted oxepin, the [2 + 4] cycloaddition competes with [4 + 6] process giving, for example a phthalazine derivative (13) besides (7) in the ratio (7) : (13) = 2 : 1. 2,7-Dimethyloxepin probably cannot undergo the [4 + 6] cycloaddition reaction owing to steric hindrances in its first step, i.e. the formation of an intermediate like (14) (Scheme 4).

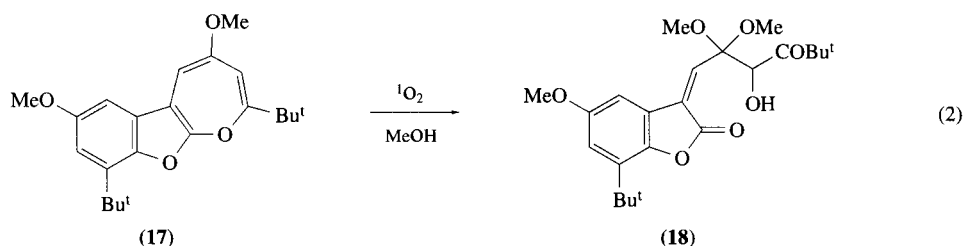


Scheme 4

9.02.5.2 Cleavage of the Oxepin Ring

Some of the processes considered above involve the cleavage of the oxepin ring, for example acid-catalyzed hydrolytic scission of one of the C—O bonds, followed by the formation of five-membered

carbocycles ((9)→(11) and (10)→(12)) or rearrangement of the intermediate 1,6-oxido-3,4-diaza[3,4]annulene (15), followed by dehydration of the formed 1,4-dicarbomethoxy-4*a*-hydroxy-4*a*,8*a*-dihydrophthalazine (16), which gives the phthalazine derivative (13) <83CB97>. However, only the former can be regarded as a true transformation of fully conjugated oxepin; while the latter takes place in the dihydrooxepin system. Another possibility in the cleavage of the oxepin ring is its opening by oxidation reactions. For example, it was shown (Equation (2)) <89JCS(P1)133> that the photooxidation of oxepino[2,3-*b*]benzofuran derivative (17) in Me₂CO—MeOH mixture containing tetraphenylporphin leads to the formation of the benzofuranone (18).

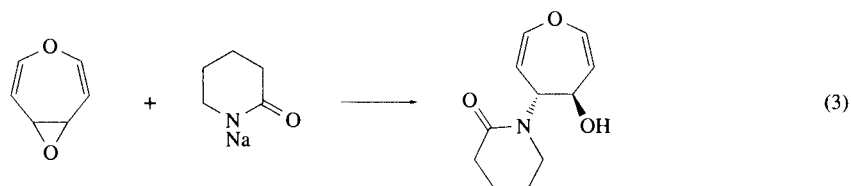


9.02.6 REACTIVITY OF NONCONJUGATED RINGS

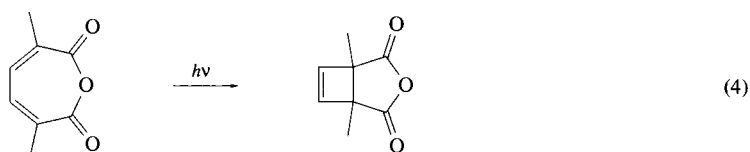
In CHEC-I <84CHEC-I(7)547>, the reactivity of oxepanes was discussed in the following subsections: (i) thermal and photochemical reactions, (ii) electrophilic attack on the ring oxygen atom, (iii) nucleophilic attack on carbon atoms, (iv) reactions with radicals or electron-deficient species, and (v) oxidations, reductions, and reactions involving cyclic transition states. These subsections practically cover all types of reactivity of oxepanes as saturated cyclic ethers. However, data concerning partially saturated oxepines was not considered in CHEC-I and this is done here. Some reactions of highly unsaturated compounds with conjugated systems which, in contrast to oxepines, cannot be even formally regarded as closed ones, namely oxepinones, oxepindiones, oxepin oxides, are also considered.

9.02.6.1 Dihydrooxepines

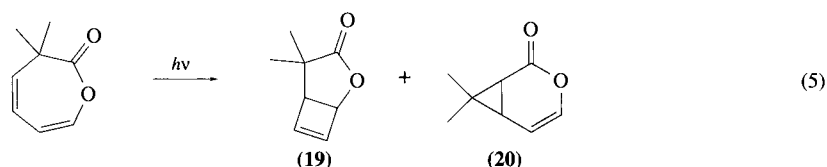
Reactions of polyunsaturated compounds, which can be formally related to dihydrooxepines, i.e. oxepinones, oxepindiones, and oxepin oxides, are noteworthy. The addition reactions of *N*-nucleophiles to both benzene oxide and symmetrical oxepin oxide were studied as models for the biogenesis of some natural epidithiadioxopiperazines of gliotoxin and aranotoxin families (Equation (3)) <82JOC1509>.



Chemical behavior of oxepin-2,7-diones is, in general, normal of anhydrides of double unsaturated conjugated carboxylic acids. Thus, methanolysis of 4-methyloxepin-2,7-dione leads to a mixture of isomeric monomethyl (2*Z*,4*Z*)-3-methyl-2,4-hexadienedioates <82JOC1212>. 3,6-Dimethyloxepin-2,7-dione undergoes photochemical ring closure to the respective bicyclic anhydride (Equation (4)) <86TL343>.



Photochemical transformations of 3*H*-oxepin-2-ones resemble that of muconic anhydrides (see above), but are complicated by side reactions. Thus, UV photolysis of 3,3-dimethyloxepin-2-one ($\sim 20^\circ\text{C}$, in acetone) gives besides the expected bicyclic lactone (**19**), an isomeric by-product (**20**); the yield of the latter was increased with increasing temperature (Equation (5)) <84JCS(P1)769>. On 2-acetylnaphthalene-sensitized photolysis of 3-acyl-3-methyloxepin-2-ones, the 1,5-acyl shift plays an important role giving, for example, 7-acetyl-3-methyloxepin-2-one, as the main product <85JCR(S)70>.



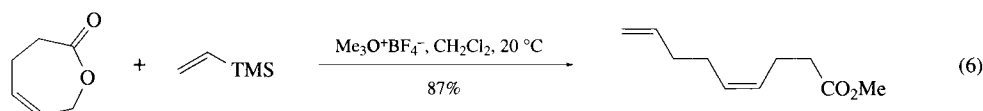
Dihydrooxepines with two isolated $\text{C}=\text{C}$ bonds can undergo selective transformations of only one, for example ethyl 3,4-dihydrooxepin-2-carboxylate on treatment with magnesium in methanol at room temperature affords in high yield (90%) the product derived from the reduction of α,β -unsaturated ester fragment, i.e. ethyl 2,3,4,5-tetrahydrooxepin-2-carboxylate <87TL5287>.

9.02.6.2 Tetrahydrooxepines

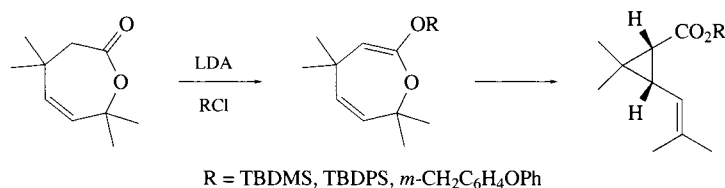
Hydroboration of 2,3,4,5-tetrahydrooxepin was studied and compared with that of 2,3-dihydrofuran and Δ^2 -dihdropyran as well as with their sulfur and carbocyclic analogues <85JOC5583>. Boron is exclusively directed to the 3 position which is probably controlled by a strong mesomeric effect of the ring oxygen.

Metallation of 2,3,4,5-tetrahydrooxepin with Bu^nLi or Bu^tLi leads to 7-lithio-2,3,4,5-tetrahydrooxepin, i.e. vinylic deprotonation occurs <82JOC3094>. It is of interest that 2,3-dihydrooxepin, like 2,5-dihydrofuran, undergoes allylic deprotonation. The readily available trimethylsilyl ketene acetal of ϵ -caprolactone is a convenient intermediate for the synthesis of 3-RO-substituted ϵ -caprolactones (R is acyl or tosyl) using, as other reagents, lead(IV) carboxylates <83JOC4940> or [hydroxy(tosyloxy)iido]benzene <89JOC1101>, respectively.

Several interesting and effective syntheses of acyclic and carbocyclic natural products are based on (Z)-4-hexenolide and its substituted derivatives. In particular, this unsaturated lactone regioselectively reacts with diorganocuprates to give (Z)-4-alkenoic acids in high yields; this transformation was used for the simple synthesis of *cis*-jasmone <84CL1795>. The other useful reagents for ring opening of (Z)-4-hexenolide are allylsilanes in the presence of trimethyloxonium fluoroborate <84TL3213, 88BCJ4051>. The importance of such transformations can be demonstrated by the stereoselective synthesis of methyl (Z)-nona-4,8-dienoate (Equation (6)).



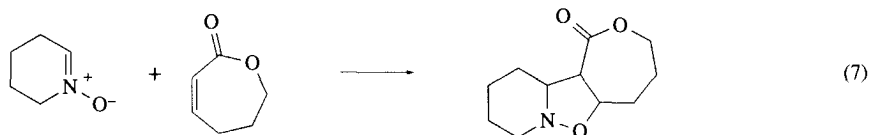
Ketene acetals obtained from unsaturated lactone enolates on mild thermolysis undergo the Claisen rearrangement leading to *cis*-2-alkenylcycloalkanecarboxylic acids <82JA4030>. Starting from 4-hexenolides, substituted 2-cyclopropanecarboxylic acids, in particular, (–)-*cis*-chrysanthemic acid (Scheme 5) can be prepared <84T2831, 85JOC707, 85TL3503>.



Scheme 5

Δ^2 -Unsaturated lactone, 2-hexenolide, enters as a dipolarophile 1,3-dipolar cycloaddition reaction with Δ^1 -piperideine giving a new heterocyclic system, 1*H*-oxepino[3'4':4,5]isoxazolo-[2,3-*a*]pyridin-1-one (Equation (7)) <90MRC947>.

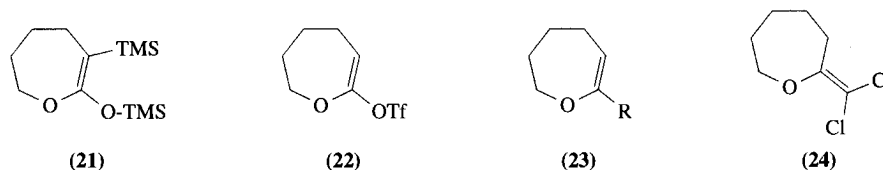
2,3,4,5-Tetrahydrooxepin-2-yl acetate undergoes "head-to-tail" polymerization promoted by chromium carbene complexes $(\text{CO})_5\text{Cr} : \text{CRPh}$, where $\text{R} = \text{Ph}$ or OMe <85JMOC279>.



9.02.6.3 Oxepanes, ϵ -Caprolactone, and Adipic Anhydride

γ -Ray induced addition of oxepan to fluorinated alkenes is described <85JCS(P1)2215>. The reaction proceeds with 100% conversion and gives, in the case of perfluoropropene, 2-(2-*H*-hexafluoropropyl)oxepin in 95% yield. As mentioned above, ϵ -caprolactone is easily converted to the corresponding trimethylsilyl ketene acetal. Using trimethylsilyl triflate and triethylamine, trimethylsilyl acetal of cyclic trimethylsilyl-substituted ketene (**21**) can be prepared <83LA816>.

Treatment of ϵ -caprolactone with *N,N*-bis(trimethylsilyl)lithium amide and then with *N*-phenyl triflimide affords 2-triflyloxy-2-hexenolide (**22**). The latter is obtained in 89% yield <89CL1313> and can be regarded as a key intermediate in the syntheses of diverse 2-substituted 4,5,6,7-tetrahydrooxepines. For instance, reactions of (**22**) with lithium dialkyl- or diphenylcuprates result in 2-butyl-substituted derivatives (**23**; $\text{R} = \text{Alk}, \text{Ph}$) <89CL1313>, while analogous interaction with hexamethyldistannane gives 2-trimethylstannyl-4,5,6,7-tetrahydrooxepin (**23**; $\text{R} = \text{SnMe}_3$) <91SL197>.



Refluxing ϵ -caprolactone in carbon tetrachloride in the presence of triphenylphosphine leads to the formation of 2-dichloromethyleneoxepin (**24**) <82JAP(K)53425>. *O*-Alkylation of ϵ -caprolactone gives the respective salt, which on treatment with sodium hydrosulfide undergoes scission of *exo*- or *endo*-C—O bonds (Scheme 6) with the formation of ϵ -thionocaprolactone and alkyl ω -hydroxythionocaproate, respectively <86JA6683>.

The reaction of adipic anhydride with (α -ethoxycarbonyl ethylidene)triphenylphosphorane <87BCJ689> gives *endo*-enol ϵ -lactone, namely 6-(α -ethoxycarbonyl ethyl)hex-5-enolide in low yield accompanied by several ring-opening products.



Scheme 6

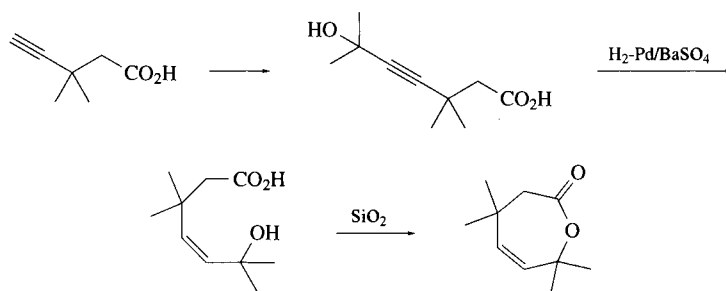
9.02.7 RING SYNTHESSES FROM ACYCLIC COMPOUNDS

Cyclization reactions giving oxepines and oxepanes are classified here according to the number of atoms in starting compounds used for building the seven-membered ring and the nature of bonds formed. In some cases, acyclic precursors are prepared from cyclic starting compounds. If such precursors are isolated before cyclization, the respective reactions are considered here, in other cases they are discussed in Section 9.02.8. Syntheses of annelated oxepines are also included if the existing ring remained unchanged.

9.02.7.1 Intramolecular Cyclizations

9.02.7.1.1 Cyclizations with formation of ester C—O bonds

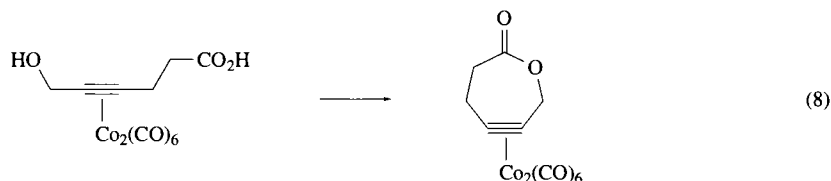
Seven-membered unsaturated lactones can be prepared in high yields by the cyclization of an appropriate ω -hydroxyalkenoic acid, for example the available 3,3,6,6-tetramethylhex-4-enoic acid gives the respective lactone in 90% yield on simple contact with silica gel under column chromatography conditions (Scheme 7) <84T2831>.



Scheme 7

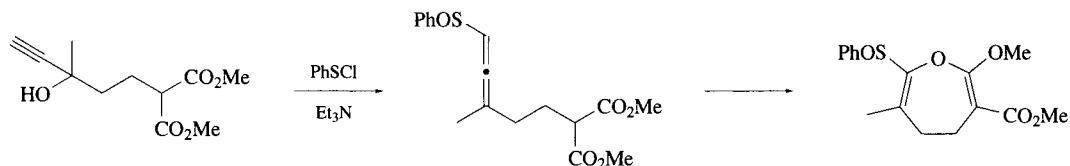
Mukaiyama cyclization promoted with 2-chloro-1-pyridinium iodide in boiling methylene dichloride <87JOC5296, 92JOM(431)335> was used for the formation of seven-membered alkynic lactones with the triple bond stabilized by complex formation from respective alkynic hydroxy acids (Equation (8)).

Refluxing 4-(5-aryl-2-oxo-4-pyrrolinyl-3-ylene)butyric acids with acetic anhydride gave the corresponding pyrrolo-3,4-dihydro-2-oxepinones, while similarly substituted crotonic acids gave pyrrolo-2-oxepinones <87AKZ189>.



9.02.7.1.2 Cyclizations with formation of ether C—O bonds

The treatment of dimethyl (3-hydroxy-3-methylpent-4-ynyl)malonate with phenylsulfonyl chloride and triethylamine in ether leads (via the respective allene sulfoxide) to a uniquely substituted 4,5-dihydrooxepin (Scheme 8) <87CC1718>.

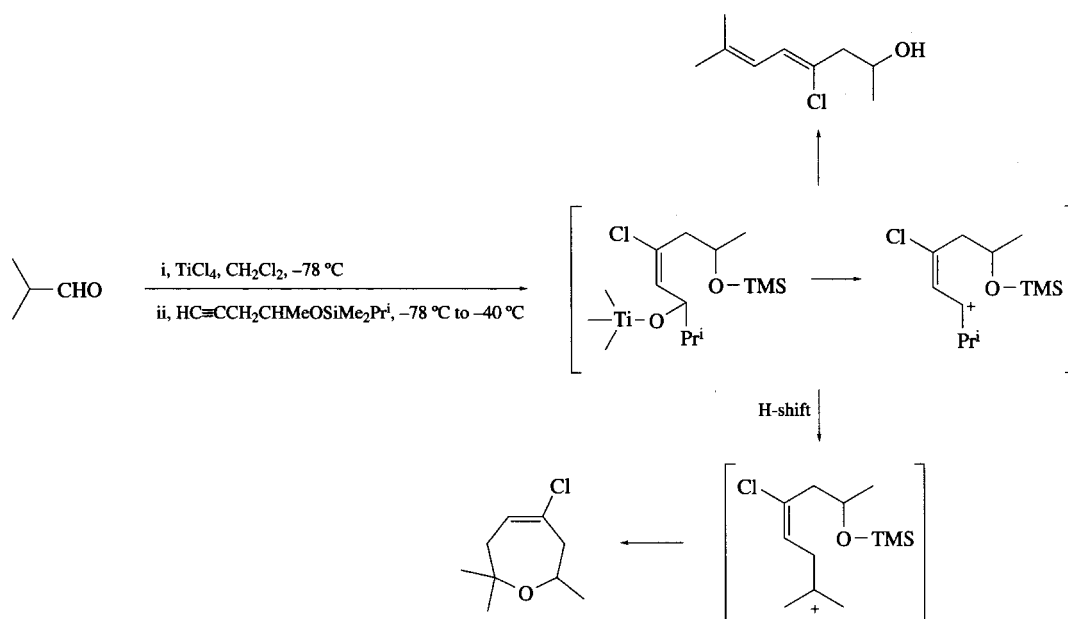


Scheme 8

An interesting route to tetrahydrooxepines, formed in good yields (50–70%), uses the TiCl_4 -promoted reaction of *O*-silylated alkynic alcohols with aliphatic aldehydes <90CC967>. As minor products, dienic carbinols are formed. The mechanism of this synthesis is shown in Scheme 9.

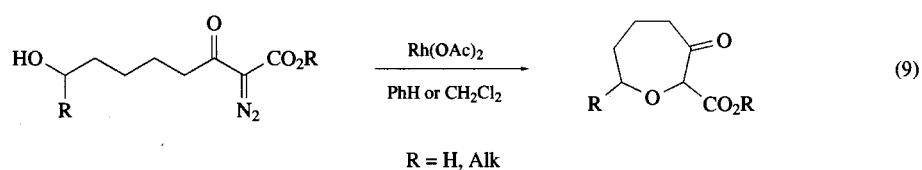
The oxidative ring closure of allylsilanes with ceric ammonium nitrate <88T3983> should also be mentioned which gave mixtures (~1:1) of 2,5,6,7-tetrahydrooxepines with 2-alkenyltetrahydrofurans. Simple dehydration of 4-hydroxy-3-(4-hydroxy-3-alkylbutyl)coumarines with Amberlyst 15 leads to the respective annelated tetrahydrooxepines in 50–70% yield <88JHC647>.

An effective synthesis of oxepanones is based on rhodium carbenoid-mediated cyclizations of



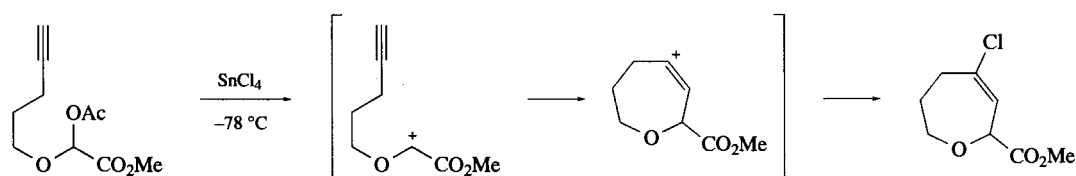
Scheme 9

appropriate diazocarbonyl compounds <86TL1403, 88JCS(P1)1417, 89JCS(P1)721, 89JCS(P1)2473>. Starting compounds can be obtained either on alkylation of the dianion of methyl acetoacetate with the $\text{Bu}^t\text{Me}_2\text{Si}$ -protected α,ω -haloalcohols, followed by diazo transfer and desilylation or on treatment of δ -valerolactones with α -lithiated diazoacetates. The key step is intramolecular carbene insertion into the O—H bond, which proceeds after the treatment of diazo carbonyl compound with rhodium diacetate (Equation (9)); the yields reach $\sim 80\%$. Starting from δ -valerolactones and α -lithiated diazomethanephosphonate or diazomethyl phenyl sulfone the respective 2-phosphorylated or phenylsulfonylated 3-oxepanones have been obtained; the latter are versatile intermediates for syntheses of various functionalized oxepanes <91JCS(P1)1>. Similar cyclization of 1-diazo-2,6-dioxoheptyl phenyl sulfone affords 7-methyl-2-phenylsulfonyl-2,3,4,5-tetrahydrooxepin-3-one <87TL6045>.



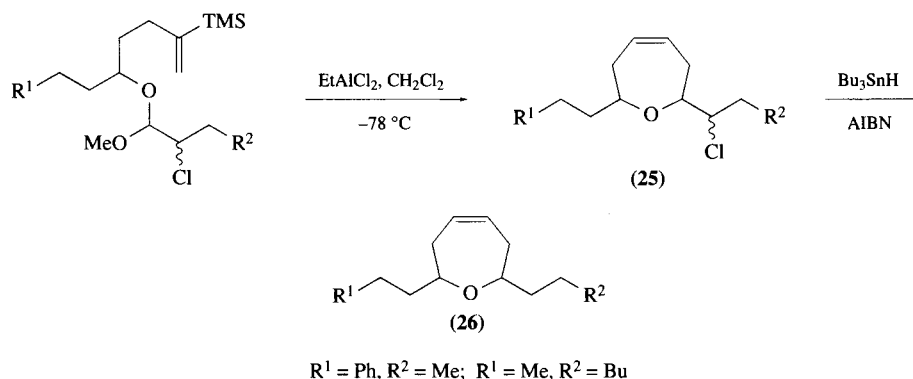
9.02.7.1.3 Cyclizations with formation of carbon–carbon bond

In the formation of carbon–carbon bonds, cyclization reactions of various types are used. As an example of electrophilic cyclization involving formation of carbon–carbon bonds and leading to tetrahydroxepines, the acetal–alkyne condensation <88TL6365> mediated by Lewis acids can be noted (Scheme 10).



Scheme 10

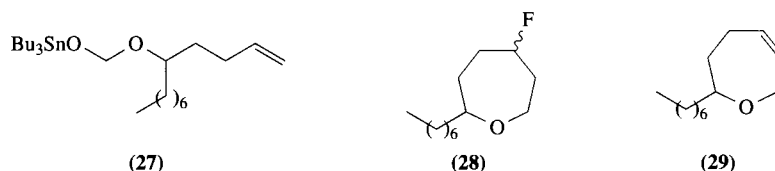
The acetal-alkene cyclization (Scheme 11) <92SL811> proceeds readily (60–70% yields) but gives mixtures (~1:1) of diastereoisomeric tetrahydrooxepines bearing halogenated side chains (**25**). However, halogen reduction results in only *cis*-isomers (**26**) in high yields (up to 85%). When a halogen atom is absent in an acetal molecule, the preparation of tetrahydrooxepines proceeds highly stereospecifically; the yields are up to 85% <89JOC5695>.



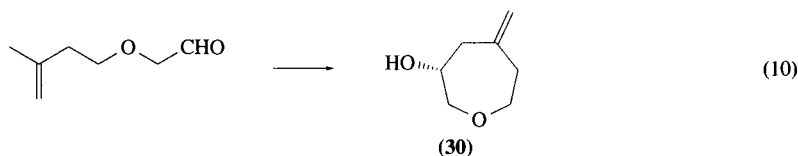
Scheme 11

Palladium-catalyzed cyclizations of bromodialkenyl ethers, in which the key step is vinylic substitution of bromine, result in low to moderate yields of tetrahydrooxepines and methylenioxepanes <83JOC3894>. γ,δ -Unsaturated seven-membered lactones are prepared in 50–60% yields from 2-phenylthio-3-butenyldiazomalonates <90CL613> on treatment of the latter with rhodium acetate; the reaction involves a [2,3]-sigmatropic rearrangement of the generated cyclic allylsulfonium ylides.

Anodic oxidation of Bu_3Sn -protected unsaturated hemi-3-acetal (**27**) with tetrabutylammonium fluoroborate, as the supporting electrolyte <92JA7594>, gave fluorinated oxepan (**28**) (61%) and its dehydrofluorination product (**29**) (28%).



Asymmetric carbonyl-ene cyclization of alkenyloxy-substituted aldehydes <91TL6571> afforded six- and seven-membered cyclic ethers of high enantiomeric purity, for example (*R*)-(**30**) possessed a 91% *ee* (Equation (10)), when chiral 2,2'-dihydroxy-1,1'-binaphthyl-based titanium perchlorate was used as a catalyst.

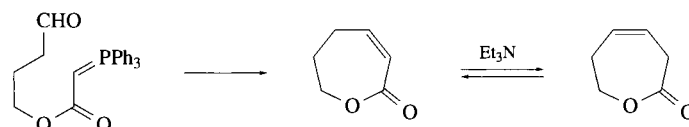


Several cycloaddition reactions leading to fused bi- and triheterocyclic systems were used for the preparation of annelated hydrooxepines such as oxepino[3,4-*c*]isoxazole <91CB1181> and oxepino[5,4,3-*hi*]indolizine <91CZ25>. In photochemical conversion of 5-(*p*-methoxyphenyl)hept-5-enyl phenanthrene-5-carboxylate, two intramolecular [2 + 2] cycloaddition reactions involving alkene double bonds compete with either the 5,6- $\text{C}=\text{C}$ bond of phenanthrene or the ester $\text{C}=\text{O}$ bond <90BCJ1049>, the latter giving phenanthryl-substituted oxetano[2,3-*b*]oxepan which undergoes degradation with loss of acetaldehyde giving 3-(*p*-methoxyphenyl)-2-phenanthr-5-yl- Δ^2 -tetrahydrooxepin. 3-(*p*-Methoxyphenyl)-2-phenanthr-5-yl-6,7-dihydrooxepin has been formed in 57% yield on photolysis of 5-(*p*-methoxyphenyl)pent-4-enyl phenanthrene-5-carboxylate <82JA6796>.

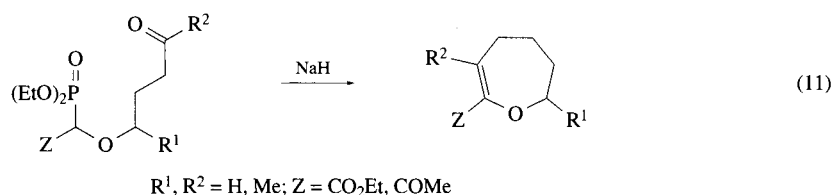
An intramolecular Wittig reaction was used in the synthesis of an α,β -unsaturated seven-membered lactone from (5-formyl-2-oxopentylidene)phosphorane <89TL7313>; however, the product

appeared to be a mixture ($\sim 1:1$) of isomeric Δ^2 - and Δ^3 -lactones (Scheme 12), as a result of an equilibrium in the presence of a base [86JOC2830].

An intramolecular Wadsworth–Emmons reaction of respective phosphonates (Equation (11)) gave substituted 2,3,4,5-tetrahydrooxepines [91TL6947, 92T3991].

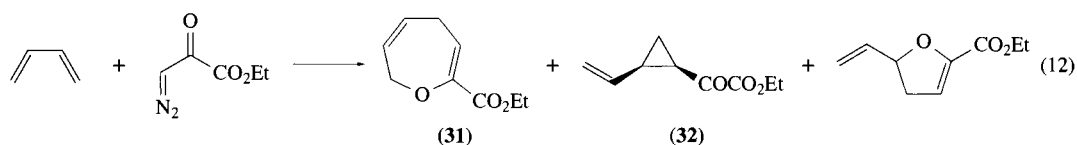


Scheme 12



9.02.7.2 Intermolecular Ring Formation

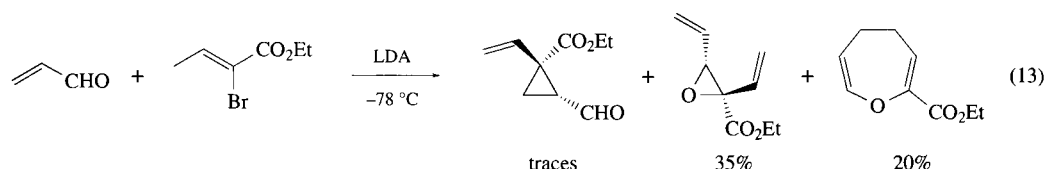
Decomposition of ethyl diazopyruvate over $\text{Cu}(\text{acac})_2$ in boiling benzene solution containing 2-methoxybuta-1,3-diene [83JOC3047] yielded ethyl 5-methoxy-5-vinyl-4,5-dihydro-2-furoate (78%) and a small amount (9%) of ethyl 5-methoxy-4,7-dihydrooxepin-2-carboxylate. It is important to note that the latter is a highly unstable compound and undergoes quantitative conversion into the former upon chromatography on silica gel. A similar reaction (Equation (12)) of ethyl diazopyruvate with 1,3-butadiene catalyzed by rhodium acetate gave a mixture of ethyl 4,7-dihydrooxepin-2-carboxylate (**31**) (26%), ethyl *trans*-(2-vinylcyclopropyl)glyoxylate (**32**) (35%) and 5-vinyl-4,5-dihydro-2-furoate (4%). The possible source of oxepin (**31**) could be its equilibrium with *cis*-(**32**), which is known to be shifted to (**31**) [87HCA2159].



The reaction, probably involving carbene formation, of acrolein with ethyl α -bromocrotonate, initiated by lithium diisopropylamide, generates α -carbanion of ethyl α -bromovinylacetate in the first step affording ethyl 4,5-dihydrooxepin-2-carboxylate, as one of products (Equation (13)) [86JOC4746].

The cycloaddition of carbon suboxide with 4-oximinopentanol [87H(26)1619] affords oxepines.

On treatment of 8-hydroxynaphthalene-1-carbaldehydes with DMA-POCl_3 , complex 2-dimethylaminonaphth[1,8-*bc*]oxepinium salts are formed [86ZOR1487].



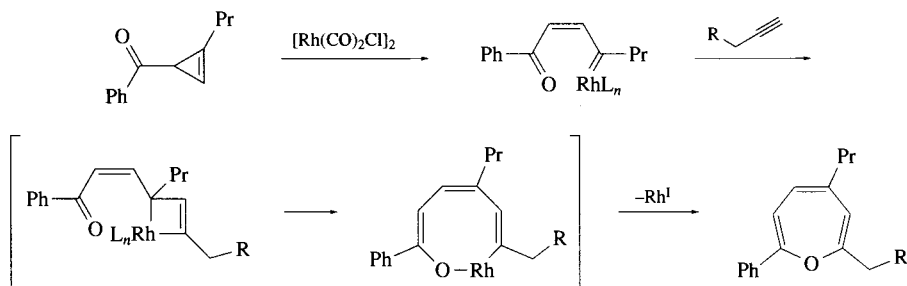
9.02.8 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

Many ring syntheses of oxepines and hydrogenated oxepines by the transformation of other rings are based on pericyclic reactions [88S569]. Below are presented various synthetic methods, which are classified by the nature and size of the starting ring.

9.02.8.1 Synthesis from Carbocyclic Compounds

9.02.8.1.1 By formation of seven- from three-membered rings

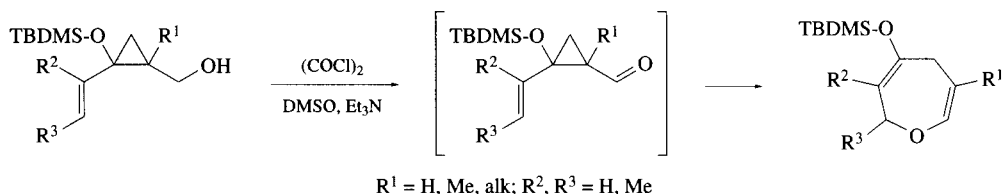
Rhodium(I)-catalyzed reaction of phenyl 2-propylcycloprop-2-en-yl ketone with terminal alkynes gives 2-alkyl-4-propyl-7-phenyloxepines (Scheme 13). The reaction involves the formation of a rhodium-carbene complex, which undergoes a [2 + 2] cycloaddition with a terminal ethyne; the resultant rhodacycle rearranges by a 1,5-sigmatropic shift, followed by reductive elimination of rhodium <92JA5881>.



Scheme 13

Swern oxidation of 2-alkenyl-2-alkylsiloxycyclopropylcarbinols involves a 3,3-sigmatropic rearrangement of the aldehydes formed and gives functionalized 2,5-dihydrooxepines (Scheme 14) in high yields <93SL27>.

Thermolysis of vinyl-1,1-cyclopropanedicarboxylic acid affords (*Z*)-4-hexenolide besides the γ -vinyl- γ -butyrolactone <86JAP(K)07270>.

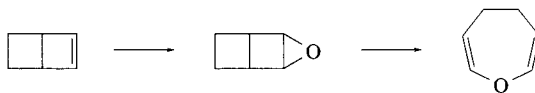


Scheme 14

9.02.8.1.2 By formation of seven- from four-membered rings

Formally, this type of transformation can be illustrated by the known syntheses of 4,5-dihydrooxepin from bicyclo[2.2.0]hex-2-ene <71JA6102, 76JOC2028> including double-bond epoxidation and rearrangement of the intermediate tricycle (Scheme 15).

Similar syntheses of perfluorinated dihydrooxepin and 4,5-(difluoromethylenedioxy)-hexafluorodihydrooxepin are also known <79JOC2813>. It should be mentioned that no equilibria with respective cyclohexadiene oxides were observed for the fluorinated dihydrooxepines.



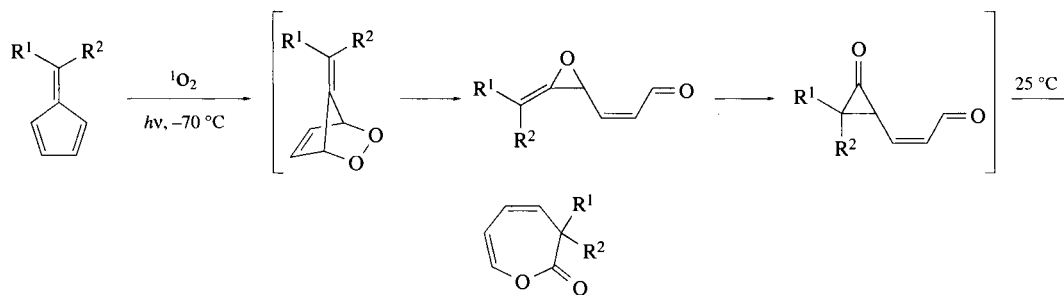
Scheme 15

9.02.8.1.3 By formation of seven- from five-membered rings

One of the routes from five-membered carbocycles to seven-membered oxygen *O*-heterocycles is the oxidation of 6-monosubstituted and 6,6-disubstituted fulvenes with singlet oxygen to give the

respective 2(3*H*)-oxepinones (Scheme 16) <71HCA913, 72CL807, 72JA1777>. The yields are rather low (20–25%) but, when one of the R groups is alkyl and the other is either alkyl or aryl, 3*H*-isomers are the only 2-oxepinones formed in the photochemical oxidation. If, however, one of the R groups is hydrogen, besides the 2(3*H*)-oxepinones, their 7*H*-isomers are formed, probably as the result of photo-induced isomerization <72CL807>. The oxidation of 6,6-diarylfulvenes gives 3,3-diaryl-2-oxepinones as the only minor products <74CL893>, while the major ones are oxygenated carbocycles.

The transformation of benzvalene into oxepin–benzene oxide tautomeric system <84CB2963> is another example of oxepin formation from five-membered rings.

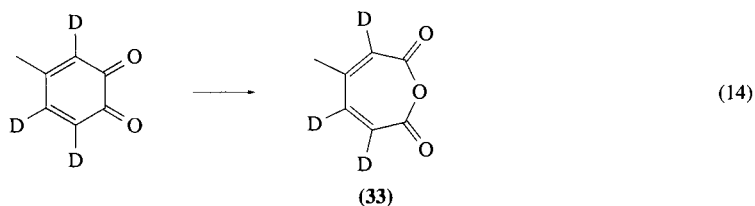


Scheme 16

9.02.8.1.4 By formation of seven- from six-membered rings

Six-membered carbocycles often play the role of starting materials in the construction of the oxepin ring system; however, for many syntheses rather stable intermediates of a different nature are known, for example those with fused six-membered carbocycles and three-membered oxygen heterocycles. The use of such systems is described in the next section. Here, several other transformations are mentioned. Some of them also may have heterocycles as intermediates but the latter are unstable under normal conditions or their structures were not studied in detail.

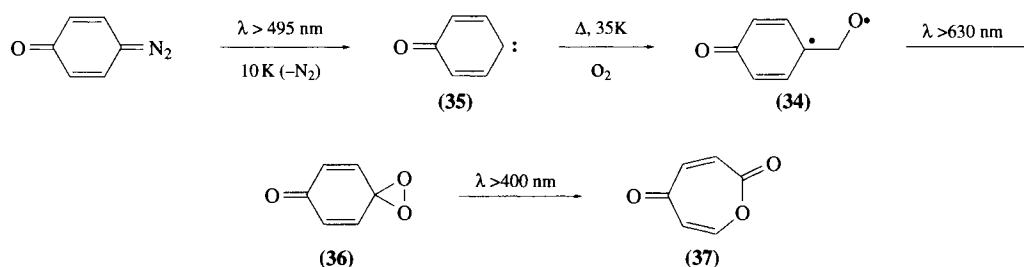
δ,ϵ -Dehydro- ϵ -caprolactone was formed in the Baeyer–Villiger oxidation of the respective unsaturated six-membered ketone using platinum(II) complexes, as catalysts <93OM148>. Oxidation of *o*-quinones can serve as a method for the synthesis of substituted muconic anhydrides <82JOC3766, 83CC518>. This process can be illustrated by the preparation of trideuterated anhydride (33), which results from the action of monoperphthalic acid on the respective deuterioquinone (Equation (14)) <89CC1629>.



Another important route to muconic anhydrides is the oxidation of 3,5-disubstituted catechols by molecular oxygen catalyzed by iron(III) salts <87CL719, 88JA8085, 91JA9200> and heteropolyvanadates <87JMOC57> as well as by a ruthenium dichloride–triphenyl phosphine complex <82JA1433, 82JAP(K)108033>; the mechanism of the process is a model for the action of catechol 1,2-dioxygenase <86JA2921, 88JA8085, 91JA9200>.

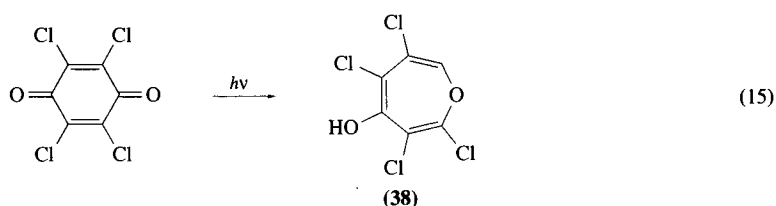
p-Benzoquinone *O*-oxide (34) was matrix isolated and shown to be a real intermediate in the reaction of cyclohexadienone carbene (35) with triplet oxygen. This reaction gave the respective dioxiranes (36), which isomerize further to the seven-membered unsaturated ketolactones (37) (Scheme 17). Similar transformations were studied also for some substituted ketolactones <88JOC2091, 92CB1851>.

Photochemical rearrangement of chloroanil in the presence of cycloheptatriene or 1,3-cyclohexadiene gives the respective oxepin (38) in 70–95% yield (Equation (15)), while in the presence of



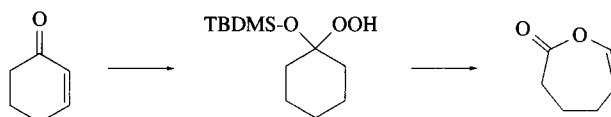
Scheme 17

cyclohexene the [2 + 2] cycloadduct of the latter with chloroanil at one of its C=O bonds is also formed <87MI 902-01>.



The formation of oxepines from some *p*-quinoid compounds is known. Thus, peroxide bond cleavage in 2,6-di-*t*-butyl-4-hydroperoxy-4-methylcyclohexa-2,5-diene-1-one with sperm whale myoglobin and myoglobin mutants gives 4,6-di-*t*-butyl-2-hydroxy-2-methyloxepin-4-one and 4,6-di-*t*-butyl-2-methylenioxepin-4-one <92JA9744>. It is of interest that the dehydration product of 2,6-di-*t*-butyl-1-*p*-methoxyphenyl-4-phenylcyclohexa-2,5-diene-1,4-diol has the 3,7-di-*t*-butyl-5-phenyl-2-*p*-tolyloxepin structure <82CB385>.

Peroxidation of cyclohexen-3-one followed by the treatment of peroxide formed with benzoic anhydride and 4-dimethylaminopyridine (Scheme 18) leads to hexen-5-olide in 70% yield <84TL2687>.



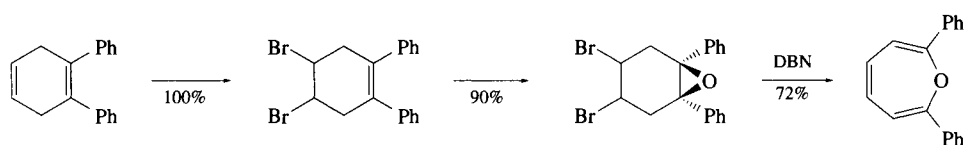
Scheme 18

9.02.8.2 Synthesis from Heterocyclic Compounds

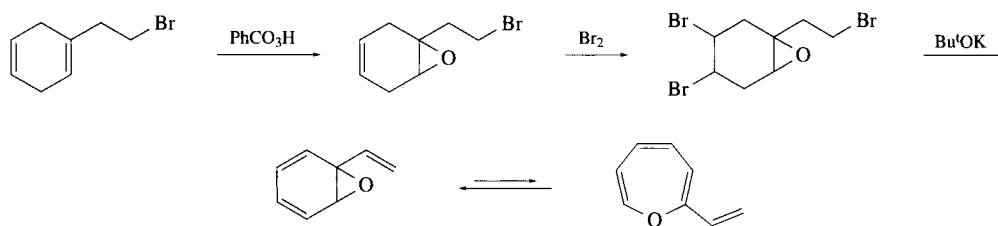
9.02.8.2.1 By formation of seven- from three-membered rings

Synthesis of benzene oxides, which are in equilibrium with oxepines, is one of the most valuable methods for their preparation. As an example of its potential, a rather simple three-step synthesis of 2,7-diphenyloxepin can be given (Scheme 19) <86JOC2784>. The equilibrium of the latter with the respective benzene oxide is shifted to the side of oxepin, but treatment of the product with trifluoroacetic acid quantitatively gives 2,6-diphenylphenol.

The same preparative route can be illustrated (Scheme 20) by the synthesis of one of less stable oxepines, 2-vinyloxepin <82TL1185>.



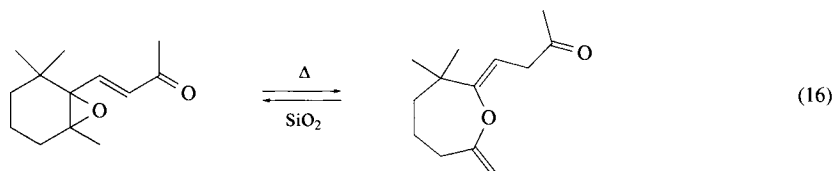
Scheme 19



Scheme 20

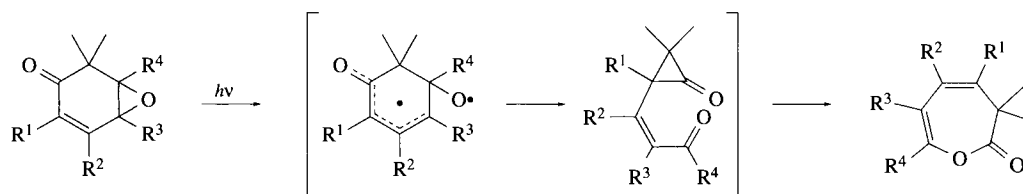
The perfluorinated oxepin has been prepared in this manner, but the content of the oxepin in the equilibrium mixture was very low <90JA6715>. A respective fused oxepin was prepared via dibenz[*a,j*]anthracene 3,4-oxide <90JCS(P1)2079>.

Some 7-oxabicyclo[4.1.0]heptanes bearing unsaturated substituents at the 1 position, for example 5,6-epoxy-5,6-dihydro- β -ionone, gave 2,7-dialkylideneoxepines (Equation (16)) under flash vacuum thermolysis at 390–585°C, the process was reversed by chromatography on silica <85HCA1089>. Similar results also gave photochemical reactions of the same compounds <86HCA555, 90JCS(P1)855>.

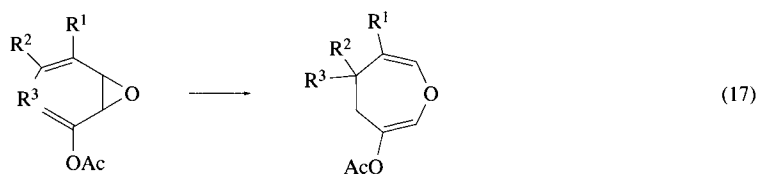


The transformation is general for different α,β -unsaturated γ,δ -epoxy ketones, for example epoxycyclohexenones <77JOC3635, 77TL1641> and epoxymethylenecyclohexanes <83HCA2489>. Its mechanism is reminiscent of the above photooxidation of 6,6-disubstituted fulvenes (Scheme 21). All R groups are H or one of them (R¹, R², R⁴) is H, while all others are Me.

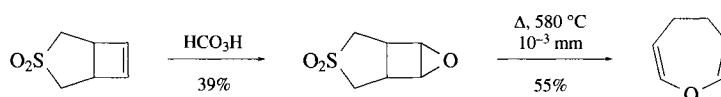
4,5-Dihydrooxepines are the products of Cope rearrangement of *cis*-2,3-divinyloxiranes (Equation (17)) <89T3021, 90JOC3975, 91TL157>.



Scheme 21

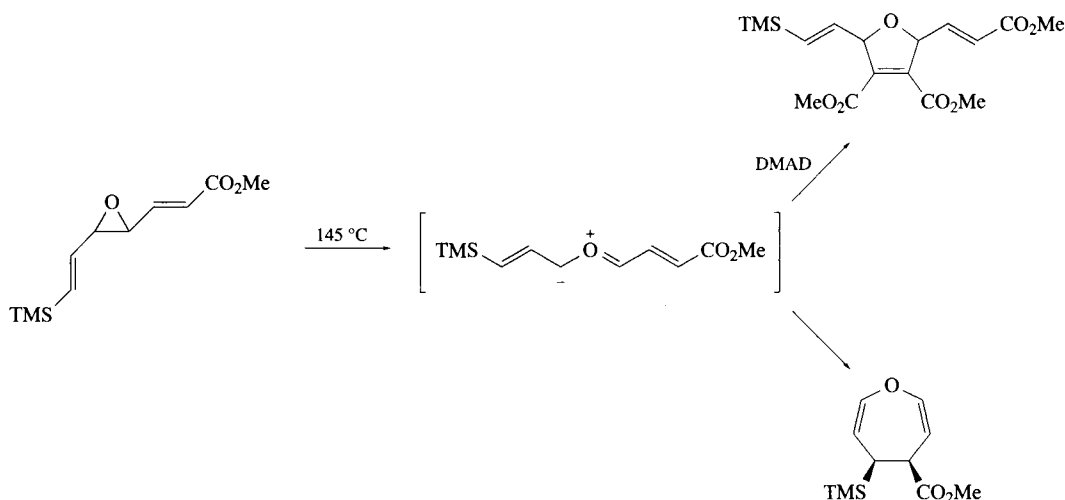


The role of one of the vinyl groups can be played by a double bond of furan ring <89T3021>, the rearrangement results in the formation of a dihydrofuro[3,2-*c*]oxepin. Sulfur dioxide extrusion from tricyclic epoxide obtained from 3-thiabicyclo[3.2.0]hept-6-ene 3,3-dioxide (Scheme 22) affords 4,5-dihydrooxepin in 55% yield <82CC1164>.



Scheme 22

Thermolysis of *trans*-2,3-divinyloxiranes to oxepines <91TL7637> can be regarded as proceeding via a carbonyl ylide, which can be trapped by dimethyl acetylenedicarboxylate (Scheme 23).



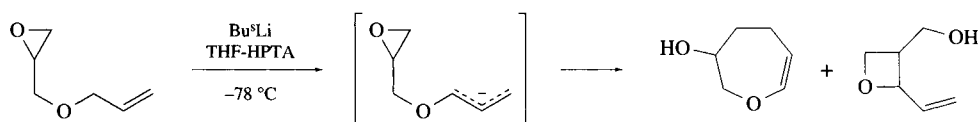
Scheme 23

exo-6,7-Diaza-3-oxatricyclo[3.2.2.0^{2,4}]non-6-ene gives 4,5-dihydrooxepin on a thermal extrusion (>180 °C) of nitrogen, while the *endo*-isomer forms a Δ^2 -cyclohexenone <90TL5129>.

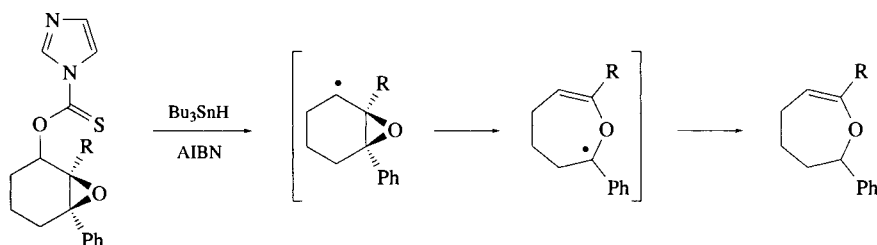
Monosubstituted oxiranes ring open on interaction with the dianion of 4-(phenylsulfonyl)butanoic acid and then cyclize by the addition of trifluoroacetic anhydride to give oxepan-2-ones, as *cis*-/ *trans*-mixtures <92SC239>.

Tetrahydrooxepinols are formed in moderate yields on cyclization of carbanions formed from allyl glycidyl ethers; the process competes with the formation of isomeric (vinyloxetanyl)carbinols <88CC625, 90TL3501>. The mechanism has been rationalized as shown in Scheme 24.

Directed ring opening of bicyclic oxiranylcarbinyl radicals (Scheme 25) affords tetrahydrooxepines in 50–70% yields <92SL987>.



Scheme 24

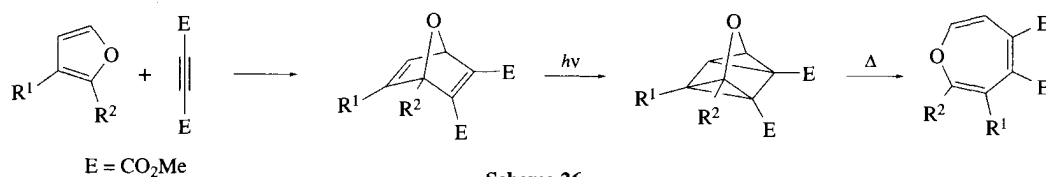


Scheme 25

9.02.8.2.2 By formation of seven- from five-membered rings

The most efficient syntheses of oxepines from five-membered *O*-heterocycles are based on Diels–Alder reaction of furans with alkynes, photolysis of 7-oxanorbornadienes obtained to respective 3-

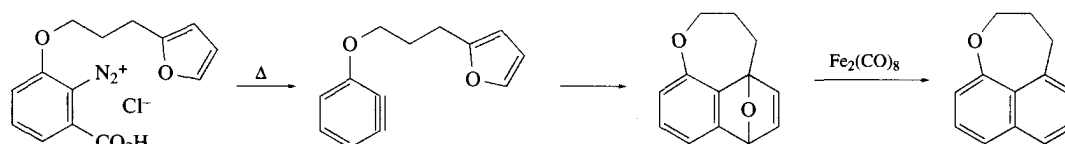
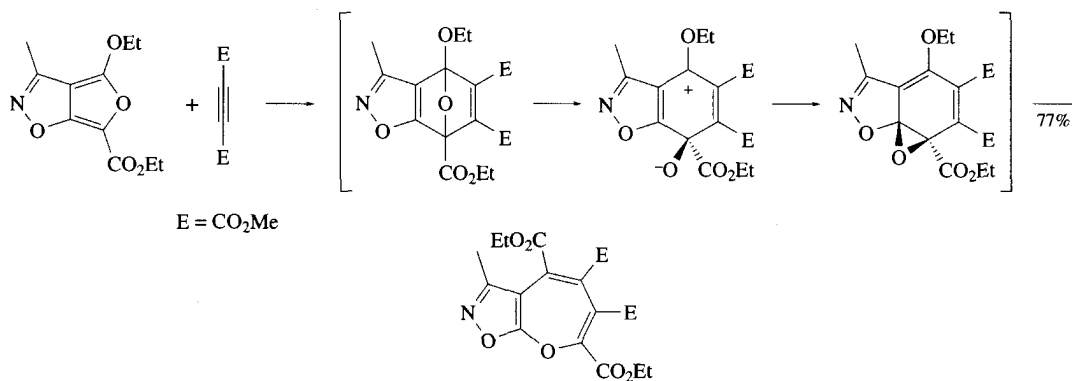
oxaquadricyclanes, and thermolysis of the latter <84CB2422, 86CB297, 86CB589, 87CB775, 91CB2465>. This route can be illustrated by Scheme 26 <87CB775>.



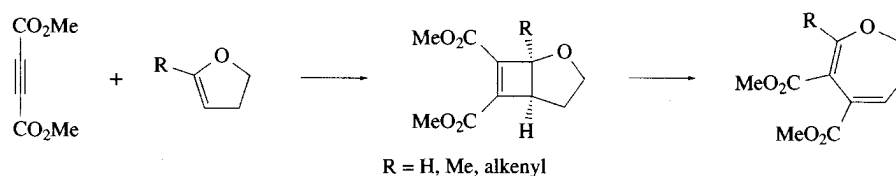
As a specific example of such syntheses, the preparation of [6]-3,6-oxepinophane starting from furan and cyclooctyne <87CB769> should be noted. The formation of 2,7-diethyl-3,4,5,6-tris(trifluoromethyl)oxepin from 2,5-diethyl-3,4-di(trifluoromethyl)furan and di(trifluoromethyl)ethyne is also of interest <92JHC113>.

The synthesis of oxepino[2,3-*d*]isoxazole system from dimethyl acetylenedicarboxylate and substituted furo[3,4-*d*]isoxazole involves Diels–Alder reaction as the key step (Scheme 27) <91TL1161>.

In an elegant synthesis of naphtho[1,8-*b,c*]oxepin, only one carbon atom of the furan ring is used for construction of oxepin cycle (Scheme 28) <86AJC635>.

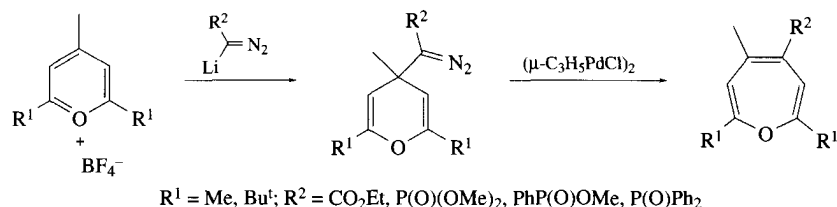


Another route from five-membered *O*-heterocycles to oxepines uses 2,3-dihydrofurans as starting materials and involves their [2 + 2] cycloaddition reaction with ethyne or ethylene compounds, followed by cleavage of bicyclic compounds formed by thermolysis or Lewis acid catalysis <83CB1691, 87TL1501, 92JOC5102>. These transformations are presented in Scheme 29 by starting from dimethyl acetylenedicarboxylate and 2,3-dihydrofuran or its 5-substituted derivatives <87TL1501>.



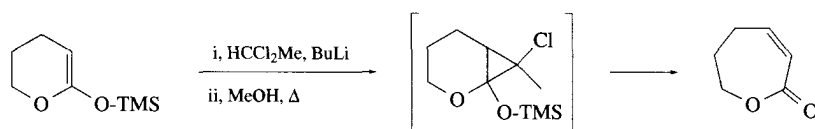
9.02.8.2.3 By formation of seven- from six-membered rings

An elegant route to oxepines starts with pyrilium salts, which add lithium derivatives of electrophilic diazoalkanes giving the respective 4-diazomethyl-4*H*-pyrans, which undergo practically quantitative ring enlargement catalyzed by allylpalladium chloride (Scheme 30) <83TL5355, 85CB3700, 87JOC3851>.

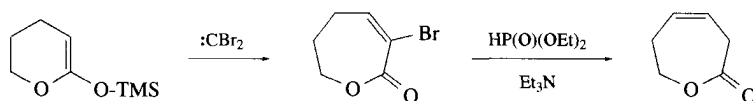


Scheme 30

2-Hexenolides can be obtained by ring enlargement of pentanolide-derived silyl ketene acetals under the action of carbenes <85T2643, 86JOC2830, 90JOC4807, 90TL197>. The transformation is illustrated by the preparation of 2-methyl-2-hexenolide in 60% yield (Scheme 31) <85T2643>. Using dibromocarbene α -halogenated 2-hexenolide can be prepared; its reductive deconjugation gave the 3-hexenolide (Scheme 32) <86JOC2830>.



Scheme 31

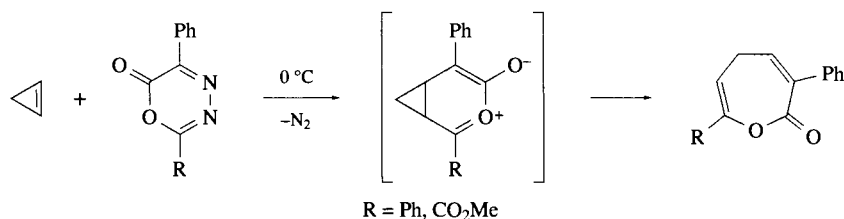


Scheme 32

2-Methyl-5,6-dihydro-2*H*-pyran in the Simmons–Smith reaction with diiodomethane and Zn–Cu couple gives a mixture of four compounds, the main component of which (50%) is 2-methyl-2,5,6,7-tetrahydrooxepin <87KGS449>. Nitrogen elimination from 6-diazo-5-methyl-3-oxabicyclo[4.1.0]heptane in methanol solution leads to the formation of the unstable *trans*- Δ^2 -tetrahydrooxepin derivatives, i.e. 5-methoxy-5-methyl-3(*E*)- and 3-methoxy-5-methyl-4(*E*)-tetrahydrooxepin mixture, which undergo further transformations affording numerous products possessing few stable oxepines <82CB220>. Di-*t*-butyl-substituted muconic anhydride is formed among other products on 5,7-di-*t*-butyl-1,4-benzodioxin oxidation with *m*-chloroperoxybenzoic acid <87JHC785>.

Intramolecular Diels–Alder cycloaddition with inverse electron demand of 3-(hex-5-ynyloxy)-6-dimethylamino-1,2,4,5-tetrazine allows formation of the respective tetrahydrooxepino-[3,4-*b*]pyridazine in moderate yield <87CZ16>. Analogous reaction of 3-(hex-5-ynyloxy)-5-trifluoromethyl-1,2,4-triazine gives 2-trifluoromethyl-5,6,7,8-tetrahydrooxepino[2,3-*b*]pyridine in 40% yield <89AP(322)561>. It should be noted that cycloaddition of 3-(hex-5-ynyloxy)-5,6-diphenyl-1,2,4-triazine followed by oxidation with nitrobenzene at 210 °C leads to the corresponding tetrahydrooxepino[2,3-*b*]pyridine but only in 8% yield <86TL2747>. As an intermolecular variant of a related synthesis, the preparation of 3,7-substituted 5*H*-oxepin-2-ones in high yields from 6-oxo-1,3,4-oxadiazines and cyclopropene (Scheme 33) can be mentioned <85CB2940, 87TL6429, 90CB2031>.

2,5-Dihydrooxepino[3,2-*a*]carbazole derivatives are formed in moderate to rather high yields on photochemical rearrangement of pyranocarbazole alkaloids, for example mahanimine <88TL6625>.



Scheme 33

9.02.9 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS

Attempts to evaluate the synthetic potential of different preparative methods are made in Sections 9.02.7 and 9.02.8. In Tables 1–4, references are given to synthetic routes to several specific groups of oxepanes and oxepines. Most references were cited in the above sections. For completeness, those from CHEC-I were also included.

Table 1 Synthetic routes to monocyclic oxepanes.

Type of compound	Ref.
Oxepan	64JOC123
2,7-Dialkyloxepanes	91JCS(P1)9
Tetrahydrooxepines	58JA3132, 60JA4087, 66TL5385
Dihydrooxepines	60JA4087, 64JOC1275, 69JA2815
Hydroxy-, alkoxy-, and acyloxyoxepanes	53JOC1356, 58CB1589, 58JA3064, 60JA4087, 65JOC335, 81JOC2267
Oxepanones and oxepanediones	30JA4110, 49JA2571, 58CB1589
Deuterated 3-methylmuconic anhydride	89CC1629
Optically active ϵ -enantholactone	89S661
Seven-Membered alkynic lactones	87JOC5296, 92JOM(431)335
Fluorinated and polyfluorinated oxepanes	85JFC(30)189, 92JA7594
Polyfluoroalkyloxepane	85JCS(P1)2215
Other halooxepanes	60JA4087
Silylated oxepanone and hydrooxepins	91JCS(P1)1, 91TL157, 91TL7637, 92JOC7010
Stannylated hydrooxepin	91SL197
Phosphorylated oxepanones	91JCS(P1)1
Sulfonylated oxepanones	87TL6045, 91JCS(P1)1, 92SC239

Table 2 Synthetic routes to monocyclic oxepines.

Type of compound	Ref.
Oxepin, alkyl-, and aryloxepines	67AG(E)385, 72B3080, 78JA6483, 78JOC2711
Vinyloxepines	82TL1185
Aminoalkyloxepines	80JOC3149
Hydroxyalkyloxepines and their esters	76TL1167, 78JA6483, 81JA898
Oxepincarbaldehydes	76TL1167, 81JA898
2-Acetyloxepin	67AG(E)385
Oxepincarboxylic acids and their esters	67AG(E)385, 74JA1193, 74JOC2088, 76ACR378, 76TL1167, 77JOC2008, 79JA2470
Cyanooxepines	76ACR378, 76TL1167, 81JOC813
Oxepinalkanoic and -alkenoic acids and esters	81JOC1191
Fluorinated and polyfluorinated oxepines	83JCS(P1)2451, 90JA6715
Perfluoroalkyloxepines	76CB2823, 83JCS(P1)2451, 92JHC113
Other halooxepines	75JA4428, 87MI 902-01
Silyloxepines	81JOC1817

Table 3 Synthetic routes to polycyclic oxepanes.

Type of compound	Ref.
Cyclopropaoxepanes	85HCA1089, 90JOC4807
Benzannelated hydrooxepines	25CB78, 53JOC801, 61JCS2516, 66CB634, 67CR(C)1665, 69TL2007, 91JHC1891
Dihydronaphth[1,8- <i>bc</i>]oxepine	86AJC635
4,5-Epoxyoxepan	60JA4087
Oxetanooxepan	90BCJ1049
Dihydrofurooxepin	89T3021
Tetrahydrooxepinobenzopyran	88JHC647
9-Oxabicyclo[4.2.1]non-6-ene	86HCA555
7,11-Dioxabicyclo[4.4.1]undeca-8,10-diene	83HCA2489
Perfluorinated dihydrooxepino-1,3-dioxolane	79JOC2813
Tetrahydrooxepinoisoxazole	91CB1181
Tetrahydrooxepino[2,3- <i>b</i>]pyridine	89AP(322)561
Dihydrooxepino[4,5- <i>b</i>]pyridine	87H(25)13
Tetrahydrooxepino[3,2- <i>c</i>]quinolin-6-one	89G367
Tetrahydrooxepino[2,3- <i>c</i>]pyridazine	87CZ16
Dihydrooxepino[4,5- <i>d</i>]pyridazine	83CB97
Dihydrooxepino[5,4,3- <i>hi</i>]indolizine	91CZ25
2,5-Dihydrooxepino[3,2- <i>a</i>]carbazoles	88TL6625

Table 4 Synthetic routes to polycyclic oxepines.

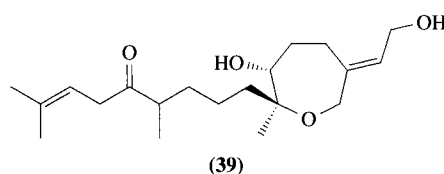
Type of compound	Ref.
Benzannelated oxepines	65CJC3433, 65TL1299, 66CB634, 68JOC2591, 73CC37, 90JCS(P1)2079
<i>peri</i> -Annellated naphthoxepinium salt	86ZOR1487
<i>ansa</i> -Derivatives of oxepines	86CB297, 87CB769
Oxepino[2,3- <i>d</i>]isoxazole	91TL1161
Dihydropyranooxepin	84CB2422
Oxepino[4,5- <i>c</i>]pyridine	83CB97

9.02.10 IMPORTANT COMPOUNDS AND APPLICATIONS

9.02.10.1 Applications and Important Compounds of Oxepanes and Hydrooxepines

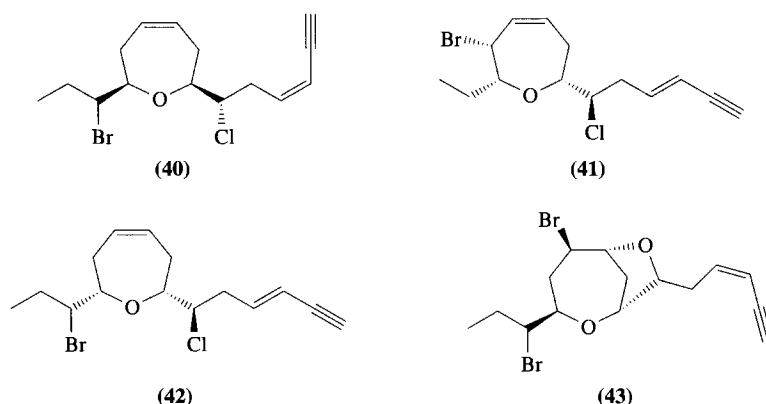
The most practically important compound from oxepanes is ϵ -caprolactone which is used as a monomer. Other oxepanes are considered following their structures from rather simple monocyclic to complicated polyheterocyclic systems.

Total synthesis of utero-evacuating oxepan, (–)-zoapatanol (**39**), has been described <81TL3027, 81USP4296035>. Deoxyzoapatanol derivatives, which are postimplant antigestational agents, have also been prepared in 24 steps <83USP4384126>.



From marine red seaweed of the *Laurencia* family, a group of metabolites was isolated whose structures are based on 2-propyl- and 2-ethyl-7-(hex-3-en-5-ynyl)-2,3,6,7-tetrahydrooxepin possessing chlorine or bromine atoms in the cycle or side chains. Among these compounds, are rogiolenynes A (**40**), B, C, D <92HCA303, 92HCA310>, laurepinnacin (**41**) and isolaurepinnacin (**42**) <81TL4081>. Closely related isoprelaufucin (**43**) having a 2,7-dioxabicyclo[4.2.1]nonane skeleton

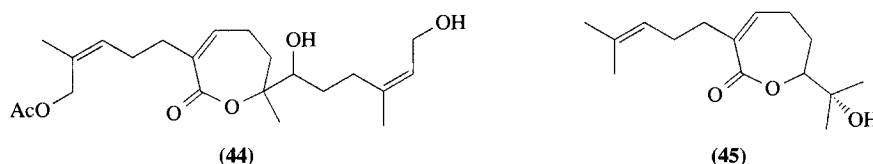
<86BCJ2953> as well as *trans*-laurencenyne <82TL1475>, a possible acyclic biosynthetic precursor of laurepinnacins (proposed in <81TL4081>), are noteworthy.



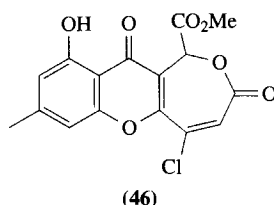
Rather simple 4-methyl-2-(3-methylbuta-1,3-dienyl)- Δ^4 -tetrahydrooxepin and -oxepan isolated from fresh fruits and prepared by synthesis have been patented as perfuming and flavoring ingredients <90EUP371347>. 3,6-Dialkyl-2-hexenolides have been claimed as cosmetic fragrant agents <88JAP(K)316776>. Organoleptic uses have been suggested for 6-alkylhexenolides and 6-alkenylhexenolides <90EUP354000>.

2-Carboxy-, 2- γ -carboxypropyl-, and 2- β -vinyl-substituted derivatives of 11-(aminoalkylidene)-6,11-dihydrodibenz[*b,e*]oxepin have been prepared and shown to have antiallergic activity <92CPB238, 92JMC2074>.

Diterpene and sesquiterpene, seven-membered lactones (44), (45) were isolated from *Melampodium longipilum* <84P829> and *Conyza hypoleuca* <91P575>. Two oxepan diterpene bicyclic lactones were isolated from *Melampodium diffusum* <84P833>. The anhydride of bis(5,6-methylenedioxy)biphenyl-2,2'-dicarboxylic acid was reduced to the respective dibenzoxepinone, which, on the action of alkanols, gave alkyl 2'-hydroxymethylbiphenyl-2-carboxylates, which were claimed to be therapeutic agents for curing liver diseases <90EUP353358, 90JAP(K)48574>.



A xanthone antibiotic, growth self-inhibitor chloromonilicin (46), was isolated from plant pathogenic fungi *Monilinia fructicola* <86MI 902-01>. Surenolactone <82LA87>, a tetranortriterpenoid A/B-dilactone with two fused seven-membered lactone units was isolated from *Toona sureni* (*Meliaceae*).

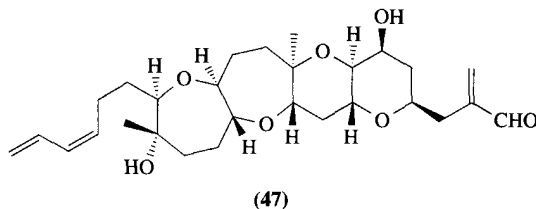


Numerous diketopiperazine antibiotics having a common partly hydrogenated oxepino[3,4-*b*]pyrrolo[1,2-*a*]pyrazine skeleton were isolated from fungi of *Emmericella* <86MI 902-02, 87H(26)475, 89MI 902-01, 90CPB73>, *Aspergillus* <86CC1495, 86JCR(S)302>, and *Ramichloridium* species <90JAP(K)62880>.

Polycyclic indole alkaloid augustilobine B has a tetrahydrooxepin moiety as one of the structural fragments <87MI 902-02>.

A vast amount of work has been devoted to structure elucidation and synthesis of polyether toxins from marine organisms, particularly, of brevetoxines <89JA6476, 90JA3040, 90JA3696, 90JA4988, 92CL1587, 92JA7935>, for example hemibrevetoxin B (47), and gambrieric acids <92JOC5448>, all of which have oxepan ring as part of their fused polycyclic skeleton.

Pyran ring enlargement in a dihydrospectinomycin derivative gave modified antibiotics, homospectinomycins are derivatives of perhydrooxepino[2,3-*b*]benz-1,4-dioxane, which exhibited bactericidal activity <88JAN1445>.



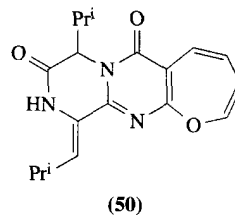
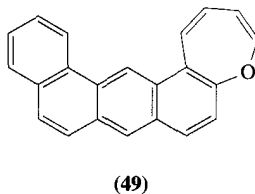
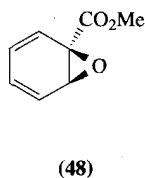
9.02.10.2 Applications and Important Compounds of Oxepines

Natural monocyclic and annelated oxepines are not as numerous as their hydrogenated derivatives; however, as mentioned in CHEC-I, <84CHEC-I(7)547> they play an important role in biosynthesis and metabolism of monocyclic and polycyclic aromatic compounds. Some new data concerning natural oxepines is given below.

1-Methoxycarbonylbenzene oxide (**48**), the valence tautomer of 2-methoxycarbonyloxepin, was isolated from liquid cultures of wood-rotting fungus *Phellinus tremulae* <93TL1589>.

Dibenz[*a,j*]anthracene-3,4-oxide together with the respective oxepin (**49**) are mammalian metabolites of dibenz[*a,j*]anthracene, their synthesis is described in <90JCS(P1)2079>.

Cinereain (**50**), a metabolite with plant growth-regulating activity from *Botrytis cinerea*, is 1-isopropyl - 4 - isobutylidene - 2,11 - dioxo - 1,2,3,4 - tetrahydro - 1*H* - oxepino[3,2 - *g*]pyrido[3,2 - *a*]pyrazine <88ABC1725>.



9.03

Thiepanes and Thiepines

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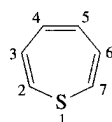
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9.03.1 INTRODUCTION

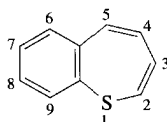
Evolution of the chemistry of thiepines has been linked to both their theoretical and biological interest. The theoretical interest is concerned with a fundamental question which relates to the net energy change associated with electron delocalization, and to whether the thiepines with $4n\pi$ electrons are aromatic, pseudoaromatic, or antiaromatic. Research activity in this area has focused mainly on simple derivatives which promise to yield information for understanding the nature of thiepines. However, investigations were confined to annelated and limited polysubstituted monocyclic thiepines in the 1970s because thiepines are generally thermally unstable. Preparation and characterization of compounds close to the parent thiepines have been achieved, but the parent remains unknown. Dibenzo[*b,f*]thiepines, prepared for their theoretical interest were found to show interesting biological activity <64USP3100207, 65M182>. The discovery opened up a new field of thiepene chemistry. The interest in fused systems, connected with the search for pharmacologically active compounds is still increasing. An immense amount of work has been carried out on condensed thiepines.

A review article for important earlier publications appeared in 1971; the preparation and properties of thiepines, their sulfoxides and sulfones are discussed <71IJS(B)267>. The chemistry of condensed thiepines, thiepanes, and partially reduced derivatives has been reviewed with comprehensive coverage of the literature up to 1970 <72HC(26)1>. In the early 1980s, two review articles dealing with benzothiepines, noncondensed thiepines and related thiepines were published <81TCC33, 82RTC277>. An article covers the literature up to 1982 <84CHEC-I(5)547>. Although no comprehensive review articles on condensed thiepines have appeared since 1972, Protiva, who has contributed greatly to research on condensed thiepines and their medicinal and biological properties, has published a review of his group's studies of thiepines and related compounds <91CCC2501>.

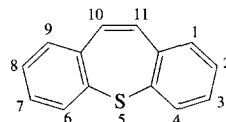
The nomenclature and numbering adopted are those used in *Chemical Abstracts*. The parent, 1-benzo, and dibenzo[*b,f*]systems are numbered as shown in compounds (1) to (4). The name for the saturated monocyclic sulfide (4) is thiepane, not hexahydrothiepene. Since the IUPAC recommendation for the nomenclature for monocyclic heterocycles in 1983 <83PAC409>, "thiepene" is optionally used for the unsaturated system; however, "thiepin" is favored by *Chemical Abstracts*; throughout this chapter "thiepene" is used.



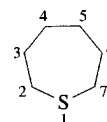
(1)



(2)



(3)

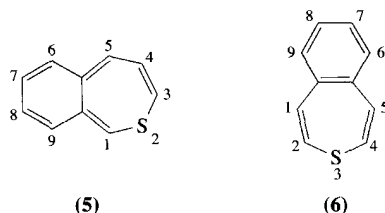


(4)

9.03.1.1 Theoretical Methods

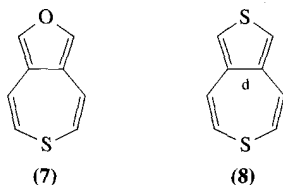
The crystal structures of some thiepines have been obtained and found to be nonplanar as described in Section 9.03.2.1. Moreover, thiepines constrained to planar, or close to planar

conformations are unknown. To understand their properties, theoretical studies associated with electron delocalization are important. Resonance energy obtained by simple (HMO) and advanced calculations (SCF-MO) for thiepine has predicted planar thiepine to be an antiaromatic molecule with negative resonance energy. The resonance energy for thiepine is $-29.7 \text{ kJ mol}^{-1}$ and $-29.8 \text{ kJ mol}^{-1}$ for 2-benzothiepine (5). 1-Benzothiepine (2) (24.7 kJ mol^{-1}) and 3-benzothiepine (6) (26.8 kJ mol^{-1}) are nonaromatic <73JA3907>.

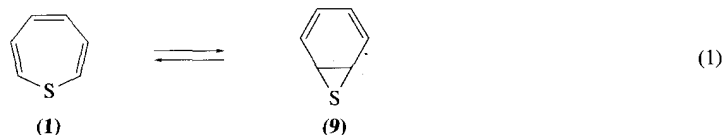


Other theoretical tests of aromaticity have been studied. The graph theory has predicted thiepine to be antiaromatic <76JA2750>. A new measure of aromaticity has been studied on the basis of absolute hardness (η) known to be an index of stability and reactivity of a molecule. The operation formula is the equation, $\eta = (I - A)/2$ where I is the ionization potential and A the electron affinity. Alternatively, the equation is $\eta = (E_{\text{HOMO}} - E_{\text{LUMO}})/2$. Absolute hardness has also predicted thiepine (1) and 2-benzothiepine (5) to be antiaromatic and 3-benzothiepine (6) to be nonaromatic. However, the prediction by this approach fails for 1-benzothiepine (2) <89JA7371>.

The degree of cyclic electron delocalization has been theoretically proposed to be a function of the mode of donor(D)–acceptor(A) arrangement of the component system as well as orbital phase continuity requirements. A novel notion of continuity–discontinuity of cyclic conjugation shows that there are nondelocalized $(4n + 2)\pi$ electron (or nonaromatic) systems and nonlocalized $4n\pi$ electron (or nonantiaromatic) systems in discontinuously conjugated systems. The notion was applied to explain the considerable stability of furano- and thieno[3,4-*d*]thiepines (7) and (8) <77JA7418, 78MI 903-01>.



Another important property of thiepine is the equilibrium between thiepine (1) and its valence isomer, benzene episulfide (9). Benzene episulfides are found to be so unstable that they can not be detected; hence theoretical treatment should provide helpful information. MNDO molecule force field calculations of the zero point energy, potential energy, and thermodynamic parameters for the valence tautomerization of benzene episulfide (9) and thiepine (1) show that (9) is more stable than (1) both in the gas phase and in polar media (Equation (1)). The equilibrium is shifted towards (1) in polar media. The vapor phase inversion barrier for (1) is $3\text{--}5 \text{ kJ mol}^{-1}$, and is reduced to zero by polar solvents <83MI 903-01>.



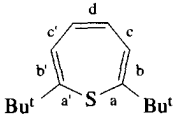
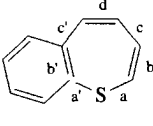
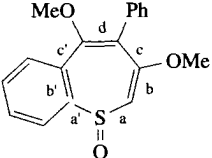
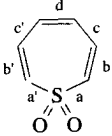
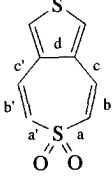
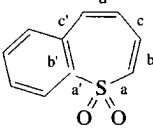
9.03.2 EXPERIMENTAL STRUCTURAL METHODS

9.03.2.1 X-Ray Diffraction

The x-ray crystal structure analysis of a monocyclic thiepine (10) stabilized by bulky groups at 2,7-positions has been conducted (Table 1) <82TL3195>. The obtained structure indicates the

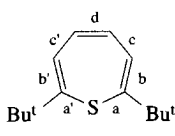
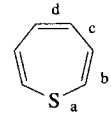
noncrystallographic mirror symmetry of the molecule passing through the S atom and the center of the C(4)—C(5) bond (a); the thiepine ring takes a boat form. The dihedral angles between the base plane (C(2), C(3), C(6), C(7)) and the bow (S, C(2), C(7)) (α) and stern (C(3), C(4), C(5), C(6)) planes (β) are 49.6° and 28.0° , respectively. The bond alternation is clearly observed in the C(2) to C(7) skeleton. The C(2)—C(3), C(4)—C(5) and C(6)—C(7) (b, d, b') are approximately equal to the C(sp²)—C(sp²) single bond. The C—S distances (a, a') of 1.808 and 1.799 Å show single bond character. The shortest nonbonded atomic distance between the *t*-butyl groups is 3.649 Å, which is shorter than the conventional van der Waals contact between the methyl groups of 4.0 Å. The steric repulsion between these methyl groups may strongly interfere with the shortening of the C(2)—C(7) distance in the expected benzene episulfide intermediate formation through sulfur extrusion. The x-ray structures of benzothiepine (**2**) <76AG(E)297>, benzothiepine 1-oxide (**11**) <78CB309>, thiepine 1,1-dioxide (**12**) <68JA4501>, thienothiepine 1,1-dioxide (**13**) <69JA3995>, and 1-benzothiepine 1,1-dioxide (**14**) <75AX(B)2729> are also shown in Table 1. These thiepine rings display bond alternation and exist in boat conformations. The oxygen of the sulfoxide function of the benzothiepine 1-oxide (**11**) possessed the *exo*(equatorial)-position. The semiempirical MO (PM3) <89JCC209> calculated

Table 1 The x-ray crystal structure analysis of thiepines.

Compound	Bond length (Å)		Bond angle (°)		α (°)	β (°)
 (10)	a	1.799	aa'	103.3	49.6	28.0
	a'	1.808	ab	119.3		
	b	1.327	a'b'	118.4		
	b'	1.328	bc	129.1		
	c	1.456	b'c'	129.5		
	c'	1.463	cd	127.3		
	d	1.328	c'd	127.7		
	a	1.781	aa'	101.1		
 (2)	b	1.321	ab	122.9	49.1	30.0
	c	1.448	bc	127.1		
	d	1.308	cd	127.8		
	c'	1.493	dc'	129.1		
	b'	1.404	c'b'	123.6		
	a'	1.773	b'a'	121.1		
	a	1.775	aa'	94		
	b	1.332	ab	118		
 (11)	c	1.485	bc	124	58.6	40.8
	d	1.345	cd	121		
	c'	1.482	dc'	127		
	b'	1.389	c'b'	121		
	a'	1.800	b'a'	117		
	a	1.723	aa'	103.3		
	a'	1.716	ab	122.8		
	b	1.344	a'b'	124.4		
 (12)	b'	1.340	bc	129.4	44.6	22.8
	c	1.429	b'c'	128.1		
	c'	1.438	cd	127.8		
	d	1.333	c'd	128.2		
	a	1.730	aa'	106.5		
	a'	1.748	ab	123.1		
	b	1.336	a'b'	122.4		
	b'	1.328	bc	128.4		
 (13)	c	1.451	b'c'	129.3	45.2	19.8
	c'	1.448	cd	127.9		
	d	1.438	c'd	126.9		
	a	1.735	aa'	108.1		
	b	1.326	ab	123.6		
	c	1.441	bc	128.2		
	d	1.328	cd	128.6		
	c'	1.456	dc'	130.1		
 (14)	b'	1.402	c'b'	126.4	47.2	24.0
	a'	1.756	b'a'	120.6		

structure of thiepine (10) reproduces the experimental structure satisfactorily (Table 2). The PM3 calculated structure of the unknown parent thiepine is also shown in Table 2.

Table 2 The PM3 calculated structure of thiepinines.

Compound		Bond length (Å)	Bond angle (°)	$\alpha(^{\circ})$	$\beta(^{\circ})$
 (10)	a	1.783	aa'	101.6	
	a'	1.783	ab	122.4	
	b	1.343	a'b'	123.7	
	b'	1.343	bc	126.2	42.7
	c	1.451	b'c'	126.6	33.4
	c'	1.451	cd	127.3	
	d	1.339	c'd'	126.7	
 (1)	a	1.744	aa	105.5	
	b	1.335	ab	130.5	26.6
	c	1.452	bc	127.6	25.0
	d	1.337	cd	128.8	

X-ray crystal analysis of thieno[3,4-*d*]thiepine (8) has been conducted <69JA3995>. A disordered structure similar to that of azulene was found, and this interfered with the complete analysis. It was reported that (8) is planar unlike most thiepinines. Only the central bond (d) is obtained as 1.46 ± 0.02 Å.

The x-ray crystal analysis of thiepine 1,1-dioxide chromium complex (15) has been conducted (Figure 1) <93JA1382>. The uncomplexed S atom is puckered and the complexed C(2)–(7) atoms are in a plane. The conformation is similar to that of (cycloheptatriene)tricarbonylchromium(0).

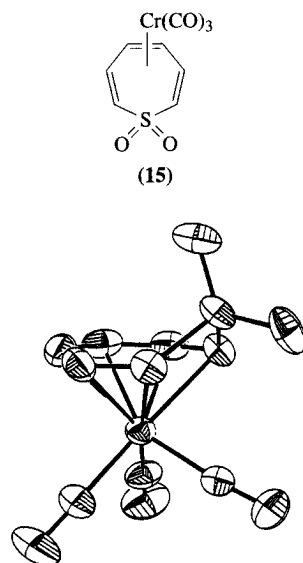


Figure 1 ORTEP drawing of (15). Reproduced by permission of the American Chemical Society <93JA1382>.

9.03.2.2 NMR Spectroscopy

Proton and ^{13}C NMR spectral data of thiepinines and related compounds are described below, and provide pertinent information on their physical and structural properties.

In the ^1H NMR spectra, the ring proton signals of a series of monocyclic thiepinines (10) and (16)–(20) appeared in the alkene region <79JA5059, 82CL1843, 82TL3195, 85CL1119>. These chemical shifts leave little doubt that the thiepine is not a paratropic but an atropic molecule. The vicinal coupling constants of the ring protons ($J_{3,4} = J_{5,6} = 5.5$ Hz and $J_{4,5} = 10.6$ Hz) of (10) were provided by

analysis of the 360 MHz NMR spectrum in decalin- d_{18} , which showed an AA'BB'-system at δ 6.10 (H-4 and 5) and 6.16 ppm (H-3 and 6). The coupling constants are consistent with an alternating triene structure and are found to be in close agreement with those of the nonplanar seven-membered trienes such as cycloheptatriene, azepine, and oxepine. The carbon chemical shifts of monocyclic thiepines are shown in Table 3.

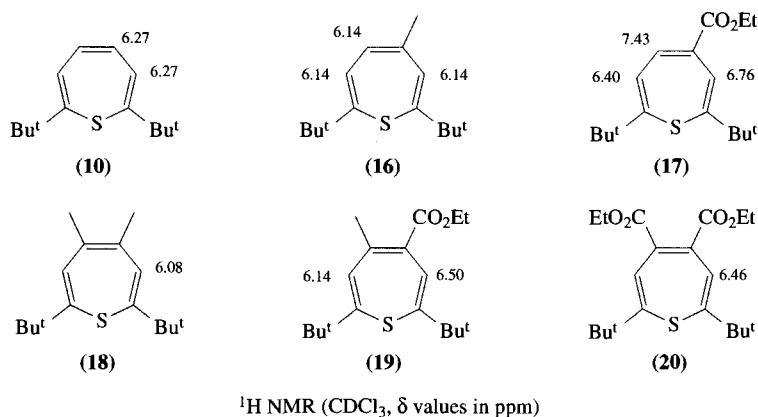


Table 3 ^{13}C NMR (CDCl_3) data for thiepines.

Compound	$C_{2,7}$	$C_{3,4,5,6}$
(10)	151.1	127.7, 132.9
(16)	148.7, 149.1	126.9, 129.1, 130.8, 141.3
(18)	148.5	131.4, 135.0
Compound	$C_{2,3,4,5,6,7}$	
(17)	126.0, 127.0, 134.0, 140.0, 151.0, 158.2	
(19)	126.8, 130.9, 132.1, 146.2, 151.4, 155.8	
(20)	125.8, 138.6, 157.5	

The ^1H NMR (400 MHz) and ^{13}C NMR (100.5 MHz) spectral data of 1-benzothiepine (2) have been reported with partial assignments (Table 4) <89ZN(B)220>.

Table 4 ^1H and ^{13}C NMR data for 1-benzothiepine (2).

H-2 5.86 (m)	H-3,4 6.40 (m)	H-5 7.06 (<i>d</i> , <i>J</i> = 12 Hz)	H-6,7,8,9 7.16 (<i>d</i> , <i>J</i> = 8 Hz, 1H), 7.28 (m, 3H)	
C-2 124.55	C-3,4 130.58, 133.99	C-5 136.94	C-6,7,8,9 127.94, 128.79, 130.14, 132.09	C-5a,9a 133.45, 140.98

The 4H-thiepinium ions (10a), (16a), and (18a), generated from thiepines (10), (16), and (18) in $\text{FSO}_3\text{H}/\text{SO}_2/\text{CD}_2\text{Cl}_2$ (-70°C) or H_2SO_4 (room temperature) have been shown by NMR examination to possess the homothiopyrylium ion structure (Table 5) <84CC604>. The ^1H NMR spectrum of (10a) indicates charge delocalization. The striking feature of the spectrum at -70°C was the fairly large chemical shift difference ($\Delta\delta = 2.5$ ppm) between the methylene protons, (4o)-H and (4i)-H, and the geminal coupling constant of 11.6 Hz for these protons (Equation (2)).

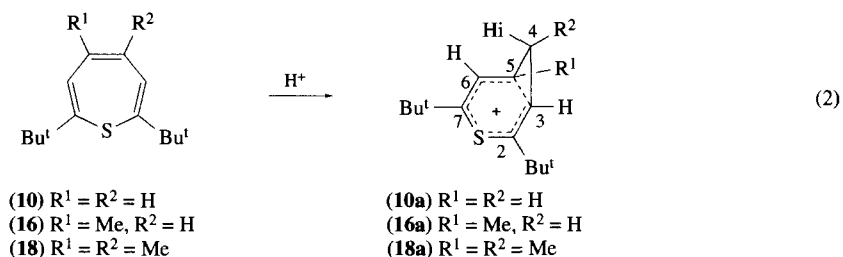
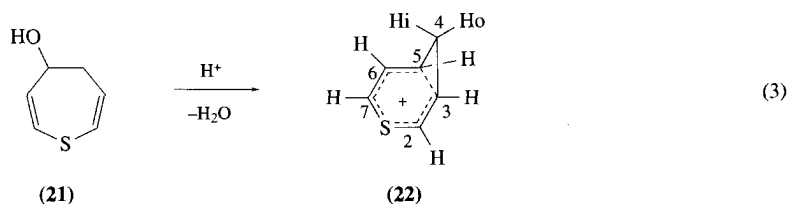


Table 5 ^1H and ^{13}C NMR data for the homothiopyrylium ions.

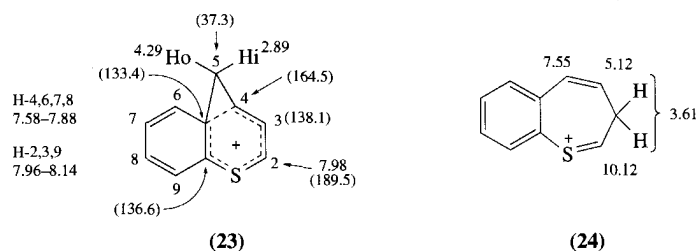
Compound	H-2	H-3	H-4o	H-4i	H-5	H-6	H-7
(10a) (-70°C) ^a		6.10 (dd)	3.81 (ddd)	1.31 (m)	7.17 (ddd)	7.65 (d)	
		$J_{3,4o} = J_{3,4i} = 7.5$, $J_{4o,4i} = 11.6$, $J_{5,6} = 9.4$, $J_{5,4o} = 8.4$, $J_{5,4i} = 8.6$ Hz					
(16a) (-70°C) ^a		6.05 (dd)	3.75 (dd)	1.66 (m)		7.61 (s)	
		$J_{3,4o} = J_{3,4i} = 7.6$, $J_{4o,4i} = 9.2$ Hz					
(18a) (-70°C) ^a		5.66 (d)		1.68 (br.s) ^c		7.63 (s)	
		$J_{3,4} = \text{ca. } 6$ Hz					
(22) (-80°C) ^a	7.99 (d)	6.32 (dt)	4.44 (m)	1.16 (m)	7.15 (dt)	7.99 (m)	10.04 (d)
	$J_{2,3} = 7.5$, $J_{3,4o} = J_{3,4i} = 7.5$, $J_{5,6} = 7.9$, $J_{5,4o} = J_{5,4i} = 7.9$, $J_{6,7} = 6.1$ Hz						
Compound	C-2	C-3	C-4	C-5	C-6	C-7	
(10a) (r. t.) ^b	162.5	144.7	31.4	130.1	120.7	216.0	
(16a) (r. t.) ^b	179.0	131.6	29.9	157.4	128.1	218.5	
(18a) (r. t.) ^b	180.6	131.3	24.2	157.2	130.4	212.0	
(22) (-70°C) ^a	131.2 ^d	129.7	33.76	150.5	133.4 ^d	178.9	

^aIn $\text{FSO}_3\text{H}-\text{SO}_2-\text{CD}_2\text{Cl}_2$. ^bIn 97% H_2SO_4 . ^cAveraged chemical shift. ^dAssignment may be reversed.

The parent homothiopyrylium ion (**22**) was generated by cleavage of the hydroxy group of 4,5-dihydrothiepin-4-ol (**21**) with FSO_3H (Table 5) <85AG(E)214>. The ^1H NMR spectrum (-80°C) of (**22**) contains two signals assigned to methylene protons at $\delta = 4.44$ and 1.16. The large chemical shift difference ($\Delta\delta = 3.28$ ppm) is mainly caused by the homoaromatic ring current. Delocalization of positive charge is also indicated by the proton chemical shift in (**22**) (Equation (3)).



Both 5H-1-benzothiepinium ion (**23**) and 3H-1-benzothiepinium ion (**24**) were generated in $\text{FSO}_3\text{H}/\text{SO}_2/\text{CD}_2\text{Cl}_2$ and characterized by ^1H and ^{13}C NMR spectra <84CL919>. The former ion can be regarded as benzohomothiopyrylium ion whereas the latter is postulated to have a localized sulfonium ion structure.



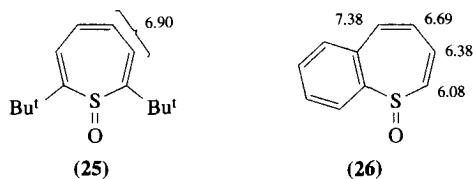
^1H NMR (δ values) and ^{13}C NMR (in parentheses, δ values)

The ^1H NMR spectrum of unstable monocyclic thiepine 1-oxide (**25**) generated by oxidation of (**10**) with *O*-benzyl *OO*-hydrogen monoperoxy carbonate ($\text{PhCH}_2\text{OCO}_3\text{H}$) has been measured at -70°C in the reaction mixture <94JCS(P1)2631>. The proton chemical shifts of benzothiepine 1-oxide (**26**), which is isolated at -40°C , are quite similar to those of benzothiepine (**2**) <88AG(E)1717>. This implies no appreciable changes in electronic and geometric structures on going from thiepine to its *S*-oxide.

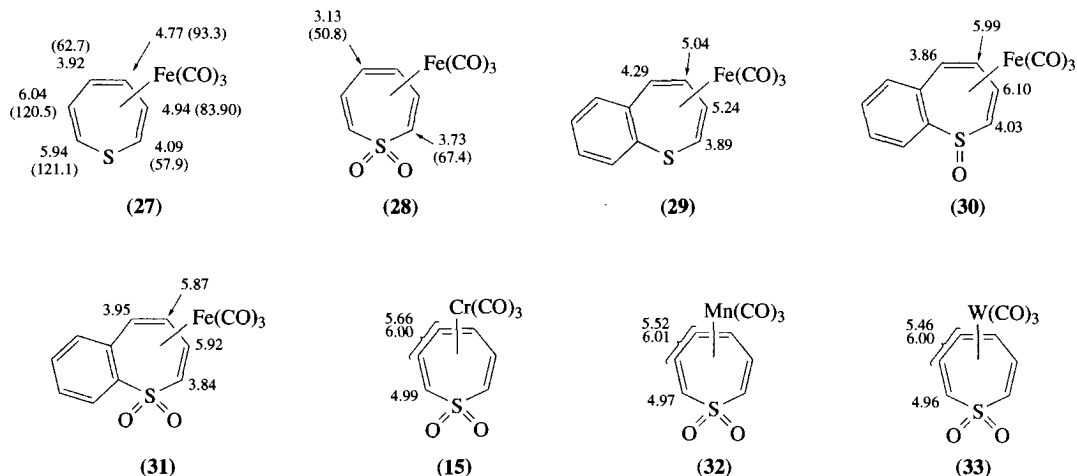
The ^1H NMR spectrum of thiepine 1,1-dioxide (**12**) shows multiple alkenic protons at 6.5–7.2 ppm <67JA1281>.

The ^1H and ^{13}C NMR signals of (η^4 -thiepine)iron tricarbonyl complexes (**27**)–(**31**) are shown

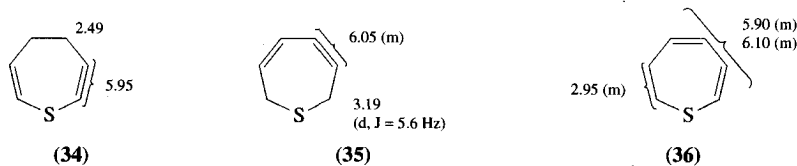
Thiepanes and Thiepines

¹H NMR (CDCl₃, δ values in ppm)

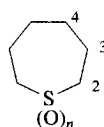
below <88AG(E)1717, 91JA5059>. The η^4 -complexation of the thiepene rings was confirmed on the basis of ¹H and ¹³C NMR spectra which exhibited signals at substantially high field for the 2- and 5-positions. The ¹H NMR spectrum of (η^6 -thiepene 1,1-dioxide)metal tricarbonyls (15), (32), and (33) (M = Cr, Mo, and W) are also shown <93JA1382>. These spectral properties are consistent with their η^6 -complexation.

¹H NMR (δ values) and ¹³C NMR (in parentheses, δ values)

The ¹H NMR spectrum of dihydrothiepanes (34)–(36) are reported as shown <79JA294>.

¹H NMR (CDCl₃, δ values in ppm)

The ¹³C chemical shifts for carbons of cyclic sulfides have been assigned by using α,α -dideutero compounds. The α -carbon signals of thiepane (4) appeared at lower field than those of the β -carbons in a similar manner as thiolane and thiane <80JOC4807, 82CPB4189>. In the ¹³C NMR spectra of the cyclic sulfoxides and sulfones, some trends have been pointed out: (1) oxidation of a sulfide to a sulfone results in a 20–25 ppm α -carbon downfield shift and a somewhat smaller upfield β -carbon shift, and (2) there is very little difference in the α -carbon shifts of the sulfoxides and the sulfones <80JOC4807>. The ¹⁷O chemical shifts for the series of cyclic sulfoxides and sulfones including thiepane derivatives (37) and (38) have been found to depend on ring size. The signals of the sulfones appear at lower field than those of the corresponding sulfoxides <80JOC4807>. The ³³S chemical shifts were measured and discussed for three, four, five, and six-membered ring sulfides, sulfoxides, and sulfones <87JOC3857>. The ³³S chemical shift for thiepane 1,1-dioxide was also recorded <89JST(186)197>. These NMR spectral data for thiepane (4) and its *S*-oxides (37) and (38) are listed in Table 6.

Table 6 ^{13}C , ^{17}O , and ^{33}S NMR data for thiepine (4) and its *S*-oxides (37) and (38).

	Chemical shift			Ref.
	(4): $n = 0$	(37): $n = 1$	(38): $n = 2$	
$^{13}\text{C}^a$				80JOC4807
C-2	33.33	52.1	55.6	82CPB4189
C-3	31.19	19.1	21.3	
C-4	26.61	—	—	
$^{17}\text{O}^b$		11	150	80JOC4807
$^{33}\text{S}^c$			339	89JST(186)197

^aIn ppm with respect to TMS as the internal reference (in CDCl_3). ^bIn ppm with respect to ^{17}O in deionized water as the external reference (in CDCl_3). ^cIn ppm with respect to CS_2 to the external reference (in CHCl_3).

9.03.2.3 UV Spectroscopy

The UV spectral data of thiepinines are shown in Table 7. The longest wavelength band of monocyclic thiepinines (10), (16), and (18) has been assigned to the $\pi_4(\text{HOMO})-\pi_5(\text{LUMO})$ transition. The observed bands in these thiepinines clearly display the successive blue shift by 12 and 26 nm for (16) and (18) compared to (10), respectively. The implication is that the coefficients at the 4- and 5-positions in the LUMO of the thiepine are greater than those at the same positions in the HOMO so that the HOMO-LUMO gap increases with increasing methylation. This causes the blue shift to be proportional to the number of methyl groups.

A more detailed measurement of UV spectra of thieno[3,4-*d*]thiepine (8) and examination by MO calculations has been conducted. The first four bands of (8) are assigned to $\pi \rightarrow \pi^*$ transitions and are correlated with the first four bands of azulene (73JA2860).

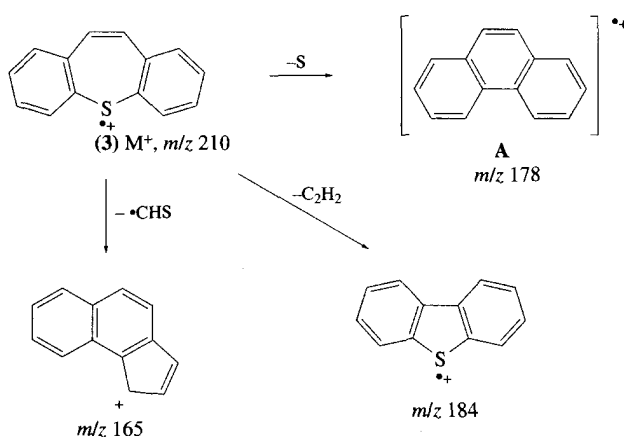
Table 7 UV spectra of thiepinines.

Compound	Solvent	λ_{max} (log ϵ)	Ref.
2,7-Di- <i>t</i> -butylthiepine (10)	cyclohexane	226 (4.02), 252 (3.35), 362 (2.51)	82TL3195
2,7-Di- <i>t</i> -butyl-4-methylthiepine (16)	cyclohexane	224 (4.04), 252 (3.51), 348 (2.60)	82CL1843
2,7-Di- <i>t</i> -butyl-4,5-dimethylthiepine (18)	cyclohexane	206 (4.26), 226 (4.00), 253 (3.58), 336 (2.68)	82CL1843
1-Benzothiepine (2)	cyclohexane	217 (4.07), 256 (4.07), 295 (2.96 sh), 345 (2.55 sh)	74AG(E)142
Dibenzo[<i>b,f</i>]thiepine (3)	EtOH	227 (4.36), 262 (4.47), 295 (3.70)	60JOC828
3-Benzothiepine (2,4-COOMe) (39)	EtOH	251 (4.46), 287 (4.24)	62JOC3224
Furano[3,4- <i>d</i>]thiepine (7)	MeOH	225 (4.19), 233 (4.24), 240 (4.43), 249 (4.38), 275 (3.04), 345 (2.67), 364 (2.71), 415 (2.15)	69TL4361
Thieno[3,4- <i>d</i>]thiepine (8)	MeOH	210 (4.13), 224 (4.12), 228 (4.15), 245 (4.29), 251 (4.41), 260 (4.41), 308 (3.23), 331 (3.27), 346 (3.03), 369 (2.56), 378 (2.49), 390 (2.43)	67JA7138
Thiepine 1,1-dioxide (12)	EtOH	262 (3.66), 232 (3.31), 215 (4.25)	67JA1281
1-Benzothiepine 1,1-dioxide (14)	EtOH (95%)	221 (4.16), 234 (4.13), 290 (3.99)	61JOC2728
3-Benzothiepine 1,1-dioxide (40)	EtOH (95%)	232 (4.5), 238 (3.9)	61JOC2728
Dibenzo[<i>b,f</i>]thiepine 1,1-dioxide (41)	EtOH	229 (4.54), 264 (3.85), 300 (4.08)	60JOC828
1-Methyl-1-benzothiepinium tetrafluoroborate (42a)	CD_3CN	234 (3.66 sh), 302 (3.47)	90ZN(B)1573
(Thiepine)iron tricarbonyl (27)	cyclohexane	262 (4.04), 335 (3.54 sh)	91JA5059
(1-Benzothiepine)iron tricarbonyl (29)	cyclohexane	276 (4.06), 310 (3.95 sh)	88AG(E)1717
(1-Benzothiepine 1-oxide)iron tricarbonyl (30)	EtOH	210 (3.43), 225 (3.42 sh), 312 (2.74)	88AG(E)1717
(1-Benzothiepine 1,1-dioxide)iron tricarbonyl (31)	EtOH	215 (3.90), 312 (2.17)	88AG(E)1717

9.03.2.4 IR and Mass Spectroscopy

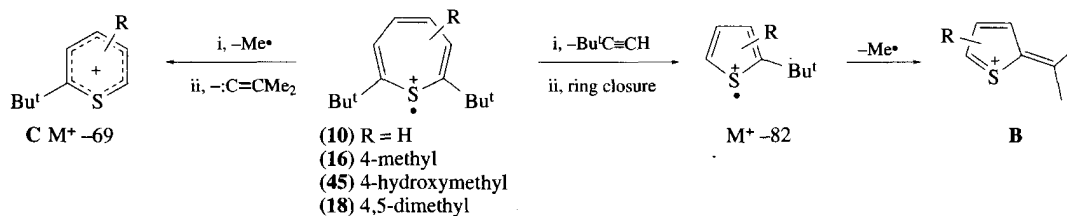
The IR spectra of thiepanes have been reported, but no systematic studies have appeared. The IR spectra of thiepan-3-one (43) and -4-one (44) were found to be suggestive for intramolecular interaction in the ground state between the ring sulfur and the CO group <75JCS(P2)1294>. However, this is not definitive evidence since there is only a small difference between the carbonyl frequency values for the thiepanones and cycloheptanone <80JPR152>.

The mass spectra of fully conjugated thiepanes including monocyclic thiepanes have been reported, but only with brief discussion. The earlier work on the mass spectrum of dibenzo[*b,f*]thiepine (3) provides important information about fragmentation processes for thiepanes. Thus, the phenanthrene radical cation **A** has been found to be a prominent feature of the spectrum, and two less important fragmentation pathways with formation of two different ring systems by loss of C₂H₂ or •CHS from the parent ion have been suggested (Scheme 1) <67JHC209>.



Scheme 1

The mass spectra of the 2,7-di-*t*-butylthiepanes show striking generalities: (1) no ions, generated from the parent ions by a loss of sulfur, are observed, and (2) the peaks at m/z ($M^+ - 97$) which may be assigned the structure **B**, generated by sequential elimination of *t*-butylethyne and a methyl radical from the parent ions, are observed. In the cases of 2,7-di-*t*-butylthiepine, the 4-methyl-, 4-hydroxymethyl-, and 4,5-dimethylthiepine derivatives, (10), (16), (45), and (18), peaks at $M^+ - 82$ are observed. A plausible fragmentation pathway involving formation of a five-membered ring is shown in Scheme 2. In the cases of (16), (45), and (18), the peaks $M^+ - 69$ assignable to the 2-*t*-butylthiopyrylium ions **C** are also observed <94UP 903-01>.



Scheme 2

The mass spectra of 1-benzothiepanes are reported to show an appreciable intensity for the parent ion and have the corresponding naphthalene radical cations as the base peak <73JOC3978>. A publication in 1989 has shown a peak at m/z 134 ($M^+ - \text{C}_2\text{H}_2$) to be observed, besides the parent ion and the ion attributed to naphthalene radical cation generated by loss of sulfur in the mass spectrum of 1-benzothiepine (2) <89ZN(B)220>.

The mass spectra of furano- and thieno[3,4-*d*]thiepines (**7**) and (**8**) were found to show abundant ions $(M^+ - 45)^+$ and m/z 45, together with the parent ions and the ions generated by a loss of sulfur. These observations suggest that the thiepine ring also follows another fragmentation pattern, attributed to the loss of a CHS group (m/z 45), with the formation of a five-membered ring $\langle 82JHC1243 \rangle$.

A detailed investigation of the mass spectrum of thiepane (**4**) was made with the aid of deuterium labeling techniques. Interesting characteristics of the fragmentation patterns of thiepane were observed. The fragment $(M^+ - C_2H_5, m/z$ 87) is the base peak. Loss of H_2S from the molecular ion gives rise to the important fragment (m/z 82). Mechanism for the formation of the major fragments (m/z 67 ($C_5H_7^+$), 60 ($C_2H_4S^+$), 61 ($C_2H_5S^+$)) is described $\langle 68AMS(4)357 \rangle$. The mass spectra of the thiepanones (3- and 4-) (**43**) and (**44**) together with their 1,1-dioxides were studied $\langle 74OMS(9)665 \rangle$. The major ions, $C_4H_6OS^+$ (m/z 102) and $C_3H_2OS^+$ (m/z 87), those stabilized by sulfur, are observed. Major fragments in the mass spectra of thiepan-3-ol, were found to be stabilized by sulfur, for example m/z 45 (CHS^+), m/z 46 (CH_2S^+), m/z 47 (CH_3S^+), m/z 58 ($C_2H_2S^+$), m/z 59 ($C_2H_3S^+$), m/z 60 ($C_2H_4S^+$), and m/z 61 ($C_2H_5S^+$). The losses of H_2O , H_2O^+ , ethene and vinyl alcohol are the major fragmentation pathways $\langle 80OMS(15)380 \rangle$.

In the mass spectrum of thiepane sulfoxide (**46**), the molecular ion eliminates OH with the initial hydrogen abstraction predominantly from the site other than the α -position to the sulfinyl group $\langle 70OMS(3)1561, 72BSJ1767 \rangle$. In the thiepane sulfone (**47**), the important modes of fragmentation are shown to involve the initial hydrogen migration to oxygen atoms and the loss of SO_2H and SO_2H_2 . The peaks due to the loss of SO_2 and $C_2H_2H^{\beta}_2$ are also observed $\langle 70OMS(3)1561 \rangle$.

9.03.2.5 Photoelectron Spectroscopy

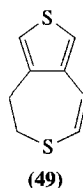
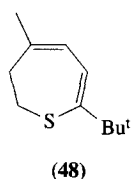
The helium(I) photoelectron spectra of monocyclic thiepines (**10**), (**16**), (**18**), and a dihydrothiepine (**48**) have been investigated $\langle 85JA6874 \rangle$. The first bands in these thiepines are assigned to ionizations from π -orbitals. The assignment is based on empirical considerations and model calculations (MNDO and *ab initio*). Comparison between the measured ionization energies, $I_{v,j}$, of (**10**), (**16**), (**18**), and (**48**) and MNDO calculated molecular orbital energies, ϵ_j , for 2,7-dimethyl analogues of (**10**), (**16**), (**18**), and (**48**) is made in Table 8. The PE spectra of thieno[3,4-*d*]thiepine (**8**) and its dihydro derivative (**49**) have been also investigated. In contrast to the spectra of (**10**), (**16**), (**18**), and (**48**), observed bands of (**8**) and (**49**) have a relatively steep onset, typically for planar π -system. The comparison between the measured ionization energies, $I_{v,j}$, of (**8**) and (**49**) with the calculated orbital energies are listed in Table 9. Furthermore, the first PE bands of (**8**) with those of azulene have been compared and the comparison shows that the energy difference between the first MOs of both compounds is similar.

Table 8 PE spectra of (**10**), (**16**), (**18**), and (**48**) and calculated molecular orbital energies, ϵ_j for 2,7-dimethyl analogues of (**10**), (**16**), (**18**), and (**48**) (all values in eV).

Compound	Band	$I_{v,j}$	Assignment	$-\epsilon_j$ (MNDO)
(10)	1	7.7	14a' (π_4)	8.71
	2		13a' (π_3)	10.41
	3	9.3	10a'' (π_2)	10.58
	4	10.2	12a' ($\pi_{1,n}$)	11.49
(16)	1	7.6	π_4	8.76
	2	8.9	π_3	10.34
	3	9.2	π_2	10.44
	4	10.0	$\pi_{1,n}$	11.31
(18)	1	7.5	11a' (π_4)	8.88
	2	8.6	16a' (π_3)	10.23
	3	8.95	13a'' (π_2)	10.25
	4	9.7	15a' ($\pi_{1,n}$)	11.09
(48)	1	7.7	π	9.25
	2	8.9	3p	9.98
	3	10.1	π	10.28

Table 9 PE spectra and calculated molecular orbital energies, ϵ_j of (8) and (49) (all values in eV).

Compound	Band	I_{vj}	Assignment	$-\epsilon_j$ (HMO)
(8)	1	7.42	$4b_1 (\pi)$	7.48
	2	8.52	$2a_2 (\pi)$	8.43
	3	9.75	$3b_1 (\pi)$	10.16
	4	10.7	$1a_2 (\pi)$	11.07
(49)	1	7.67	$7a'' (\pi)$	7.92
	2	8.73	$6a'' (\pi)$	9.12
	3	9.38	$5a'' (\pi)$	9.96
	4	11.0	$4a'' (\pi)$	11.22



9.03.3 THERMODYNAMIC ASPECTS

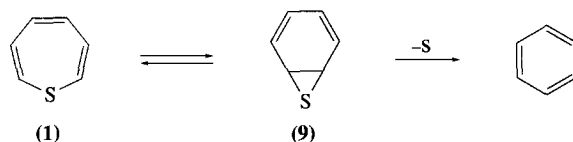
9.03.3.1 Antiaromaticity and Aromaticity

A thiepine is formally isoelectronic with the 8π -electron cyclooctatetraene and cycloheptatrienide anion as well as other heteropines, and if planar, should be antiaromatic as the Hückel rule predicts. However, as discussed under x-ray diffraction (Section 9.03.2.1), the thiepine ring is boat shaped. ^1H NMR spectral analysis indicates that thiepines are not paramagnetic but atropic (Section 9.03.2.2) (see also Section 9.01.1).

As an example of heterocyclic homoaromatic species, homothiopyrylium ions (10a), (16a), (18a), (22), and (23) have been directly observed by NMR spectroscopy (see Section 9.03.3.2). Their NMR spectra have shown 6π -electron delocalization and existence of homoaromatic ring current.

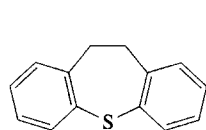
9.03.3.2 Stability and Stabilization

In general, simple thiepines are known to be thermally unstable owing to ready sulfur extrusion. The widely accepted mechanism of sulfur extrusion involves valence isomerization of the thiepine ring to its corresponding thianorcaradiene (benzene episulfide) isomer, followed by irreversible loss of sulfur. Because of the thermal instability, the parent thiepine has never been characterized, even as a transient species (Scheme 3).

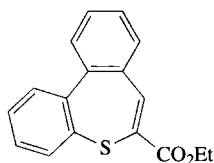
**Scheme 3**

Thiepines can be stabilized by electronic effects such as aromatic ring annelation. In the transition state to a thianorcaradiene the aromatic ring resonance is cancelled. The thermal stability of the

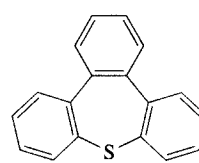
thiepine ring increases with an increasing number of annelated benzene rings. Thiepinines with more than two benzene rings (**3**), (**50**), and (**51**) are quite thermally stable compounds <60JOC828, 65T1299>.



(3)



(50)



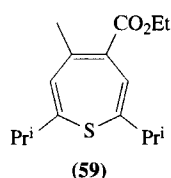
(51)

The half-lives of aromatic and heteroaromatic rings annelated thiepinines are shown in Table 10 <81TCC33>. The differences in thermal stability between (**55**) and (**56**) can be explained in terms of total loss of aromaticity in thianorcaradiene isomer in (**55**). Comparison of aromatic and heteroaromatic rings ((**53**), (**57**), and (**58**)) clearly shows that the thermal stability of these thiepinines increases with increasing aromatic character of the annelated rings.

Table 10 Half-lives of annelated thiepinines.

 (2) 58 min/47°C	 (52a) 352 min/47°C	 (53) 57 min/25°C
 (54) 49 min/146°C	 (55) 72 min/94°C	 (56) 33 min/-27°C
 (57) 52 min/-27°C	 (58) 19 min/-27°C	

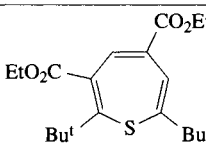
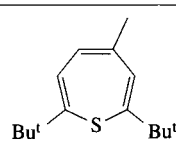
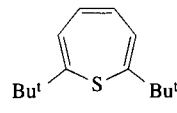
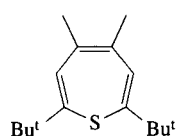
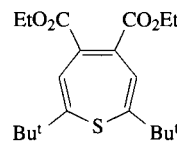
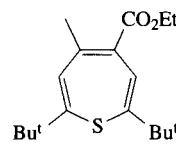
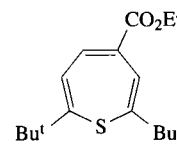
Thiepinines can be also stabilized by steric effects. Monocyclic thiepinines (**10**) and (**16**)–(**20**) with a bulky group at both C₂ and C₇ positions of the thiepine ring are sufficiently stable and show no tendency to extrude sulfur at room temperature. Thus, these thiepinines possess substantial thermal stability arising from the steric repulsion between two *t*-butyl groups. Thiepine (**59**) possessing an isopropyl group at both C₂ and C₇ positions is unstable even at -70°C <78CL723>.



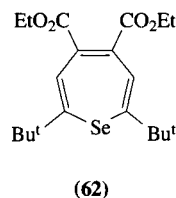
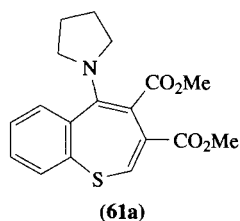
(59)

The effect of a variety of electron donating or withdrawing substituents on the thermal stability of thiepinines has been examined in the 1-benzothiepine and 2,7-di-*t*-butylthiepine systems <79JA5059, 81TCC33, 82TL3195, 85CL1119, 90CE853>. The half-lives of substituted 2,7-di-*t*-butylthiepinines to the corresponding benzene derivatives at 130°C in toluene-d₈ are listed in Table 11. It has been suggested that the difference in their thermal stability is explained mainly by the steric effects of the substituents <85JA6874>.

Table 11 Half-lives of 2,7-di-*t*-butylthiepines at 130°C in toluene-*d*₈.

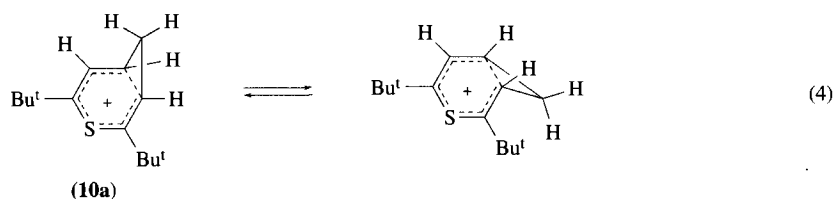
Compound	$t_{1/2}$, h	Compound	$t_{1/2}$, h
 (60)	> 1000	 (16)	105
 (10)	365	 (18)	15
 (20)	254	 (19)	7
 (17)	157		

Thermodynamic parameters have been obtained from kinetic studies of the thermal decomposition of ethyl 2,7-di-*t*-butyl-5-methyl-4-thiopenecarboxylate (**19**) <90AG(E)424> and 1-benzothiepine (**61a**) <74T2431>. The activation parameters for the sulfur extrusion reaction of (**19**) and (**61a**) are $\Delta H^\ddagger = 93.7 \pm 14 \text{ kJ mol}^{-1}$ for (**19**), $\Delta H^\ddagger = 75 \pm 13 \text{ kJ mol}^{-1}$ for (**61a**), and $\Delta S^\ddagger = -112.5 \pm 15 \text{ JK}^{-1} \text{ mol}^{-1}$ for (**19**), $\Delta S^\ddagger = -100 \pm 42 \text{ JK}^{-1} \text{ mol}^{-1}$ for (**61a**), respectively. The large negative $\Delta S^\ddagger$ values are well in accord with a decrease in entropy in the transition state which would be anticipated to be close to a thianorcaradiene structure. In contrast, $\Delta S^\ddagger$ value for the selenium extrusion reaction from selenepine (**62**) is $9.3 \text{ JK}^{-1} \text{ mol}^{-1}$, which implies that the reaction pathway is different to that of thiepines. A pathway via incipient fission of a C—Se bond has been suggested <90AG(E)424>.

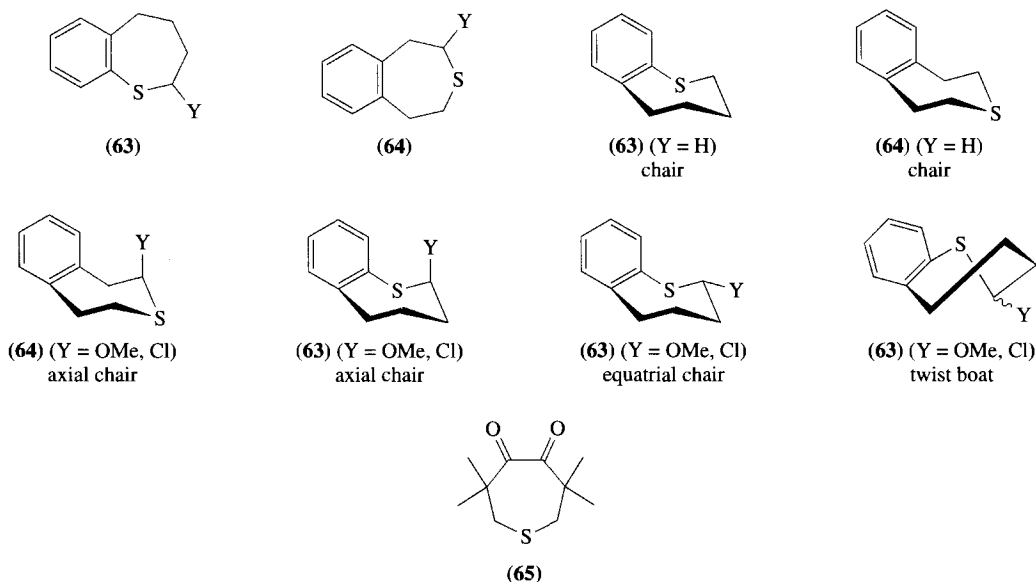


9.03.3.3 Conformation

The ring flipping process in the 4H-thiepinium ion (**10a**), which is considered as the homothiopyrylium ion, has been studied by NMR spectroscopy and a barrier of 54.4 kJ mol^{-1} has been determined <84CC604>. The value is intermediate between 93.3 and 35.1 kJ mol^{-1} for those of the homotropyrylium ion and the homocyclopropenium ion, respectively (Equation (4)).



The conformational properties of 1-benzo- and 3-benzothiepine derivatives were studied by ^1H and ^{13}C -high field NMR spectroscopy in $\text{CHF}_2\text{Cl}-\text{CD}_2\text{Cl}_2$ solution at low temperature. Both parent compounds (**63**; $\text{Y} = \text{H}$) and (**64**; $\text{Y} = \text{H}$) were found to exist in the chair conformation. The 2-substituted derivatives of (**64**; $\text{Y} = \text{OMe}$ and $\text{Y} = \text{Cl}$) showed the presence of axial chair form only. The 2-substituted derivatives of (**63**; $\text{Y} = \text{OMe}$ and $\text{Y} = \text{Cl}$) showed mixtures of three conformers (axial chair : equatorial chair : twist boat; ($\text{Y} = \text{OMe}$) 93 : 5 : 2; ($\text{Y} = \text{Cl}$) 85 : 12 : 3). The predominance of the axial chair form in both series argues in favor of a strong anomeric effect $\langle 92\text{CJC}2650 \rangle$. The dynamic stereochemistry of 3,3,6,6-tetramethyl-4,5-thiepanedione (**65**) was studied with other seven-membered α -diketones by ^1H NMR spectroscopy and by molecular mechanics calculations $\langle 83\text{JCS(P}2\text{)1351} \rangle$. The preferred conformer of the α -diketone was found to be a distorted chair with a carbonyl-carbonyl dihedral angle of 102° . The inversion barrier of the seven-membered ring system was found to be 47.5 kJ mol^{-1} , and the value is 8.4 kJ mol^{-1} higher than those of other α -diketones.

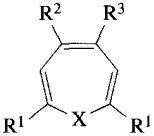
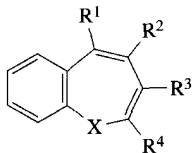
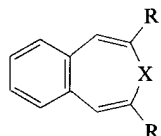
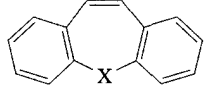


9.03.3.4 Melting and Boiling Points

Melting points of certain organic compounds such as alkanes have been discussed $\langle \text{B-55MI 903-01, B-78MI 903-02} \rangle$; however, correlation between molecular structures and melting points depending on intermolecular association of molecules in the liquid and solid states is not generally clear. Melting points of thiepinines and thiepanes have not been studied systematically yet.

Melting points of thiepinines obtained are summarized in Table 12. Certain members of 2,7-di-*t*-butylthiepinines, having sufficient symmetry, are isolated as crystals showing low melting points without loss of sulfur atom. Dibenzo[*b,f*]thiepine (**3**) shows a melting point higher than that of 1-benzothiepine (**2**); melting points increase normally with molecular weight. In the 1-benzothiepine series, introduction of the phenyl group into the ring tends to raise the melting point, but not introduction of halogen. No reports appear of thiepinines tending to sublime. A sulfone invariably has a higher melting point than the corresponding thiepine. Because fully conjugated thiepine oxides are thermally less stable than the corresponding thiepinines, limited melting points are reported due to difficulty in isolation. Lower members of thiepanes and partially reduced thiepinines are mostly liquid under normal conditions.

Table 12 Melting points of thiepines.

Compound		Mp. (°C)	Ref.
	X = S (10): R ¹ = Bu ^t , R ² = R ³ = H; (18): R ¹ = Bu ^t , R ² = R ³ = Me; (19): R ¹ = Bu ^t , R ² = Me, R ³ = CO ₂ Et, X = SO ₂ , (12): R ¹ = R ² = R ³ = H	36–36.5 59.5–61 23.5–24.5 117–118	82TL3195 82CL1843 79JA5059 67JA1281
	X = S (2): R ¹ = R ² = R ³ = R ⁴ = H; (66a): R ¹ = Ph, R ² = Cl, R ³ = R ⁴ = H; (66b): R ¹ = Ph, R ² = Br, R ³ = R ⁴ = H; (67): R ¹ = R ² = R ³ = H, R ⁴ = Cl; (68): R ¹ = Me, R ² = Cl, R ³ = R ⁴ = H X = SO, (11): R ¹ = R ³ = OMe, R ² = Ph, R ⁴ = H, X = SO ₂ , (14): R ¹ = R ² = R ³ = R ⁴ = H	23.5–24.5 86–88 81–82 (oil) (oil) 105 140–141	74AG(E)142 78JOC3379 78JOC3379 73JOC3978 78JOC3379 75AG(E)812 61JOC2728
	(39): X = S, R = CO ₂ Me (69): X = SO ₂ , R = H	95–97 161.5–163.5	56CB2608 56JA848
	(3): X = S (41): X = SO ₂	89–90 171–172	60JOC828 60JOC828

^a2,7-Di-*t*-butylthiepene 1-oxide (25) was detected at low temperatures, but not isolated (94JCS(P1)2631). ^b1-Benzothiepene 1-oxide (26) was isolated, but its melting point was not measured due to its instability (88AG(E)1717). ^cDibenzo[*b,f*]thiepene 5-oxide was isolated, but its melting point was not described (70JPC2236).

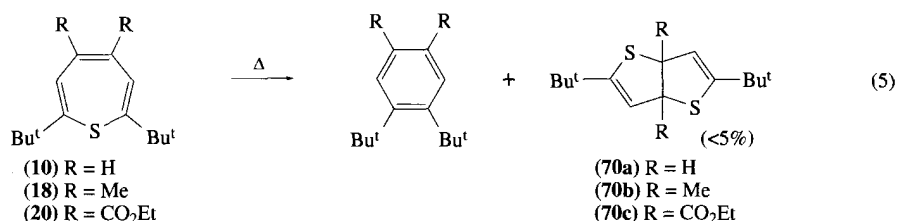
9.03.4 REACTIVITY OF FULLY CONJUGATED RINGS (THIEPINES)

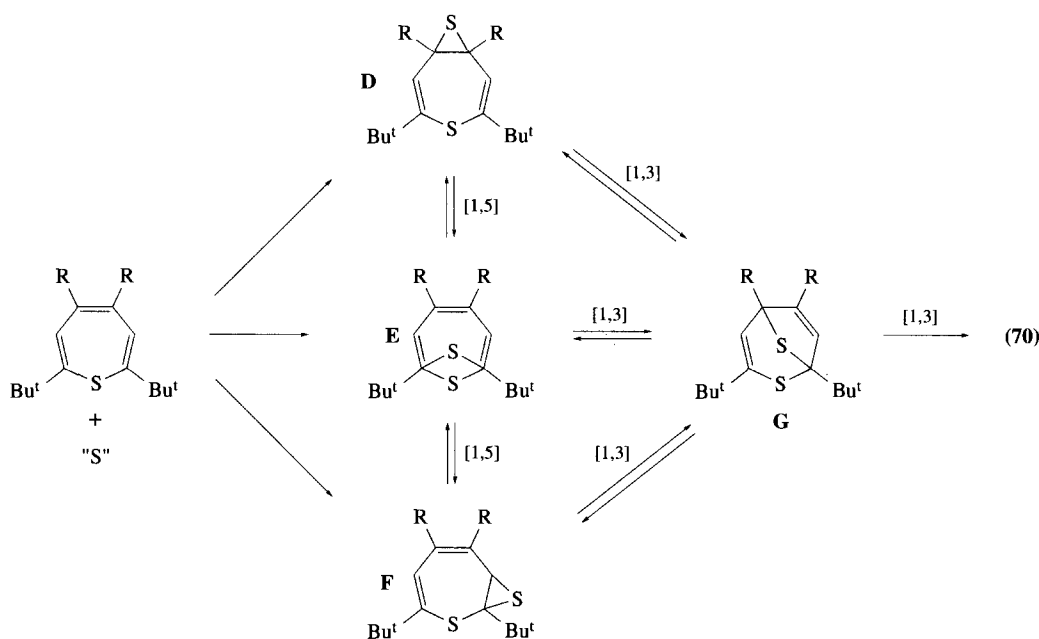
9.03.4.1 Introduction and General Survey

As has already been discussed in Section 9.03.3.2, thiepines are thermally unstable. Most reactivity studies have been carried out on monocyclic thiepines stabilized by 2,7-*t*-butyl groups, annelated thiepines, thiepene 1,1-dioxides and their metal complexes.

9.03.4.2 Thermal and Photochemical Reactions

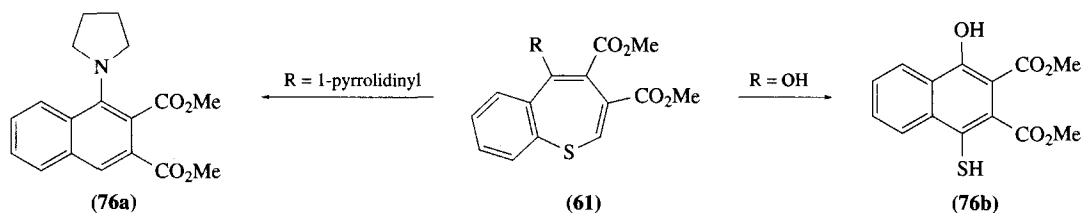
As discussed in Section 9.03.3.2, thiepines thermally change to the benzene derivatives through valence isomerization to the corresponding thianorcaradienes followed by irreversible cheletropic loss of sulfur. When 2,7-di-*t*-butylthiepines (10), (18), and (20) were thermolyzed, *o*-di-*t*-butylbenzene derivatives were major products; however, a small amount of sulfurated products (70) was also obtained. The structure of (70c) was confirmed by x-ray analysis (Equation (5)). A plausible mechanism for the formation of (70) is shown in Scheme 4. The thermally extruded sulfur, which is in a highly reactive monomeric form, adds to a thiepene to produce intermediates **D**, **E**, **F**, or **G**. **D**, **E**, or **F** can be transformed into **G**. Subsequent [1,3] shift of **G** may afford the compound (70) (89PS(43)243).





Scheme 4

Benzothiepine derivatives (**61**) extrude sulfur or rearrange to a thionaphthol in toluene, depending on the 5-substituents (Scheme 5).

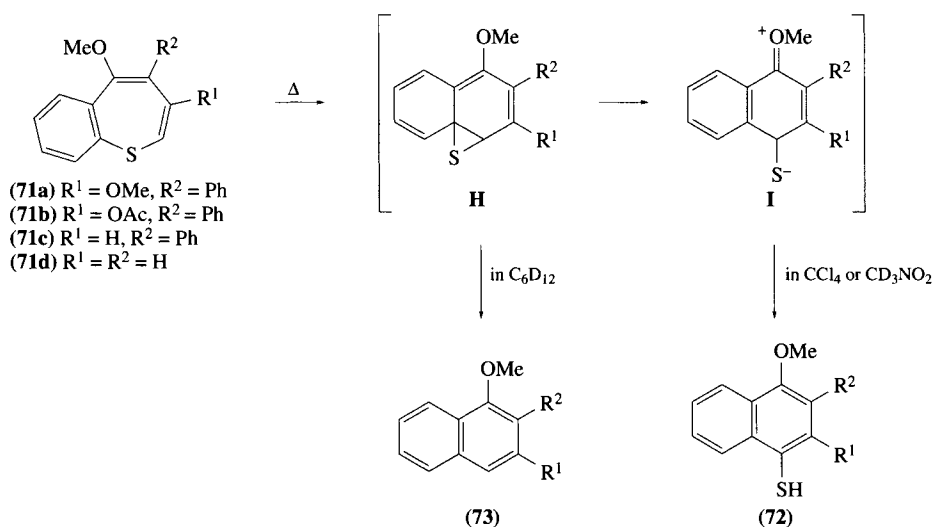


Scheme 5

On the other hand, benzothiepinines (**71**) extrude sulfur or rearrange to thionaphthols, depending on the solvent. Thus, on heating in carbon tetrachloride or nitromethane benzothiepinines (**71**) isomerize to the corresponding thionaphthols (**72**); whereas in cyclohexane from (**71**), the usual desulfuration products (**73**) arise <90ZN(B)1059>. Kinetic and thermodynamic data have been examined for the reactions (**71**) → (**72**). A reaction mechanism via thianorcaradiene intermediate **H** to intermediate **I** was assumed (Scheme 6).

Thiepine 1-oxides are less thermally stable than thiepinines. 1-Benzothiepine 1-oxide (**26**) is converted to naphthalene within 1 h at -15°C in CD_2Cl_2 <88AG(E)1717>. 2,7-Di-*t*-butylthiepine 1-oxide (**25**) generated *in situ* formed the corresponding benzene derivative at -15°C <94JCS(P1)2631>. The half-life at this temperature was found to be 5.5 h. Considering steric repulsion by two *t*-butyl groups, it was deduced that (**25**) has an *endo*(axial)-sulfoxide conformation, while the reported x-ray structure of stable benzothiepine 1-oxide (**11**) was an *exo*(equatorial)-sulfoxide <78CB309> (see Section 9.03.2.1).

Most 1-methyl-1-benzothiepinium salts (**42**) are thermally more stable than the corresponding benzothiepinines (Table 13). Thermolysis of the salts gave naphthyl thioethers (**79**) (Equation (6)) <77TL1985, 83LA425, 90ZN(B)1573>.



Scheme 6

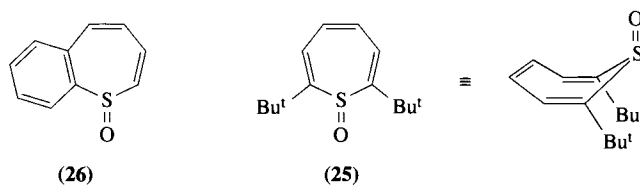
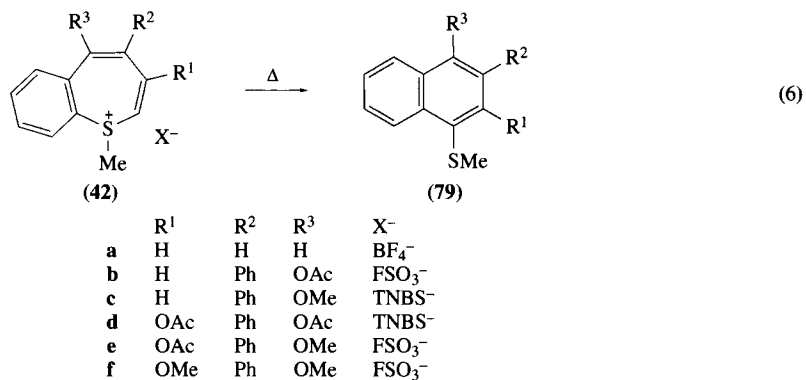
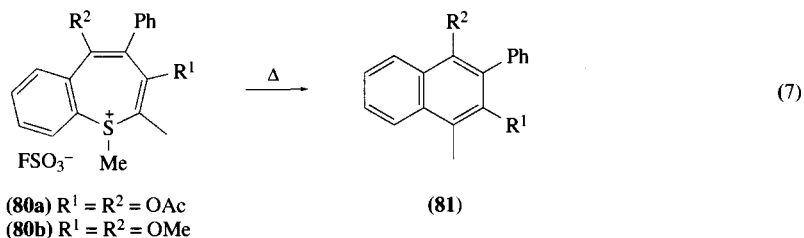


Table 13 Rate constants and half-lives of 1-methyl-1-benzothiepinium salts (**42**) $\rightarrow$ (**79**) and comparative data for thermolysis of the corresponding benzothiepinines.

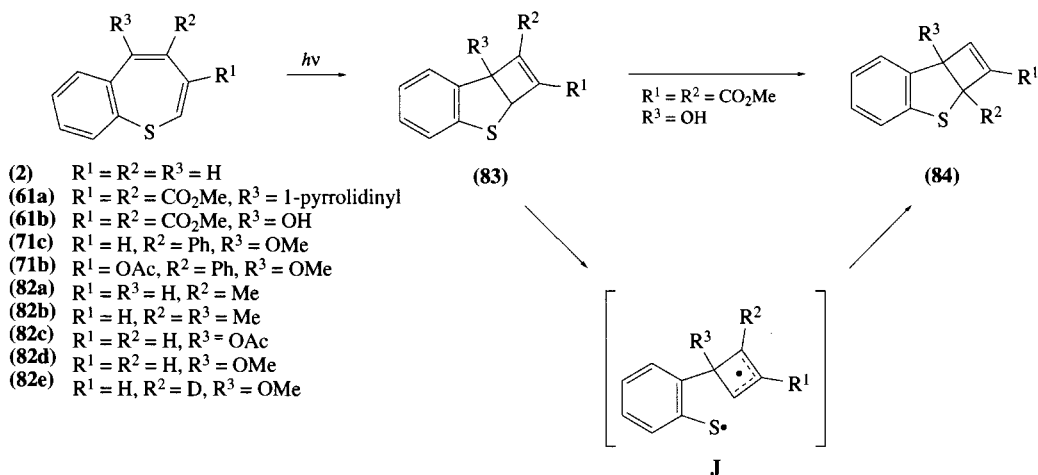
Compound	k for (42) $\rightarrow$ (79) [s^{-1}]	Compound	k for thermolysis of (2) and (74) [s^{-1}]
(42a)	$k_{75^\circ\text{C}} = 2.6 \times 10^{-4}$ (CD_3CN) $t_{1/2} = 44$ min	(2)	$k_{47^\circ\text{C}} = 1.99 \times 10^{-4}$ (CCl_4) $t_{1/2} = 58$ min
(42b)	$k_{50^\circ\text{C}} = 8.7 \times 10^{-5}$ (CD_3OD) $t_{1/2} = 133$ min	(74b)	$k_{48.5^\circ\text{C}} = 2.4 \times 10^{-5}$ (CCl_4) $t_{1/2} = 49$ min
(42c)	$k_{60^\circ\text{C}} = 5.5 \times 10^{-5}$ (CD_3NO_2) $t_{1/2} = 208$ min	(71c)	$k_{59^\circ\text{C}} = 2.7 \times 10^{-4}$ (CCl_4) $t_{1/2} = 43$ min
(42d)	$k_{80^\circ\text{C}} = 3.5 \times 10^{-4}$ (CD_3NO_2) $t_{1/2} = 33$ min	(74d)	$k_{75^\circ\text{C}} = 9.8 \times 10^{-4}$ (CD_3OD) $t_{1/2} = 12$ min
(42e)	$k_{70^\circ\text{C}} = 8.7 \times 10^{-5}$ (CD_3NO_2) $t_{1/2} = 133$ min	(71b)	$k_{59^\circ\text{C}} = 6.4 \times 10^{-5}$ (CDCl_3) $t_{1/2} = 180$ min
(42f)	$k_{80^\circ\text{C}} = 2.8 \times 10^{-6}$ (CD_3NO_2) $t_{1/2} = 68$ h	(71a)	$k_{82^\circ\text{C}} = 7.8 \times 10^{-5}$ (CD_3OD) $t_{1/2} = 148$ min



Thermolysis of the 1,2-dimethyl-4-phenyl-1-benzothiepinium salts (**80a,b**) gave sulfur-free reaction products (**81a,b**) (Equation (7)) <84ZN(B)985>.

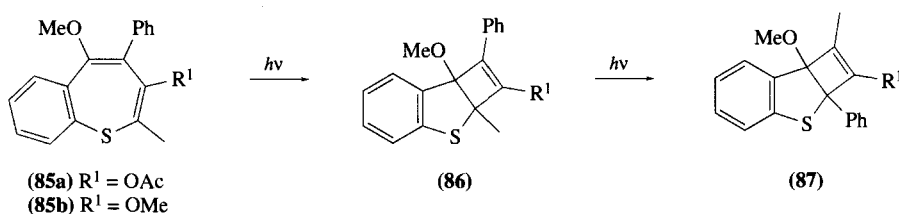


The photoreaction of 1-benzothiepine (**2**) and the substituted 1-benzothiepinines (**61**), (**71c**), (**71b**), and (**82**) yields the products (**83**) arising from the butadiene–cyclobutene cyclization <72TL4597, 74AG(E)142, 76BCJ825, 87LA505>. On prolonged irradiation of (**61b**), it was converted into another isomer (**84**). The conversion of (**61b**) into (**84**) was considered to proceed via a rupture of C—S bond to give a stabilized diradical *J* which reacts further to form a new C—S bond, yielding (**84**) (Scheme 7).



Scheme 7

The photoreaction of the 2-methyl-4-phenyl-1-benzothiepinines (**85**) leads to the primary photo-products (**86**), which were not isolated, but rather transformed to the secondary photoproducts (**87**) in the course of the irradiation (Scheme 8) <82ZN(B)1344>.

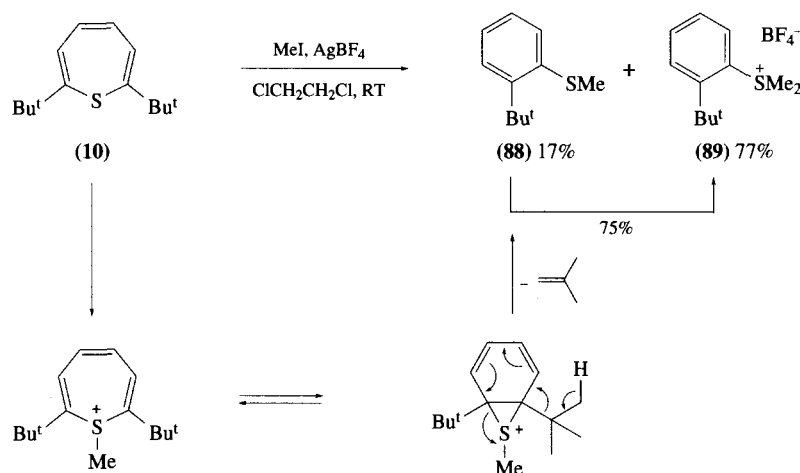


Scheme 8

9.03.4.3 Electrophilic Attack at Sulfur

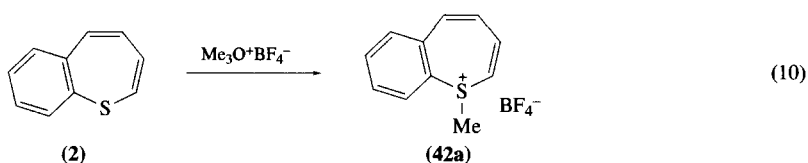
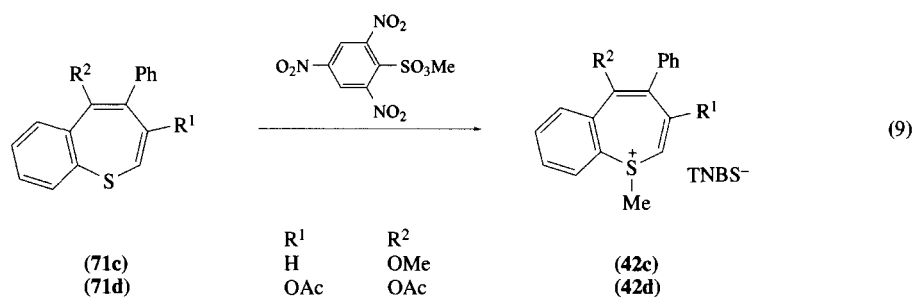
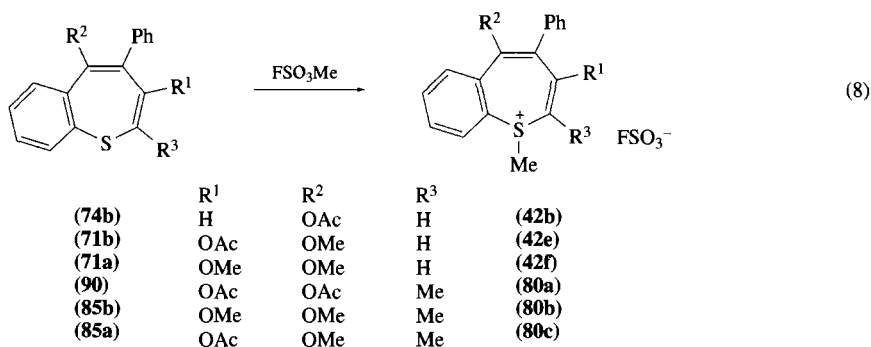
Reaction of 2,7-di-*t*-butylthiepine (**10**) with methyl iodide in the presence of AgBF_4 at room temperature gave (**88**) and (**89**). Under the same conditions (**88**) was converted to (**89**). The plausible

reaction mechanism for the formation of (88) and (89) involves generation of 1-methyl thiepinium ion and its valence isomer as shown <94JCS(P1)2631> in Scheme 9.



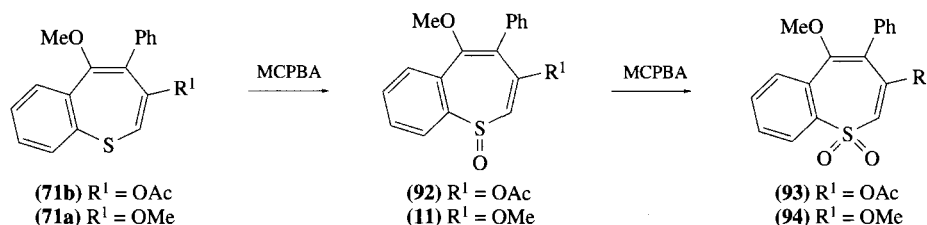
Scheme 9

Methyl fluorosulfate, methyl 2,4,6-trinitrobenzosulfonate, and trimethyloxonium tetrafluoroborate have been shown to serve as methylating reagents for the formation of S-methyl benzo-thiepinium salts (Equations (8)–(10)) <77TL1985, 83LA425, 84ZN(B)985, 90ZN(B)1573>.



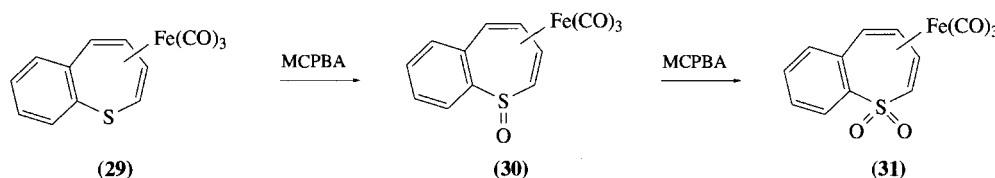
Oxidation of thiepine (19) with MCPBA at -78°C gave only the benzene derivative by loss of SO. Oxidation of thiepine (10) with *O*-benzyl *OO*-hydrogen monoperoxycarbonate ($\text{PhCH}_2\text{OCO}_3\text{H}$) gave unstable thiepine 1-oxide (25) <94JCS(P1)2631>. Further oxidation of (25) to the thiepine 1,1-dioxide was unsuccessful presumably because of the steric hindrance of the two *t*-butyl groups.

While oxidation of benzothiepine (**2**) to labile benzothiepine 1-oxide failed, (**2**) was directly oxidized with two equivalents of MCPBA to the stable benzothiepine 1,1-dioxide (**14**) <74AG(E)142, 88AG(E)1717, 89ZN(B)220>. Oxidation of the substituted benzothiepinines (**77**), (**78**), and thieno[3,4-*d*]thiepine (**8**) by MCPBA gave the corresponding 1-oxides and 1,1-dioxides, respectively (Scheme 10) <68TL3017, 75AG(E)812>.



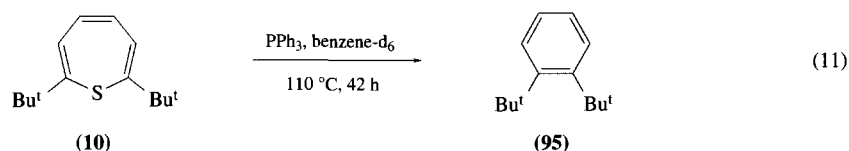
Scheme 10

On oxidation with MCPBA, 1-benzothiepine(tricarbonyl)iron (**29**) was converted into sulfoxide (**30**). Further oxidation of (**30**) with MCPBA provided dioxide complex (**31**) (Scheme 11) <88AG(E)1717>.

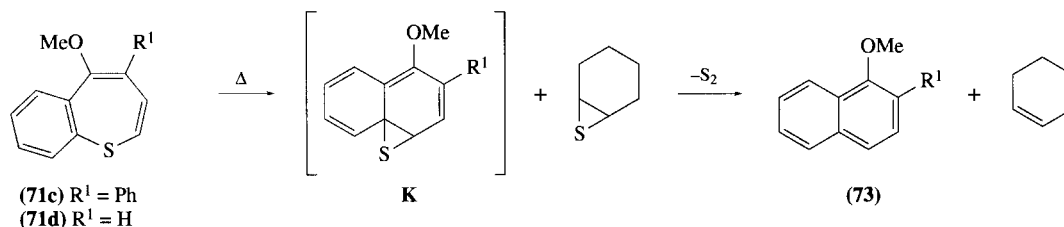


Scheme 11

Although thiepine (**10**) is quite stable in toluene- d_8 or decalin- d_{18} at 130°C , thermolysis of (**10**) in benzene- d_6 in the presence of an equimolar amount of triphenylphosphine at 110°C for 42 h gave *o*-di-*t*-butylbenzene (**95**) quantitatively (Equation (11)) <82TL3195>.



When thermolysis of benzothiepinines (**71c,d**) is carried out in the presence of cyclohexene sulfide in carbon tetrachloride or nitromethane as solvent, the desulfuration products (**73c,d**) together with an equimolar amount of cyclohexene are produced. This behavior leads to the assumption of S_2 -species as the primary elimination product of sulfur from the thianorcaradiene intermediate **K** (see Section 9.03.4.2) (Scheme 12) <90ZN(B)1059>.

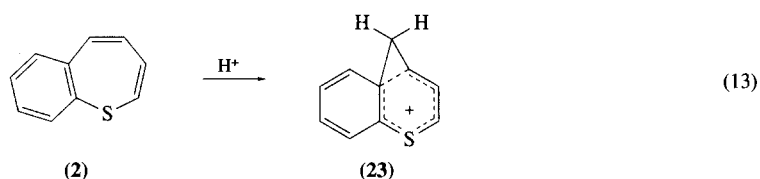
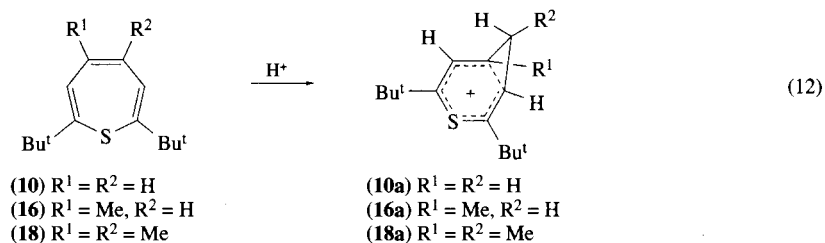


Scheme 12

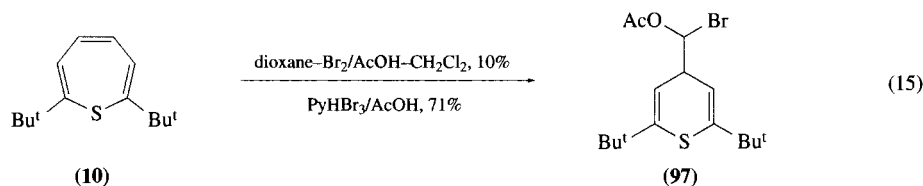
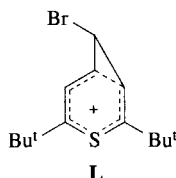
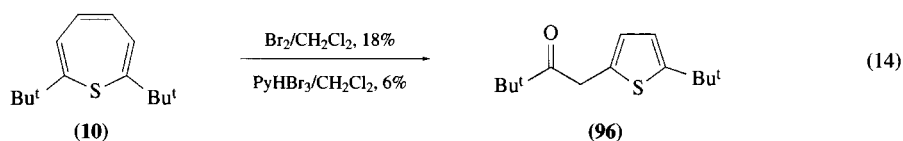
9.03.4.4 Electrophilic Attack at Carbon

Treatment of thiepinines (**10**), (**16**), and (**18**) with $\text{FSO}_3\text{H}-\text{SO}_2$ or H_2SO_4 gave 4H-thiepinium ion (**10a**), (**16a**), and (**18a**), respectively (Equation (12)). Treatment of 1-benzothiepine (**2**) with

$\text{FSO}_3\text{H}-\text{SO}_2$ or H_2SO_4 gave 5H-1-benzothiepinium ion (**23**) (Equation (13)). The generated ions (**10a**), (**16a**), (**18a**), and (**23**) are considered as homothiopyrylium ions by ^1H NMR examination (Section 9.03.2.2) <84CC604, 84CL919>.

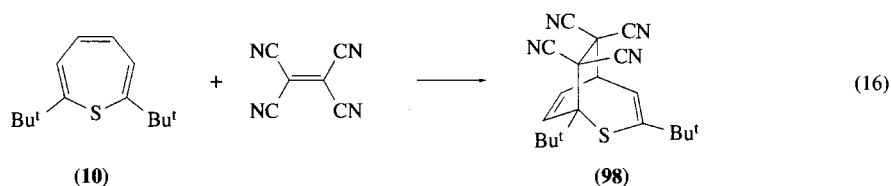


Bromination of the thiepine (**10**) with bromine in CH_2Cl_2 or pyridinium hydrotribromide in CH_2Cl_2 gave the thiophene derivative (**96**) in low yield (Equation (14)). On the other hand, reaction of (**10**) with a dioxane-bromine complex in $\text{AcOH}-\text{CH}_2\text{Cl}_2$ or pyridinium hydrotribromide in AcOH gave the thiopyran (**97**) in 10% and 71% yields, respectively <94JCS(P1)2631> (Equation (15)). In both reactions, the same homothiopyrylium ion intermediate **L**, which is analogous to a protonated species of thiepine (**10**), was postulated.

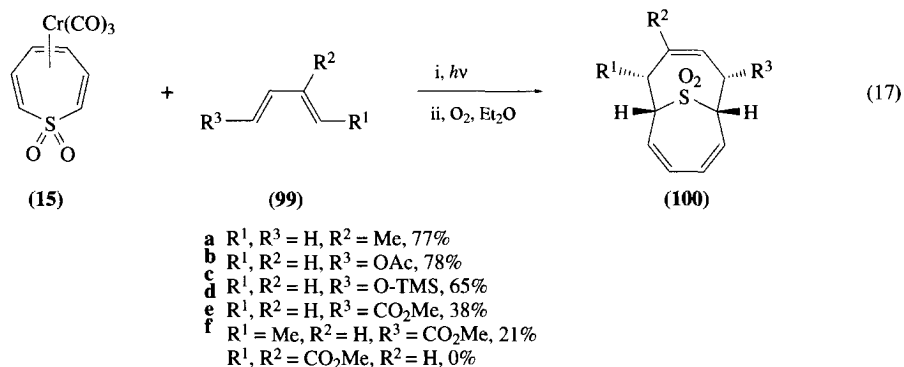


9.03.4.5 Cyclic Transition State Reaction with a Second Molecule

Reaction of (**10**) with TCNE in toluene at 60°C under high pressure (8500 atm) gave [4 + 2] cycloadduct (**98**). The same reaction occurred in acetonitrile at room temperature under atmospheric pressure to give (**98**) <94JCS(P1)2631> (Equation (16)). Since the rate of the cycloaddition is dependent upon solvent polarity, the reaction intermediate may be a charge transfer complex or a zwitterion.

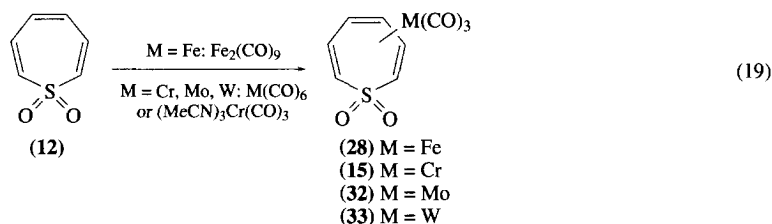
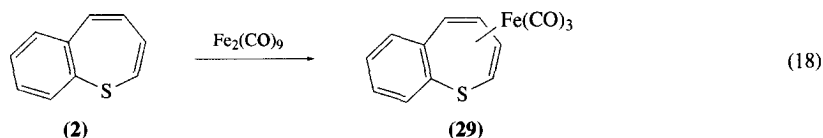


Irradiation of a solution of thiepine 1,1-dioxide chromium complex (**15**) in the presence of diene (**99**), followed by metal decomplexation with oxygen provided [6 + 4] cycloadducts (**100**) <92TL5873, 93JA1382>. The relative stereochemistry of the products (**100**) was shown to be derived from an *endo* transition state. The electronic character of the diene (**99**) appears to offer a moderate influence on reaction efficiency. For example, yields were uniformly lower for reactions involving electron-deficient diene partners relative to those employing electron-rich dienes (Equation (17)).



9.03.4.6 Other Reactions

Reaction of 1-benzothiepine (**2**) with Fe₂(CO)₉ (large excess) in hexane gave iron tricarbonyl complex (**29**) (Equation (18)) <88AG(E)1717>. The reaction of thiepine 1,1-dioxide (**12**) with Fe₂(CO)₉ (1.5 equiv.) in THF at 50 °C gave (η⁴-thiepine 1,1-dioxide)iron tricarbonyl complex (**28**) in high yield (Equation (19)) <91JA5059>. On treatment of (**12**) with (MeCN)₃Cr(CO)₃ at room temperature (η⁶-thiepine 1,1-dioxide)chromium tricarbonyl complex (**15**) was obtained. The corresponding thiepine 1,1-dioxide molybdenum and tungsten complexes (**32**) and (**33**) were also prepared <93JA1382>.

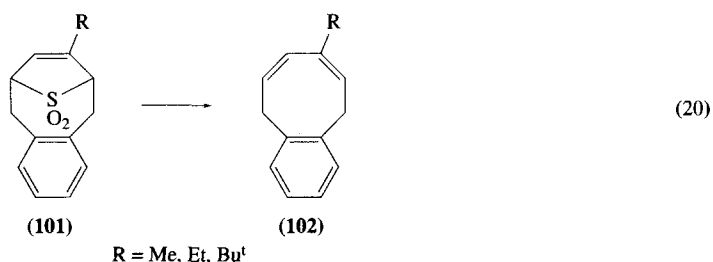


9.03.5 REACTIVITY OF NONCONJUGATED RINGS (DIHYDRO- AND TETRAHYDROTHIEPINES AND THIEPANES)

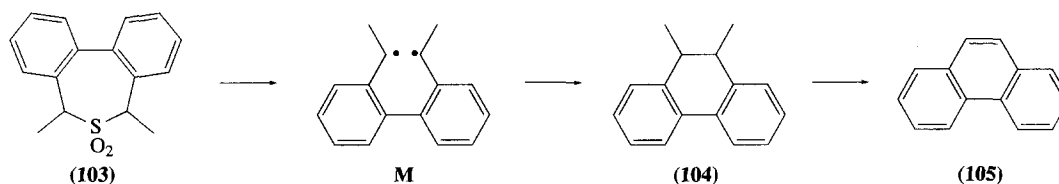
The reactions of thiepanes and related compounds fall into two categories: (1) reactions on the sulfur atom; and (2) those occurring at another part of the molecule. The first category includes transannular reactions in which the sulfur atom participates, and the second category includes reactions of thiacycloheptyne with the alkyne part being able to form adducts and reactions of the substituents on the sulfur atom (see Section 9.03.7). These reactions are of synthetic and mechanistic interest.

9.03.5.1 Thermal and Photochemical Reactions

Lithium aluminum hydride was found to promote thermal extrusion of SO₂ from sulfolenes <77TL947>. This reaction was extended to thermal extrusion of SO₂ from bridged sulfolenes (**101**). The reactions proceeded smoothly at room temperature in high yields to give (**102**) <91JOC4560>. Although the mechanism for this reaction is not clear, it is postulated that the reaction proceeds by thermal cleavage through considerable lowering of the transition state for a cheletropic elimination of SO₂ (Equation (20)).



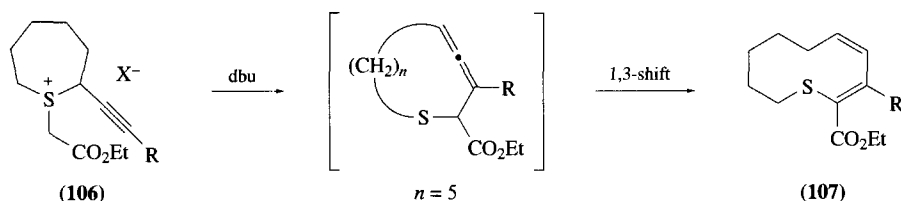
The thermal reaction of 5,7-dimethyl-5,7-dihydrodibenzo[*c,e*]thiepine 6,6-dioxide (**103**) was conducted <88JOC4333>. Thermolysis of (**103**) at 550°C (0.2 mmHg) gave 9,10-dimethyl-9,10-dihydrophenanthrene (**104**) (86%) with loss of SO₂; however under more extreme conditions (735°C, 1 mmHg), phenanthrene (**105**) was a major product. The thermolysis of (**103**) together with labelling studies provided the mechanism of phenanthrene formation involving the biradical **M** as shown in Scheme 13. The generated biradical **M** underwent ring closure to (**104**), followed by loss of two methyl radicals, to give (**105**).



Scheme 13

[2,3]-Sigmatropic rearrangement has received much attention due to its theoretical interest and its potential synthetic usefulness. [2,3]-Sigmatropic rearrangements of sulfonium ylides have formed a ring-growing sequence. The reactions of cyclic α -ethynyl sulfonium ylides prepared from thiepane derivatives were investigated. Thus, the sulfonium salts (**106**) were treated with dbu to result in ring expansion, and gave thionines (**107**) (Scheme 14). The formation of (**107**) was suggested to involve an initial sigmatropic rearrangement to the allenic intermediate, followed by a 1,3 hydrogen shift <82H(19)2147, 86CPB3644>.

The flash photolysis of 2,7-diphenylthiepane sulfur dioxide was found to generate the corresponding biradical <85JA6724>.

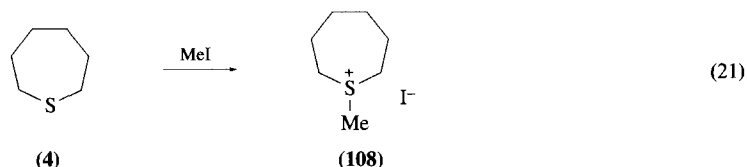


Scheme 14

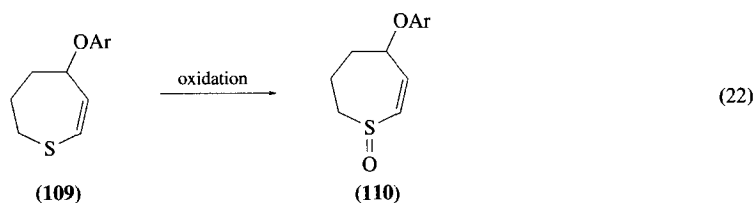
9.03.5.2 Electrophilic Attack at Sulfur

Dialkyl sulfides including cyclic sulfides react with electrophiles such as alkyl halides or tosylates to give the corresponding sulfonium ions which have been extensively investigated <B-76MI 903-01>.

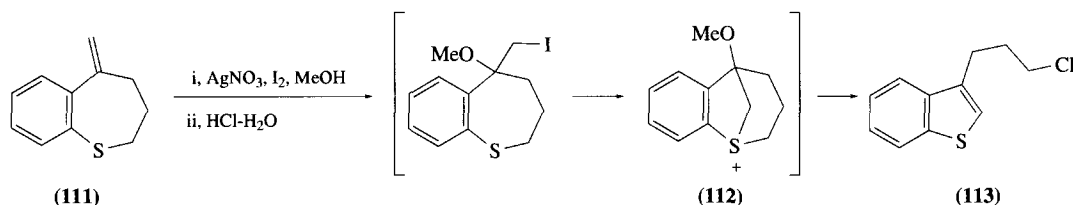
Sulfonium salts can be converted to the corresponding sulfonium ylides promising useful reactions. Thiepane (4) reacted with methyl iodide to yield the sulfonium iodide (108) (Equation (21)) <53M1206>. Thiepanes reacted with sulfonates to give the corresponding sulfonium salts in high yields <82H(19)2147, 86CPB3644>.



Thiepanes and partially hydrogenated thiepinines are easily oxidized with oxidants such as MCPBA to give the corresponding sulfoxides or sulfones. For example, on treatment of (109) with MCPBA or sodium periodate, (110) was obtained (Equation (22)) <85AG(E)214>; oxidation of thiepinines with two equivalents of MCPBA yielded the corresponding sulfones <84JCS(P1)515>.



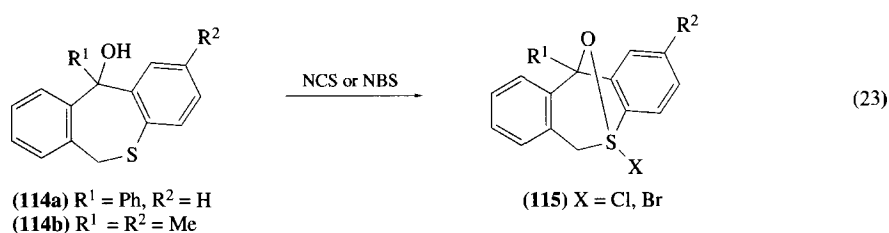
When 5-methylene-2,3,4,5-tetrahydro-1-benzothiepine (111) was subjected to ring expansion reaction conditions (treatment with silver nitrate in the presence of iodine in methanol), intramolecular attack by sulfur at the initially formed halomethyl group led to the bicyclo[3.2.1]octane intermediate (112), which yielded the benzothiophene derivative (113) without formation of any ring expansion products (Scheme 15) <89TL4279>.



Scheme 15

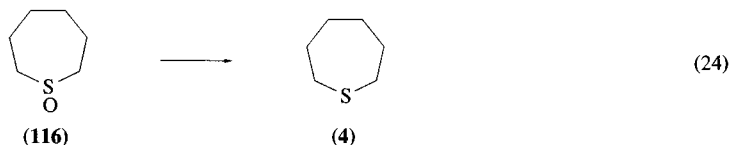
9.03.5.3 Nucleophilic Attack at Sulfur

On treatment of 6,11-dihydrodibenzo[*b,e*]thiepin-11-ols (114) with one equivalent of NCS or NBS at room temperature in CH_2Cl_2 , the halosulfonium ions initially formed were attacked by the hydroxy group to give the corresponding halosulfuranes (115), as stable crystals (Equation (23)). The covalency of the sulfur-halogen bond was established by $^1\text{H-NMR}$, mass spectral, and x-ray crystal structure analysis <83TL4337>.



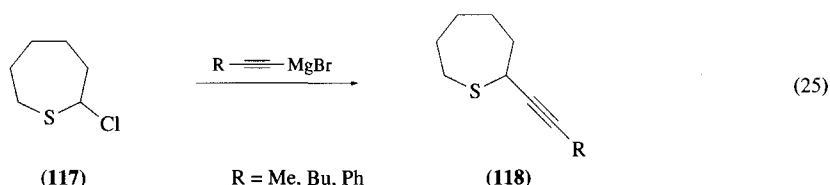
Reduction of sulfoxides to sulfides has been extensively studied <77OPP63, 88T6537>. Thiepane 1-oxide (116) can be reduced to thiepane (4) (Equation (24)). Reactions with hydrogen halides have

been suggested to proceed by a S_N2 type attack at the sulfur atom. The reactivity of sulfoxides towards acid-catalyzed reduction has been studied and found to be in the order of five- > four- > open > seven- > six-membered cyclic sulfoxides <71BCJ2456>.

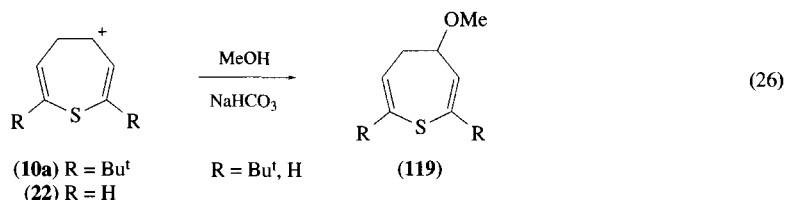


9.03.5.4 Nucleophilic Attack at Carbon

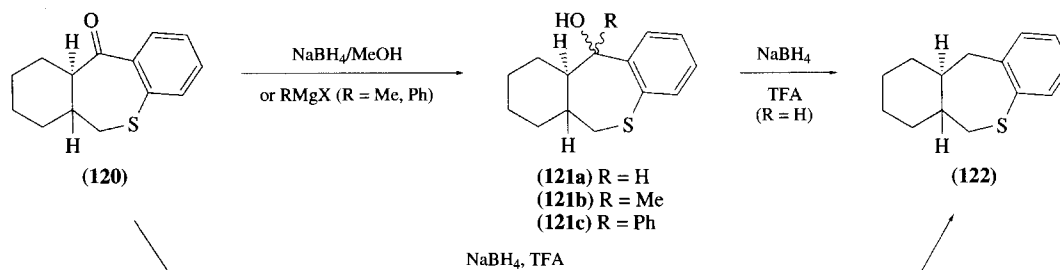
Nucleophilic substitution of the chlorine atom present in 2-chlorothiepane using Grignard reagents has provided a standard synthetic route to 2-alkylthiepanes. 2-Chlorothiepane (117) reacted with alkynylmagnesium bromides in ether affording the 2-alkynyl thiepanes (118) in good yields (Equation (25)) <86CPB3644>.



Thiepinium ions (10a), (22) were allowed to react with methyl alcohol in the presence of sodium hydrogen carbonate yielding the 4,5-dihydro thiepines (119) in moderate yield (Equation (26)). It is interesting that 2,5-dihydro derivatives were not obtained <84CC604, 85AG(E)214>. 3*H*-1-Benzothiepinium ion gave also 2-methoxy-2,3-dihydro-1-benzothiepine upon treatment with methanol in the presence of sodium hydrogen carbonate; however, 5*H*-1-benzothiepinium ion (23) was found to give no products under the same conditions, probably due to instability of the corresponding product <84CL919>.

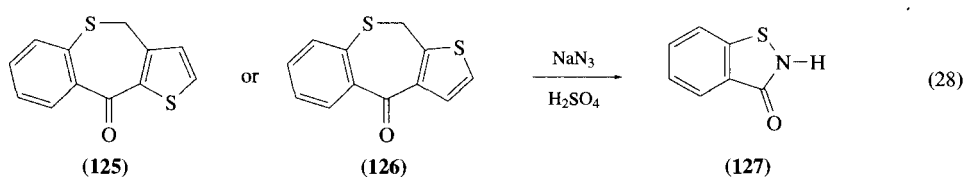
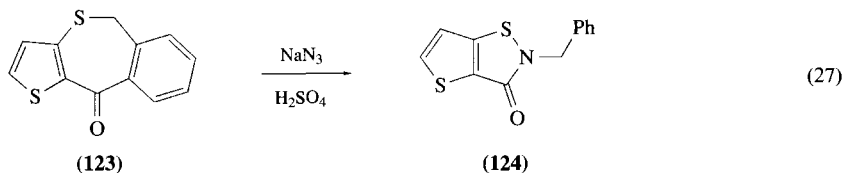


Thiepanones may react with nucleophiles to provide the corresponding products. Reactions of 6,6a,7,8,9,10,10a,11-octahydro-11-oxo-dibenzo[*b,e*]thiepine (120) with certain nucleophiles was reported. The ketone (120) reacted with $NaBH_4$ to give the alcohol (121a), which was reduced with $NaBH_4$ in TFA at $-10^\circ C$ to give the 6a-H, 10a-H-deoxo derivative (122). Compound (122) was also obtained directly from (120) under the same conditions <91JHC1891>. Reactions of the ketone (120) with Grignard reagents gave the corresponding alcohols (121b, c). The Leuckart reaction of the ketone (120) yielded the corresponding amino derivative (Scheme 16) <91JMC593>.



Scheme 16

Thienobenzothiepine derivatives were found to give rearranged products under the Schmidt reaction conditions. Thus, the ketone (**123**) gave the isothiazoline (**124**) (Equation (27)), in contrast ketones (**125**) and (**126**) yielded only isothiazoline (**127**) (Equation (28)). The most plausible mechanism for these ring contractions is shown (Scheme 17). It involves the cleavage of the thiepanone with migration of a hydrogen, and the subsequent formation of a five-membered ring. The lower stability of the ion $[^+ - \text{CH}_2 - (3\text{- or } 2\text{-thienyl})]$ (corresponding to intermediate **N**) is responsible for the formation of the dealkylated product (**127**) with preferential migration of a proton <91JHC1881>.



When the thioacetal (**128**) was treated with allylmagnesium bromide and subsequently with $\text{BF}_3 \cdot \text{etherate}$, nucleophilic addition on the carbonyl carbon and a subsequent cationic cyclization took place; the product (**129**) was obtained by aromatization with loss of methanethiol (Scheme 18) <84TL5095>. The reaction of (**128**) under the Simmons–Smith reaction conditions gave the thienothiepine derivative (**130**). The proposed mechanism for the formation of (**130**) involves a nucleophilic attack of the initially formed sulfonium ylide intermediate, intramolecular aldol type condensation, aromatization and demethylation (Scheme 19) <89TL3093>.

The reactive alkyne (**131**) was allowed to react with *t*-butyllithium in THF at -78°C affording the addition product (**132**) in good yield (Scheme 20). No addition of *t*-butyllithium was observed in less polar solvents. The reaction of the lithio derivative (**132**) or the corresponding cuprate with electrophiles gave poor results except for the case involving methyl iodide <86T1693>.

4,5-Dihydro-4-alkyl-3H-dinaphtho[2,1-*c*:1',2'-*e*]thiepinium salts react with nucleophiles to afford dihydrothiepine and/or 1,1'-binaphthalene ligands <94JOC1326>.

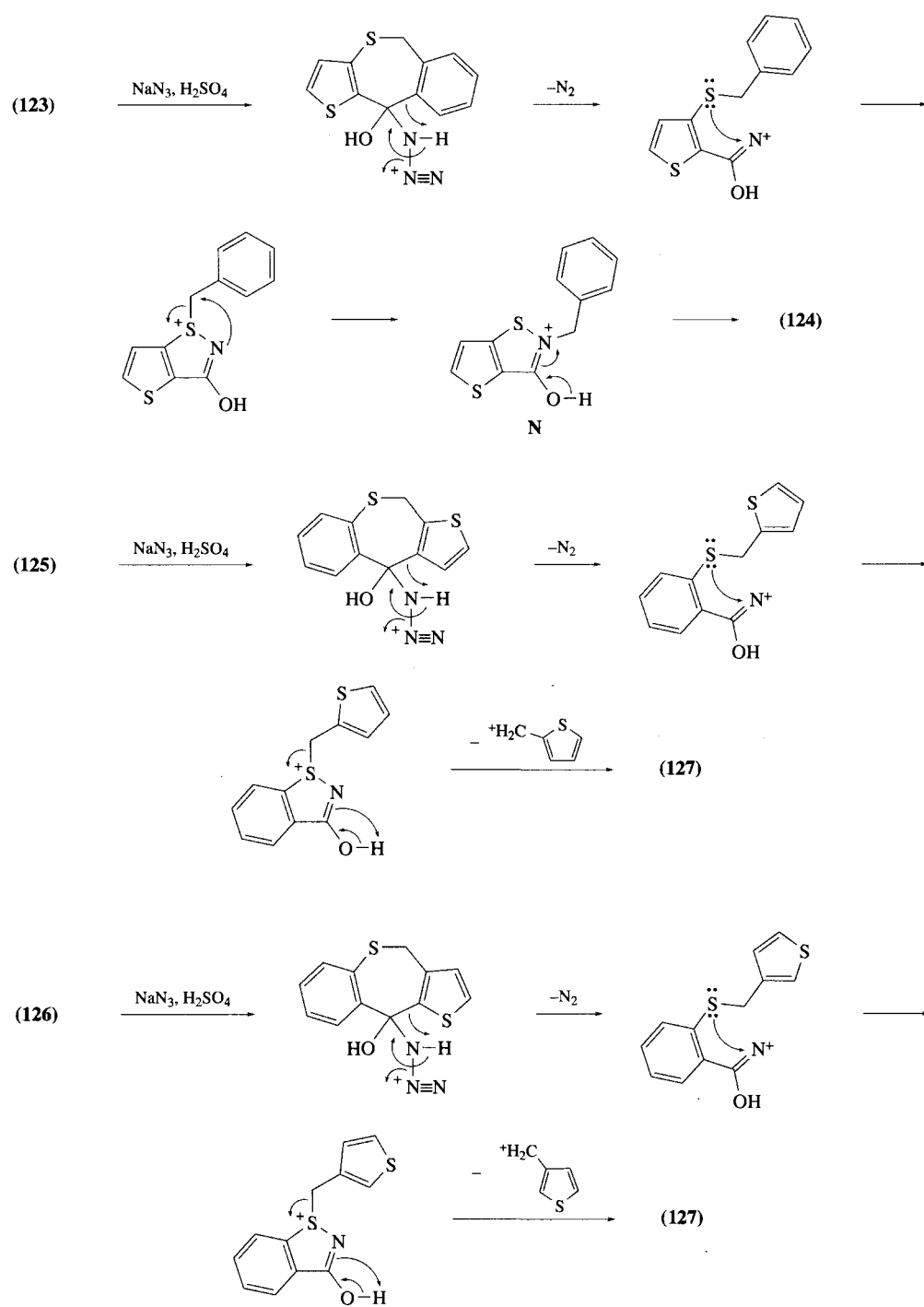
9.03.5.5 Reactions with Radicals or Electron Deficient Species

α -Chlorination of thiepanes by using NCS has been explored as a route to α -chlorothiepanes which hold promise for further transformations <69JHC115, 86CPB3644, 89JA2652>. The relative rates of hydrogen atom abstraction from cyclic sulfides were investigated. The results show that reaction occurs only at the position adjacent to the sulfur atom, and the reactivity was in the order $\text{C}_4\text{H}_8\text{S}$ (tetrahydrothiophene) $>$ $\text{C}_5\text{H}_{10}\text{S}$ (tetrahydrothiopyran) $>$ $\text{C}_6\text{H}_{12}\text{S}$ (thiepane). In contrast, for cyclic ethers the order was $\text{C}_4\text{H}_8\text{O} > \text{C}_6\text{H}_{12}\text{O} > \text{C}_3\text{H}_6\text{O} > \text{C}_5\text{H}_{10}\text{O}$. These results imply little influence of ring strain. The major structural effect could be that of variable electron donating ability of the sulfur atom <89JPO367>.

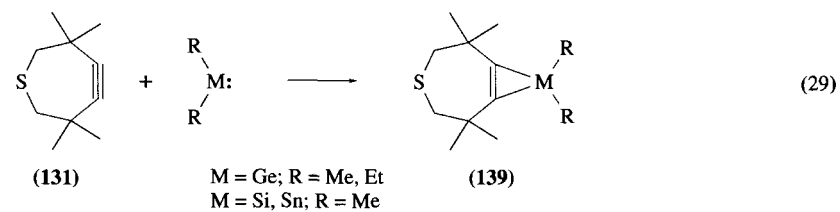
Alkynes are usually reluctant to undergo addition by alkyl radicals; however, the strained alkyne (**131**) was expected to be a good substrate for radical addition reactions. Thus, when a mixture of (**131**) and AIBN in benzene was heated, the adducts (**134**) (39%) and (**135**) (51%) were obtained. Compound (**134**) can be converted to (**135**) on heating (Scheme 21) <86T1693>.

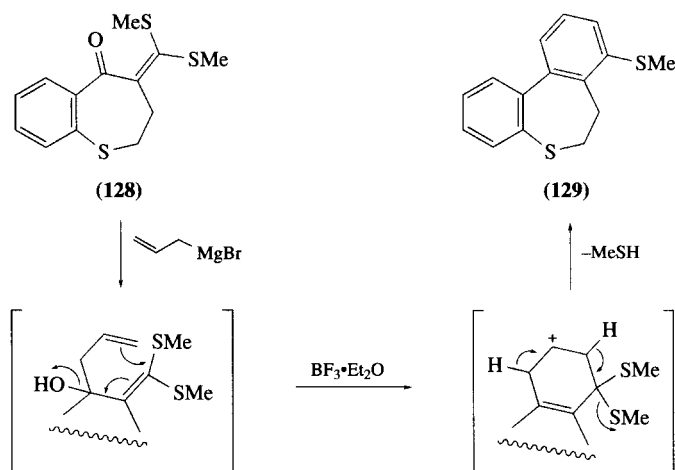
On irradiation of a suspension of the thiadiazole (**136**) in excess 1-thiacycloheptyne (**131**), the thiophene (**138**) was obtained in 94% yield. The formation of (**138**) was suggested to involve the generation of the diradical (**137**) (Scheme 22) <92TL5947>.

Reactions of the alkyne (**131**) with the main group carbene analogues, R_2M : ($\text{M} = \text{Si}, \text{Ge}, \text{Sn}$) were found to give the corresponding silacyclopropenes <83TL4083>, germacyclopropenes <83TL4083, 85JOM(290)C27>, and stannacyclopene <88JA5208>, respectively (Equation (29)).

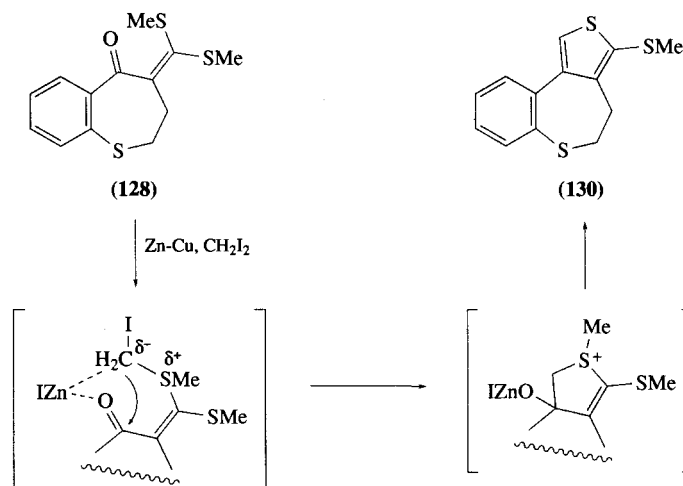


Scheme 17

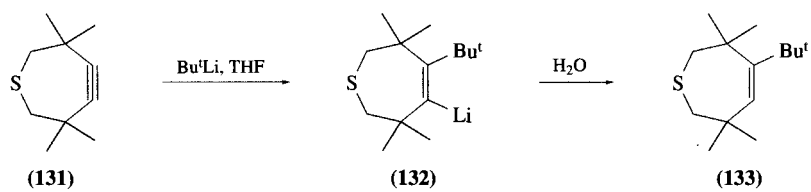




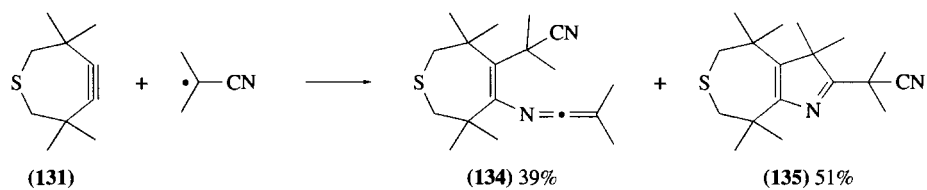
Scheme 18



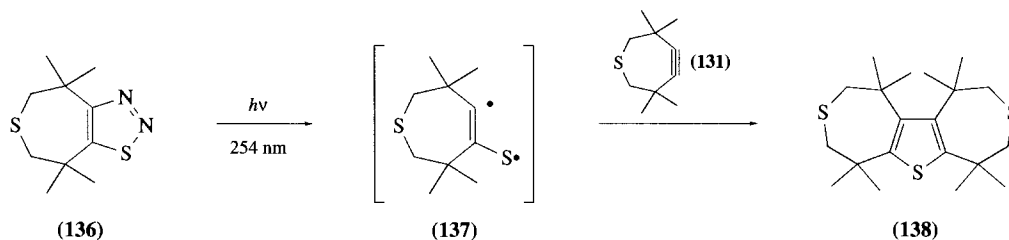
Scheme 19



Scheme 20



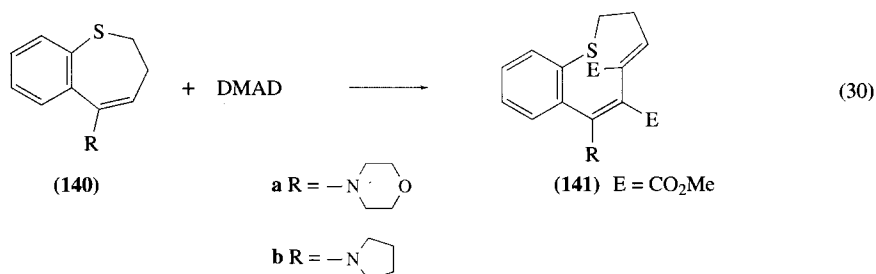
Scheme 21



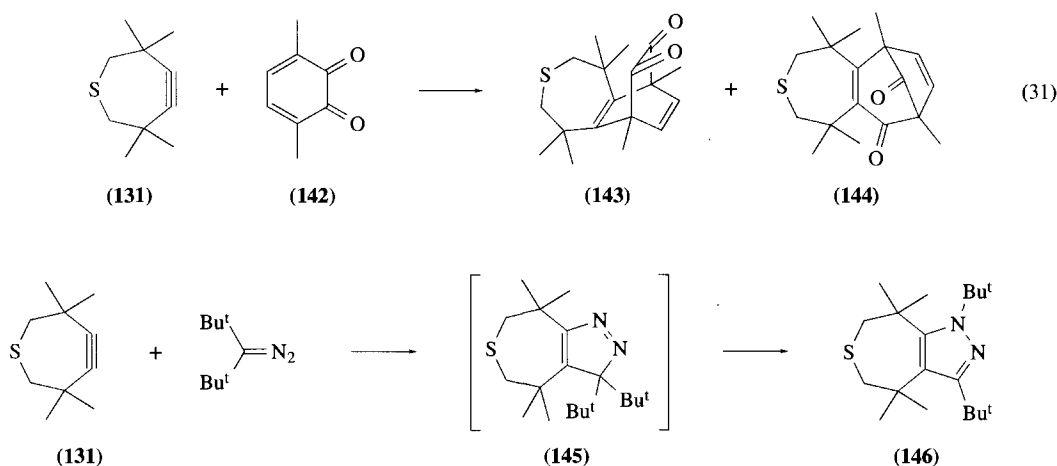
Scheme 22

9.03.5.6 Reactions Involving Cyclic Transition States

The dihydro-1-benzothiepine (140a) reacted with DMAD at room temperature to give an adduct, *cis*, *trans*-benzo[*b*]thionine in good yield, which isomerized to a *cis,cis*-isomer in refluxing toluene over 4 h. No initial cyclobutene adducts were obtained (<84CC411>). With (140b), the corresponding cyclobutene derivative was, however, obtained (Equation (30)) (<82ACS(B)435>).



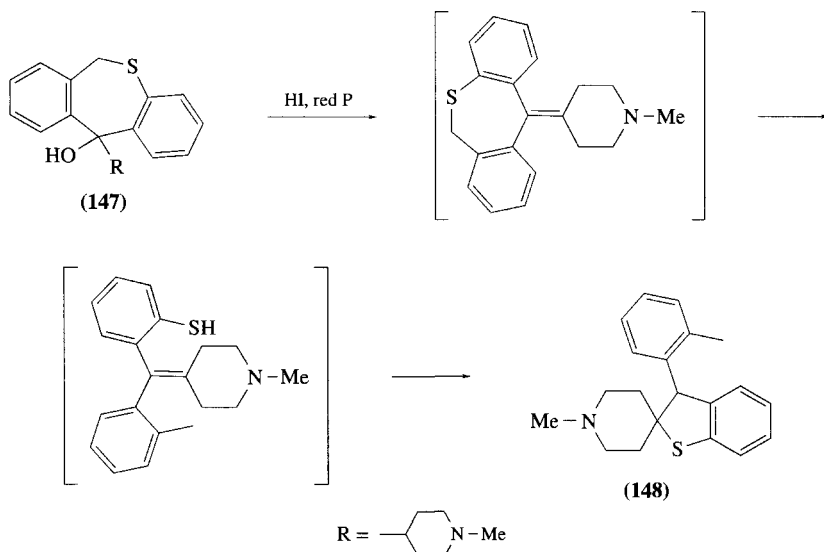
The cycloaddition reactions of the thiacycloheptyne (131) were further studied. When (131) was allowed to react with the quinone (142) at 40°C for 7 days, the normal adduct (143) (25%) and the rearranged product (144) (25%) were obtained (Equation (31)) (<83TL4821>). Reaction of (131) with di-*t*-butyldiazomethane in refluxing heptane for 4.5 h gave the pyrazole (146). The formation of (146) is explained by a migration of a *t*-butyl group in (145), which is the likely intermediate (Scheme 23) (<92TL5947>).



Scheme 23

9.03.5.7 Other Reactions

Attempted reduction of (147) with HI in the presence of red phosphorus in boiling acetic acid for five hours gave almost quantitatively the rearranged spirocyclic aminosulfide (148). The most likely mechanism for this reaction involves the dehydration of (147), the reductive cleavage of the ArCH₂ SAr bridge, and a subsequent intramolecular cyclization (Scheme 24) (<89CCC235>).

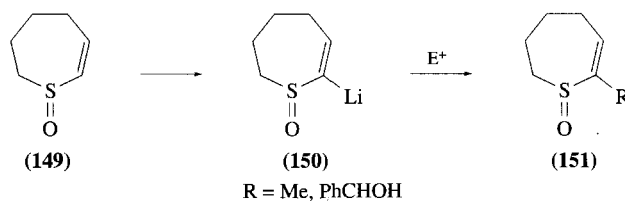


Scheme 24

9.03.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

9.03.6.1 Attack at Hydrogen

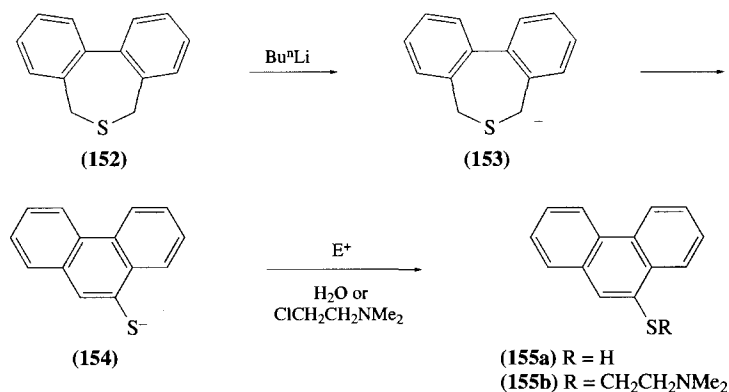
It is of interest to determine which proton of 1-thiacyclohept-2-ene-1-oxide (149) is removed by bases. (149) was found to generate 2-metalated derivative (150) with bases in THF in the presence of TMEDA. The anion (150) reacted rapidly with CH_3I and benzaldehyde as well as substituted benzaldehydes to give the alkylated compound and the corresponding alcohols in high yields. In the absence of TMEDA, the anion rapidly polymerizes even at -78°C (Scheme 25) <81AJC1027>.



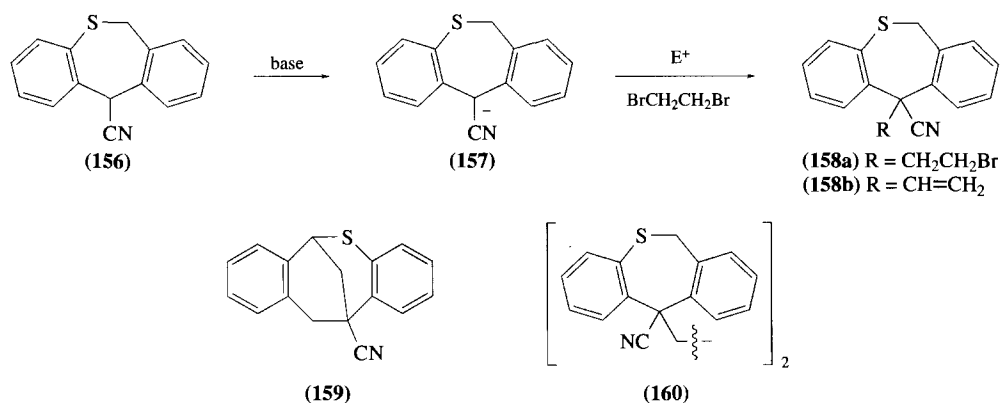
Scheme 25

The carbanion (153) was found to undergo immediate rearrangement to the stable thiolate anion (154) <86CCC2848>. The reaction of (152) with *n*-butyllithium in ether-hexane resulted in formation of red solution. When the solution was allowed to stand at room temperature for 48 h and hydrolyzed with water, phenanthrene-9-thiol (155a) and the disulfide derived from (155a) were obtained. Treatment of the solution with 2-dimethylaminoethyl chloride gave the 9-phenanthrylthioether (155b). The mechanism for the rearrangement (153) $\rightarrow$ (154) is not known with certainty; however, it may well be similar to the Wittig rearrangement as postulated by the authors <54AG10, 70AG(E)763>. The corresponding sulfone generated the expected carbanion with *n*-butyllithium (Scheme 26).

Generation of the carbanion (157) from the thiepine (156) and its reaction with electrophiles were studied. Reaction of (156) with sodium hydride in DMF, followed by treatment with 1,2-dibromoethane yielded the normal product (158a) in 21% yield. However, the reaction of (156) with 1,2-dibromoethane and 50% sodium hydroxide solution in the presence of tetrabutylammonium bromide gave three products, (158b) (31%), (159) (8%), and (160). A plausible mechanism for the formation of (159) is proposed (Scheme 27) <87CCC2281>.



Scheme 26

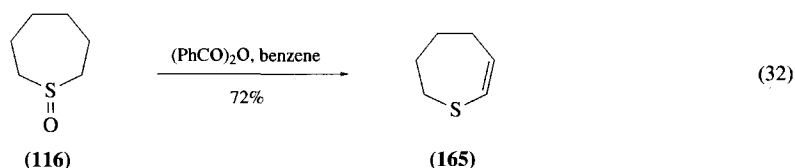


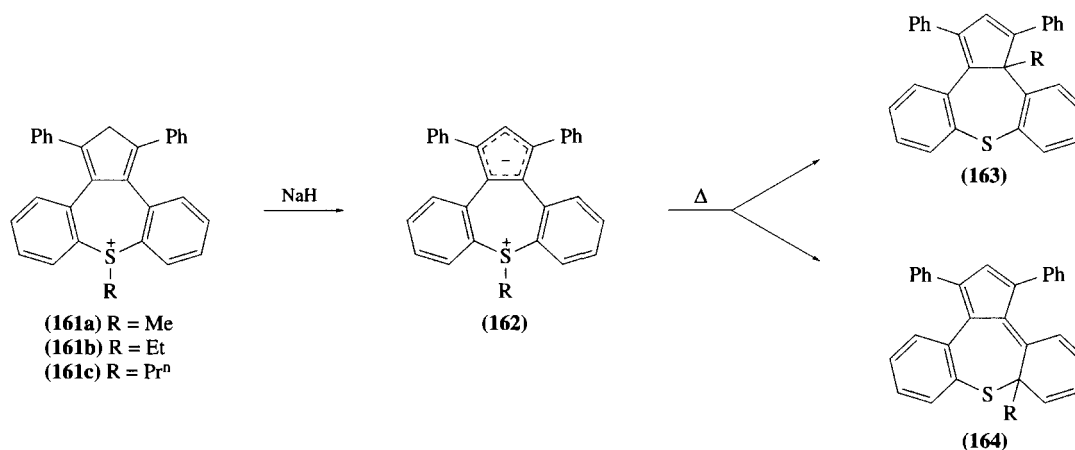
Scheme 27

9.03.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO THE RING SULFUR ATOM

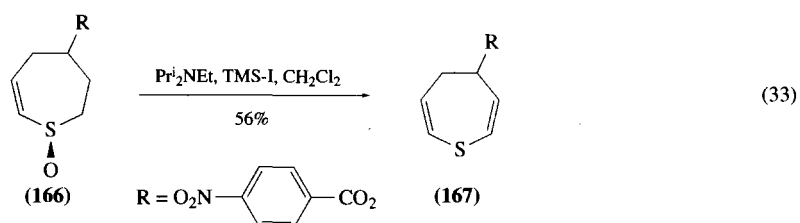
Thermal reactions of cyclic sulfur ylides were studied. A thiaazulenecyclone was reduced with LAH–AlCl₃ to give 1,3-diphenyl-2,8-dihydrodibenzo[*e,h*]-8-thiaazulene, which was treated with alkyl iodides and AgClO₄ in dichloromethane yielding thiaazulenium salts (161). Deprotonation of the thiaazulenium salt (161a) with NaH in THF gave 1,3-diphenyl-8-methyldibenzo[*e,h*]-8-thiaazulene (162a) as orange plates. Thermal reaction of (162a) in refluxing THF gave the 1,4-migrated product (163a) in 64% yield together with formation of a dealkylated compound (12%). The ylides (162b) and (162c), prepared following similar reactions gave (163b) (34%), (164b) (14%), (163c) (29%) and (164c) (47%), respectively (Scheme 28). These results show that bulkier groups favor a 1,2-migration <80TL4287>. The reactions of more stable ylides which were derived from the ylides (162b) and (162c) with DMAD, are reported to need higher temperatures for rearrangement. These ylides did not rearrange on refluxing in THF for 1 h, but when heated at 170–200 °C for 3–5 min without solvent did give the 1,4-rearranged products <81H(16)721>.

Sulfoxides bearing an α -hydrogen react with electrophiles such as carboxylic acid anhydrides, yielding products in which sulfur is reduced while an adjacent carbon is oxidized (Pummerer reaction). This reaction is applied to the preparation of partially hydrogenated thiepines as shown (Equation (32)) <81AJC1027>. Although the conversion of (166) to (167) was not achieved under the usual conditions, a modified Pummerer reaction was found to be effective <83TL2619, 85AG(E)214>. When (166) was treated with diisopropylethylamine in dichloromethane and then upon addition of freshly distilled TMSI under nitrogen, (167) was obtained (Equation (33)).

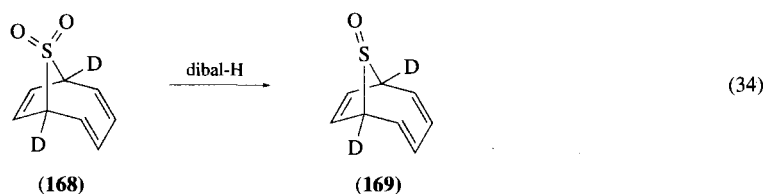




Scheme 28



Chemical reduction of a sulfonyl group is not easy, in part because most reducing agents are soft. Dibal-H has been shown to be effective for reduction of certain sulfones. The reagent is harder and its uncharged Al atom permits interaction with the hard oxygen atoms of the sulfone group <73CJC1419>. A bridged thiepine dioxide (168) was reduced with dibal-H in dichloromethane to give the sulfoxide (169) in 92% yield (Equation (34)) <75JA1124>.

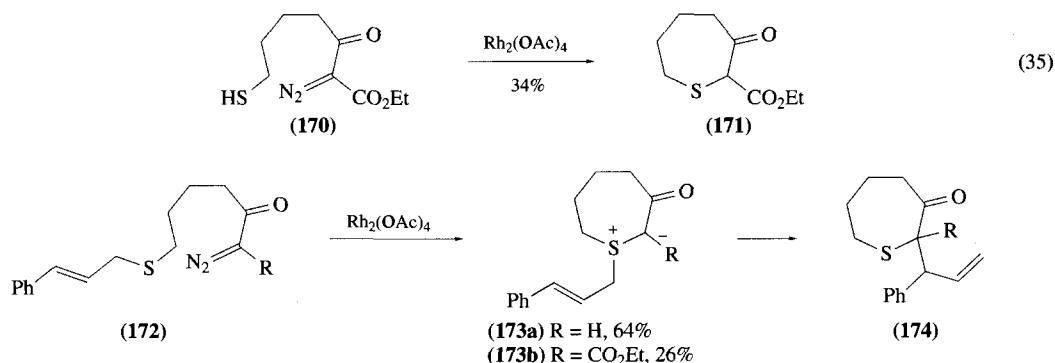


9.03.8 RING SYNTHESSES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

9.03.8.1 Synthesis of Dihydro- and Tetrahydrothiepinines, and Thiepanes

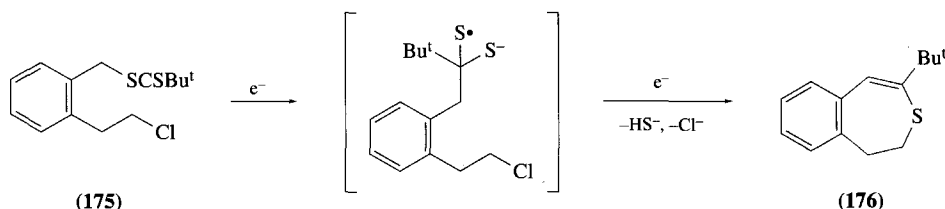
9.03.8.1.1 By formation of one bond

Although carbon-carbon bond formation provides versatile methods for synthesis of thiepane derivatives, limited attention had been paid to methods involving carbon-sulfur bond formation. New synthetically interesting cyclizations involving carbon-sulfur bond formation have been reported. The reaction of electrophilic carbenes and carbenoids with divalent sulfur compounds to give the corresponding sulfonium ylides is well known. This reaction has been applied to synthesis of thiepanes. Thus, upon treatment of the diazo thiol (170) with rhodium(II) acetate in boiling benzene, the thiepanone (171) was obtained in 34% yield (Equation (35)) <90T6501>. Similarly, diazo sulfides (172) gave the thiepanones (174) via subsequent [2,3]-sigmatropic rearrangement of the resulting sulfur ylides (173) (Scheme 29) <87TL5351>.



Scheme 29

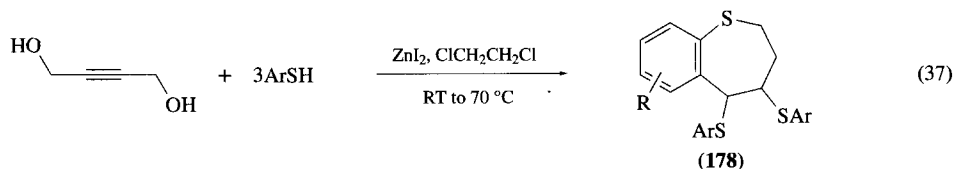
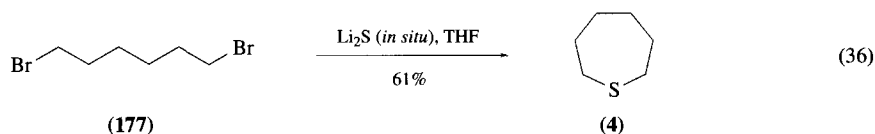
Intramolecular cathodic cyclization of dithiocarboxylic esters was studied; the cathodic reduction of (175) was found to give the benzothiepine (176) as shown (Scheme 30) <92CB127>.



Scheme 30

9.03.8.1.2 By formation of two bonds

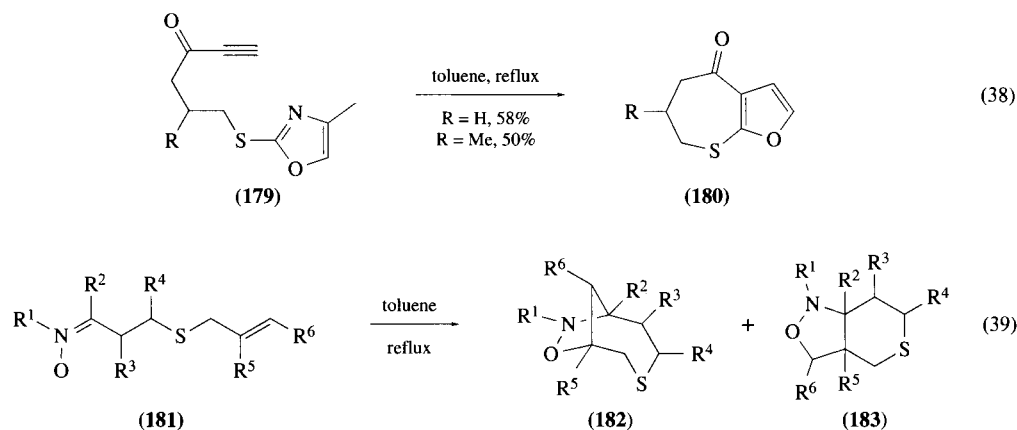
Modified methods were reported for the synthesis of thiepane rings involving a double nucleophilic reaction. The procedure in dipolar aprotic solvents was found to improve the yield even under the normal dilution concentration <79SC857>. Li_2S generated *in situ* from hexamethyldisilathiane and methyllithium was found to be a convenient reagent for carbon-sulfur bond formation (Equation (36)) <85JOC4969>. 2-Butynediol was allowed to react with arenethiols in the presence of zinc iodide in 1,2-dichloroethane, giving 4,5-bis(arylthio)-2,3,4,5-tetrahydro-1-benzothiepinanes (178) in good yields. The most likely mechanism for this reaction involves the intramolecular cyclization of a cationic intermediate generated *in situ* (Equation (37)) <87S827>.



When alkynic ketones (179) were heated in toluene at reflux for several hours, reactions involving the intramolecular Diels-Alder and the retro-Diels-Alder sequence proceeded with formation of the thiepine derivatives (180) (Equation (38)) <89TL6607>. When the *N*-aryl-substituted nitrones (181) (which are in equilibrium with the dimer) were heated in toluene, 1,3-dipolar reaction took place to give bicyclothiepanes (182) and/or thiopyranes (183). The ratio of the products depends on the substituents. Reductive cleavage gave the corresponding thiepanes with amino and alcohol groups (Equation (39)) <88TL5755, 90CB1999>.

4,5-Dihydro-3H-dinaphtho[2,1-*c*:1',2'-*e*]thiepine was synthesized by reaction of racemic dibro-

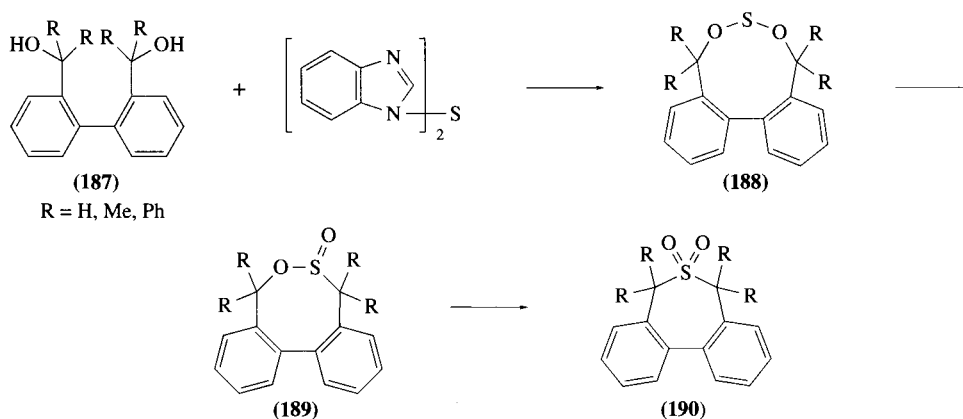
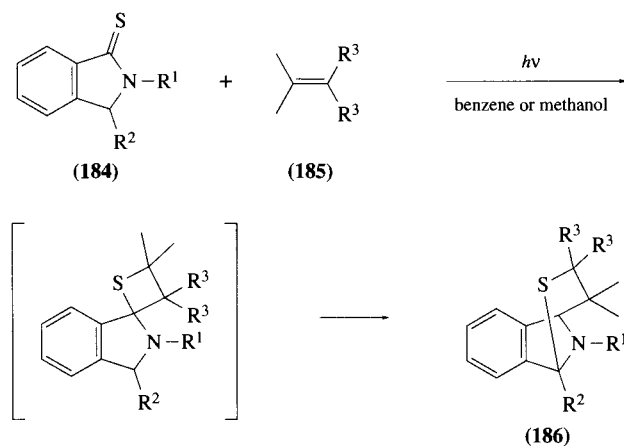
mide with Na_2S . The dihydrothiepine was resolved into enantiomers by preparative chromatography <94JOC1326>.



Irradiation of 2-arylisoindoline-1-thiones (**184**) in the presence of alkenes (**185**) afforded photochemical cycloaddition and subsequent rearrangement to give the bridged thiepines (**186**) <92JOC4000>. A reasonable mechanism for the reaction is postulated in Scheme 31.

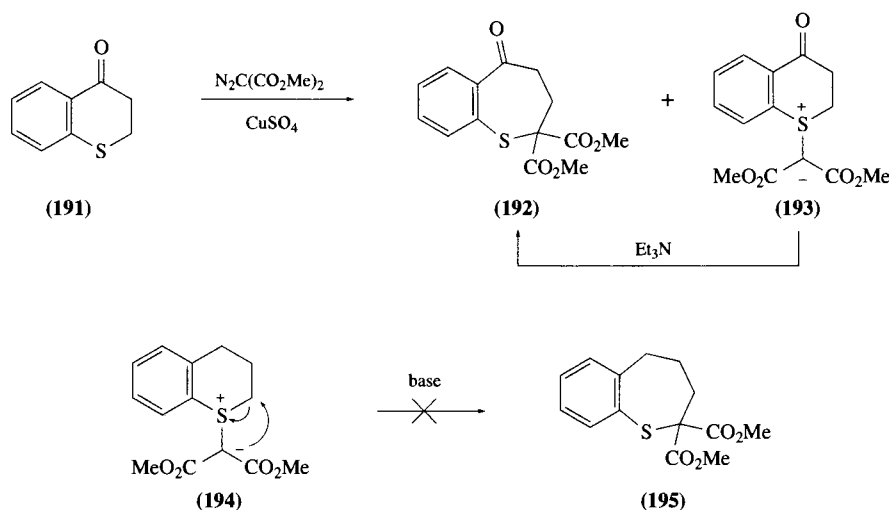
Dibenzo[*c,e*]thiepine dioxides (**190**) were prepared by using a sulfur-transfer reagent as shown <83CJC757> (Scheme 32).

Dibenzo[*b,d*]thiepine derivatives were synthesized via reaction of cyclopalladated thioether complexes with alkynes <95JOC1005>.



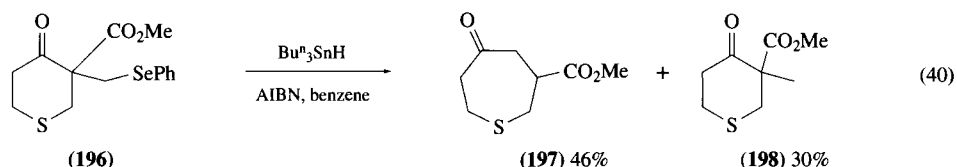
9.03.9 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

Ring expansion of thiopyranones by the use of diazo reagents (i.e., diazomethane, ethyl diazoacetate) is a standard method for the preparation of thiepanones (see Section 9.03.10.2). The reaction has also been applied to annelated derivatives with moderate success. A different version of ring expansion by diazo reagents, in which the sulfur atom plays a role, has been reported. The mechanism involves thermal rearrangement of unstable sulfonium intermediates (Scheme 33) <81JCS(P1)2978, 82JCS(P1)917, 89CL485>. The base-induced rearrangement of the ylide (**193**) seems to involve formation of an intermediate via β -elimination and a subsequent Michael addition. The Stevens-type rearrangement was eliminated since ylide (**194**) was recovered under the reaction conditions used for the rearrangement of (**193**).

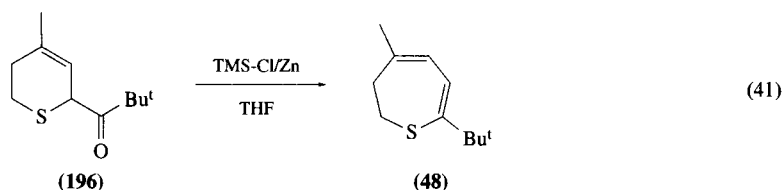


Scheme 33

Free radical reactions have been applied to the formation of seven-membered heterocycles. When the β -ketoester (**196**) was treated with tributyltin hydride and a catalytic amount of AIBN, the thiepanone (**197**) was obtained together with the reductive product (**198**) (Equation (40)) <91T4847>.

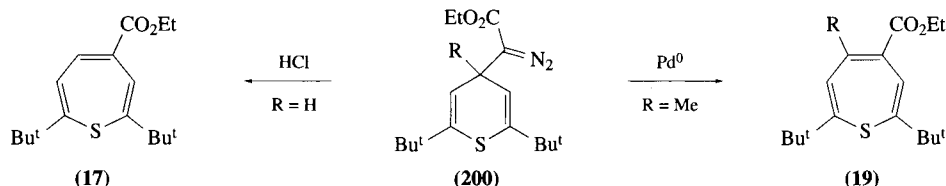


The ring transformation reaction is important for the preparation of medium- and large-membered rings and heterocycles including thiepinines since methods of preparation of these compounds by direct cyclization are limited. 2,6-Di-*t*-butylthiopyran was prepared from an acylthiophene derivative with the TMS-Cl/Zn reagent; the mechanism for the reaction is not clear. A similar ring expansion reaction was successfully applied to the synthesis of a dihydrothiepine. When TMS-Cl was added to a solution of the ketone (**199**) in THF in the presence of excess active zinc at 0°C , the thiepine (**48**) was obtained (Equation (41)) <82BCJ3057>.

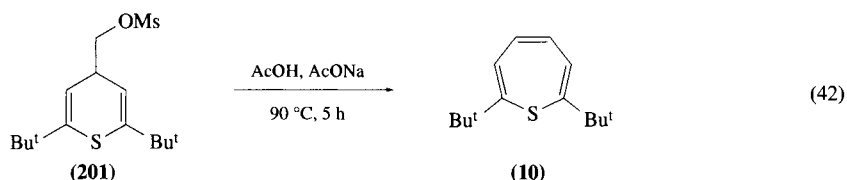


The thermal instability of fully conjugated thiepinines dictated the search for mild methods for their preparation. 2,7-Di-*t*-butylthiepine (**19**) was prepared for the first time via a carbene intermediate

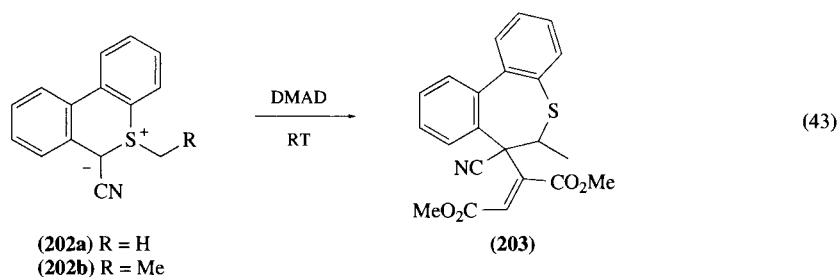
generated at low temperatures <79JA5059>. Subsequently, thiepinines were found to be stable under mildly acidic conditions, and thus a variety of acidic conditions was examined for their preparation. Although compound (**200**; R = H) did not give (**17**) on treatment with a palladium(0) catalyst, thiepine (**17**) was obtained in 13% yield on treatment with dry hydrogen chloride in ether at -20°C (Scheme 34) <82CL1843>. Since these results indicated that a carbenium ion could undergo a ring expansion reaction, the methanesulfonate (**201**) was subjected to solvolysis conditions. A solution of (**201**) in acetic acid in the presence of sodium acetate and acetic anhydride was heated at 90°C to give the thiepine (**10**) in 30% yield (Equation (42)). The major by-product is acetate, which can be converted to the starting compound <82TL3195>.



Scheme 34



The reaction of (**202b**) with DMAD gave (**203b**) in 38% yield; whereas, (**202a**) gave other compounds under similar conditions <85CC883>. A plausible mechanism for the formation of (**203**) is proposed. Nucleophilic attack of (**202b**) onto the electron-deficient ethyne forms a zwitter ionic intermediate, which leads to a sulfonium ylide upon intramolecular proton abstraction from the proximate alkyl group. The ylide undergoes a Stevens-type rearrangement resulting in formation of (**203b**) (Equation (43)); however, the preferential formation of (**203**) was not explained.



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

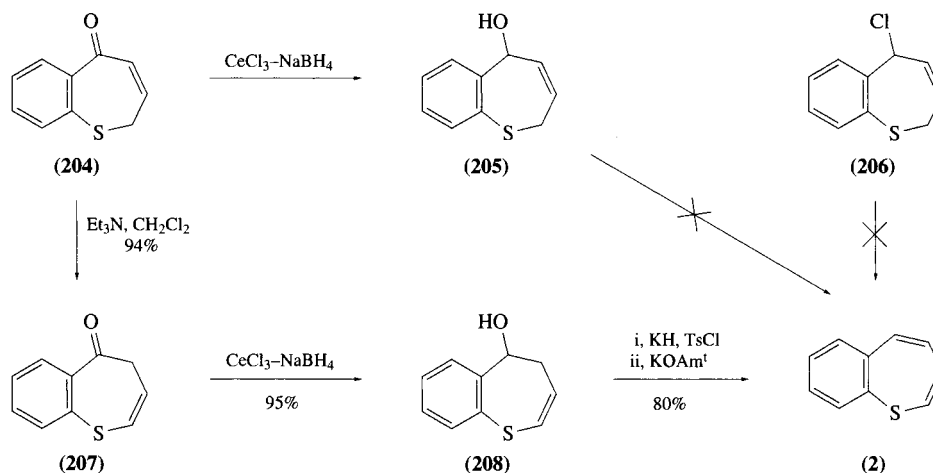
9.03.10.1 Synthesis of Thiepinines

Some established methods have been reported for the preparation of 1-benzothiepinines including the parent member.

9.03.10.1.1 Methods by sequential introduction of double bonds from tetrahydro or dihydro derivatives

1-Benzothiepinines stabilized with substituents are obtained by this method <73JOC3978, 78JOC3379, 90CE853>; however, it was difficult to achieve the synthesis of the parent member from the alcohol (**205**) or the halide (**206**). A convenient route to 1-benzothiepine (**2**) was found. Thus, ketone (**204**),

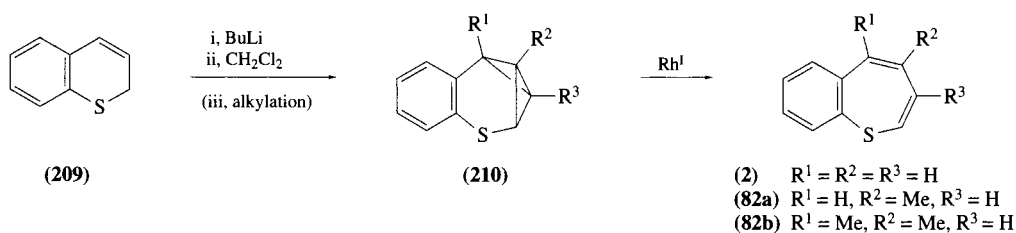
when treated with triethylamine in CH_2Cl_2 at room temperature, isomerized to the more stable ketone (**207**) in 85% ((**207**) is more stable than (**204**) by 7.9 kJ mol^{-1}) <90ZN(B)1573>. The ketone (**207**) is reduced with $\text{CeCl}_3\text{-NaBH}_4$ in methanol to give alcohol (**208**) in 95% yield, which is treated with potassium hydride and subsequently with *p*-toluenesulfonyl chloride, then without isolation of the intermediate, reaction with potassium *t*-amylate at -12°C for 3 h gives thiepine (**2**) in 80% yield. All operations, workup and removal of the solvent were performed at -20°C (Scheme 35) <89ZN(B)220>.



Scheme 35

9.03.10.1.2 Methods by rhodium(I)-catalyzed rearrangement from 4,5-benzo-3-thiatricyclo[4.1.0.0^{2,7}]heptene derivatives

Compounds (**210**) are prepared from 2H-1-benzothiopyran (**209**) by metalation with *n*-butyllithium and subsequent reaction with dichloromethane (and alkylation of (**210**) via the anion). Treatment of (**210**) with dicarbonyl-2,4-pentanedione/rhodium(I) gives the isomerized 1-benzothiopynes (**2**) and (**82a,b**). The last step is mild enough ($\sim 0^\circ\text{C}$) to enable isolation of even the labile 1-benzothiopyne (**2**) (Scheme 36) <74AG161, 75TL2697, 76BCJ825>.

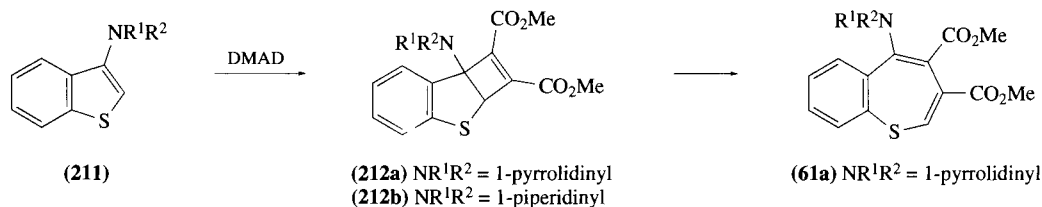


Scheme 36

9.03.10.1.3 Methods by ring enlargement of the five-membered ring of benzo[b]thiophenes

Compounds stabilized by substituents are prepared by this method. Benzo[b]thiophene (**211a**) reacts with DMAD in nonpolar solvents even at -20°C to give the adduct (**212a**). However, (**211b**) reacts only sluggishly and requires 140°C to give only the naphthalene derivative. Compound

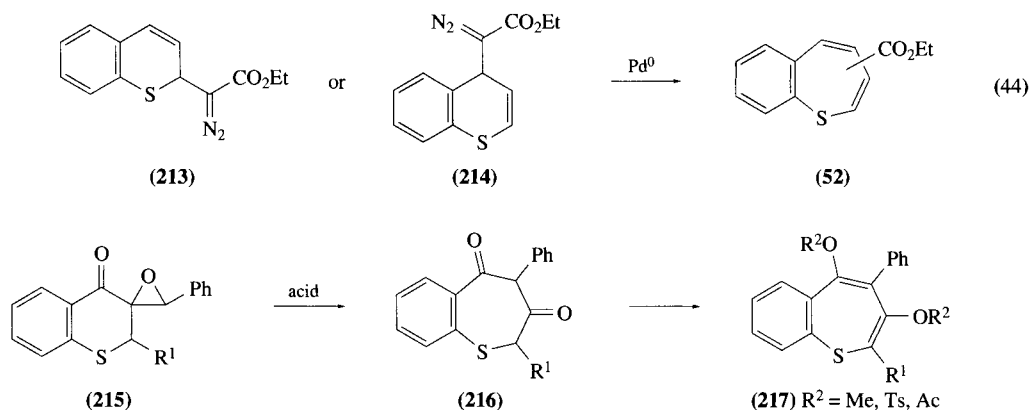
(**212a**) gives (**61a**) in 60% yield in refluxing ether (Scheme 37) <72CC1232, 74T2431>. Reactivity of benzo[*b*]thiophenes was found to depend on substituents; the synthesis suffers from a lack of generality <74TL2503>.



Scheme 37

9.03.10.1.4 Methods by ring enlargement of 1-benzothiepyrans

Preparation of ethoxycarbonyl-substituted 1-benzothiepinines (**52**) is reported. Treatment of the diazo compounds, (**213**) or (**214**) prepared by reaction of benzo-1-thiopyrylium tetrafluoroborate with ethyl lithiodiazoacetate, with π -allylpalladium chloride dimer yields four 1-benzothiepinines (**52**) with an ethoxycarbonyl group (Equation (44)) <78TL3576>. The acid-catalyzed rearrangement of the spirooxiranes (**215**) gives 2,3,4,5-tetrahydro-1-benzothiepine-3,5-diones (**216**); the spirooxiranes are easily synthesized from the corresponding α -benzylidene ketones. The further transformation of (**216**) yields the fully conjugated 1-benzothiepinines (**217**) with enol ether fragments (Scheme 38) <66AG980, 75CB3596, 84AP(317)385>.

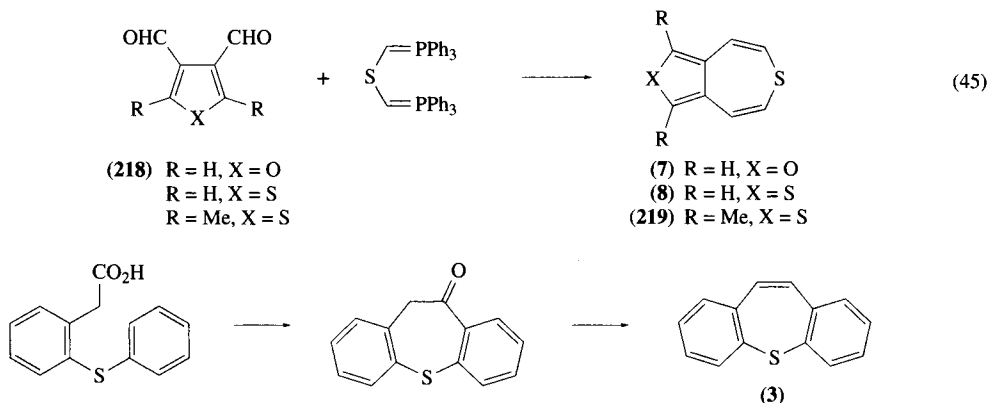


Scheme 38

The stable 2,7-di-*t*-butylthiepinines are prepared following the methods described in Section 9.03.9. An annelated thiepine is synthesized by the Diels–Alder reaction of a furano[3,4-*d*]thiepine with *N*-phenylmaleimide <70JA5263>. A thiepine stabilized by electronic effects is synthesized by the thermal ring opening reaction of 2-thiabicyclo[3.2.0]heptadiene <74T2093>. Although 3-benzothiepinines are expected to be as stable as 1-benzothiepinines, simple derivatives are unknown. A stable 2,4-dicarboxylic acid derivative can be obtained from phthalaldehyde by a double Knoevenagel condensation reaction <53JA6332>. This reaction has been applied to the preparation of naphtho[2,3-*d*]thiepinines <62JCS3262>.

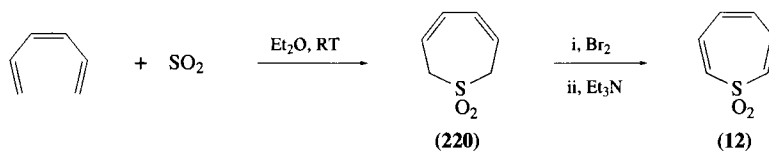
Stable furano and thieno[3,4-*d*]thiepinines (**7**), (**8**) and (**219**), which were prepared in multisteps <67JA7138, 69TL4361>, can be prepared by the bis-Wittig reaction in one pot (Equation (45)); however, preparation of thieno[2,3-*d*]thiepine failed <82JHC1243>. Since the reaction proceeds even at -50°C , this method is more suitable for the synthesis of moderately stable thiepinines. Annelated thiepinines, such as 2-benzothiepinines and dibenzo[*c,e*]thiepinines which are present as the unstable *o*-quinodal structures, structurally similar to monocyclic thiepine, are unknown. The first synthesis of dibenzo[*b,f*]thiepine (**3**) was successfully achieved from readily available thioxanthene in three steps involving ring enlargement <60JOC828>. Dibenzo[*b,f*]thiepinines with methyl groups in the 2-, 3-, 4-,

and 5-positions were also prepared by a similar ring expansion reaction <67JA5931>. Another general synthetic route to dibenzo[*b,f*]thiepinines via dibenzo[*b,f*]thiepin-10(11H)-ones was explored (Scheme 39) <65M182>.

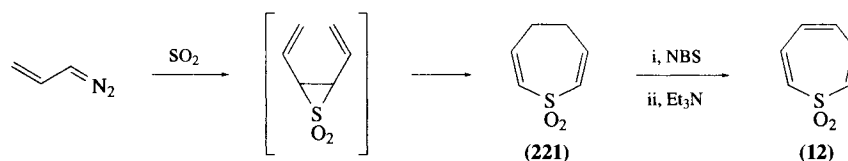


Scheme 39

Stable thiepine 1,1-dioxide (**12**) was prepared from *cis*-hexatriene <67JA1281>. Reaction of *cis*-hexatriene with sulfur dioxide at room temperature yields 2,7-dihydrothiepine 1,1-dioxide (**220**), which reacts with excess bromine in chloroform to give 3,4-dibromo-2,3,4,7-tetrahydrothiepine 1,1-dioxide. Treatment of the dibromide with two equivalents of triethylamine at 25°C gives thiepine 1,1-dioxide (**12**) (Scheme 40). Another method involving an episulfone was reported <71CC313>. Reaction of vinyl diazomethane with sulfur dioxide at -20°C gives a divinyl episulfone, which undergoes the Cope rearrangement at room temperature to give 4,5-dihydrothiepine 1,1-dioxide (**221**). Bromination with NBS and subsequent treatment with triethylamine yields (**12**) (Scheme 41).



Scheme 40



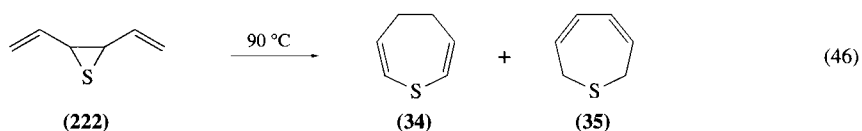
Scheme 41

Thiepine oxides are thermally less stable than the corresponding thiepinines and thiepine dioxides; 2,7-di-*t*-butylthiepine 1-oxide (**25**) was detected only at low temperatures <94JCS(P1)2631>. 1-Benzo-thiepine 1-oxides stabilized by substituents were prepared and isolated by oxidation of the corresponding thiepinines <75AG(E)812> (see Section 9.03.4.3). However, synthesis of labile 1-benzothiepine 1-oxide (**26**) failed under either oxidative or traditional reaction conditions. Alternatively, (**26**) was derived from 1-benzothiepine 1-oxide (**30**) (tricarbonyl)iron at -50°C by oxidative removal of Fe(CO)₃ <88AG(E)1717>.

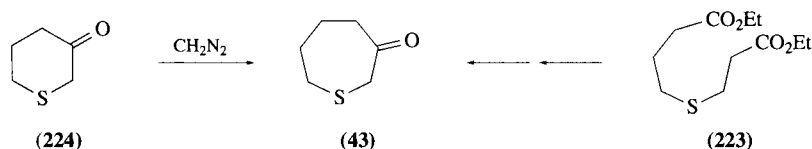
9.03.10.2 Synthesis of Thiepanes

Thiepanes can be conveniently prepared by a classic ring closure reaction (see Section 9.03.8.1.2 and 9.03.11.1).

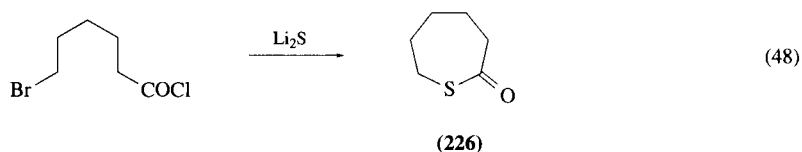
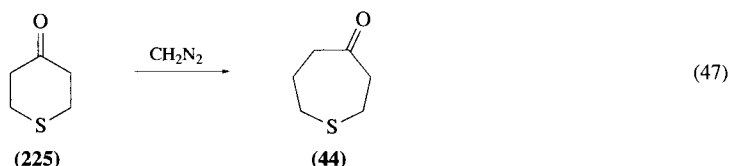
Partially reduced thiepinines are known. The thermal reaction of divinyl episulfide (**222**) was shown to be useful for the preparation of 4,5- (**34**) and 2,7-dihydrothiepine (**35**) <79JA294>. The product ratio is variable and temperature/time dependent (Equation (46)). A 2,3,4,5-tetrahydro- and a 4,5-dihydrothiepine are prepared from a thiepane derivative by the Pummerer reaction (see Section 9.03.7).



A Dieckmann-type cyclization of a diester (**223**), acid-catalyzed hydrolysis and decarboxylation affords thiepan-3-one (**43**) (Scheme 42) <56JA1965>. Thiepan-4-ones are prepared by rhodium(II)-catalyzed cyclization of diazo sulfides (see Section 9.03.8.1.1). Thiepan-4-one (**44**) was prepared from thiacyclohexan-4-one (**225**) by ring enlargement reaction using diazomethane (Equation (47)) <56JA1965>. Methyl 4-oxothiepane-6-carboxylates were prepared by a radical ring expansion reaction (see Section 9.03.9). Reaction of thiacyclohexan-3-one with diazoalkanes yields mixtures of thiepan-3-ones and -4-ones, which can be separated by distillation; for example, (**43**) is obtained from (**224**) (Scheme 42) <67AG(E)872>. Thiepan-2-one (**226**) is obtained by an intramolecular condensation of 6-thiolhexanoic acid <64MI 903-01>, or by cyclization of 6-bromohexanoic acid chloride using Li_2S generated *in situ* (Equation (48)) <85JOC4969>.

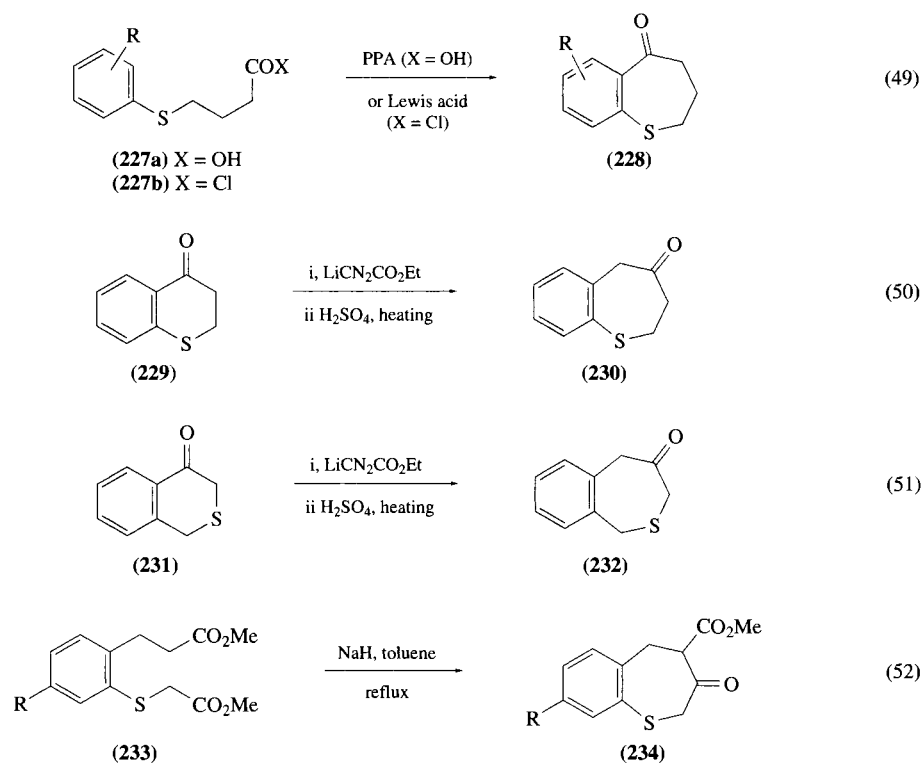


Scheme 42



3,4-Dihydro-1-benzothiepin-5(2H)-one (**228**) occupies a prominent position in the synthetic work on 1-benzothiepinines. The established method for preparation of (**228**) is the route from γ -thio-phenoxybutyric acid (**227a**) by the PPA cyclization (Equation (49)) <61JOC2728>. Substituted derivatives can be prepared by the Friedel–Crafts ring closure reaction of the corresponding acid chlorides (**227b**) <66BSF3674, 68BRP1112681>. 2,3-Dihydro-1-benzothiepin-4(5H)-one (**230**) was prepared by the ring expansion of the ethyl diazoacetate derived from thiochroman-4-one (**229**) followed by hydrolysis and decarboxylation (Equation (50)) <77JCS(P1)1822>. Similar procedures were applied to the preparation of 1,3-dihydro-2-benzothiepin-4(5H)-one (**232**) (Equation (51)). Preparation is reported of 3-oxo-2,3,4,5-tetrahydro-1-benzothiepinines (**234**) by the Dieckmann reaction of methyl 3-(2-methoxycarbonylmethylthiophenyl)propionate derivatives (**233**) (Equation (52)) <87CPB1930>.

Sulfoxides and sulfones of thiepanes and partially hydrogenated thiepinines are generally prepared from the corresponding sulfides by oxidation with appropriate oxidants (see Section 9.03.4.3 and 9.03.5.2).

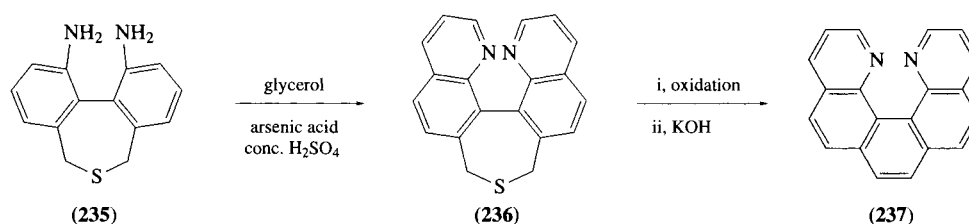


9.03.11 IMPORTANT COMPOUNDS AND APPLICATIONS

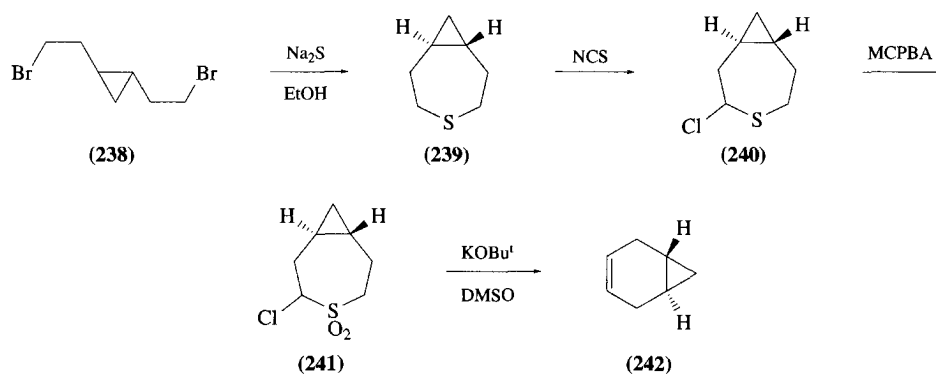
Although heterocycles enjoy well-established synthetic application, limited use of thiepinines and thiepanes is reported in laboratory synthesis. Heterocyclic compounds occupy a prominent position in modern pharmaceuticals, pesticides, and dyestuffs; many thiepinines and thiepanes are also widely used in these areas.

9.03.11.1 Dihydro- and Tetrahydrothiepinines and Thiepanes

Benzo[1,2-*h*:4,3-*h'*]diquinoline ('1,14-diaza[5]helicene') (**237**), found to be an example of a kinetically active 'proton sponge,' has been synthesized. 1,11-Diaminodibenzo[*c,e*]thiepine (**235**) was converted into (**236**) in a double Skraup reaction (glycerol/arsenic acid/conc. sulfuric acid) (24%). Oxidation with trifluoroperoxyacetic acid, and the subsequent modified Ramberg–Backlund rearrangement with KOH and CCl₄ in Bu^tOH resulted in formation of (**237**) (Scheme 43) <89AG(E)86>. Much attention has been paid to molecules with twist bent bonds, one of which, *trans*-bicyclo[4.1.0]hept-3-ene was prepared via *trans*-4-thiabicyclo[5.1.0]octane. Otherwise, it would be difficult to make them. The thiepane (**239**) was prepared under high-dilution conditions. Treatment of (**239**) with NCS yielded the labile α -chloro sulfide (**240**), which was oxidized with MCPBA to give the sulfone (**241**). Treatment of (**241**) with potassium *t*-butoxide gave (**242**) in 24% yield. The same sequence was used for preparation of substituted derivatives (Scheme 44) <89JA2652>.

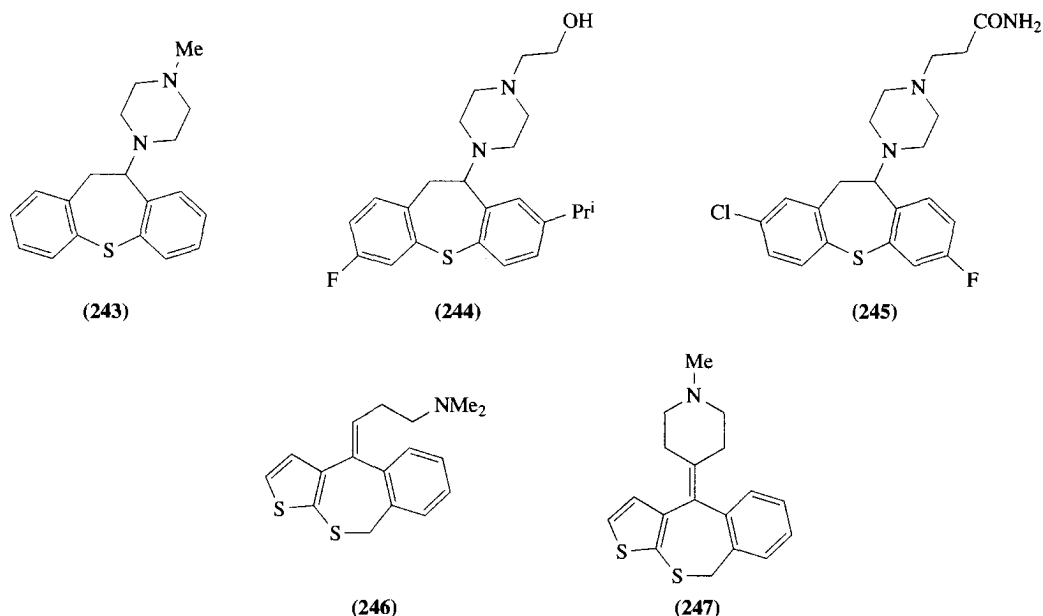


Scheme 43

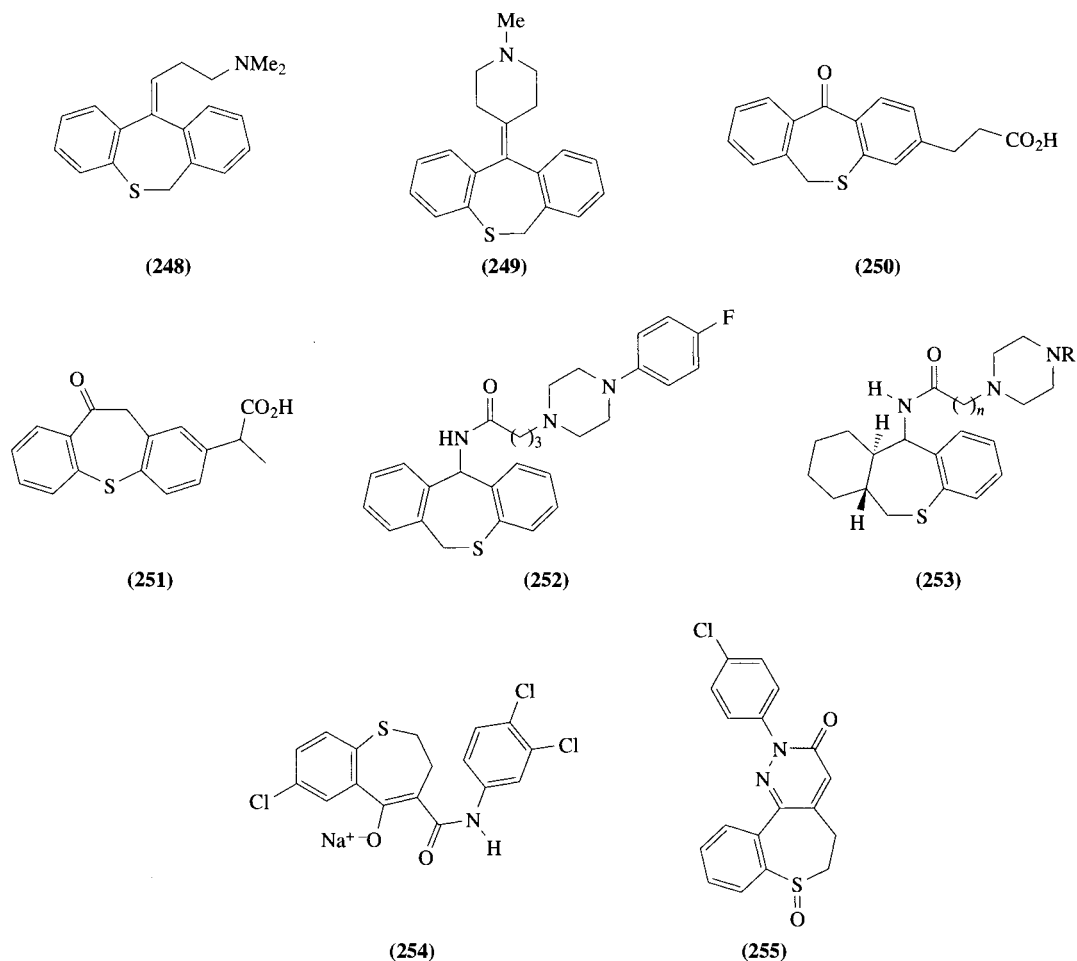


Scheme 44

Condensed thiepanes are well known to show physiological activity. In the 10,11-dihydro-dibenzo[*b,f*]thiepine system, 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepine (perathiepin) (**243**) derivatives exhibit significant antidepressant activity <65FES721, 68CZP121337>. Derivatives with different substituents on the 4-nitrogen of piperazine and benzene rings, such as Isofloxythiepin (**244**) <84CCC2638, 86CCC698, 90CCC2282>, and cloflumide (**245**) <86CCC2598, 87MI 903-01, B-89MI 903-01> are neuroleptics drugs. Attention has been paid to similar tricyclic systems in the search for new drugs. In the thieno[2,3-*c*]-2-benzothiepine series, dithiadene (**246**) <74CCC1366, 83CCC623> was found to show antihistamine activity, and pipethiadene (**247**) to show antidepressant activity <83CCC623>.

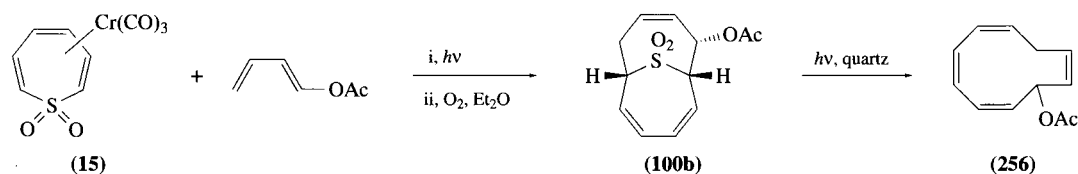


In the dibenzo[*b,e*]thiepine series, dothiepin (**248**) <62E326, 62HCA1860> and perithiadene (**249**) <63AF1039, 65MI 903-01>, showing antidepressant activity, are well known. Dibenzo[*b,e*]thiepin-11-(6*H*)-one derivatives, tiopinac (**250**) <78JMC1035, 86JMC2347> and zaltoprofen (**251**) <80GEP(O)2941869, 82JAP(K)82106678, 93MI 903-01> are antiinflammatories. A dibenzo[*b,e*]thiepine, AD-2615 (**252**) <91JMC927> and octahydrodibenzo[*b,e*]thiepinones (**253**) <91JMC593> are reported to be a new class of calcium antagonists. A benzothiepine derivative, enolicam sodium (**254**), is an antiinflammatory and antirheumatic agent <80USP4185109>. A sulfoxide, Y-23684 (**255**), was found to have an anxiolytic activity <92CPB117>.



9.03.11.2 Thiepinines

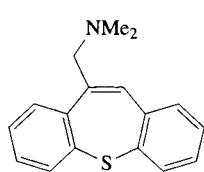
The use of fully conjugated thiepinines as starting materials or synthetic intermediates is rare since only a limited number of thiepinines stabilized with substituents are available. Metal-promoted high-order cycloaddition reactions of thiepine dioxide have been found to give substituted ten-membered carbocycles, which are potential intermediates for the synthesis of certain natural products. When (η^6 -thiepine 1,1-dioxide)tricarbonylchromium(0) (**15**) was irradiated (450 W Canrad Hanovia high pressure Hg vapor lamp, uranium glass filter) in dichloromethane–hexane (1 : 1) at room temperature in the presence of excess diene, followed by metal decomplexation with oxygen, (**100b**) was obtained. Photolysis of (**100b**) gave the all *Z*-cyclodecatetraene (**256**) in 54% yield via cheletropic extrusion of sulfur dioxide (Scheme 45) <92TL5873, 93JA1382>.



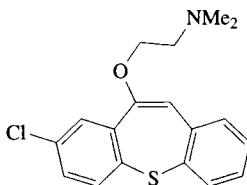
Scheme 45

Since damotepine (**257**) was found to show sedative activity <66NEP6514187>, a variety of modified dibenzo[*b,f*]thiepinines have been prepared and their physiological activities have been researched. Zotepine (**258**) has psychosedative and antipsychotic activity <78CPB3058>. Citatepine (**259**) was found to have neuroleptic, psychosedative activity, and to be a potential dopamine antagonist. <83EUP125484>. A 1H-dibenzo[2,3:6,7]thieno[4,5-*c*]pyrrole derivative (**260**) (CGP-19865) was

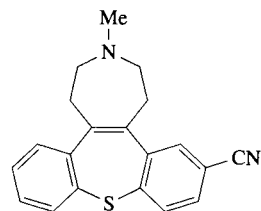
reported to be neuroleptic and a psychosedative <83EUP125484>. Dibenzo[*b,f*]thiepine-3-carboxylic acid 5,5-dioxide (**261**) has been reported to be a thromboxane antagonist <84MI 903-01, 85USP4536507, 86USP4558037>. No significant applications of simple thiepinines such as monocyclic derivatives and 1-benzothiepinines have emerged.



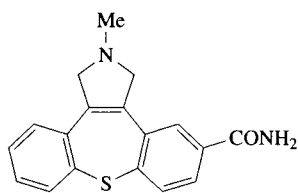
(257)



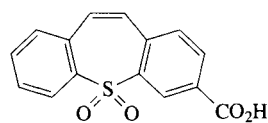
(258)



(259)



(260)



(261)

ACKNOWLEDGMENT

We are grateful to Dr David Barrett for his critical reading of this review. We also thank Professor I. Murata of Fukui Industrial University for his useful suggestions. The PM3 MO calculations of compounds (**1**) and (**8**) were performed on the CONVEX C-220 computer at the Information Processing Center of Nara University of Education.

9.04

1,2-Diazepines

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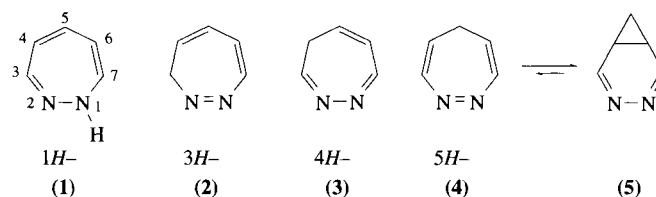
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9.04.1 INTRODUCTION

1,2-Diazepines have received much attention since the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(7)593>, primarily because of continued interest in the psychopharmacological activity of their bicyclic and tricyclic derivatives, and because of the thermochromic properties of the fully unsaturated, parent ring system. Authoritative chemical reviews were given previously <67AHC(8)21, 68CRV747, 76H(4)1509, 81ACR348>. Later reviews are found in extensive book chapters on dibenzodiazepines and other tricyclic diazepine systems <84HC(43)1> and bicyclic 1,2-diazepines <91HC(50)1>, both of which review the literature up to the late 1970s and early 1980s, and in the annual updates since 1989 on seven-membered ring compounds <89PHC297, 91PHC276, 92PHC253, 93PHC290, 94PHC301>. Several specialized reviews, and others written in languages other than English, have appeared <83MI 904-01, 85MI 904-01, 86MI 904-01, 86MI 904-02, 86MI 904-03>. The chemistry of 1,2-diazepines has also been described on numerous occasions together with that of related 1,3-diazepines and the more thoroughly investigated 1,4-diazepines, and with emphasis on pharmacology <83MI 904-02, B-89MI 904-04>.

This chapter focuses on substituted derivatives of the parent 1*H*-, 3*H*-, and 4*H*-1,2-diazepines (1)–(3) and their benzo- and dibenzo-fused ring systems. Mention is also made of less common systems bearing 1,2-diazacycloheptane rings. The 5*H*-isomer (4) is not normally isolated because its valence tautomeric equilibrium with the 3,4-diazanorcaradiene (5) lies far to the right, although the equivalent of the 5*H*-isomer can be found in 11*H*-dibenzo[*c,f*][1,2]diazepines <84CC832>.



9.04.2 THEORETICAL METHODS

The energies and coefficients of the LUMO and HOMO of diazepine (6) (Figure 1) have been determined by MNDO calculations and used to explain the preference for addition of *N*, α -diphenylnitrone at the 4,5-positions of (6). Consideration of these factors indicates that interactions between the LUMO of the diazepine (6) and HOMO of the nitrone control the reaction but do not explain the regiochemistry of the addition <92H(34)497>. However, the major formation of the C—O bond at position 5 is explained by examination of the electron densities of positions in (6).

The potential energy surface relevant to the known photoinduced ring expansion of 1-iminopyridinium ylides to isomeric 1,2-diazepines (see Section 9.04.10.1) has been examined by AM1 semiempirical molecular orbital calculations with the finding that the *N*-formyl derivative proceeds through an initial excited singlet state which then undergoes internal conversion to a ground-state bicyclic intermediate, the 1,7-diazanorcaradiene, and then to the diazepine <90JPC4464>.

9.04.3 EXPERIMENTAL STRUCTURAL METHODS

Spectroscopic and x-ray crystallographic data portray the 1*H*-1,2-diazepine ring as a cyclic polyalkene having no propensity to achieve planarity <81ACR348>. Perhaps the most thoroughly investigated and characterized 1,2-diazepine is the tranquilizer Tofizopam (Grandaxin), a 5*H*-2,3-benzodiazepine. Key spectroscopic data for this compound have been compiled <B-89MI 904-04>.

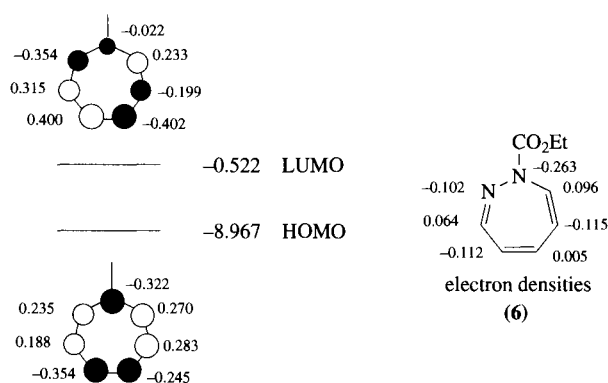


Figure 1

while less common data, such as ¹³C NMR chemical shifts <83MI 904-03> and circular dichroism <84MI 904-01>, and its determination by fluorimetry <81MI 904-01>, phosphorimetry <81MI 904-01>, and polarography <85AP(318)271> are found elsewhere.

9.04.3.1 X-ray Crystallographic Analysis

The x-ray crystal structure of the 1-tosyl derivative (7) shows that the ring exists in a boat conformation with N(1) at the prow (Figure 2) <72T581>. Double bonds are clearly localized at N(2)—C(3) 1.255 Å, C(4)—C(5) 1.326 Å, and C(6)—C(7) 1.333 Å, and the imine bond is isolated, whereas bond delocalization is present in the butadiene-like part C(4)—C(5)—C(6)—C(7). In contrast, when the diazepine is complexed with Fe(CO)₃, for example (8), the iron atom is bound to the butadiene moiety C(4) to C(7), as also occurs in the 1*H*-azepine and 1-methoxycarbonyl-1*H*-azepine complexes; the N(1) atom adopts a planar *sp*² configuration and the seven-membered ring consists of the two planar parts bent along the C(4)⋯C(7) line by 40° <70AG(E)958>.

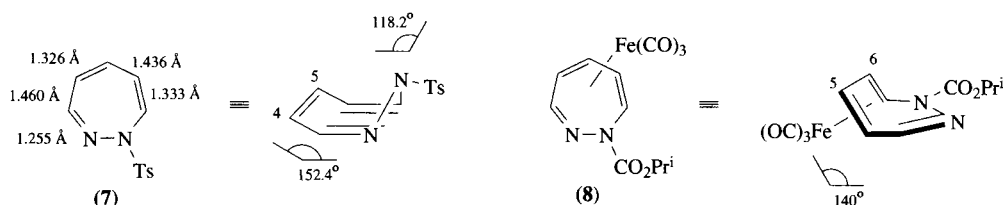
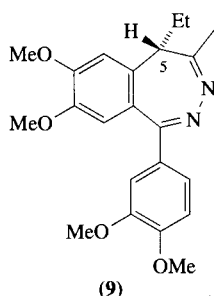


Figure 2

The x-ray crystal structure data for other 1,2-diazepines, for example 2,3,4,7,8,9,10,11a-octahydro-11-(4-methoxyphenyl)-4-[(4-methoxyphenyl)methylene]-1*H*-dibenzo[*c,f*][1,2]diazepine <83JST(101)333> and 9-bromo-2,3-dimethyl-1,2,3,4,5,6-hexahydro[1,2]diazepino[5,4-*b*]indole <83JCS(P1)1937>, indicate similarly puckered rings and reveal single (N—C and C—C) and double (N=C and C=C) bonds that are close to expected values. For 4-phenyl-6,7,8,9-tetrahydro-1*H*-2,3-benzodiazepine 2-oxide, the degree of puckering is very similar to that of structurally related 1-methyl-4-phenyl-1*H*-2,3-benzodiazepine <85AX(C)1253>. There is evidence of some delocalization around the seven-membered ring and, as a consequence, ring inversion of the seven-membered ring in the oxides is much easier than in the parent diazepines <84JCS(P1)2611>.

Two crystallographically independent molecules have been found in the crystal lattice of (–)-1-(3,4-dimethoxyphenyl)-5-ethyl-4-methyl-7,8-dimethoxy-5*H*-2,3-benzodiazepine (9) (Tofizopam (Grandaxin)) hydrobromide <86JST(147)143>. The molecules are related by a pseudo-centre of symmetry by virtue of the conformation of their seven-membered rings and the attendant methoxy groups and dimethoxyphenyl substituents, but they have the same stereogenicity (5*S*). This results in a different orientation for the C(5) substituent: the ethyl group is equatorial in one and axial in

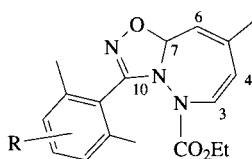
the other. The relative stability of these conformations has a profound effect on the optical rotation of freshly prepared solutions of the sample (see Section 9.04.4.2).



(9)

In an unusual case, the structure of 1,3,4-trifluoro-7,9-dimethyl-11*H*-pyrido[4,3-*c*]benzo[1,2]diazepine has been found by x-ray crystallography to comprise two planar units intersecting at an angle of 117° along a line joining C(11) and the midpoint of bond N(5)—N(6) <84CC832>. Equally, the gas-phase electron diffraction data for perfluoro(1,4-dimethyl-2,3-diazacyclohepta-1,3-diene) are consistent with a *C*₂ conformer with a torsional angle around the single N—N bond of 52.4° <85JST(130)55>.

Elsewhere, x-ray crystallographic analyses have been used to define the structure of a dimeric product from *N*(2)-acetylation of 4-phenyl-5*H*-2,3-benzodiazepine <84JCS(P1)2027>, and confirm 2-ethoxycarbonyl-5-methyl-10-aryl-1,2,9-triaza-8-oxabicyclo[5.3.0^{1,7}]-3,5,9-decatrienes (10), as the main class of products from cycloaddition of aryl nitrile oxides and 1-ethoxycarbonyl-5-methyl-1*H*-1,2-diazepine <92H(34)1583>.



R = H, 4-OMe, 4-Me, 4-Br, 3,5-Cl₂-4-Me

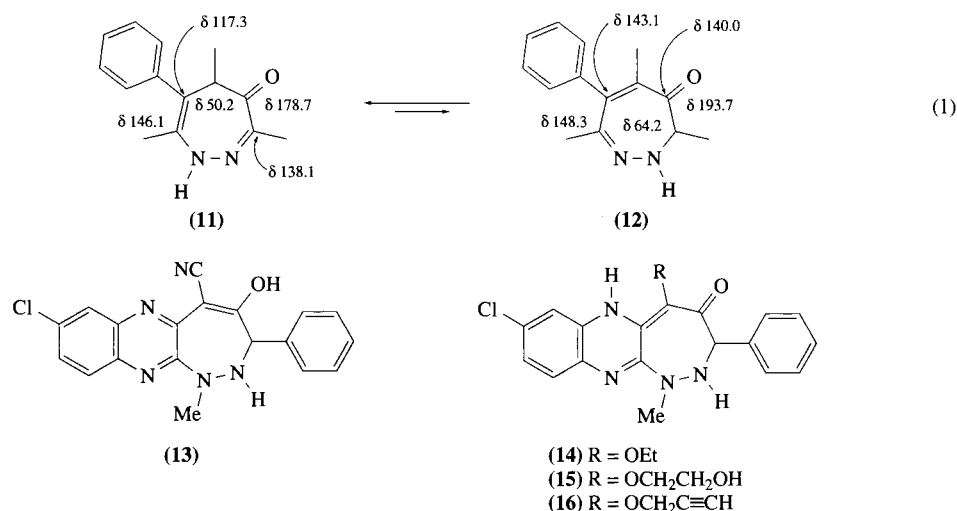
(10)

9.04.3.2 Spectroscopic Methods

Proton and ¹³C NMR spectra have been used extensively in the structural characterization of 1,2-diazepines. In addition, NMR studies have been instrumental in defining conformations of these structures and their tautomeric forms, and in demonstrating the occurrence of dynamic behavior. Thus, variable-temperature ¹H NMR studies have been used to confirm the occurrence of ring inversion in 4*H*-3,5,7-triaryl-1,2-diazepines, and to determine a decrease of 29 kJ mol⁻¹ in the activation energy to ring inversion in the corresponding salts <74CJC2805>. Similarly, flexibility of the seven-membered ring of 1*H*- and 5*H*-2,3-benzodiazepines has been studied by temperature-dependent NMR spectroscopy, and the free energies of activation for inversion have been determined to be approximately 63 and 79–92 kJ mol⁻¹, respectively (see Section 9.04.4) <73JCS(P1)2543>. The anxiolytic 5*H*-1,2-diazepine, Tofizopam (9), bears a C(5)-ethyl substituent and was revealed by ¹H and ¹³C NMR spectroscopy to have two conformations in solution <74CB3894>. The difference in free energies of the two conformations was estimated to be 4 kJ mol⁻¹, and the major conformer assigned with a pseudo equatorial C(5)-ethyl group. Variable-temperature NMR studies of fully unsaturated 1*H*-1,2-diazepine–Fe(CO)₃ complexes, for example (8), by the groups of Streith <72T581> and Snieckus <73JA6835> have demonstrated fluxional behavior in these molecules only when the nitrogens are unsubstituted. A mechanism, involving a bimolecular, intermolecularly *H*-bonded species has been proposed to explain this behavior <73JA6835>.

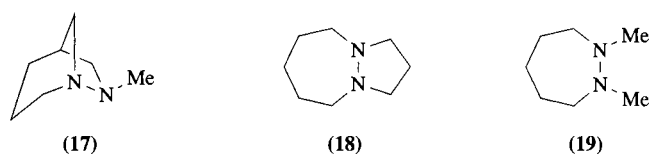
The ¹H NMR spectroscopic assignment of protons in (10) has been made through a complete series of double-resonance experiments, and the signals at δ ca. 6.0 and 5.7 assigned to H(6) and H(7), respectively <92H(34)1583>, contrary to an earlier report in which assignments, in similar

compounds, were less rigorously made <77T1349>. Tautomeric 1,5-dihydro and 2,3-dihydro forms of 1,2-diazepin-4-ones are distinguishable by the higher chemical shift of the carbonyl carbon in the ^{13}C NMR spectrum of the latter, for example (11) and (12) (Equation (1)) <85JOC2141>. The 2,3-dihydro-4-hydroxy form of (13) and the 2,3,4,6-tetrahydro-4-oxo form of (14)–(16) were also assigned by means of NOE and ^{13}C NMR spectroscopic data <90JHC2197>.



The ultraviolet and fluorescence spectra of 1-acetyl-3,5,7-triaryl-1*H*-1,2-diazepines have been compared with those of arylcycloheptatrienes <81ZN(A)1213>. Consequently, the heterocycles, and various 4*H*-1,2-diazepine derivatives, have been examined for photoimaging compositions <87MI 904-01>. A series of 3,8-dihalo-substituted 2,9-dimethyldibenzo[*c,f*][1,2]diazepin-11-one 5-oxides, 2,9-dimethyldibenzo[*c,f*][1,2]diazepin-11-ones, and 2,9-dimethyldibenzo[*c,f*][1,2]diazepin-11-one 5,6-dioxides were prepared by photolysis of the corresponding 5,5'-dimethyl-2,2'-dinitrodiphenylmethanes and their IR, UV, NMR, and mass spectra recorded <82AJC2377>. The compounds showed strong molecular ions, usually the base peak, IR absorption at 1660–1680 cm^{-1} , as expected for highly conjugated carbonyl group, and electronic absorption at around 250 and 335 nm as befits the extended conjugation between the aromatic rings. An analysis of the electron impact mass spectra of 3,5,7-triaryl- and trialkyl-4*H*-1,2-diazepines has concluded that the occurrence of dinitrogen expulsion from triaryldiazepines and absence of similar fragmentation from trialkyldiazepines probably originates from the better stabilization by the aryl substituents of neighboring unpaired electrons <83OMS(18)433>. Previously, the difference was attributed to steric inhibition of N₂ expulsion <69ACS3125>. Tautomeric pairs of 1,5-dihydro- and 2,3-dihydro-1,2-diazepin-4-ones, for example (11) and (12), are most readily distinguished through the appearance of congruent mass spectral fragmentation pathways <85JOC2141>. In the 1,5-dihydro series, the two most abundant fragment ions arise from loss of a (in (11) MeCN, CO, H) fragment or from loss of the 5-Me group followed by loss of CO and then MeCN. The spectra of 2,3-dihydro compounds are more complex and the congruence within the series is less complete. Prominent fragmentation appears to be loss of methylketene from C(3)—C(4) or loss of MeCH=NH from C(3)—N(2).

Nelsen found that trialkylamine, tetraalkylhydrazine, dialkyl ether, and dialkyl peroxide ionization potentials, including those of hexahydro-1,2-diazepines (17), (18), and (19), could be predicted using empirically-derived substituent parameters, but, in contrast to relatively insensitive ether and peroxide values, hydrazine values were noticeably affected by ring size, CNC angle, CNN angle, and lone-pair–lone-pair dihedral angle <84JOC1891>. The ionization potential, oxidation potential, and electron-transfer equilibrium of hexahydro-1,2-dimethyl-1*H*-1,2-diazepine have also been measured in the gas phase by high-pressure mass spectrometry <88JA7945>.



9.04.4 THERMODYNAMIC ASPECTS

9.04.4.1 Chromatographic Behavior

Interest in the biological impact of benzo- and dibenzodiazepines has led to numerous studies on the detection of their derivatives and metabolic products. Those methods pertaining to 1,2-diazepine derivatives refer mostly to Tofizopam (**9**) and include detection and separation by high-pressure liquid chromatography <87JC303, 90JC361, 91MI 904-01, 91MI 904-02>, thin-layer chromatography <90JC45, 90JC361>, gas chromatography–mass spectrometry <87MI 904-02, 87MI 904-03> and spectrofluorimetry <81MI 904-01, 89MI 904-02, 89MI 904-03, 91MI 904-03>. The influence of eluant composition and temperature effects on the retention mechanism of Tofizopam (**9**) in reverse-phase liquid chromatography has been explored <94JLC2809> and the enantiomeric separation of benzodiazepines, using microcolumn chromatography techniques, has been examined <94JC(A)139>.

9.04.4.2 Conformation and Tautomerism

1*H*-1,2-Diazepines contain 8π electrons and as such are antiaromatic in their planar form. Unsubstituted 1*H*-1,2-diazepines are unknown, but *N*-substituted derivatives have been isolated; they have a shallow boat structure according to x-ray crystallographic analysis data (see Section 9.04.3.1) <70JA7436, 72HCA2159>. The structure of the corresponding cation has also been discussed <72CC504>. Proton affinity (956 kJ mol^{-1} at 550K) and pK_a (6.66) values of hexahydro-1,2-dimethyl-1*H*-1,2-diazepine (**19**) are comparable with those of other saturated tetraalkylhydrazines <88JA6303>. The proton-transfer equilibria of saturated hydrazines have also been compared with electron-transfer equilibria data from earlier work <87JA1373>.

Annular tautomerism between one or more NH forms and various CH forms of 1,2-diazepines are possible with the favored species dependent upon the nature and position of substituents <69ACS3125, 70T739>. Unlike monocyclic azepines and tautomeric 1,2-diazepines, 5*H*-1,2-diazepines (**4**) exist preferentially in their bicyclic diazanorcaradiene form (**5**) <72JA2770>. Such is not the case in 4*H*-1,2-diazepines, for example (**20**), where NMR data are inconsistent with the 2,3-diazanorcaradiene form (**21**) and indicate the presence of a conformational equilibrium with a comparatively high barrier to ring inversion (Figure 3) <69ACS3125>.

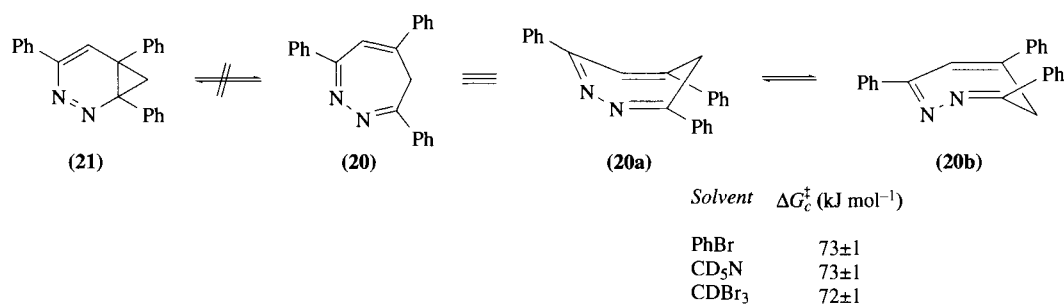
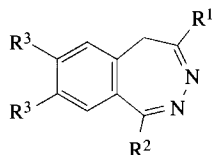


Figure 3

Annular tautomerism of 1*H*-1,2-benzodiazepines <74CC640> and several 2,3-benzodiazepines has received attention <70CC1197, 72CC823, 72CC827, 73JCS(P1)2543>. The 2,3-benzodiazepines appear to increase in stability in the order 3*H*- < 4*H*- < 1*H*- < 5*H*-isomers <B-76MI 904-01>. NMR data from 1*H*-2,3-benzodiazepines are best explained in terms of a conformational equilibrium between two boat forms with C(1) at the prow. The free energy of activation at the coalescence temperature of the methylene protons at C(1) is $63 \pm 4 \text{ kJ mol}^{-1}$. In a multisubstituted derivative, the proportion of one conformer may be higher than the other <73JCS(P1)2543, 74CB3894>. 1*H*-2,3-Benzodiazepines are readily tautomerized to their 5*H* isomers under basic conditions and the 5*H* isomers, for example (**22**)–(**25**), are found to have the higher barriers to ring inversion ($\Delta G^\ddagger$ values of the order $80\text{--}90 \text{ kJ mol}^{-1}$) <73JCS(P1)2543>. This high barrier to inversion is the factor responsible for an anomaly in the specific rotations of freshly prepared solutions of Tofizopam (**9**). The magnitude of the optical rotation is determined almost entirely by the resulting helicity of the benzodiazepine moiety, which changes slowly upon dissolution of the substance, and the stereogenic center (C(5)) does not

seem to contribute significantly to the rotation value <83JHC709>. The resolution and kinetics of conformational change have been studied extensively by high-pressure liquid chromatographic methods <86JST(147)143, 88MI 904-01, 89JLC2719> and by NMR spectroscopy <93MI 904-01>.

	R^1	R^2	R^3	$\Delta G_c^\ddagger$ (kJ mol ⁻¹)
(22)	H	Ph	H	82±1
(23)	H	Ph	OMe	80±1
(24)	Ph	Me	H	83±1
(25)	Ph	<i>p</i> -Tol	H	93±1



Substituents, such as OH, SH, and NH₂, can also participate in tautomeric equilibria, for example compare (13) with (14)–(16). The tautomerism of 1,2-diazepin-4-ones has been thoroughly investigated by Moore *et al.* and the two keto tautomers (11) and (12) found to predominate in an equilibrium ratio of ca. 8:1, respectively (Equation (1)) <68JA1369, 73JOC2939>. 5*H*-2,3-Benzodiazepin-1-ones and benzodiazepine-1-thiones have also been established to exist in their oxo and thiono tautomeric forms <70BSF2237>.

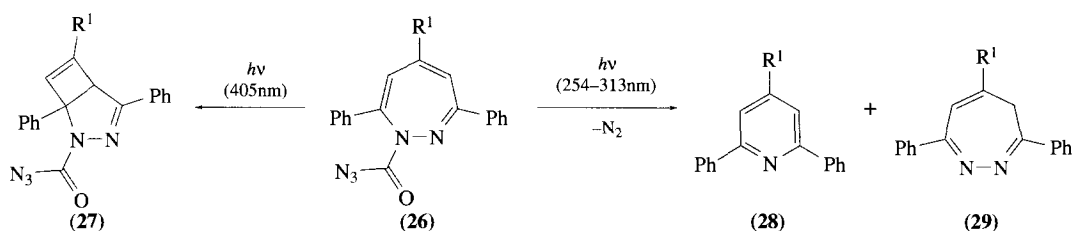
9.04.5 REACTIVITY OF FULLY CONJUGATED RINGS

9.04.5.1 Unimolecular Reactions

The chemistry of 1*H*-, 3*H*-, and 4*H*-1,2-diazepines has been examined mostly from the standpoint of their photochemical and thermally induced ring contractions and reactivity in cycloaddition processes. As nonaromatic substances, the heterocycles have a high degree of double-bond character and react accordingly.

9.04.5.1.1 Photochemical reactions

Photoinduced [$\pi_2 + \pi_2$]-electrocyclization of 1-acyl-1*H*-1,2-diazepines, like that of 3*H*- and 4*H*-diazepines, continues to provide a convenient route to dihydrodiazabicyclo[3.2.0]heptenes <86H(24)77>. However, in photolysis of 1-azidocarbonyl-3,5,7-triaryl-1,2-diazepines, for example (26), this pathway is optimal at an excitation wavelength of 405 nm where it gives the carbamoylazide (27) (Scheme 1) <88ZC189>. Excitation at lower wavelength (254–313 nm) yields varying proportions of 2,4,6-triarylpyridines, for example (28), and 3,5,7-triaryl-4*H*-1,2-diazepines, for example (29), through acylnitrene formation and ring contraction to diazanorcaradiene intermediates in a solvent dependent process.

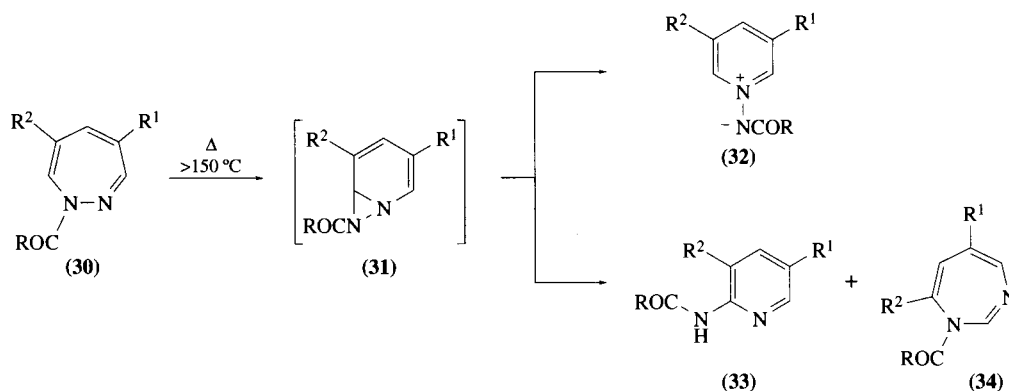


Scheme 1

9.04.5.1.2 Thermally induced reactions

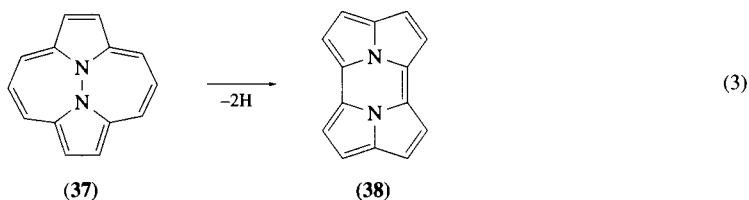
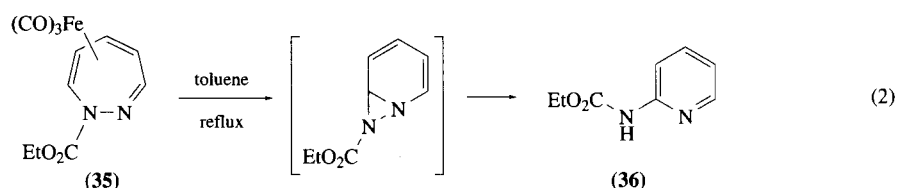
1-Acyl-1*H*-1,2-diazepines (30) undergo [$\pi_2 + \pi_2 + \pi_2$] electrocyclization at >150 °C to give diazanorcaradiene (31) followed either by ring opening to give pyridinium *N*-imides (32) when no other groups or electron-withdrawing groups are present, or by rearrangement and ring opening to give 2-acylaminopyridines (33) and 1,3-diazepines (34) when four- and/or six-electron-donating groups are present (Scheme 2) <81ACR348, 81CPB3688, 81CPB3696>. The activation parameters for this process,

when the acyl group is a benzoyl, mesitoyl, or benzenesulfonyl group, exclude a room-temperature equilibrium between (30) and (31). Instead, the rate-determining step is the thermal isomerization to an excited, short-lived 1,7-diazanorcaradiene, like (31), which rapidly aromatizes; the rearrangement is highly exothermic <84NJC223>.



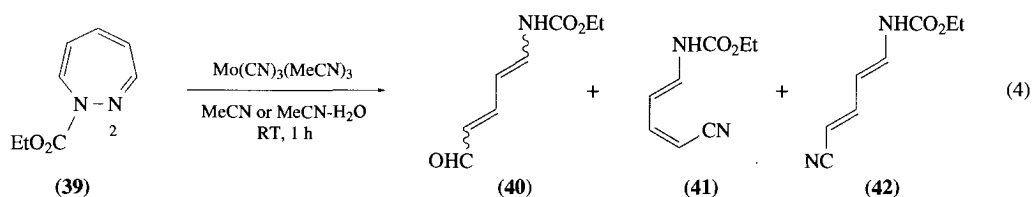
Scheme 2

Thermal decomposition of the [diene]-Fe(CO)₃ complex (35) (Equation (2)), leads to 2-ethoxycarbonylaminopyridine (36) in addition to some loss of the ethoxycarbonyl group <86H(24)1411>. A thermal electrocyclic rearrangement of [10*b*,10*c*]diazapyraceheptylene (37) has also been proposed as one component in a possible mechanism for formation of the unusual bridged [14]annulene (38) (Equation (3)) <85TL5429>.

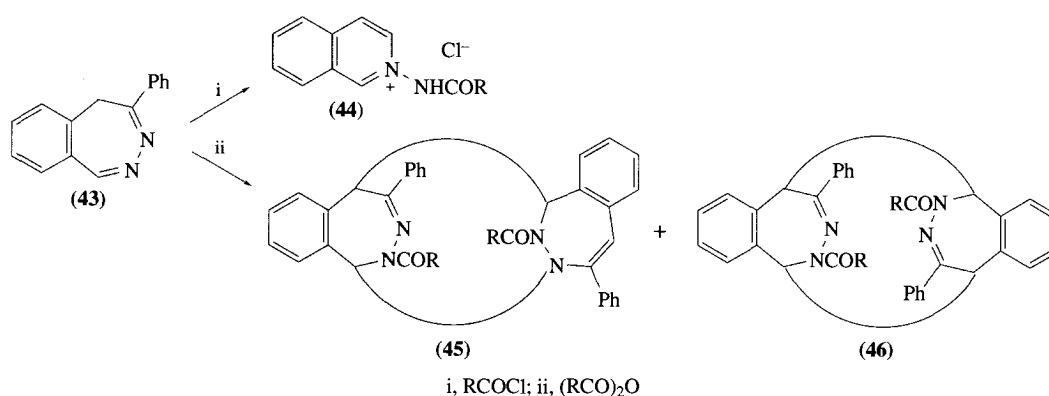


9.04.5.2 Electrophilic Attack at Nitrogen

The metallation of 1-ethoxycarbonyl-1*H*-1,2-diazepines with iron carbonyls has generally led to [diene]-Fe(CO)₃ complexes, such as (35), as the only isolated products <85H(23)1399>. A report that 1-arenesulfonyl derivatives react with Fe₂(CO)₉ by iron coordination on N(2) to give pyrrole derivatives following ring contraction therefore appeared exceptional <78H(11)461>. However, product analysis of the reaction of 1-ethoxycarbonyl-1*H*-1,2-diazepine (39) with Fe₂(CO)₉ at room temperature reveals ring-opened compounds consistent with coordination of iron at N(2), in addition to formation of the major diene complex (35). Simultaneously, (albeit to a smaller extent), coordination takes place at the diene moiety to yield ring-opened products. Similarly, 1-ethoxycarbonyl-1*H*-1,2-diazepine (39) with Mo(CO)₃(MeCN)₃ at room temperature in anhydrous or moist acetonitrile affords ring-opened products (40)–(42) (Equation (4)) supposedly by initial Mo-complexation at N(2) <86H(24)1411> and reaction with Pd(OAc)₂ in AcOH gave traces of (41) in addition to resinous material <90H(31)1491>.



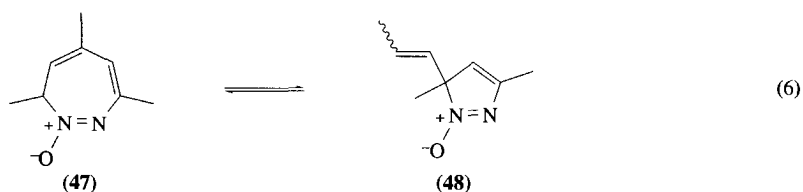
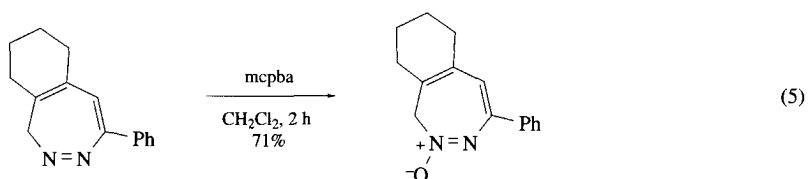
Acylation of 4-phenyl-5*H*-2,3-benzodiazepines (**43**) with acyl chlorides, chloroformate esters, and toluenesulfonyl chloride, in benzene or toluene, a procedure previously communicated $\langle 84\text{CHEC-I(7)602} \rangle$, occurs at N(2) and is accompanied by ring contraction to isoquinolinium *N*-imides (**44**) and/or [6 + 4] dimerization to acylated dimers (**45**) and (**46**) (Scheme 3) $\langle 82\text{TL345, 84JCS(P1)2027} \rangle$. The nature of the acylating agent, the order of mixing, and the reaction temperature all influence the reaction pathway. Benzoylations in pyridine proceed, as do those with acetic anhydride in benzene or toluene, to give products of addition and have been used to prepare 1-alkoxy-2-benzoyl derivatives.



Scheme 3

9.04.5.3 Oxidation

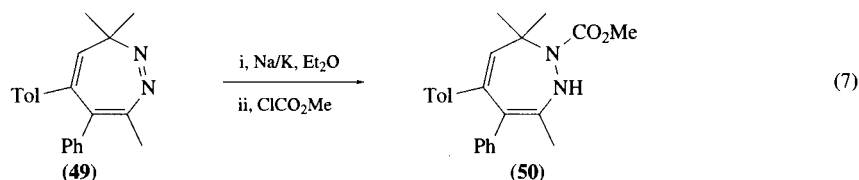
Oxidation of 3*H*-1,2-benzodiazepines with MCPBA affords a mixture of 1- and 2-oxides $\langle 78\text{CPB1896} \rangle$, whereas, monocyclic and other fused 3*H*-1,2-diazepines appear to give only the 2-oxides (Equation (5)) probably for thermodynamic reasons $\langle 84\text{JCS(P1)2611} \rangle$. The diazepine oxide (**47**), prepared from the corresponding diazepine, rearranged readily at room temperature to give an equimolar equilibrium mixture of (**47**) and pyrazole oxide (**48**) (Equation (6)) $\langle 84\text{JCS(P1)2611} \rangle$. Proton NMR studies of the 3*H*-1,2-diazepine 2-oxides have revealed that the activation barrier to ring inversion is 12–16 kJ mol⁻¹, lower than that for the parent diazepines.



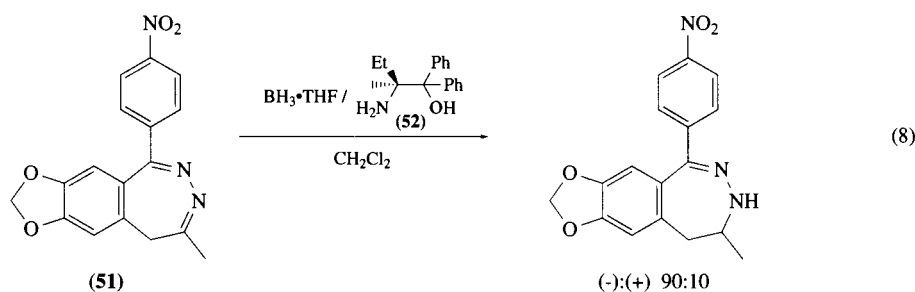
9.04.5.4 Reduction

In general, 1,2-diazepines are preferentially reduced at C=C bonds during catalytic hydrogenation and at the C=N bonds during hydride reduction $\langle 84\text{CHEC-I(7)604} \rangle$. Reductive silylation at

C(4) and C(5) of 1-ethoxycarbonyl-1*H*-1,2-diazepine (**39**) with Ph_2SiCl_2 , Me_2SiCl_2 , and Me_3SiCl in $\text{P}(\text{O})(\text{NMe}_2)_3$ in the presence of Mg, has been reported to give in the former two cases oxadisilane derivatives $\langle 83\text{BCJ}175 \rangle$. Meanwhile, reduction of 3*H*-1,2-diazepine (**49**) with Na–K alloy in ether, and acylation of the product (Equation (7)) gave the 2-methoxycarbonyl-1,2-dihydro-3*H*-1,2-diazepine (**50**), which was used for mechanistic studies $\langle 85\text{JOC}2539 \rangle$. This outcome contrasts with the behavior of less substituted 4*H*-1,2-diazepines, which yield pyridines upon treatment with Na–K alloy $\langle 72\text{TL}4891 \rangle$.

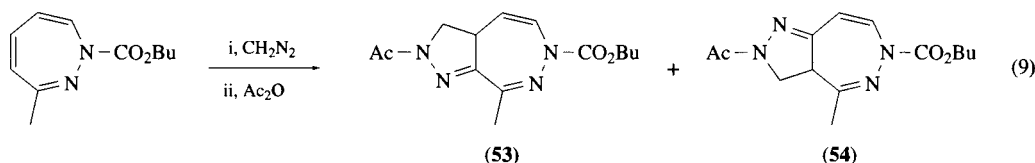


A new development has been the asymmetric reduction of 1-aryl-4-methyl-5*H*-2,3-benzodiazepine (**51**) by an adduct from various chiral amino alcohols, for example (**52**), and borane (Equation (8)) $\langle 95\text{MIP}01357 \rangle$.

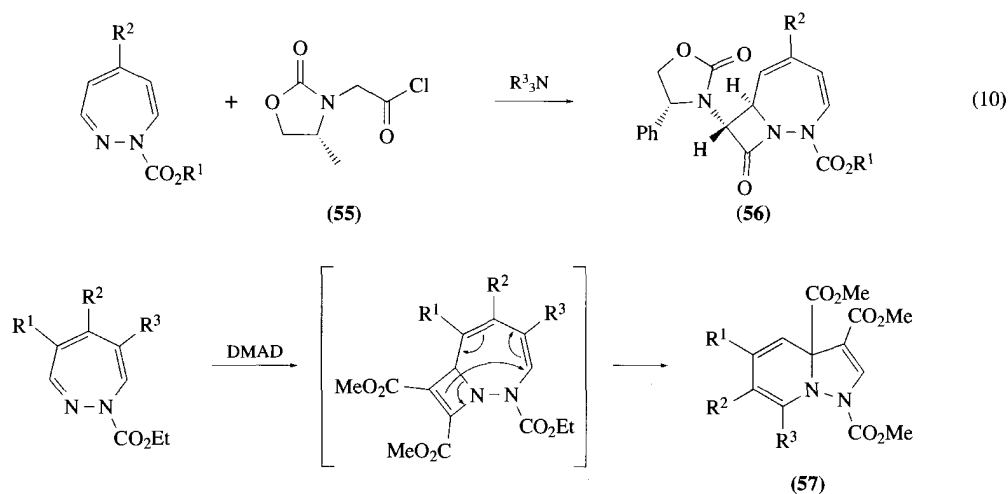


9.04.5.5 Cycloaddition

Cycloaddition reactions of 1,2-diazepines bearing 1-acyl or 1-sulfonyl substituents have been studied extensively since the mid-1980s. Conjugated diene reactants possessing electron-withdrawing groups react at the 4,5- and 6,7-double bonds of the diazepines and give [4 + 2] cycloadducts or benzodiazepines derived from them $\langle 84\text{BCJ}3483 \rangle$. An interesting adaptation of this work has been the reaction of *o*-chloranil, as a heterodiene, to give benzodioxano products $\langle 82\text{H}(19)1197, 86\text{BCJ}2485 \rangle$. Diazoalkanes react with 1-acyl ($\text{R} = \text{CO}_2\text{Et}$, CO_2Bu^t , COPh), and 1-tosyl-1,2-diazepines to form direct and inverse pyrazolinodiazepines, for example (**53**) and (**54**), respectively (Equation (9)). During this process there is a dramatic rate increase that occurs in the order $\text{CH}_2\text{N}_2 < \text{MeCHN}_2 < \text{Me}_2\text{CN}_2$, in accord with MNDO calculations $\langle 85\text{CB}4682 \rangle$. The atomic orbital coefficients of the frontier molecular orbital involved in the interaction are similar in value so that regioselectivity is unlikely to occur, and only slight regioselectivity is observed.

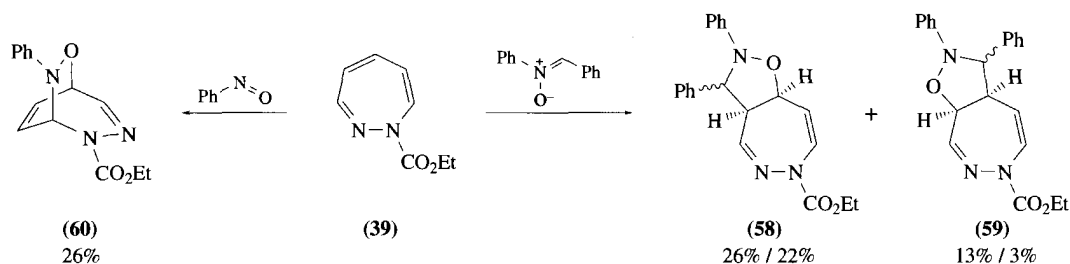


Streith *et al.* have reported numerous examples of cycloadditions to 1,2-diazepines by ketenes prepared from acid chlorides in the presence of base or with ketenes directly $\langle 83\text{LA}1361, 83\text{LA}1374, 83\text{LA}1393 \rangle$. The reactions give azetidinones through a highly selective [2 + 2] addition to the $\text{C}(2)=\text{C}(3)$ double bond of the diazepines. Application of this approach using the Evans–Sjogren ketene, derived from the chiral oxazolidinone (**55**) $\langle 83\text{TL}3783 \rangle$, gave non-concerted stereospecific [2 + 2] cycloaddition with good diastereoselectivity to give azetidinone (**56**), (Equation (10)) $\langle 91\text{HCA}767 \rangle$. Use of dimethyl ethynedicarboxylate also appears to give [2 + 2] adducts but the initial products rearrange to give indazole derivatives (**57**) (Scheme 4) $\langle 87\text{CC}1880 \rangle$.



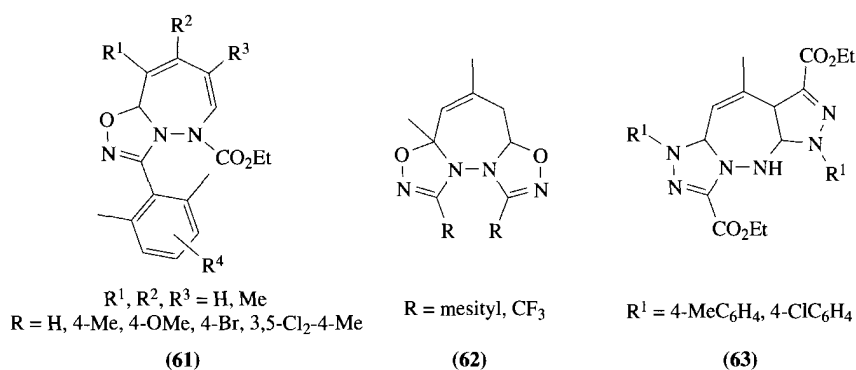
Scheme 4

The reactions of 1-ethoxycarbonyl-1*H*-1,2-diazepine (**39**) with *N*, α -diphenylnitrone and nitrosobenzene have been compared with those of 1-ethoxycarbonylazepine <92H(34)497>; however, the products from the diazepine gave more insightful mechanistic information. These studies revealed the preference in the former case for reaction at the C(4)=C(5) double bond, with one preferred regiochemistry, (**58**) versus (**59**), but little or no stereochemical control due to secondary orbital overlap (Scheme 5). In contrast, nitrosobenzene behaved as a dienophile and gave a [4 + 2] adduct (**60**) in 26% yield.



Scheme 5

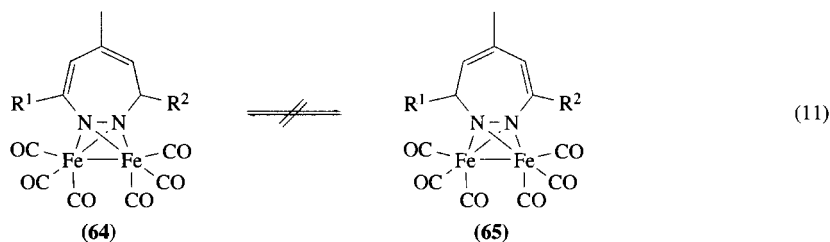
Benzonitrile oxides with 1-ethoxycarbonyl-4-methyl-, 5-methyl-, and 6-methyl-1,2-diazepines undergo 1,3-dipolar cycloaddition to give 1,2,4-oxadiazole derivatives (**61**), as the most abundant products <92H(34)1583, 93T7001>. In contrast, reactions of mesitylnitrile oxide, CF₃CBr=NOH and R¹NHN=CBrCO₂Et (R¹ = 4-MeC₆H₄, 4-ClC₆H₄), with 5,7-dimethyl-4*H*-(or 2*H*)diazepine afford only products resulting from condensation of two moles of dipole, for example (**62**) and (**63**) <94SC513>. The reactions leading to dicycloadition (**62**) gave mainly monocyclization products, that can be explained by a zwitterionic intermediate.



9.04.6 REACTIVITY OF NONCONJUGATED RINGS

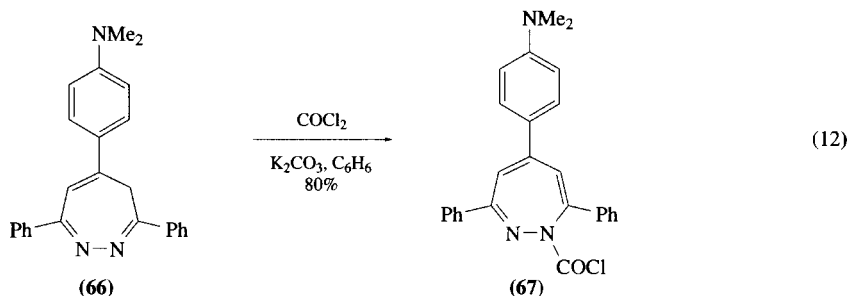
9.04.6.1 3*H*-1,2-Diazepines

Reactions of 3*H*-1,2-diazepines and their benzo equivalents, 1*H*-2,3- and 3*H*-1,2-benzodiazepines, with $\text{Fe}_2(\text{CO})_9$ give dinuclear iron complexes, for example (64) and (65). The complexes are noteworthy because they undergo ring inversion more readily than their precursors. Moreover, complexation of the azo group also stops the easy [1,5]-sigmatropic hydrogen shift (Equation (11)) which allows dynamic equilibrium of the precursors at room temperature <84JCS(P1)1581>.



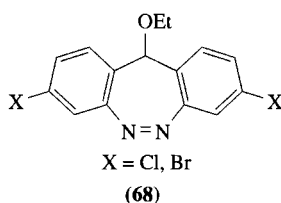
9.04.6.2 4*H*-1,2-Diazepines

Phosgene reacts at nitrogen in 3,7-diphenyl-5-(4-dimethylaminophenyl)-4*H*-1,2-diazepine (66) (Equation (12)) and other 4*H*-1,2-diazepines to give high yields of chloroformyl derivatives, for example (67), that have been used for the preparation of carbamoyl azides as microlithographic agents <87GEP252824>.



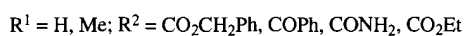
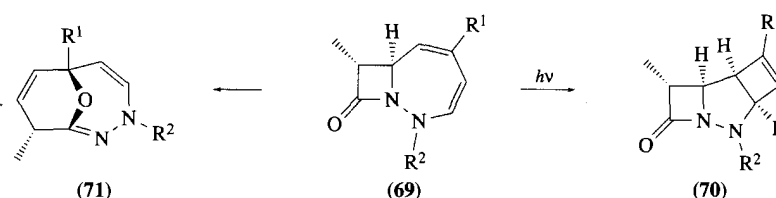
9.04.6.3 5*H*-1,2-Diazepines

The photolysis of 11*H*-dibenzo[*c,f*][1,2]diazepine in acidified EtOH has given the corresponding dibenzodiazepin-11-one and minor amounts of 2,2'-diaminobenzophenone and 2,2'-diaminodiphenylmethane <67AJC2229>. Similar treatment of the 3,8'-dichloro- and 3,8'-dibromo-11*H*-dibenzodiazepines, in the same solvent, also affords their 11-ethoxy derivatives (68), which adds support to the proposed photoinduced intermolecular hydride-transfer mechanism <91JIC299>.



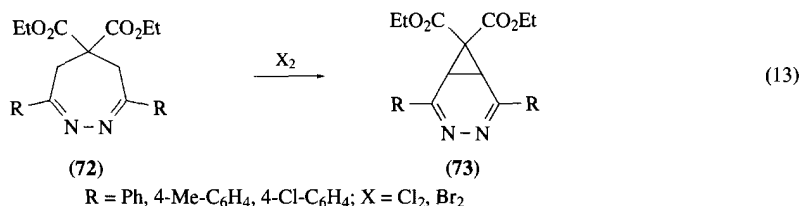
9.04.6.4 Dihydro Derivatives

Photoinduced ring closure of 2,3-dihydro-1*H*-1,2-diazepines to cyclobutanopyrazolines readily occurs and has been used in the synthesis of azo compounds for diradical generation <85JOC2539>. There are numerous examples of a similar process that takes place upon direct irradiation of azetidinone derivatives (69) to give tricyclic isomers (70), but in the presence of a triplet sensitizer, the reaction takes a different course to yield cyclic imidates (71), whose structures have been confirmed by x-ray crystallography (Scheme 6) <84CJC2440>.

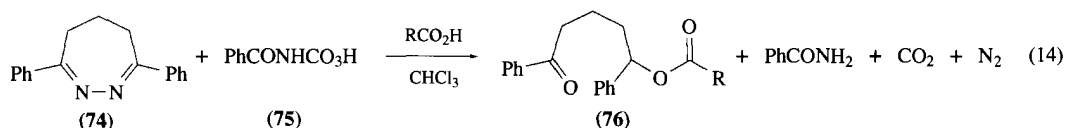


Scheme 6

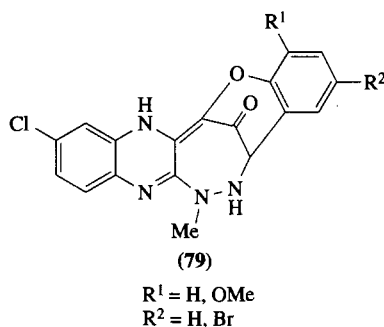
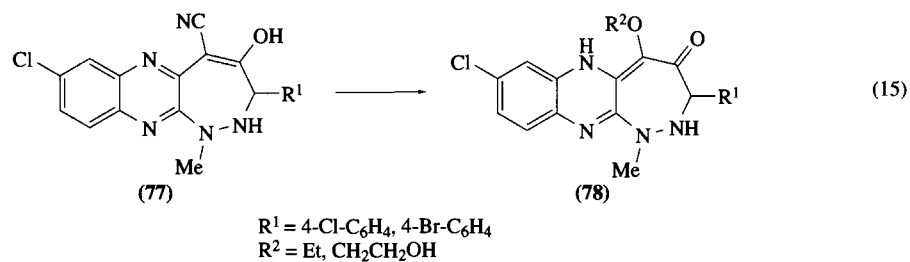
5,5-Bis(methoxycarbonyl)-3,7-diaryl-5,6-dihydro-4*H*-1,2-diazepines (72), upon halogenation, afford substituted 3,4-diazanorcaradienes (73) in excellent yields (Equation (13)) <B-92MI 904-04>, but the types of products are strongly dependent upon the nature of the 5-substituents, for example 5-CO₂Me, 5,5-(CO₂Me)₂, and 5,5-(CN)(CO₂Me), and the reaction conditions <86H(24)3059, 86JHC557>; other products include pyridazines and polyhalogenated dihydrodiazepines.



Acid hydrolysis of 5,5-diaryl analogues of (72) did not cleanly give the dicarbonyl compounds, but rather gave ketones and unsubstituted ketones by a retro-Michael reaction <87CC582>. The 5,5-unsubstituted cyclic azines, for example (74), with *N*-benzoylperoxycarbamic acid (75) in the presence of a carboxylic acid, generated the corresponding carboxylic acid keto ester (76) in high yield together with innocuous by-products (Equation (14)). The reaction is described as easy to run and has been presented as a useful synthetic method for the selective reduction of one carbonyl group in dicarbonyl compounds via the cyclic azine derivatives <89MI 904-04>.

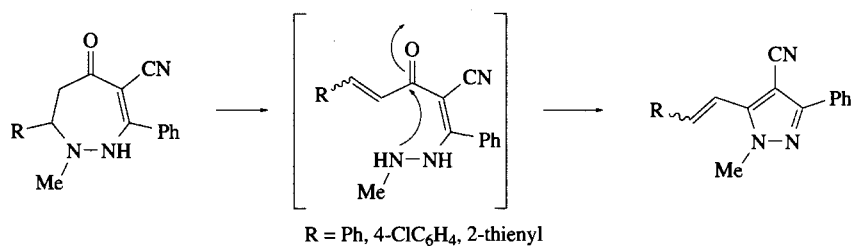


A series of reactions pertinent to quinoxaline fused 2,3-dihydro-1*H*-1,2-diazepines (77) has been published <90JHC819, 90JHC2197>. These involve intermolecular displacement of the 5-cyano group of (77) by alkoxides, a reaction that proceeds with spontaneous tautomerism to yield diazepinones (78) (Equation (15)) (see Section 9.04.3.2). When the aryl group, R^1 , bears an *ortho* hydroxyl moiety, the resultant intramolecular reaction yielded compounds, such as (79) <90JHC2209, 91JHC787>. Treatment of (79) with dead leads to dehydrogenation; however, attempted oxidation of (78; $R^2 = \text{CH}_2\text{CH}_2\text{OH}$) with NBS in aqueous medium gave the diazepine ring contraction affording the 4-oxopyridazino derivative <91JHC199>.



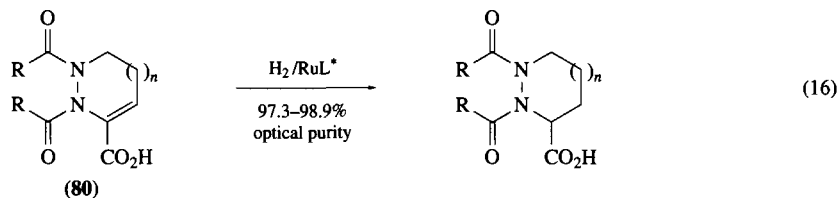
9.04.6.5 Tetrahydro Derivatives

Tetrahydrodiazepin-5-ones, when heated with HCl, are transformed by retro-Michael addition and recondensation into alkenylpyrazoles (Scheme 7) <84H(22)2265>.

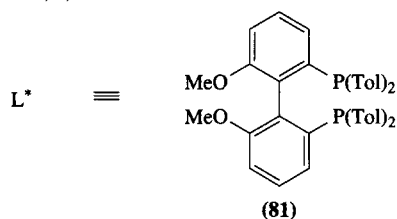


Scheme 7

Asymmetric hydrogenation of 1,2-diacyl- and 1,2-bis(alkoxycarbonyl)-2,3,4,5-tetrahydro-1*H*-1,2-diazepine-7-carboxylic acids (**80**), using optically active ruthenium diphenylphosphine catalysts, for example (**81**), proceeds in high yields and optical purities (Equation (16)) in a process that has been applied to the synthesis of an intermediate to the antihypertensive drug, cilazapril <93EUP570764>.

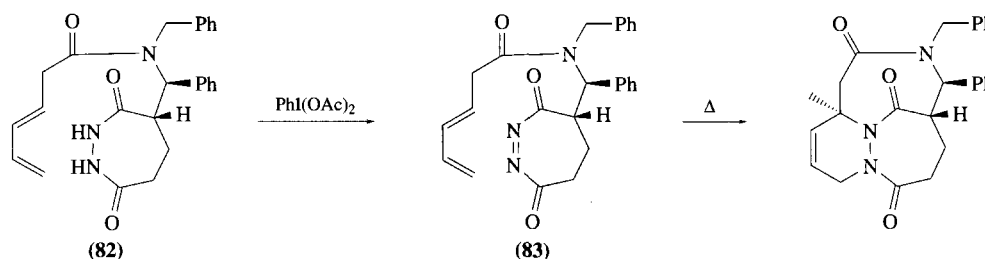


$R = \text{alkyl, arylmethyl, aryl, alkoxy, arylmethoxy, aryloxy}$
 or $R, R = \text{CH}_2, \text{CH}_2\text{CH}_2, 1,2\text{-C}_6\text{H}_4$
 $n = 0, 1, 2$



9.04.6.6 Hexahydro Derivatives

Oxidation of the optically active hexahydro-1,2-diazepine-3,7-dione (**82**) with $\text{PhI}(\text{OAc})_2$ gives a diacyldiazo compound (**83**) which undergoes intramolecular Diels–Alder cycloaddition in a synthesis of mimics of the β -turn in peptides (Scheme 8) <88JA1638>. This innovative strategy has now been used in the synthesis of several mimics of folded peptides.

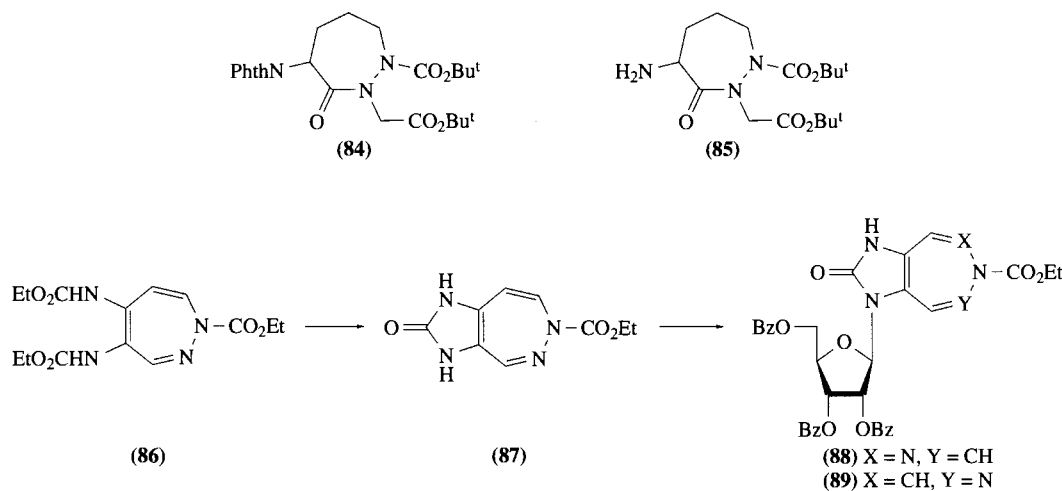


Scheme 8

9.04.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

The relative reactivity of the 1,2-diazepine ring system has limited the extent to which substituents can be manipulated.

It is noteworthy that the 4-phthalimido group in hexahydro-1,2-diazepin-3-one (**84**) has been selectively cleaved using hydrazine. This has permitted the 4-amino group of (**85**) to be reductively alkylated in a synthesis of antihypertensives <84USP4465679>. Moreover, 1-ethoxycarbonyl-4,5-bis(ethoxycarbonylamino)-1*H*-1,2-diazepine (**86**), but not its 5,6-isomer, undergoes internal cyclization, and the resulting imidazo[4,5-*d*][1,2]-diazepine derivative (**87**) has been *N*-ribosylated with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- β -D-ribofuranose to give two monoribosylated products (**88**) and (**89**), and a diriboside (Scheme 9) <86T1511>. Deprotection of (**88**) and (**89**) to yield novel ribonucleosides proceeds cleanly with methanolic ammonia, but the diriboside undergoes concomitant contraction of the diazepine ring with the same reagent.



Scheme 9

9.04.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING NITROGEN HETEROATOMS

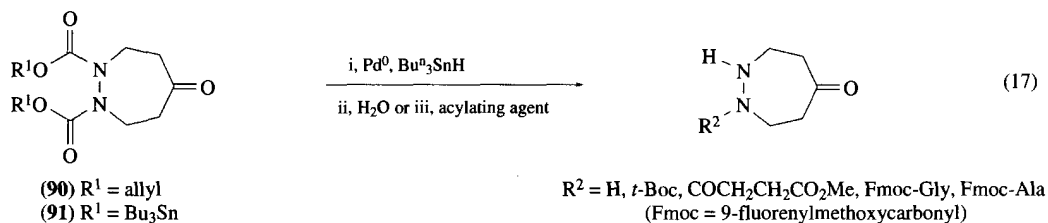
Acyl groups have been the most heavily studied of 1,2-diazepine ring nitrogen substituents.

9.04.8.1 Monocyclic 1,2-Diazepines

Diverse carbamoyl azides have been prepared as potential microlithographic agents from the corresponding carbamoyl chlorides <87GEP252824>. Derivatives of this kind undergo photolysis

to give 2,4,6-triarylpyridines and 3,5,7-triaryl-4*H*-1,2-diazepines (see Section 9.04.5.1.1) in ratios depending upon the solvent used <88ZC189>.

It has been reported that *N*-allyloxycarbonyl-protected hydrazines, including (90), react with a palladium(0) catalyst and Buⁿ₃SnH to give versatile intermediate tin carbamates (91) that can be converted either into the corresponding deprotected or acylated hydrazines (Equation (17)) <91TL6629>.

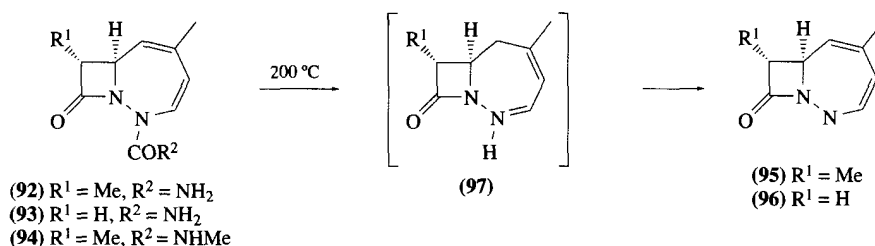


The reactions of hexahydro-1,2-diazepine and its *N*-ethoxycarbonyl derivative with aryl-isocyanates and arylisothiocyanates have also been reported in the patent literature <84EUP104484, 93JAP(K)5213970>. Urea derivatives or products of secondary cyclization can be obtained.

A scheme for the preparation of (3*R*)- and (3*S*)-piperazic acid derivatives, including those fused to a 1,2-diazepine ring, using Evan's chiral auxiliary methodology have been reported <94MIP11353>.

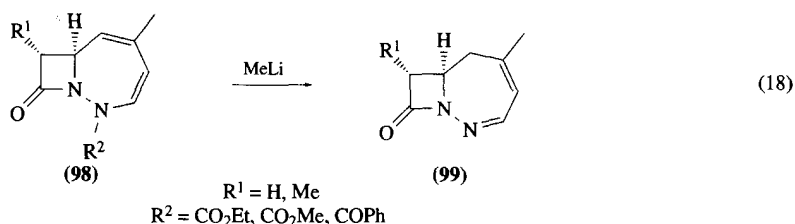
9.04.8.2 Azetidinodiazepines

Azetidinodiazepines (92)–(94) at 200 °C afford the enamines (95), (96), and (95) respectively, and fragmentation proceeds by way of the short-lived diazepine (97) and subsequent prototropic shifts (Scheme 10) <83LA2141>. Benzoylazetidinodiazepines, when heated with TFA, lead in a similar way to the corresponding enamines, as well as to benzoic acid, but ammonolysis of *N*-ethoxycarbonylazetidinodiazepines leads to products from ring opening of the β-lactam ring as well as cleavage of the ethoxycarbonyl group. The latter result is interesting because ammonolysis of monocyclic 2-acetyl-1-ethoxycarbonyl-2,3-dihydro-1*H*-1,2-diazepine yields an enamine through selective loss of the carbamoyl group.



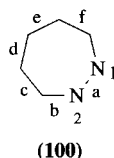
Scheme 10

Methyl lithium has proved to be a useful alternative to ammonia as a basic reagent for deacylating *N*-alkoxycarbonyl- and *N*-benzoyl-substituted 1,2-diazepines. This methodology has found application with azetidinodiazepines (98) in which the NR⁴ group is cleaved selectively to give (99) without destruction of the β-lactam moiety (Equation (18)) <90H(30)551>.



9.04.9 RING SYNTHESSES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

Numerous reported syntheses of 1,2-diazepines have been found to be in error and in fact give different heterocycles. These reports and their corrections are highlighted in the following sections. Syntheses are discussed in the order used in CHEC-I and are referred largely to methods described since publication of the first edition. Thus, preparations from non-heterocyclic precursors are classified according to the bonds formed, using the convention of labeling ring sides by lower-case italic letters according to structure (100).

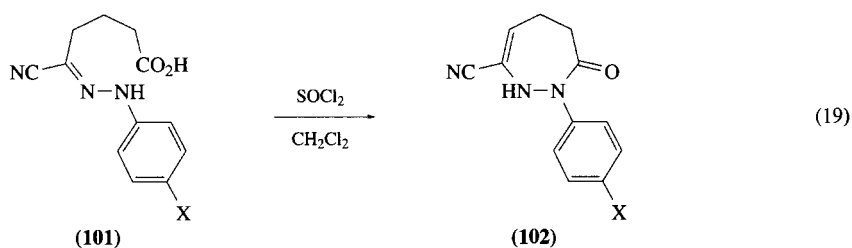


9.04.9.1 Type *a* (N—C—C—C—C—C—N)

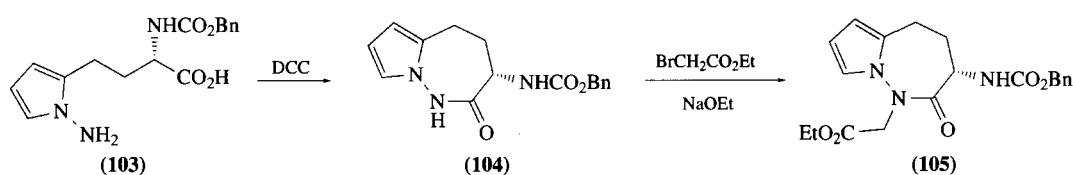
Formation of the *a* bond has been achieved by irradiation of acetyl esters of 2,2'-dinitrodiphenylcarbinols in protic solvents, such as Pr^iOH , to give dibenzo[*c,f*][1,2]diazepin-11-one 5-oxides (91MI 904-05). The corresponding dibenzo[*c,f*][1,2]diazepin-11-ones, 2,2'-dinitrobenzophenones, 2-amino-2'-nitrobenzophenones and *N*-hydroxyacridones are also formed in varying amounts; the reaction becomes more complex in aprotic solvents.

9.04.9.2 Type *b* (C—C—C—C—C—N—N)

Despite the statement in CHEC-I that 1,7-electrocyclization of $\alpha,\beta,\gamma,\delta$ -unsaturated diazoalkanes provides a good general route to 1,2-diazepines (84CHEC-I(7)595), the method has rarely been used since the mid-1980s. Arylhydrazones, for example (101), obtained through treatment of 2-cyanocyclopentanone with $\text{PhN}_2^+\text{Cl}^-$, have been cyclized with SOCl_2 in CH_2Cl_2 and with PCl_3 in benzene to 2-aryl-2,3,4,5-tetrahydro-1,2-diazepin-3-ones (102) via formation of the *b* bond (Equation (19)) (84CR(B)929). Treatment of (101) with ppa in AcOH afforded its *N*-acetyl derivatives and (102) in 20% and 50% yields, respectively. Notably, the same hydrazones when treated with HCl in EtOH afford Fischer indole products (87BSF361).



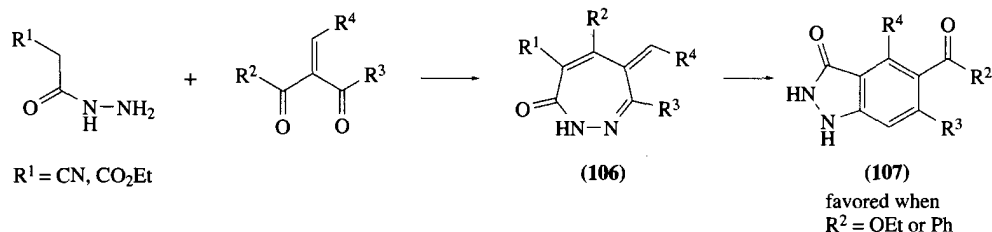
Chiral 1,2-diazepines, for use as conformationally restrained peptide mimics, have been synthesized by preformation of aminopyrrole (103), from glutamic acid, then cyclization using conventional dcc coupling to diazepinone (104) (Scheme 11) (92JOC3535). Subsequent alkylation on the amide nitrogen has provided an acetic acid derivative (105), that was also prepared by the type *bg* synthesis (see Section 9.04.9.5.2).



Scheme 11

9.04.9.3 Type *be* (C—C—C + C—C—N—N)

Acetohydrazides with α,β -unsaturated 1,3-diketones gave 1,2-diazepinones (**106**) (Scheme 12), but the reaction course depends upon temperature and the relative reactivity of the carbonyl groups of the reactants. When one of the carbonyl groups is of low reactivity, for example benzoyl or ethoxycarbonyl, the reaction does not yield diazepinones but only pyrazolo[3,4-*b*]pyridines (**107**) and/or acetohydrazones <90LA841>.

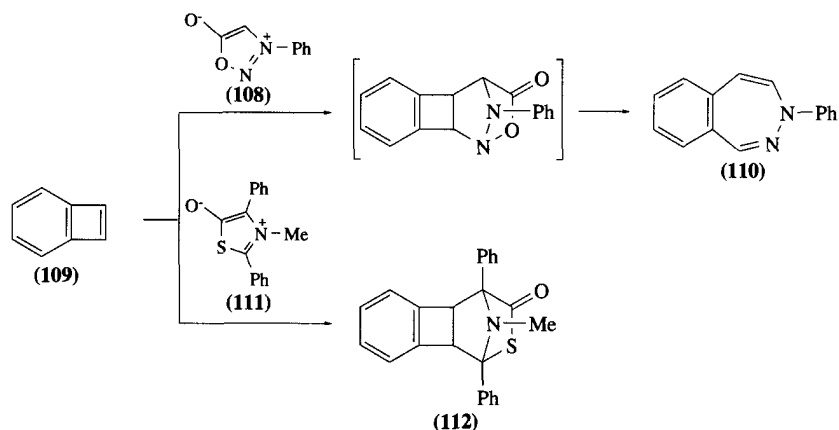


Scheme 12

An earlier reported synthesis of benzodiazepinoquinolines by reaction of hydrazinobenzoquinolines with 1,3-dicarbonyl compounds <74BCJ1786> has been shown to be in error; the reaction actually affords pyrazolylbenzoquinolines <93BCJ1703>.

9.04.9.4 Type *bf* (C—C—C—C + N—N—C)

The dipolar cycloaddition of sydnone (1,2,3-oxadiazolidin-5-one derivatives) (**108**) with benzocyclobutene (**109**) has been used to synthesize 3*H*-2,3-benzodiazepines (**110**). This synthesis involves a cycloaddition–extrusion–ring-expansion sequence, and with other mesionic compounds, for example the thiazolium-4-olate (**111**), primary cycloadducts (**112**) were isolated (Scheme 13) <93JCS(P1)1055>.



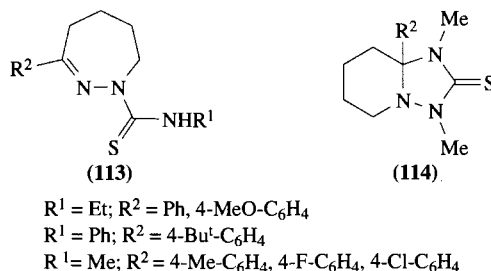
Scheme 13

9.04.9.5 Type *bg* (C—C—C—C—C + N—N)

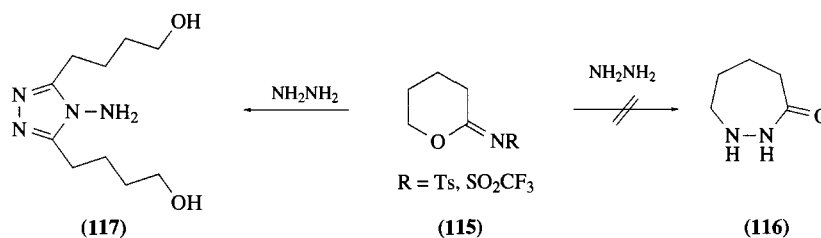
Construction of the diazepine ring through reaction of a preformed 5-carbon fragment and hydrazine, a substituted hydrazine, or a hydrazide, is a popular approach that has been achieved in several ways. Cases in which an intermediate (often a hydrazone) has been isolated and subsequently cyclized are dealt with in Section 9.04.9.2.

9.04.9.5.1 1,5-Halogenocarbonyl compounds and related precursors

The four-substituted thiosemicarbazides with 5-halovalerophenones give 3-aryl-4,5,6,7-tetrahydro-1*H*-1,2-diazepine-1-carbothioamides (**113**), but similar treatment using 2,4-dimethylthiosemicarbazide affords [1,2,4]triazolo[1,5-*a*]pyridine-2(3*H*)-thiones (**114**) <88JHC1471>.



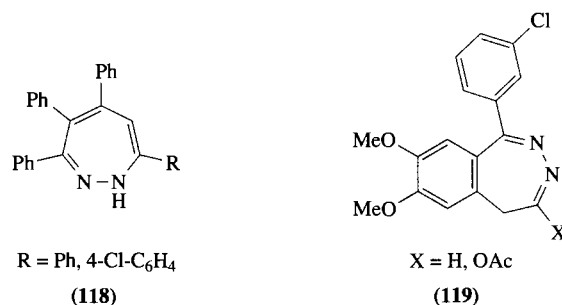
The lactone sulfonylimine (**115**), when treated with hydrazine, was previously claimed <65CB1138> to give hexahydro[1,2]diazepin-3-one (**116**), but in fact leads to aminotriazolodibutanol (**117**) (Scheme 14) <91HCA2024>.

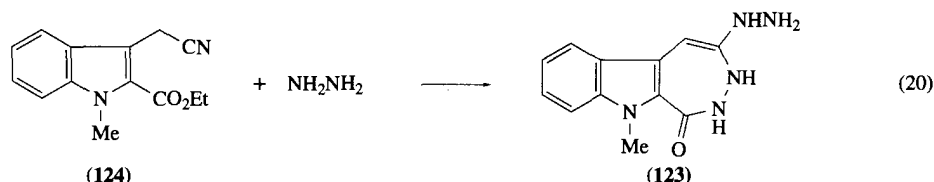
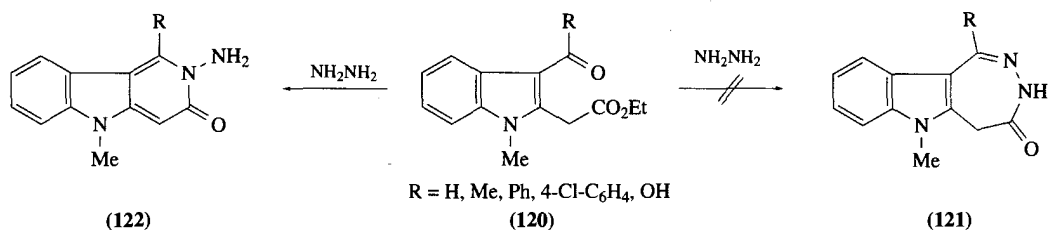


Scheme 14

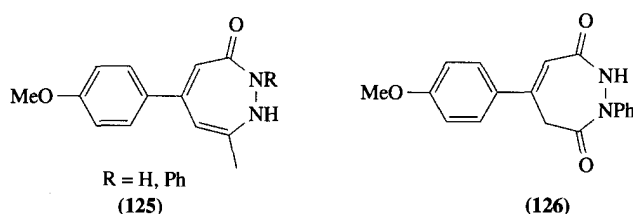
9.04.9.5.2 1,5-Dicarbonyl compounds

Reactions of 1,5-dicarbonyl compounds with hydrazines and their anions continue to provide a general route to 1,2-diazepines, and have yielded aryltriphenyldiazepines (**118**) in 40% yield <88MI 904-02> and a CNS agent, 5*H*-2,3-benzodiazepine (**119**), in 80% yield and high purity <92BRP2248838, 92BRP2255338>. Indole aldehydic and keto esters, and diesters, (**120**), that have been reported to yield structurally related diazepino[5,6-*b*]indoles (**121**) <84JHC381, 85JHC1445>, have, however, been shown to give aminopyrido[4,3-*b*]indolones, for example (**122**) (Scheme 15) <86JHC1055>. This result explains the apparent failure of methods that require cyclization of certain semicarbazides to provide similar compounds <85JHC1445>, and sheds some doubt on the structure of (**123**), which was prepared in a similar manner from the ester nitrile, (**124**) (Equation (20)) <84JHC381>; there has been no correction of structure (**123**).



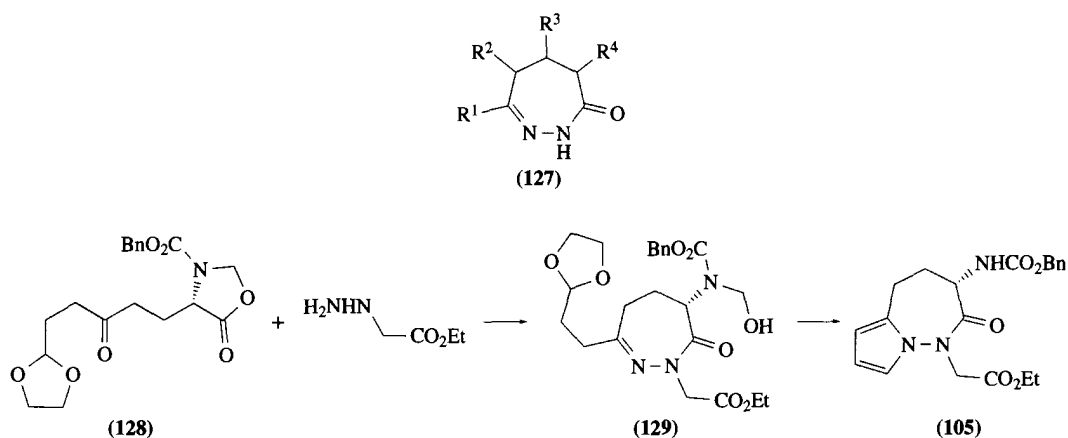


Glutaroyl chloride and *N,N'*-diarylhydrazine have been used to prepare hexahydro-1,2-diazepine-3,7-diones <89CB1503>. Hydrazine and phenylhydrazine with 5-acetyl-4-anisylpyran-2,6-dione afforded different diazepinones (**125**) and (**126**), while with 4-anisyl-6-methyl-2-pyrones, they yield the same diazepine, of the type (**125**) <84H(22)1979>.



Similarly, use of 5-ketoacids with hydrazine provides a direct route to a wide range of substituted 2,4,5,6-tetrahydro-3*H*-1,2-diazepin-3-ones (**127**) <92EUP478195>. An amino acid-derived 5-keto-lactone (**128**) has also been transformed in this manner into an optically active diazepinone (**129**) in an alternative approach to (**105**) (Scheme 16) (see Section 9.04.9.2) <92JOC3535>.

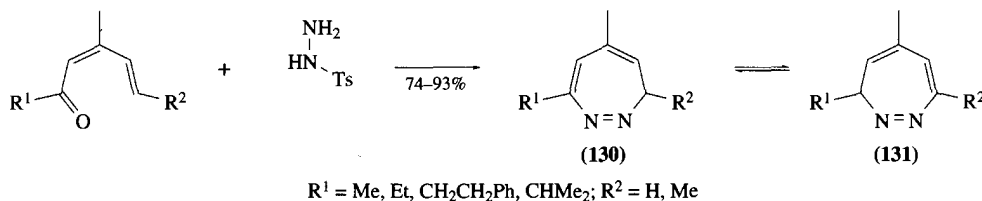
A related cyclocondensation has been used to prepare 3-oxo-hexahydro-1,2-diazepine-2-acetic acids for use in the treatment of hypertension <84USP4465679>.



Scheme 16

9.04.9.5.3 $\alpha,\beta\text{-}\gamma,\delta$ -Unsaturated carbonyl compounds

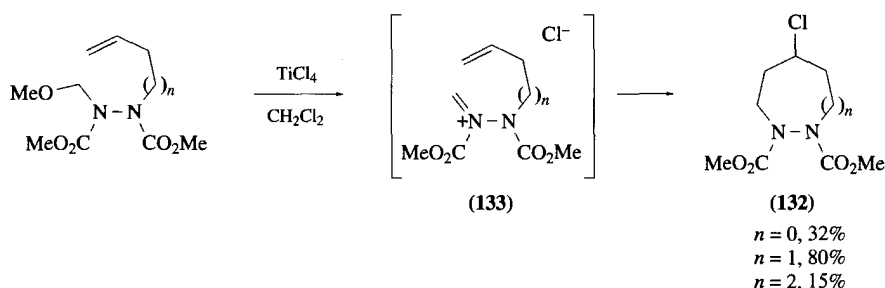
Tosylhydrazide with $\alpha,\beta\text{-}\gamma,\delta$ -unsaturated ketones, followed by dehydrotoluenesulfonylation, has afforded a good source of 3*H*-1,2-diazepines, for example Scheme 17 <84JCS(P1)1581>. The tautomeric products (**130**) and (**131**) from the reaction were in dynamic equilibrium at room temperature but in some cases could be separated by high-pressure liquid chromatography at 0°C.



Scheme 17

9.04.9.6 Type *c* (C—C—C—C—N—N—C)

While relatively uncommon, construction of the 1,2-diazepine skeleton through formation of the *c* bond has considerable potential. A 5-chlorohexahydro-1,2-diazepine derivative (132) has been prepared in this manner by the TiCl₄-catalyzed alkenyl ring closure to an iminium ion (133) (Scheme 18); the reaction seems optimal for formation of the seven-membered ring of diazepines <88TL6975>. The bisallyloxy ketone (90) (see Section 9.04.8.1) was prepared similarly by ring closure of an alkynylsilane in HCO₂H <91TL6629>.



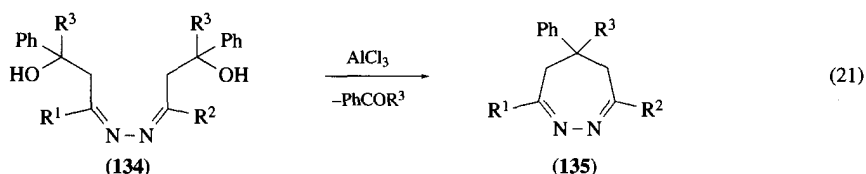
Scheme 18

9.04.9.7 Type *ce* (C—C + C—C—N—N—C)

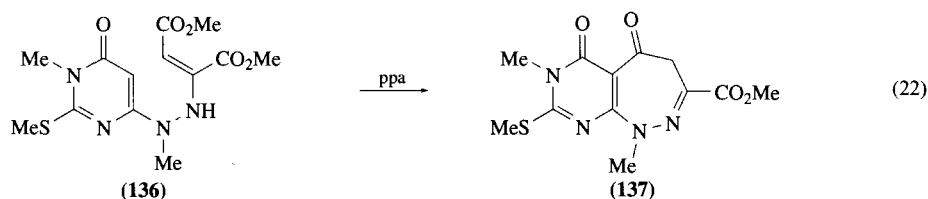
The 1,3-dipolar cycloaddition of quinoxaline-4-oxides with 2-chloroacrylonitrile gives 2,3-dihydro-1*H*-1,2-diazepino[3,4-*b*]quinolines, for example (14)–(16), in what is formally formation of the diazepine *c* and *e* bonds <90JHC819, 90JHC2197, 93JHC537>. The products exist predominantly in their enol form, but, subsequent displacement of the C(5)-cyano group with alkoxy groups in the presence of base (see Section 9.04.3.2) brings about a shift in the tautomeric equilibrium to give mostly the keto form <90JHC2197>.

9.04.9.8 Type *d* (C—C—C—N—N—C—C)

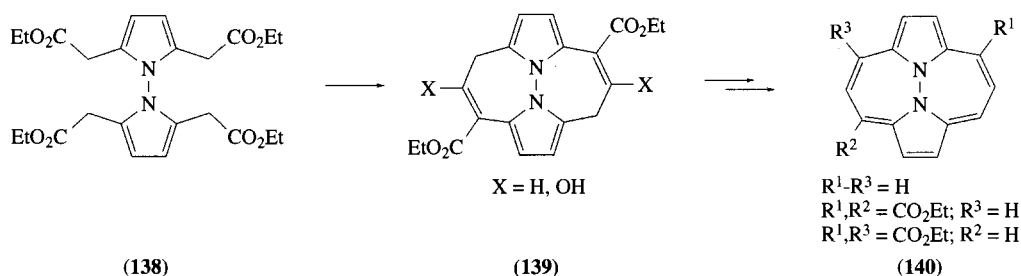
Treatment of dihydroxydihydrazine (134) with AlCl₃ promotes cyclization to dihydrodiazepines (135) in 80–90% yield (Equation (21)) <87CC582>. Formation of the *d* bond occurs with concomitant loss of a PhCOR³ fragment.



Cyclization of the Michael adducts formed from enehydrazines and DMAD, for example (136), in the presence of ppa proceeds to give pyrimidone-fused 1,2-diazepines (137) through formal closure of the *d* bond (Equation (22)) <92JCS(P1)1287>. In contrast, thermolysis of the adducts (136) in tetralin preferentially provides fused pyridine and pyrrole ring products.



In a related process, Dieckman cyclization of the 1,1'-bipyrroletetraacetic ester (**138**) affords [10b,10c]diazapyracehylene derivatives (**139**) and (**140**) (Scheme 19) <85TL5425, 85TL5429>.



Scheme 19

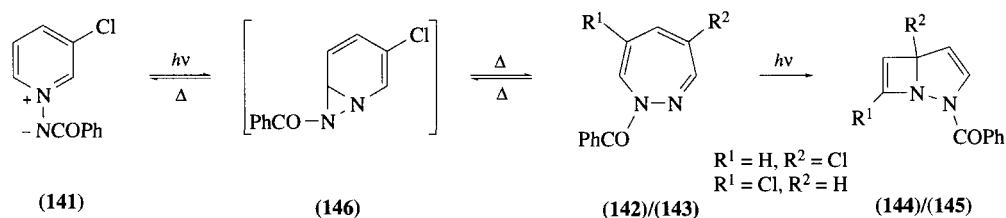
9.04.9.9 Type *de* (C + C—C—N—N—C—C)

The condensation of α -bromoacetophenone azines with dimethyl malonate in the presence of NaOMe affords 5,5-bis(methoxycarbonyl)-3,7-diaryl-5,6-dihydro-4*H*-1,2-diazepines <77BCJ2153, 92MI 904-01>; this method has been extended to reactions involving malononitrile and ethyl cyanoacetate in the presence of NaOEt to give similar 5,6-dihydro-3,7-diphenyl-4*H*-1,2-diazepines in 70 and 75% yields, respectively <86JHC557>.

9.04.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

9.04.10.1 From Pyridine *N*-Imides

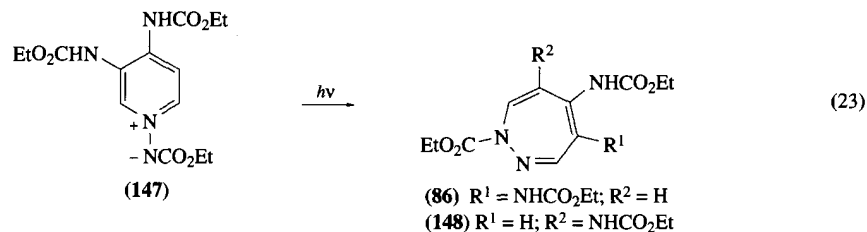
The photochemical conversion of pyridine *N*-imides to 1*H*-1,2-diazepines has been used on numerous occasions to prepare monocyclic and bicyclic heterocycles <83LA1374>. Photoinduced ring enlargement of the 3-chloro-*N*-iminopyridinium ylide (**141**) leads to simultaneous formation of two chlorodiazepines, (**142**) and (**143**) (Scheme 20). The major secondary photochemical step is formation of bicyclic isomers (**144**) and (**145**), and not a [1,7] sigmatropic shift of the benzoyl group <83TL3327>. 1,7-Diazanorcaradiene intermediates (**146**) have not been detected in this rearrangement process, but there is much evidence for their existence as short-lived species <84NJC223>.



Scheme 20

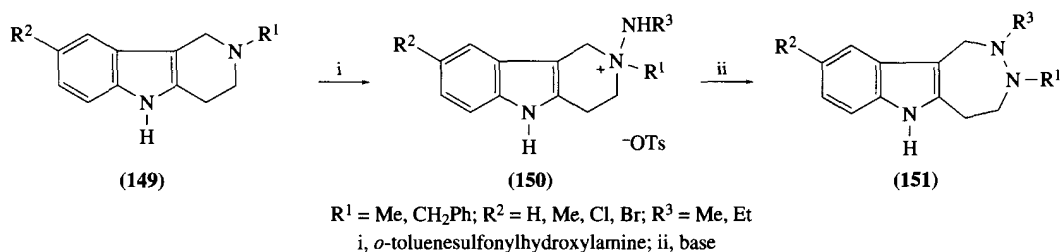
The photochemical reaction of *N*-iminopyridinium ylide (**147**) has given isomeric 1,2-diazepines (**86**) and (**148**) (Equation (23)); the ratio of which was solvent-dependent. The success of this reaction contrasts with the photoinduced rearrangement of similar *N*-iminopyridinium ylides from bicycles,

such as imidazo[4,5-*c*]pyridine, which gave alternative regiospecific formation of 4-amino-imidazo[4,5-*c*]pyridine derivatives <86T1511>. Azetidinodiazepines have also been prepared by treating pyridinium ylides with methylketene <85H(23)2589>.



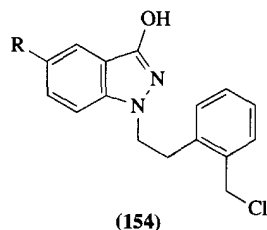
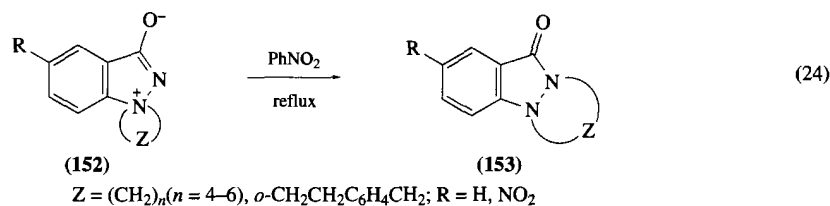
9.04.10.2 From Tetrahydro- γ -carbolines

Carbolines (149) react with *O*-toluenesulfonylhydroxylamine derivatives to give ammonium salts (150) which on treatment with base undergo ring enlargement to hexahydro-2,3-diazepino[5,4-*b*]indoles (151) (Scheme 21) <82H(17)163>.



Scheme 21

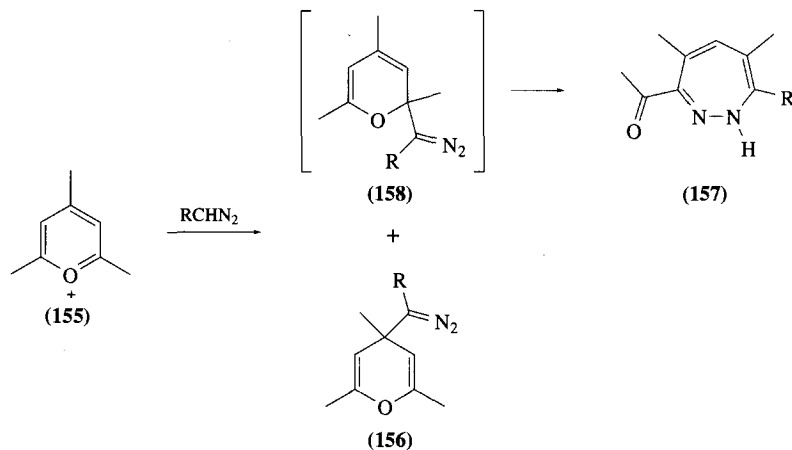
In a similar thermal process, rearrangement of spiro 1,1-disubstituted indazole oxides (152) gave variable yields of 1,2-disubstituted indazolinones (153), including diazepines (Equation (24)) <85JHC1743, 93JCS(P1)1119>. The overall neutral spirane (152; $\text{Z} = o\text{-CH}_2\text{CH}_2\text{C}_6\text{H}_4\text{CH}_2$, $\text{R} = \text{NO}_2$), gave a single product (154) in 95% yield, but thermolysis of the hydrochloride salt of (152) gave (154) (73% yield) in addition to its regioisomer (12%) <93JCS(P1)1119>.



9.04.10.3 From Pylidium Salts

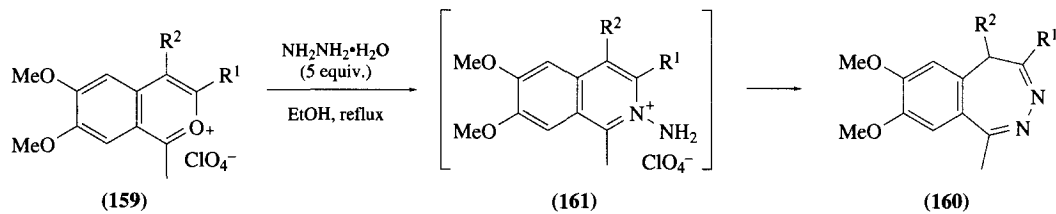
Electrophilic diazoalkane substitution of RCHN_2 ($\text{R} = \text{CO}_2\text{Et}, \text{P}(\text{O})(\text{OMe})_2$) with 2,4,6-trimethylpyrilium tetrafluoroborate (155) gave 4-diazoalkylpyrans (156) and 1,2-diazepines (157) (Scheme

22). The latter were formed by spontaneous isomerization of the intermediate 2-diazoalkyl-2H-pyrans (**158**) <87JOC3851>. In contrast, the analogous 4-methyl-2,6-diphenylpyrilium tetrafluoroborate gave only 4-diazoalkylpyrans.



Scheme 22

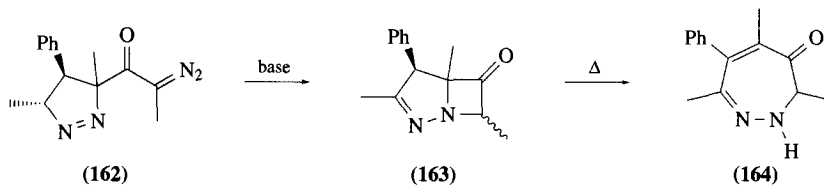
Treatment of benzopyrilium perchlorates (**159**) with excess hydrazine hydrate in refluxing EtOH has provided 5H-benzo-2,3-diazepines (**160**) in 63–75% yield (Scheme 23) <93KGS1475>. Reaction of (**159**; R¹ = Me, R² = CO₂Et, CN) with one equivalent of hydrazine hydrate affords 2-amino-isoquinolinium perchlorates (**161**) in 90% yield, which, in the case of the 4-cyano compound, proceeds to the benzodiazepine (**160**; R¹ = Me, R² = CN) in 73% yield.



Scheme 23

9.04.10.4 From Pyrazoles, Pyrazolines, and Related Species

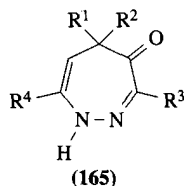
Sequential base-catalyzed ring closure of diazopropionylpyrazolone (**162**) and thermal rearrangement of the diazabicycloheptanone (**163**) gave diazepinone (**164**) and its 1,5-dihydro isomer (Scheme 24) <85JOC2141>.



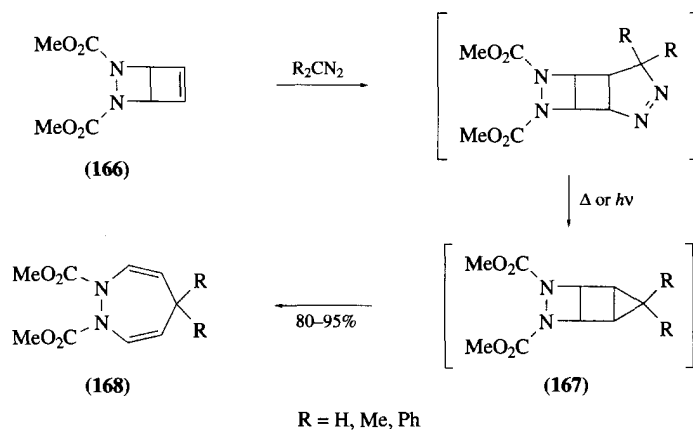
Scheme 24

1H-Pyrazolines formed by cycloaddition of diazoalkanes to unsaturated carbonyl compounds have been studied vigorously for their conversion into 1,2-diazepinones <83TL5469, 91JHC369>.

whereas diazoalkanes with substituted cyclobutenones afforded intermediates that generally form 4,5-dihydro-1*H*-1,2-diazepin-4-ones (**165**) in good to excellent yield <83TL5469>. Regioisomeric intermediates prepared by reaction with 2-diazopropane and 2-diazodiphenylmethane do not, however, undergo rearrangement.

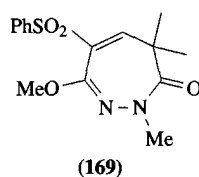


Cycloaddition of diazoalkanes to diazabicyclo[2.2.0]hexanes (**166**) and subsequent extrusion of nitrogen also affords diazatricyclo[3.2.0.0^{2,4}]heptanes (**167**) that are easily valence-isomerized to novel dihydrodiazepines (**168**) (Scheme 25) <84TL297>.

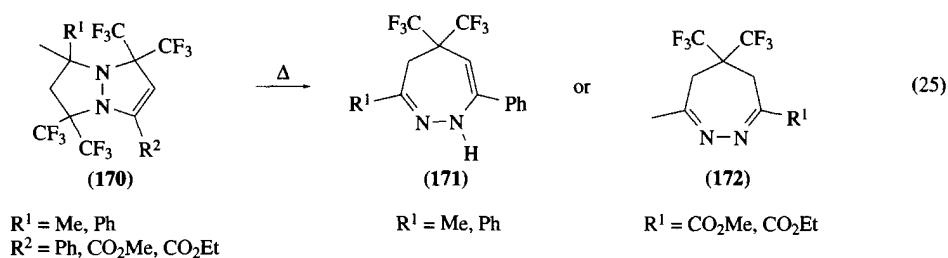


Scheme 25

A similar approach has been used in the synthesis of diazepinone (**169**) from a phenylsulfonylpyradiazinone precursor <91JHC369>.

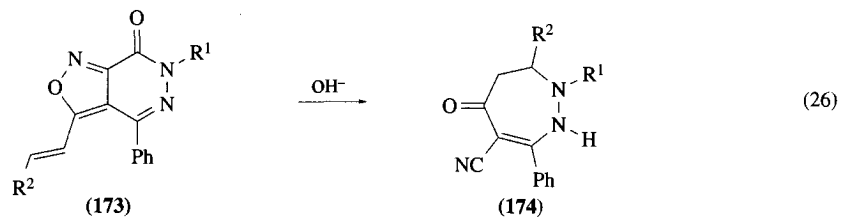


The thermolysis of 1,5-diazabicyclo[3.3.0]oct-2-enes (**170**) (Equation (25)) also provides a relatively simple synthesis of 4,5-dihydro-1*H*-1,2-diazepines (**171**) and 5,6-dihydro-4*H*-1,2-diazepines (**172**) through ring cleavage or a [3 + 2]-cycloreversion, depending upon the substitution pattern of the bicyclic skeleton <82LA1741>.



9.04.10.5 From Isoxazolo[3,4-d]pyridazin-7(6H)-ones

Vinylisoxazolopyridazinones (173), prepared by condensation of methylisoxazolopyridazinones with $R^1\text{CHO}$, are converted with alkali into 2,3,4,5-tetrahydro-1*H*-1,2-diazepin-5-ones (174) through a Michael-type addition (Equation (26)) <84H(22)1741>.



9.05

1,3-Diazepines

DAVID J. LE COUNT
Congleton, UK

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9.05.1 INTRODUCTION

The chemistry of monocyclic 1,3-diazepines is frequently the chemistry of ureas, thioureas, guanidines, and their various derivatives. With this in mind it should be noted that much of the chemistry reported in this chapter may well be applicable to smaller and, occasionally, larger ring analogues. Partially unsaturated 1,3-diazepines, notably formed by the ring expansion of cyclopropyluracils, have been reviewed by Wamhoff *et al.* <92AHC(55)130>.

No doubt arising from their similarity with the pharmacologically interesting and important 1,4-benzodiazepines, considerable attention has been devoted towards 1,3- and 2,4-benzodiazepines and analogues where the aryl ring has been replaced by a heterocyclic system. These and other bicyclic systems have been reviewed by Fryer and Walser <B-91MI 905-01>. A more general review of the field of 1,3-diazepine chemistry has been produced by Sharp <B-89MI 905-01>.

9.05.2 THEORETICAL METHODS

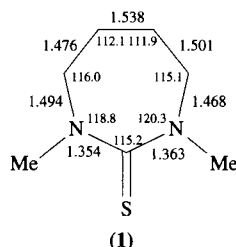
A study of the tautomerization of 2,2'-bis(4,5,6,7-tetrahydro-1,3-diazepine) within the context of a theoretical study of oxalamidines by semiempirical PM3-MNDO calculation <94CCA431> has revealed *syn* and *anti* forms which differ in the conformation about the methylene bridges. The geometry of the *anti* form is reported to agree remarkably well with the crystal geometry.

The dipole moment of 5,7-diazaazulene has been calculated by CNDOVSB, STO-3G and 4-31G *ab initio* methods <89JCS(P2)103>. As would be expected, the presence of the electron-attracting nitrogen atoms means that it has a lower ground state dipole moment than either azulene or 1- and 2-azaanulenes.

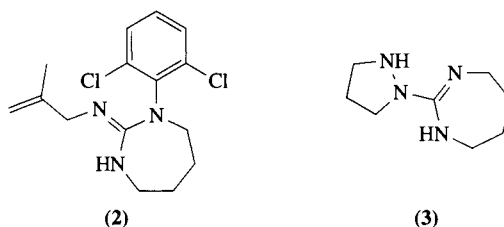
9.05.3 EXPERIMENTAL STRUCTURAL METHODS

9.05.3.1 X-ray Studies

Numerous useful x-ray crystallographic studies have been published, the simplest being that of hexahydro-1,3-dimethyl-1,3-diazepin-2-thione (**1**) <84DOK(277)868>.



Other structures include the aminoguanidines (**2**) <88JCS(P1)3311> and (**3**) <94JCS(P2)2407>, 2-methylene-1,3-diazepines <88JPR724, 92JOC235, 92JOC3026>, and a number of 1*H*-2,4-benzodiazepine derivatives <89CSC521, 92CSC97, 93JMC3361>.



9.05.3.2 NMR Studies

Although NMR studies are firmly established as part of the armory used for structural determination and verification of organic materials, there are few reports of systematic studies of 1,3-diazepines. The most useful emerges from a study of the electronic and conformational properties of cyclic ureas and thioureas in which ^{13}C -spectra of hexahydro-1,3-diazepines are presented <90JST(222)265>. The chemical shifts measured in CDCl_3 are shown, as reported, in Figure 1. The photoelectron spectra of these compounds have also been reported <89JST(196)181>.

9.05.4 THERMODYNAMIC ASPECTS

NMR studies have been used to investigate the conformational preferences of a number of fused 1,3-diazepine systems. The preferred conformation of *N,N'*-dimethyl-2,3,4,6-tetrahydro-2,4(1*H*)-diazepine is reported to be the chair-axial-equatorial conformer (**4**) <85TL13>; whereas the perhydro-system (**5**) is predominantly the *trans*-fused conformer <90MRC426>. An extensive NMR study of a number of hexahydropyrimidines *N,N'*-bridged by methylene groups has been undertaken in support

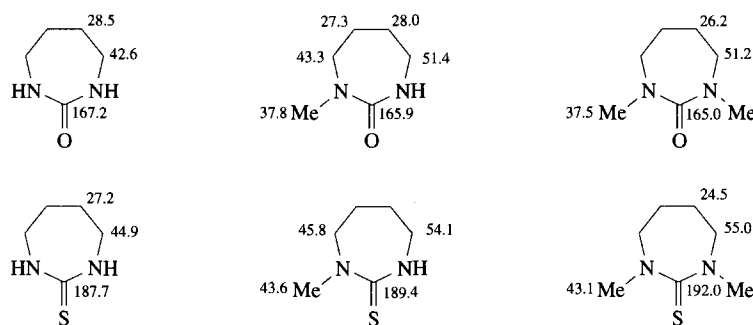
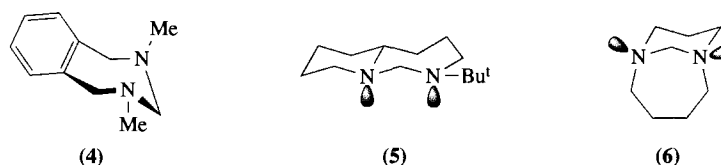


Figure 1 Carbon-13 NMR chemical shifts of hexahydro-1,3-diazepines.

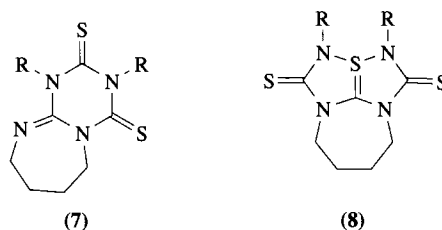
of photoelectron spectroscopy and theoretical methods (93JA6580). From data obtained from force field calculations 6-diazabicyclo[4.3.1]decane favors an *ax,ax* (or *out,out*) conformation (6), which is supported experimentally by both NMR and PE spectra.



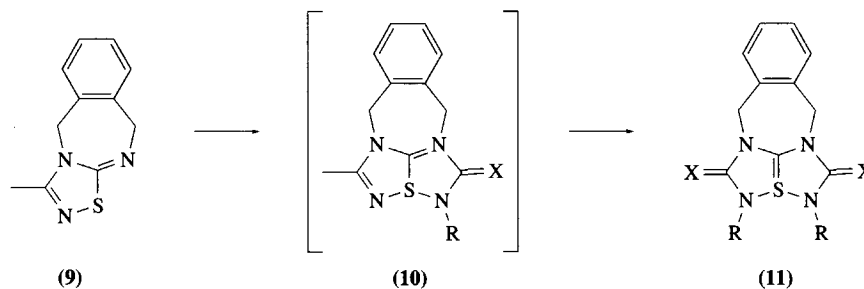
High performance thin layer chromatography (HPTLC), a useful technique for the study of the mechanisms and kinetics of organic reactions, has been applied to the base hydrolysis of a series of 4,5,6,7-tetrahydro-1,3-diazepines when pseudo first-order rate constants were observed (95MI 905-01).

9.05.5 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

All significant reports in this area concern reactions of reduced 1,3-diazepines with a 2-substituent. Thus the dilithium dianion of hexahydro-1,3-diazepin-2-thione reacts with methyl- and ethyl-isothiocyanates to yield the diazepinotriazindithiones (7; R = Me or Et) in modest yield (86BCJ3693). If the reaction is carried out in the presence of phenacyl chloride the hypervalent tricyclic tetraazapentalene system (8) is obtained in a one-pot reaction (88BCJ2419). In the corresponding pyrimidine series, it was shown that thermolysis or oxidation results in loss of one molecule of isothiocyanate which may then be replaced by a second, different group, causes the formation of asymmetric ring systems. This reaction was apparently not conducted in the diazepine system but that such a reaction might occur comes from the observation that (9) reacts with thiocyanates or isothiocyanates to give the tetracyclic analogues (11; X = O or S) (94HAC149). The reaction is proposed to proceed via intermediate (10) which loses acetonitrile and adds a further molecule of iso(thio)cyanate (Scheme 1).



It has also been observed that bromomagnesium complexes of hexahydro-1,3-diazepin-2-one, prepared using Grignard reagents, undergo the fixation of carbon dioxide. The resulting carbamate complexes transfer the fixed carbon dioxide to active methylene compounds such as acetophenone

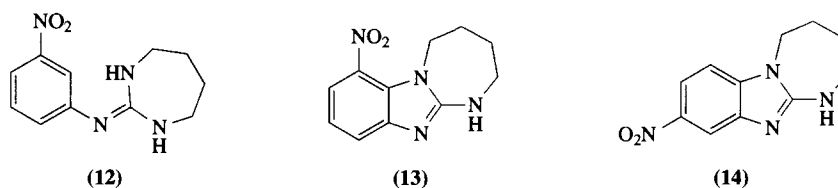


Scheme 1

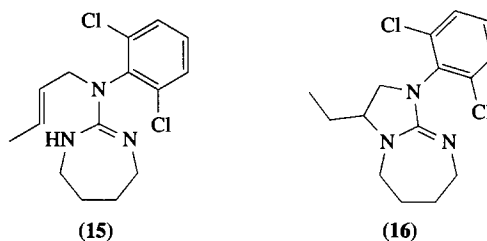
or propiophenone <83CC1487, 85NKK310>. The bis-magnesium complex is more effective in this process than the corresponding mono-complex.

Hexahydro-1,3-diazepin-2-thione may be conveniently converted into the *N,N'*-dialkyl-hexahydro-1,3-diazepin-2-one by treatment with alkyl halides in the presence of aqueous sodium hydroxide and a catalytic amount of benzyltriethylammonium chloride <82S464> and its reaction with (2-bromo-1-phenylethylidene)malononitrile affords 7-amino-8-cyano-9-phenyl-2,3,4,5-tetrahydropyrido[1,2-*a*][1,3]diazepine <90JOC4740>.

Appropriately substituted guanidines undergo oxidation leading to the formation of polycyclic derivatives. Thus (12) is oxidized by potassium *t*-butoxide in DMSO to give a 28 : 1 mixture of the isomers (13) and (14) in 58% yield <92S596>. If a ring nitrogen atom is alkylated the ratio changes to 19 : 1, whereas if the exocyclic nitrogen atom is further alkylated, only the *para* isomer is formed.

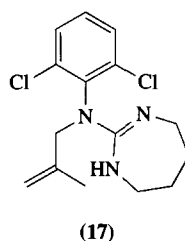


Bicyclic guanidines may be conveniently prepared by intramolecular Hg(II)-induced amination of alkenes <87S460>. Thus, the alkene (15) forms the bicyclic derivative (16) in 92% yield. The reaction also proceeds equally smoothly with 1-alkenyl derivatives.

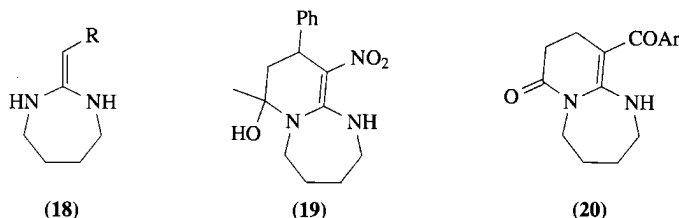


N-Substituted 2-arylamino-4,5,6,7-tetrahydro-1*H*-1,3-diazepines undergo aryl migrations in the presence of base, as exemplified in the formation of (2) from (17) <88JCS(P1)3311>. The reaction does not proceed, however, in the absence of the second substituent on the exocyclic nitrogen atom.

2-Alkylidene derivatives have been utilized in the formation of numerous bicyclic derivatives.



Thus in examples from the early 1990s, (**18**; R = NO₂) affords the hemiaminal (**19**) with benzylidene acetone <93AP(326)335>, whilst the ketone (**18**; R = COAr) yields (**20**) with methyl acrylate in boiling dioxan <89SC1801> or by UV-irradiation <93SC1039>.



9.05.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO NITROGEN

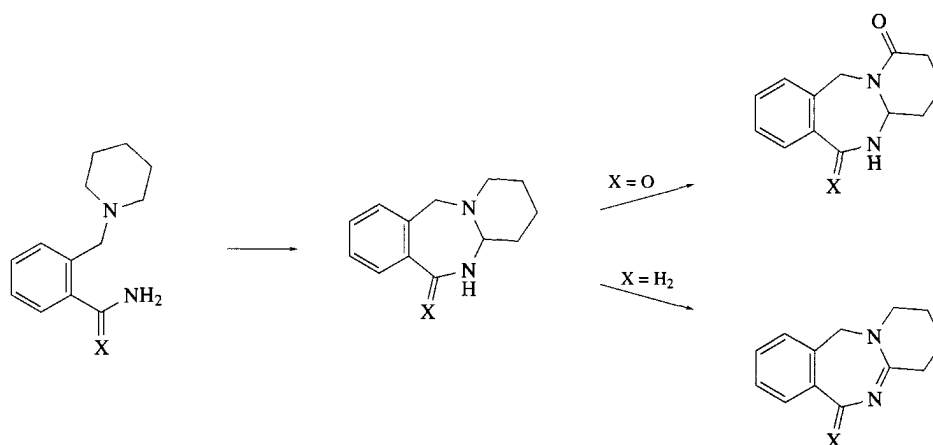
Treatment of 1-benzyloxycarbonyl-1*H*-1,3-diazepine and 3-benzyloxycarbonyl-3*H*-1,3-diazepines with trimethylsilyl iodide followed by hydrolysis yields in each instance the *N*-unsubstituted 3*H*-1,3-benzodiazepine, an indication that the 3*H*-tautomer is the most stable of the three possible tautomers <83H(20)2173>. Similar results were observed with thienodiazepines.

9.05.7 SYNTHESIS OF 1,3-DIAZEPINES BY RING CLOSURE

9.05.7.1 Formation of a Single Bond

9.05.7.1.1 Type a (N—C—C—C—C—N—C)

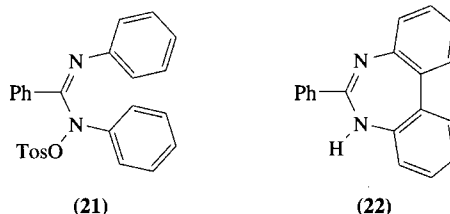
Chlorination of the bis-amide of glutaric acid followed by treatment of the resulting *N,N'*-dichloro derivative with base affords 2,4-dioxohexahydro-1,3-diazepine <82S973>. Hg(II)-edta oxidation of benzylamines containing an *ortho*-nucleophilic substituent offers a convenient route to annelated 2,4-benzodiazepines as illustrated in Scheme 2 <91AP(324)367>. Introduction of a methyl group into the α -position of the amino group suppresses the secondary oxidation step and increases the yield of the cyclization significantly such that it is essentially quantitative <92AP(325)177>. The reaction is not limited to cyclic amines, however, as the reaction also proceeds with 2-dimethylaminoethyl benzamides.



Scheme 2

9.05.7.1.2 Type c (C—C—N—C—N—C—C)

There are few instances where this mode of ring closure offers convenient syntheses of 1,3-diazepines. However, the preparation of 6-phenyl-5*H*-dibenzo[*d,f*][1,3]diazepine (**21**) in 35% yield by thermolysis of *N,N'*-diphenyl-*N*-(4-tosyloxy)benzaminidine (**22**) is a good example of this class of cyclization <83CB1822>.

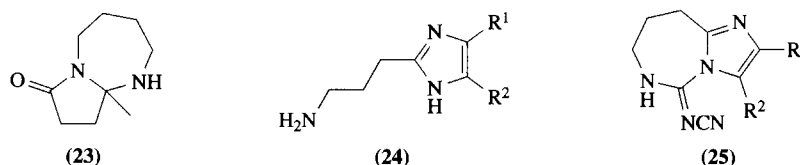


9.05.7.2 Formation of Two Bonds

9.05.7.2.1 Type ab (N—C—C—C—C—N + C)

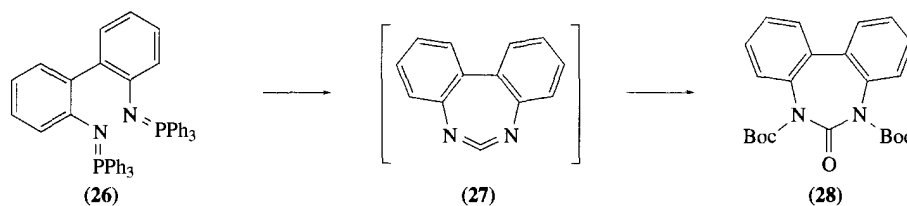
It is without doubt that the insertion of a C1 unit into 1,4-diaminobutanes is the most frequently used method for the formation of both monocyclic and bicyclic 1,3-diazepines systems. Examples include the use of aldehydes <84JOC5147, 87CZ179, 89TL6323, 91ACS1064>; acids and acid derivatives <82JMC340, 84JMC401, 88HCA77>; carbon disulfide <84JMC401, 90TL4003, 90TL5467, 91CZ224, 93JMC3361>; orthoesters <84JMC401, 91TL5031, 93JMC3361>; 1,1-carbonyldiimidazole (CDI) <86JOC267, 93JMC3361>; cyanogen bromide <93JMC3361>; urea <92PJC801>; dibromomethane <84PJC251>; dichloromethane <90AG(E)933>; diiododinitroethylene <92JOC235>; aryl nitriles <91CCC2288>, a reaction which appears to be catalyzed by the presence of La³⁺ ions <87JOC1017>; carbonimidic dichlorides <83SI033>; benzamidate <90M821>; and dithioates <88JPR724, 89SC943, 91CZ224, 93BCJ148>.

In addition to these more familiar methods, a number of novel approaches have been described. 1,4-Diaminobutane is reported to react with 1-chloro-2-alkylthioethyne to yield 2-alkylthiomethyl-3,4,5,6-tetrahydro-1,3-diazepines <89IZV906>. 1,4-Diaminobutane absorbed onto alumina or montmorillonite K₁₀ reacts with ethyl 4-oxopentanoate under microwave conditions to yield the fused pyrrolodiazepine (**23**) <92SL219>. Acylation of 2-(3-aminopropyl)imidazoles (**24**) with *N*-cyano-diphenyl-imidocarbonate offers an efficient synthesis of imido[1,2-*c*][1,3]diazepines (**25**) <84JHC753>. In an alternative approach to the use of carbon disulfide for the preparation of hexahydro-1,3-diazepin-2-thione, a method employing the use of carbon tetrachloride and sodium sulfide in the presence of the phase-transfer catalyst triethylbenzylammonium chloride (TEBA) has been described <83LA1839>; the yield is quoted as 70%. 1,3,4,5-Tetrahydro-1,3-benzodiazepin-2(*2H*)-one is reported to be formed in 81% yield by the high pressure reaction of 2-(2-aminophenyl)ethylamine with carbon dioxide in the presence of stoichiometric quantities of selenium and an oxidizing agent such as oxygen or DMSO <87BCJ1793> and 6,7-dihydrodibenzo[*d,f*][1,3]diazepin-6(*5H*)-one is isolated by the catalytic reduction of 2,2'-dinitrobiphenyl in the presence of CO, Bu^tOH, and Rh(CO)₄[−] <91JOM(420)119>.



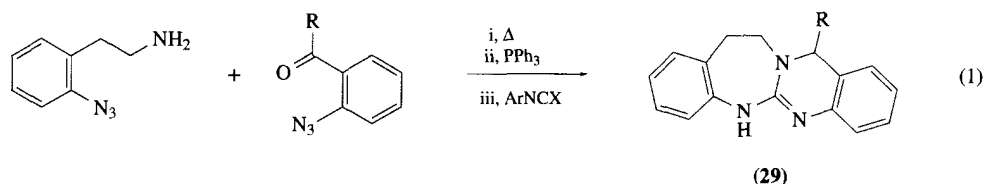
In a comprehensive series of papers, Molina *et al.* have demonstrated the usefulness of the aza-Wittig reaction in the formation of a number of annelated heterocycles, including 1,3-diazepines <93JOC1687, 94CB1641, 94JOC7306>. In a simple example, when the bis(iminophosphorane) (**26**), prepared from 2,2'-azidobiphenyl and triphenylphosphine, is allowed to react with two equivalents of Boc₂O and one equivalent of DMAP, the dibenzo-5,7-diazepin-6-one (**28**) is produced in 28% yield. The reaction is considered to proceed (Scheme 3) via the conversion of one of the iminophosphorane groups into isocyanate which cyclizes to afford the highly reactive carbodiimide (**27**). Further

reaction with a second equivalent of Boc_2O followed by rearrangement under the reaction conditions leads to the formation of (28).

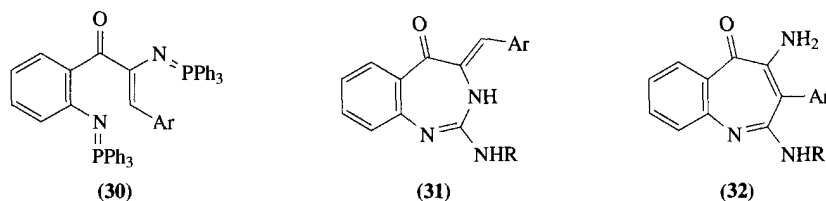


Scheme 3

The methodology can be utilized in the preparation of quite complex derivatives such as the bicyclic guanidine outlined in Equation (1). In this example, in a one-pot reaction, 2-(*o*-azidophenyl) ethylamine and an *o*-azidoaryl carbonyl compound react to form the corresponding imine which upon subsequent treatment with triphenylphosphine and an arylisocyanate affords the cyclic guanidine (29) in a consecutive aza-Wittig/($2\pi + 2\pi$) cycloaddition/transannular annelation reaction sequence.



The reaction is not limited to biaryl derivatives <94TL3817>. Treatment of the bisiminophosphorane (30) with an alkyl isocyanate or isothiocyanate furnished the 1,3-benzodiazepin-5-one (31). However, if an aryl iso(thio)cyanate is used, the reaction takes a different course, resulting in the formation of (after hydrolysis) the benzazepin-5-one (32).

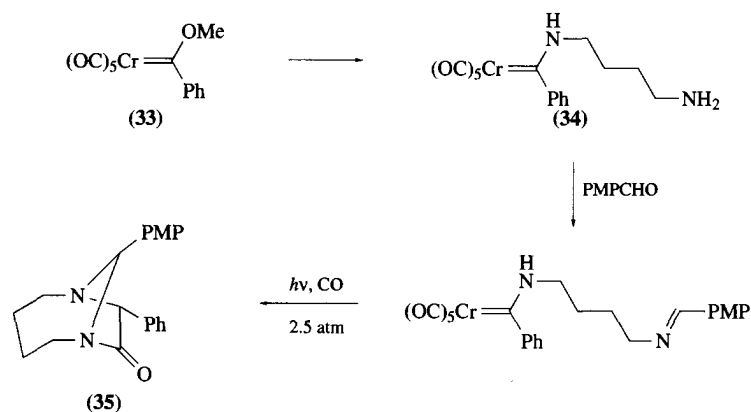


The formation of the bridged system (35) from 1,4-diaminobutane with concomitant insertion of carbon monoxide is a novel method for the preparation of a 1,3-diazepine by insertion of an aldehyde function (Scheme 4) <95JA5604>. The chromium(0) complex (33) is treated with the diamine to form the new complex (34) which when reacted with 4-methoxybenzaldehyde (PMPCHO) at room temperature followed by irradiation with carbon monoxide under pressure furnishes the diazepine (35) in an overall yield of about 60%.

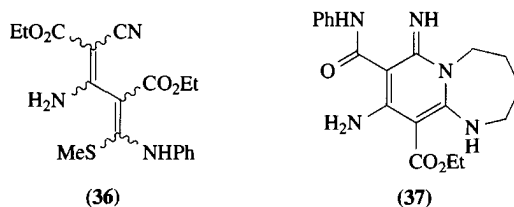
In a complex series of transformations, reaction of the diene (36) with 1,4-diaminobutane results in the formation of the bicyclic pyrido[1,2-*a*][1,3]diazepine (37) in what is a formal insertion of a Cl fragment into the diamine <95JHC477>. Initial nucleophilic replacement of the thiomethyl group by the diamine and subsequent cyclization is followed by a Smiles-type rearrangement, then sequential ring-opening and ring-closure transformations.

9.05.7.2.2 Type ad ($\text{C}-\text{C}-\text{C}-\text{C} + \text{N}-\text{C}-\text{N}$)

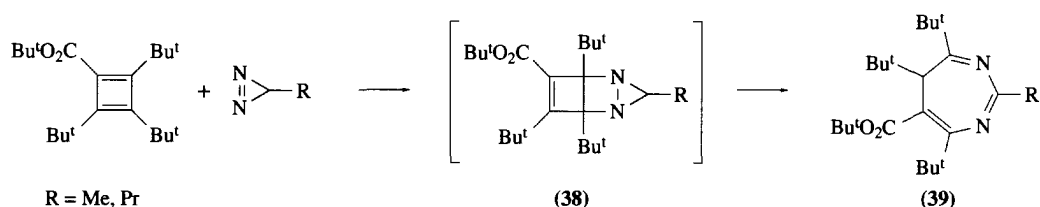
Reports of fully unsaturated monocyclic 1,3-diazepines are rare but the formation of 5*H*-1,3-diazepine is reported by Regitz and co-workers <88CB357>. A [$4\pi + 2\pi$] cycloaddition of 3-alkyl diazarines with *t*-butyl 2,3,4-tri-*t*-butyl-cyclobutadiene-1-carboxylate is the key step in this procedure, which affords the 1,3-diazepine (39). Clearly the initial step is the formation of the



Scheme 4



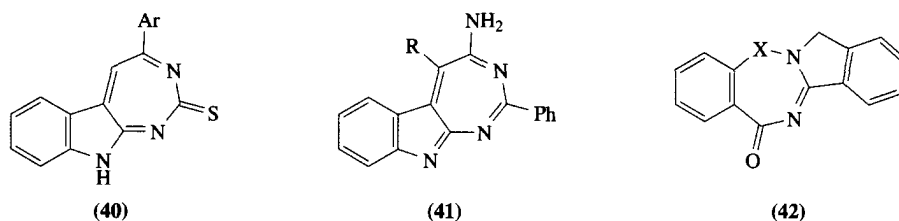
valence tautomer (38) which undergoes ring opening and a hydrogen shift to give the final product (Scheme 5).



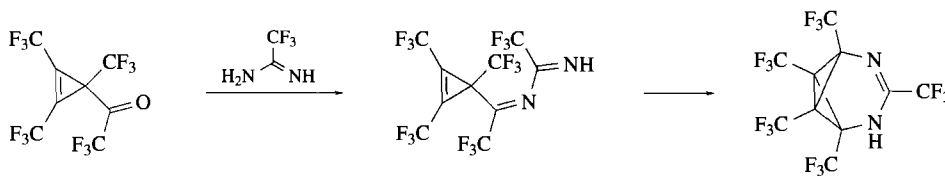
Scheme 5

Further examples of the reaction of electrophiles with thioureas and amidines have been reported. These include, for example, formation of 1,3-diazepino[4,5-*b*]indole-2-thiones (40) by the reaction of 3-aroylemethylenindol-2-ones with thiourea (90IJC(B)369) and 2-phenyl-1,3-diazepino[4,5-*b*]indoles (41; $R = CN$ or CO_2Et) by the reaction of 3-dicyanomethylene- or 3-ethoxycarbonylcyanomethyleneindole-2-one with benzamidine (92IJC(B)280). The latter reaction fails with *N*-substituted indolones, spiropyrimidines being formed instead. Annelated 2,4-diazepines (42; $X = CO$ or CH_2) are obtained by treatment of 1-amino-3*H*-isoindole with respectively phthaloyl chloride or 2-bromomethylbenzoyl bromide (93PHA812).

An interesting valence tautomer of 1,3-diazepine is claimed for the reaction of tris(trifluoro-



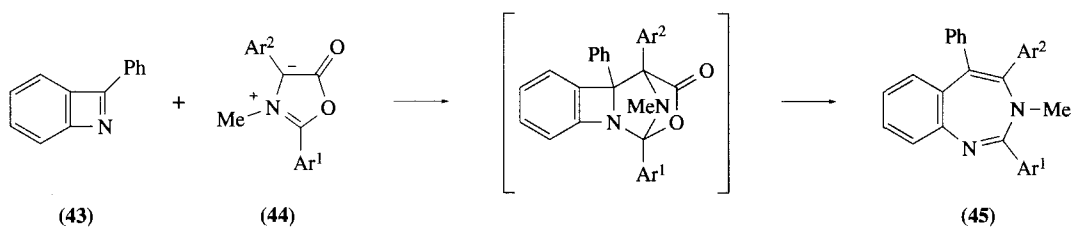
methyl)cyclopropenyl trifluoromethyl ketone with acetamidine in the presence of TiCl_4 <81TL1113>. The intermediary bis-imine readily undergoes a $\pi 2s + \pi 2s + \pi 2s$ rearrangement to form the diazepine (Scheme 6).



Scheme 6

9.05.7.2.3 Type ae ($\text{C}-\text{C}-\text{C}-\text{N} + \text{C}-\text{N}-\text{C}$)

Cycloaddition of the benzazete (43) to the munchnone (44) gives the 3*H*-1,3-benzodiazepine (45) <83CC1007>. The reaction is presumed to proceed by way of extrusion of carbon dioxide from the initially formed cycloadduct accompanied by rearrangement of the resulting dihydroazete (Scheme 7).



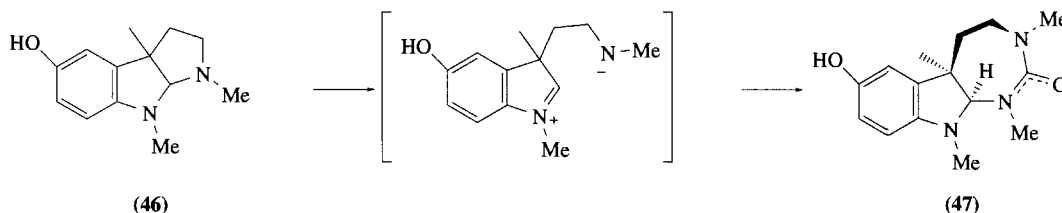
Scheme 7

9.05.8 SYNTHESIS OF 1,3-DIAZEPINES BY RING TRANSFORMATION

9.05.8.1 Transformation of a Five-membered Ring

Physostigmol (46) is transformed into isoserine (47) by reaction with methyl isocyanate <89TL61>. The reaction is presumed to proceed by way of a zwitterionic intermediate (Scheme 8) and the conformation of isoserine was determined by means of computer supported simulation of the NMR shifts of the protons on C_4 and C_5 .

6-Methylamino-5*H*-dibenzo[*d,f*][1,3]-diazepine is formed as a minor product in the irradiation of 1-methyl-4-phenyl-5-phenyliminotetrazole <85CB2164>.



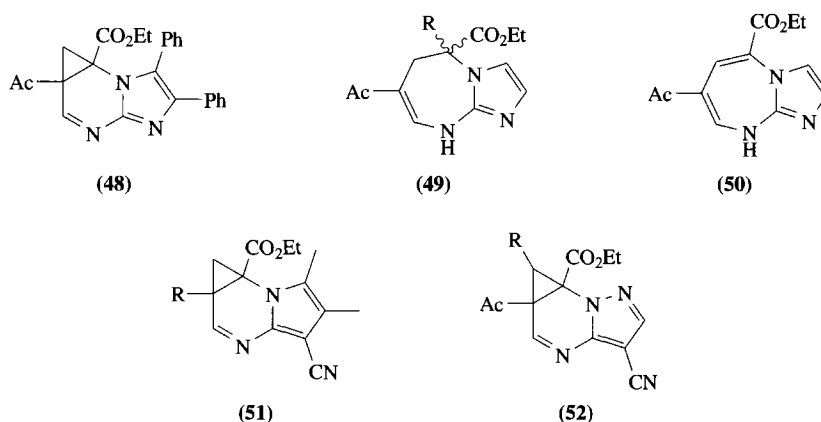
Scheme 8

9.05.8.2 Transformation of a Six-membered Ring

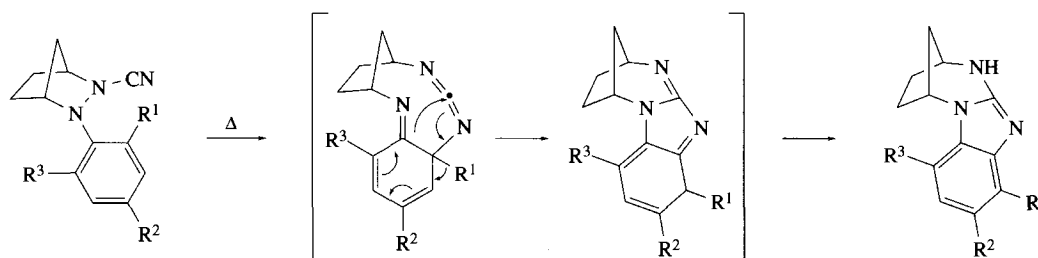
The ring expansion of aromatic azides, long established as a preparative procedure for azepines, has been applied to the formation of benzo-2,4-diazepines. Photolysis of 4-isoquinolyl azides in the

presence of primary amines is reported to afford the corresponding 5-alkylamino-1*H*-benzo-2,4-diazepines <82JCS(P1)421> and it is claimed by Suschitzky and co-workers <82JCS(P1)431> and also by Tsuchiya and co-workers <85CPB4564> that 5-methoxy-2,4-diazepines are obtained by photolysis in the presence of methanol, although there does seem a disparity in the identity of the products claimed by both sets of authors. The Japanese workers report to be unable to repeat the work of Suschitzky and co-workers, and claim that in their hands dihydroisoindoles are formed under the acidic conditions used by the Suschitzky group.

There are further reports on the ring expansion of pyrimidines to form 1,3-diazepines. Treatment of the cyclopropa[*e*]imidazo[1,2-*a*]pyrimidine (**48**) with acetic acid affords the imidazo[1,2-*a*][1,3]diazepine (**49**; R = OAc) whilst treatment with hydrogen in the presence of 5% palladium on charcoal gives the derivative (**49**; R = H) <82CPB1289>. In a bromination/debromination sequence, the fully unsaturated derivative (**50**) is formed from (**49**; R = H). Similar transformations have been reported from cyclopropa[*e*]pyrrolo[1,2-*a*]pyrimidines (**51**; R = CO₂Et, OAc) <83JHC81> and cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidines (**52**; R = H, Ph, CO₂Et) <82JHC519, 83H(20)1913, 85JHC785>.



A tris-aza-Cope rearrangement of *N*-cyano-*N'*-aryl or vinylhydrazines leads to the formation of polycyclic imidazo[1,3]diazepine derivatives <92T5249>. In the example shown (Scheme 9), the rearrangement requires the migration of the substituent in the *ortho* position of the aryl ring. The nature of the substituent does not appear to affect the reaction as migration is observed with hydrogen, chlorine, bromine, alkylthio, cyano, and methyl groups. Electron-withdrawing substitution in the *para* position decreases the reaction rate but not the final yield which is high in all cases.

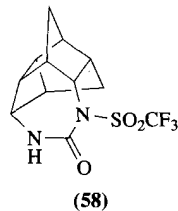
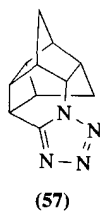
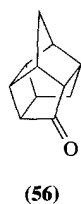
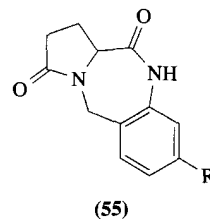
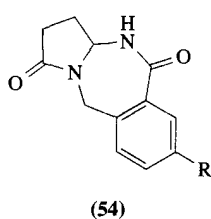
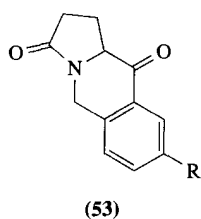


Scheme 9

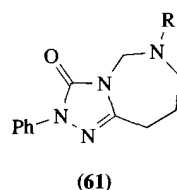
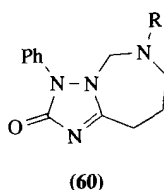
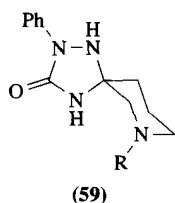
Schmidt rearrangement of the tetrahydroisoquinolone (**53**) has been shown to give a mixture of the 1,3- and 1,4-benzodiazepines (**54**) and (**55**) <94JHC87>. The 1,4-benzodiazepine is the predominant product, such that when R = H it is the only product. When R = F, however, the 1,4-diazepine is still the major product (60%) but the yield of the 1,3-diazepine is increased to 40%.

An unusual Schmidt reaction has been observed with ketone (**56**) <95H(40)223>. When the reaction is carried out using hydroxylamine *O*-sulfonic acid/formic acid, the expected ring expansion to the tetrahydropyridinones occurs. With hydrazoic acid, however, the unexpected 1,3-diazepine system is obtained (**58**). This observation is rationalized by the intermediate (**57**), formed by addition of hydrazoic acid to the initially formed lactam, which then undergoes a Huisgen rearrangement.

An interesting variation of the ring expansion of 3-oxopiperidines has been observed by Gstach

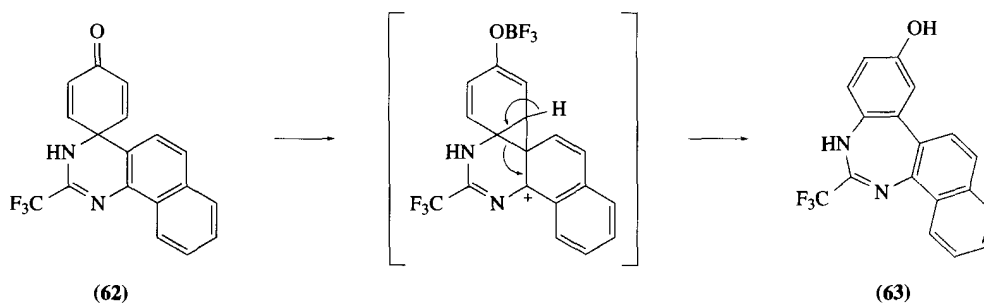


and Seil which is dependent on the nature of the substituent on the nitrogen atom (90S1048). Thus treatment of *N*-substituted piperidones with phenyl hydrazine followed by reaction with KNCO gives the spirotriazolinone (59). Oxidation with KMnO_4 affords the two annulated triazolo[1,3]diazepines (60) and (61). Where $\text{R} = \text{COPh}$, the 1,5-annulated product is obtained in high yield, with only a small amount of the 4,5-isomer, in the case of $\text{R} = \text{Me}$, it is the 4,5-annulated system which is the major product.



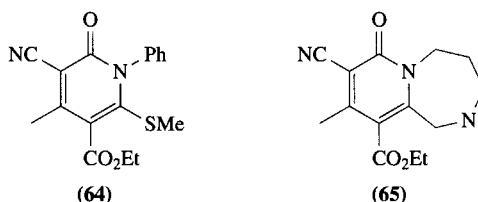
The spirolactone (62) undergoes a Lewis acid dienone-phenol rearrangement with BF_3 etherate to afford the 5*H*-diaryl[*d,f*][1,3]diazepine system (63) (Scheme 10) (94TL5235). It had previously been recorded that 1-methyl isoquinoline *N*-acylimides rearrange to form 1*H*-1,3-benzodiazepines (80CPB2602, 84CHEC-I(7)605), but the rearrangement failed with 2-methylquinoline *N*-acylimides, although the furano-, thieno-, and pyrrolo-analogues did undergo the rearrangement. It has now been demonstrated that the rearrangement will proceed if the quinoline carries electron-donating substituents in the 6- and/or 8-positions (82CPB3757).

Reaction of the thiomethylpyridine (64) with 1,4-diaminobutane is reported to afford the pyrido

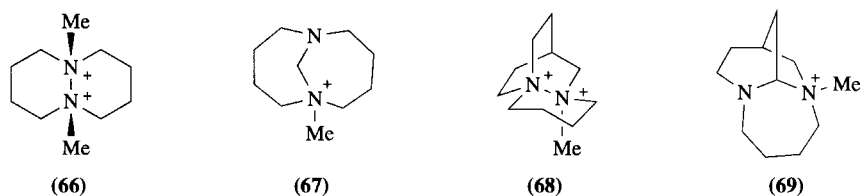


Scheme 10

[1,3]diazepine derivative (**65**) <94JHC393>. The mechanism proposed is identical in essence to the preparation of (**37**) from the diene (**36**).

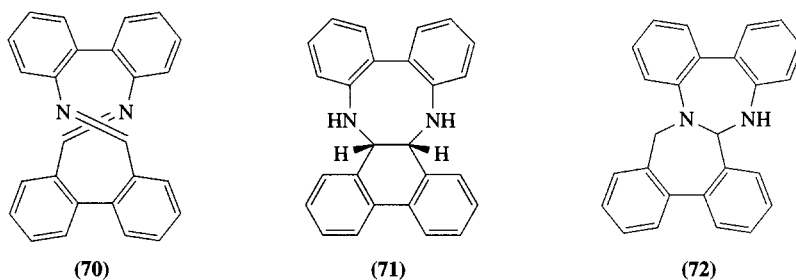


Deprotonation of the dication *cis*-1,6-dimethyl-1,6-diazoniabicyclo[4.4.0]decane (**66**) results in products derived from deprotonation at a methyl group, including 1-methyl-1-azonia-6-bicyclo[4.4.1]undecane (**67**) <84JCS(P2)411, 86JOC3169>, and deprotonation of the dication of 6-methyl-1,6-diazoniatriacyclo[6.2.2.0^{1,6}]dodecane (**68**) affords the monoion of 1-methyl-1-azonia-6-azatriacyclo[7.2.1.0^{6,11}]dodecane (**69**) <86JOC3169>.



9.05.8.3 Transformation of an Eight-membered Ring

Whilst most ring transformations in the synthesis of 1,3-diazepines involve ring-expansion reactions, there are isolated reports of ring contraction. Thus irradiation of the bis-imine (**70**) affords the diazocine (**71**) which, after *meso-dl* transformation, is converted into the bis-1,3-diazepine (**72**) <95LA657>. The product is identical to that obtained by the electrochemical reduction of (**70**) <82JOC4452>.



9.06

1,4-Diazepines

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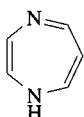
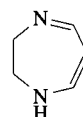
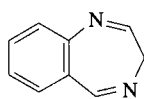
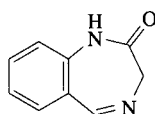
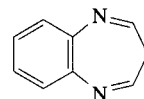
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9.06.1 INTRODUCTION

Undoubtedly the driving force for much of the 1,4-diazepine chemistry has been the commercial success of the important central nervous system (CNS)-active 1,4-benzodiazepines. By contrast, the monocyclic 1,4-diazepines have received much less attention and the lion's share of this has been on 2,3-dihydro-1,4-diazepines and their salts.

In this chapter, the general outline used for 1,4-diazepines in *Comprehensive Heterocyclic Chemistry, First Edition* (CHEC-I) <84CHEC-I(7)593> is followed but with an expanded section on theoretical methods, experimental structural methods and thermodynamic aspects. The format of CHEC-I is followed in discussing synthetic methods and the examples are drawn mainly from the literature since 1982. The reactions of the 1,4-diazepines are presented in the following order: fully unsaturated monocyclic systems first, then dihydro, tetrahydro, and hexahydro systems followed by the benzodiazepines again in the same order of unsaturation in the seven-membered ring.

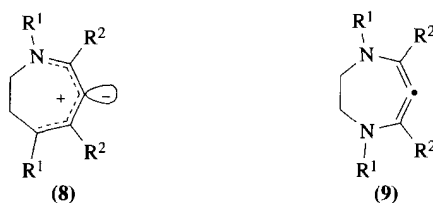
The ring numbering and accepted system of nomenclature for the 1,4-diazepines are illustrated in the structures (1)–(7). These structures are representatives of the tautomeric forms that have been most studied. Examples of all the fully unsaturated monocyclic 1,4-diazepines have been described and all are very unstable. In the dihydro-1,4-diazepines, the 2,3-dihydro-1*H* compounds have been studied most. For the benzo analogues the 3*H* series are usually more stable than the 1*H* and although the parent compounds of both series are unknown, there is an extensive chemistry on substituted analogues especially in the 3*H* series. The benzodiazepin-2-ones have been widely studied as befits their commercial importance. The syntheses and reactions of the 1,5-benzodiazepines are considered separately in the appropriate sections. This chapter does not deal specifically with hetero-fused diazepines, dibenzodiazepines, and the various pharmacologically interesting tricyclic systems derived by ring fusion usually between N-1 and C-2 of the benzodiazepines.

1*H*-1,4-diazepine (1)2*H*-1,4-diazepine (2)6*H*-1,4-diazepine (3)1*H*-2,3-dihydro-1,4-diazepine (4)3*H*-1,4-benzodiazepine (5)1*H*-1,4-benzodiazepin-2(3*H*)-one (6)3*H*-1,5-benzodiazepine (7)

Reviews of interest are listed below: general interest <84CHEC-I(7)593, B-89MI 906-01>; 2,3-dihydro-diazepinium salts, syntheses, and reactions <93AHC(56)1>; 1,4- and 1,5-diazepines and reduced derivatives, syntheses, and reactions <B-91MI 906-01>; 1,4-benzodiazepines spectroscopic aspects, medicinal chemistry, and clinical aspects <B-83MI 906-01>.

9.06.2 THEORETICAL METHODS

Photodebromination of 6-bromo-2,3-dihydro-1,4-diazepinium ions has been assumed to involve the intermediate formation of an onium ion (8) rather than an allene (9), the formation of which would involve the loss of delocalization energy of ca. 80 kJ mol⁻¹ <82JCR(S)80>. MNDO calculations, however, suggest that for the isolated molecule, intermediacy of the allene (9) should be preferred.



The vibrational and electronic spectra of a number of 2,3-dihydro-5-trifluoromethyl-7-aryl-1,4-diazepines have been measured and the various absorption bands and the electronic transitions of the latter assigned using INDO/S calculations of electronic transition energies (93CJS82). In a similar investigation, the gas-phase photoelectronic spectra of the therapeutically important benzodiazepines, medazepam, diazepam, and chlordiazepoxide have been measured and correlations made on the basis of EHT and HAM/3 calculations (88SA(A)1079). The changes in electronic structure brought about by the formation of the seven-membered ring relative to acyclic comparitors are emphasized, notably in the energy and composition of the molecular orbitals.

MM2 calculations have been used to estimate the conformational contribution to the observed differences in protonation behavior of fully ionized 1,4-diazacycloheptane-*N,N'*-diacetic acid with respect to its six- and eight-membered analogues (90JCS(P2)2211). These calculations indicate that the observed differences are conformationally dependent. Conformational aspects of 2,3-dihydro-1*H*-1,4-diazepines and the corresponding benzodiazepines have been studied using PM3 methodology (92JOC3320). These studies include the effect of substitution and protonation. A half-chair conformation is preferred, although increasing substitution increases the contribution of a boat conformation which becomes the most stable conformation in 5-substituted 1*H*-1,4-benzodiazepines.

Numerous investigations to correlate the molecular parameters with pharmacological activity have been reported (77JMC1206, 79MI 906-01, 84MI 906-01).

9.06.3 EXPERIMENTAL STRUCTURAL METHODS

This section seeks to present the salient features of those experimental structural methods which have proved of general use in establishing the structure of 1,4-diazepines. There is a large body of literature on the mass spectra and UV spectra of benzodiazepine based drugs, concentrating on the detection of these drugs and their metabolites in biological fluids but this aspect is not considered here.

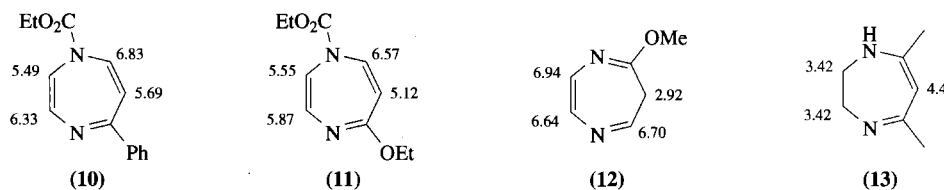
9.06.3.1 Infrared Studies

The infrared spectra of a series of 1*H*-, 2*H*-, and 6*H*-1,4-diazepines all show C=N absorptions in the range 1615–1640 cm⁻¹ (87CPB3175, 87CPB1179, 90CPB2911). The amide carbonyl of 1-ethoxycarbonyl 1,4-diazepin-5-one is observed at 1674 cm⁻¹ which is within the range expected for a cyclic lactam. 2,3-Dihydro-1,4-diazepines do not exhibit a normal C=N absorption; characteristic N—H bands are found between 3150 and 3190 cm⁻¹ (65CB2701). The infrared spectra of 2,3-dihydro-diazepinium salts are more complicated than those of the free bases and have been reviewed (93AHC(56)1).

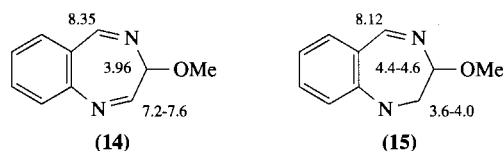
9.06.3.2 NMR Studies

In the proton NMR, the chemical shifts of all the ring protons of the fully unsaturated 1,4-diazepines are found at the lower end of the range expected for alkenic protons (δ 5.0–7.0). In the structures presented below, the chemical shifts of the protons are listed alongside the appropriate atom. Typically, the coupling constant for the 2,3-protons is 6 Hz and for the 6,7-protons 9 Hz (87CPB3166, 90CPB2911). The structure of the 6*H*-1,4-diazepine (12) was assigned from its NMR spectrum; the 6-methylene protons appeared as a doublet at δ 2.92 (J = 5 Hz) and the 7-proton at δ 6.70 (J = 5 Hz) (87CPB3175). This contrasts with the 6-proton of 1-ethoxycarbonyl-5-ethoxy-1*H*-1,4-diazepine (11), which is found as a doublet at δ 5.12 (90CPB2911). For 2,3-dihydro-1,4-diazepines

(e.g. (13)), the 2- and 3-methylene protons are found in the range δ 3–4 <65CB2701>. A characteristic of these compounds is that the 5- and 7-protons appear downfield of the 6-proton (δ 6.5–7.0 and 4.4–4.8, respectively) and a similar relationship is seen also with the related 1,2-dihydro-1,4-diazepinium salts <93AHC(56)1>.



The key chemical shifts for a number of pharmacologically important 1,4-benzodiazepines have been tabulated <80JHC1483, 85MRC280>. However, since for the most part, these compounds have an aryl substituent in the 5-position and a carbonyl group in the 2-position data on the diazepine ring protons are restricted to the 3-protons, which when methylene, are found between δ 4.3 and 4.9. In the less heavily substituted benzodiazepines (14) and (15) the 5-benzylic alkenic proton is shifted downfield to δ 8.35 <87CPB4110>.



Carbon-13 NMR is a powerful adjunct to proton NMR in assigning the structures of 1,4-diazepines and the characteristic chemical shifts for some representative compounds are listed in Table 1.

Table 1 Carbon-13 chemical shifts for representative 1,4-diazepines.

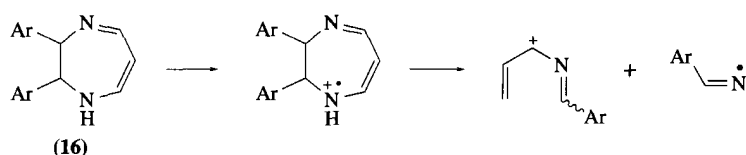
Structure	2C	3C	5C	6C	7C
	50.01	53.78	162.65	91.23	155.66
	46.51	54.43	173.41	45.55	49.09
	127.66	128.36	146.30	38.65	139.36
	169.90	57.0	168.8		

In the case of 5-methoxy-6H-1,4-diazepine, the 6H structure rather than the tautomeric 2H, 3H, and 7H structures was assigned from the proton and ^{13}C spectra <87CPB3175>. The ^{13}C spectra of

the various benzodiazepine based drugs have been recorded <78JHC1083, 81OMR(15)99, 81AP(314)186, 85MRC280, 87MRC642>. In a ^{15}N study of a number of 5-aryl benzodiazepin-2-ones, the signal at -54.5 ppm was assigned to N-4 and the high field signal at -253.0 ppm to N-1 <83OMR(21)621>. The influence of substituents in the 5-aryl ring on the N-4 chemical shift and the influence of substituents in the fused phenyl ring on the ^{15}N chemical shift has been recorded <81AP(314)733, 83OMR(21)621>.

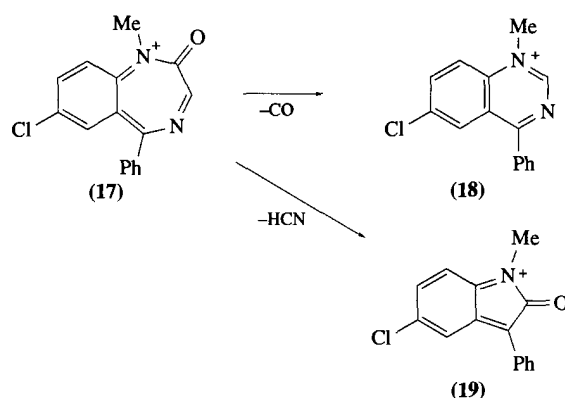
9.06.3.3 Mass Spectrometry

Electron impact mass spectrometry of a series of 2,3-diaryl-2,3-dihydro-1,4-diazepines (**16**) showed an intense molecular ion peak and in all the cases studied the initial fragmentation step was the same, namely cleavage of the N(1)—C(2) bond with the loss of an $\text{ArCH}=\text{N}$ radical <65CB3479>. The other major peaks arose by cleavage of the initially formed cation fragment (Scheme 1).



Scheme 1

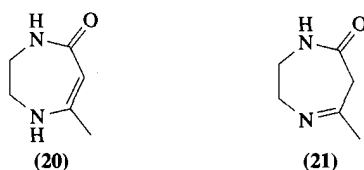
It was shown for diazepam and some of its close analogues that the main fragmentation pathway involved the loss of H from the parent ion (**17**) followed by the loss of CO to give a quinazoline (**18**) or HCN to give an indolone (**19**) (Scheme 2) <70JMC475>. These fragmentation pathways are analogous to the known chemical reactions of benzodiazepinones following proton abstraction from C-3. The mass spectra of 2,3-dihydrodiazepinium salts are generally similar to those of the free bases <93AHC(56)1>.



Scheme 2

9.06.3.4 Electronic Spectra

In an early paper, the diazepinone (**20**) was assigned this structure rather than the isomeric (**21**) based on the similarity of its UV spectrum to that of ethyl β -methylaminocrotonate <62JOC3565>.

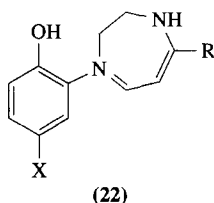


The electronic spectra of a series of 2,3-dihydro-5-aryl-7-alkyl-1,4-diazepines have been measured and analyzed in conjunction with a correlation energy diagram for some of the important molecular

orbitals as calculated by the INDO/S method for the various tautomeric forms. It was concluded that the compounds exist in the conjugated rather than the bis-imine tautomer <93CJS82>. The observed absorption bands were assigned to various intramolecular charge-transfer transitions involving the aryl and diazepine rings and to locally excited transitions in the diazepine ring.

The important absorption bands for a number of benzodiazepines have been reported (typically, bands are found at 200, 230, and 315 nm). The effects of substituents in the aryl rings on these absorption bands were investigated and these were not only dependent on electronic properties of the substituent but also on the stereochemical changes they induce in the molecule <75EJM433>. The electronic spectra of 2,3-dihydrodiazepinium salts have been reviewed <93AHC(56)1>.

5-(2-Hydroxyaryl)-7-substituted-2,3-dihydro-1*H*-1,4-diazepines (**22**) show brilliant yellow-green, yellow, or orange fluorescence when irradiated in the solid state at 365 nm. Solutions of these compounds do not fluoresce but fluorescence reappears when the solutions are made more viscous, for example, by addition of glycerine <85S339>.

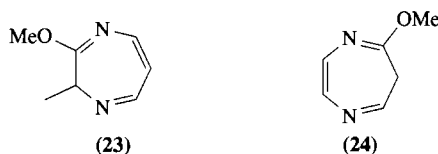


9.06.4 THERMODYNAMIC ASPECTS

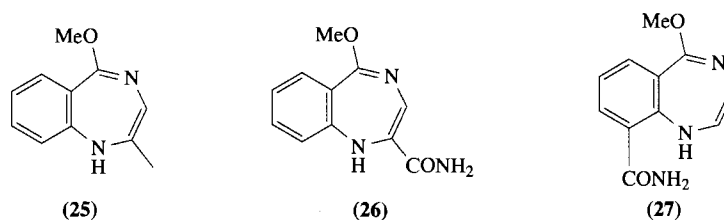
9.06.4.1 General Aspects

By analogy with azepines and 1,2-diazepines <81H(15)1569>, the fully unsaturated 1,4-diazepines with their 8π electron system should not be aromatic but should behave as cyclic polyenes and, like cycloheptatriene should have a chair or boat conformation. If the ring system were able to become planar, one would expect the fully unsaturated 1,4-diazepines to be anti-aromatic. Additional evidence for the nonaromatic nature of the 1,4-diazepines is provided by the NMR spectra, where the ring protons are found in the typical range for alkenic protons, i.e. δ 5.0–7.0.

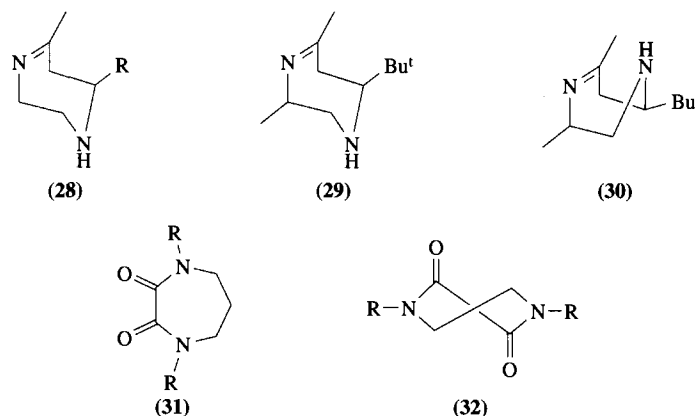
For monocyclic fully unsaturated 1,4-diazepines, the NH forms are extremely unstable and have been isolated only as their acylated derivatives, for example, (**10**). The CH forms, 2*H*- and 6*H*-1,4-diazepines (**23**) and (**24**), are more stable and can be isolated but are found to decompose on standing, even at low temperature <87CPB1179>. Although (**23**) can be purified by chromatography on silica, (**24**) is extremely susceptible to decomposition on both silica and alumina but can be chromatographed on sephadex or kieselguhr <87CPB3175>.



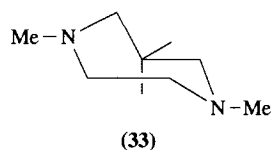
The fully unsaturated 1,4-benzodiazepines (e.g. (**25**)) also are unstable to chromatography and decompose on storage. By contrast, the analogues with an amide group at C-2 (**26**) or C-9 (**27**) are stable crystalline solids and it is suggested that this stability is a result of an intramolecular bond between the 1-NH and the adjacent amide group <90CPB2919>.



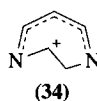
From a detailed analysis of the NMR spectra (proton and ^{13}C) of some 5-methyl-7-alkyl-1*H*-2,3,5,6-tetrahydro-1,4-diazepines (**28**), it was concluded that these compounds adopt a chair conformation with the 7-alkyl substituents ($\text{R} = \text{Me}, \text{Pr}^i, \text{Bu}^t$) in an equatorial position. The introduction of a methyl group at C-3, when the C-7 substituent is Bu^t , gave two separable isomers one of which was considered to have a chair conformation (**29**) and the other a boat or twist-boat conformation (**30**) $\langle 84\text{PJC}721 \rangle$. The conformation of the saturated 1,4-diazepine ring is sensitive to the nature and position of substituents in the ring. Proton NMR and molecular mechanics calculations for some *N,N'*-dialkylamino-1,4-diazepine-2,3-diones (**31**) and their monothio and dithio analogues point to a twist-boat conformation with C-2 symmetry (**32**) $\langle 81\text{JCS(P2)}1344 \rangle$.



Conformational studies on alkyl substituted hexahydro-1,4-diazepines have shown that these exist in a chair conformation (**33**) $\langle 79\text{PJC}2135 \rangle$.



The 2,3-dihydrodiazepinium system has been studied extensively and the conformations deduced from proton NMR, UV spectroscopy, and x-ray crystallography $\langle 93\text{AHC}(56)1 \rangle$. These salts have a flat, helical delocalized vinamidinium portion $[\text{N}(1)-\text{C}(5)-\text{C}(6)-\text{C}(7)-\text{N}(4)]$ whose ends are linked by a puckered dimethylene bridge (**34**).



As would be expected for this important class of drug, the benzodiazepines have been the subject of intense study, much of it driven by a desire to relate biological activity to molecular shape. The benzodiazepin-2-ones adopt a cycloheptatriene-like boat conformation while their reduced analogues and compounds lacking the 2-carbonyl group adopt a cycloheptadiene-like pseudo boat conformation $\langle \text{B-83MI } 906-01 \rangle$. The use of NMR spectroscopy and x-ray crystallography in determining the conformations of benzodiazepines has been reviewed $\langle \text{B-83MI } 906-01 \rangle$. X-ray studies on diazepam and two closely related but biologically relatively inactive analogues have shown that despite their disparate biological activity, the three compounds have very similar conformations $\langle 74\text{JMC}374 \rangle$.

9.06.4.2 Ring Inversion

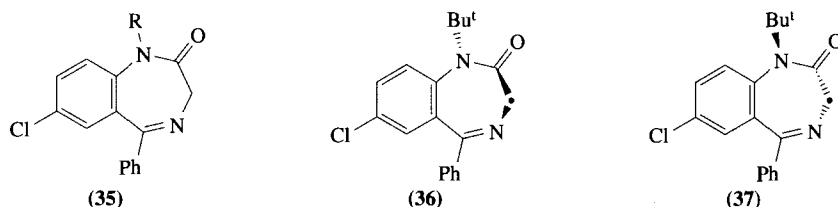
2,3-Dihydrodiazepinium salts, which do not have large substituents at the 2- and 3-positions, undergo rapid ring inversion at room temperature. This is clearly seen in their NMR spectra where the 2,3-methylene protons appear as singlets at room temperature but as AA'BB' multiplets at lower

temperatures. The factors governing the barriers to inversion in these systems are mainly the size of the substituents on the planar part of the ring rather than their electronic effects (73JCS(P2)1729, 93AHC(56)1). Ring inversion is inhibited by large substituents at the 2,3-position of the diazepine ring and for *cis*-2,3-di-*t*-butyldihydrodiazepinium cation the NMR spectrum is unchanged even on heating to 100°C (93AHC(56)1).

The conformations and ring inversions for alkyl-substituted tetrahydrodiazepines have been studied using ¹H NMR; for 5,7,7-trimethyl-2,3,6,7-tetrahydro-1*H*-1,4-diazepine, a ring inversion between two equivalent chair conformations has been reported and this process is hindered at a temperature of -120°C (84PJC721).

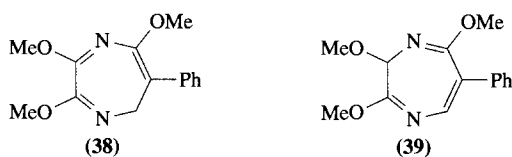
The influence of the 2,3-substituents on the energy barriers to inversion for *N,N'*-dialkyl-perhydrodiazepines (31) has been studied using a combination of ¹H NMR and molecular mechanics calculations. These compounds have a twist-boat conformation and ring inversion would involve passage through a planar *s-cis*-(thio)oxamide conformation where there would be a greater energy cost for the bulkier thiocarbonyl substituents compared to the carbonyl substituents. The relative barriers to inversion for (31) and the analogue in which the 2,3-carbonyls are thiocarbonyl are 11.1 and 24.1 kcal mol⁻¹, respectively (81JCS(P2)1344).

In benzodiazepin-2-ones, there is an inversion of the seven-membered rings between two nonplanar, energetically equivalent forms and although these compounds have no asymmetric centre they have conformational asymmetry. A detailed ¹H NMR study (67BSF992) has shown that the inversion is rapid at room temperature for desmethyldiazepam (35; R = H) but slow for diazepam (35; R = Me) itself and for related N(1)-substituted analogues. The ring inversion of benzodiazepines and the effects of substituents on the energy barriers to inversion have been reviewed (B-83MI 906-01). Although the ring inversion of N(1)-substituted diazepam analogues is slow on the NMR timescale, it is too rapid to permit isolation of the two enantiomers at room temperature (the calculated barrier to inversion is 17.6 kcal mol⁻¹). Calculations and modeling indicated that the use of the *t*-butyl group as a conformational "lock" would raise the barrier to inversion above 24 kcal mol⁻¹, which should permit the separation of the two enantiomers (36) and (37). This was achieved and the absolute configuration of enantiomer (36) was established by x-ray crystallography (90JA3969). The single enantiomers were stable in the solid state but slowly racemized in solution over a period of 3 days.

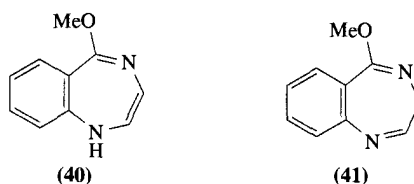


9.06.4.3 Tautomers

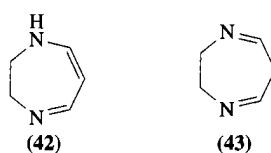
As mentioned already, for the fully unsaturated monocyclic 1,4-diazepines, the 1*H* isomer can only be isolated when acylated at the N-1 atom, and hence further tautomerization is precluded. The structures of the 2*H* and 6*H* isomers have been assigned by NMR but there is no evidence of a dynamic equilibrium between the forms (87CPB3175, 87CPB1179). The highly substituted 2-methoxy-5*H*-1,4-diazepine (38) could be isolated but the related 2-alkyl or 2-aryl analogues rearranged spontaneously to the 2*H* isomer; on heating (38) underwent an irreversible 1,5-hydride shift to the 2*H* isomer (39) (89AG(E)613).



The fully unsaturated 1*H*-benzodiazepine (**40**) is very unstable but can be converted into the more stable 3*H* isomer (**41**) on stirring with excess sodium methoxide in methanol <87CPB3182>.



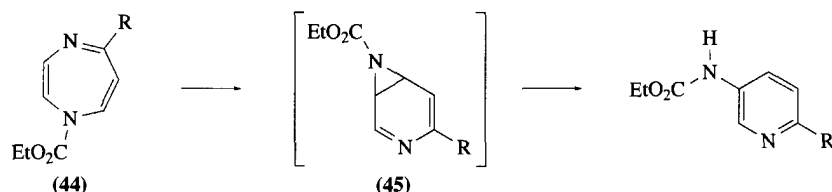
There is a wealth of evidence (¹H NMR, ¹³C NMR, UV) on 2,3-dihydro-1,4-diazepines which supports the conjugated tautomer (**42**) over the bis-imino tautomer (**43**) <62JOC3565, 65CB2701, 86CJS127, 93CJS82>. Although the bis-imine tautomer cannot be detected spectroscopically its presence has been invoked to explain aspects of the reactivity of 6-halo-2,3-dihydro-1,4-diazepines <93AHC(56)1>.



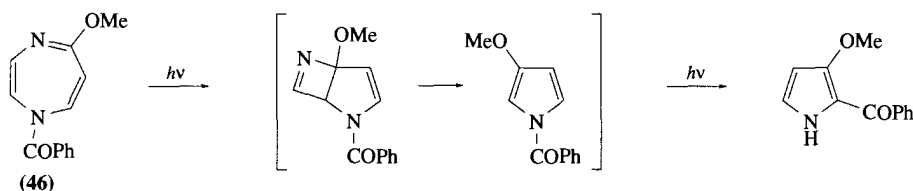
9.06.5 REACTIVITY OF FULLY UNSATURATED SYSTEMS

9.06.5.1 Monocyclic

The thermolysis of fully unsaturated 1,4-diazepines (**44**) at temperatures between 120 and 180°C in inert solvents such as xylene or *o*-dichlorobenzene gives pyridines in high yields when R is alkoxy <87CPB3175, 90CPB2911> but in only 20% yield when R is phenyl (Scheme 3) <87CPB3166>. The pyridines are formed by C(4)—N bond cleavage in an azanorcaradiene intermediate (**45**). The photolysis of 1-benzoyl-5-methoxy-1*H*-1,4-diazepine using a 400 W high-pressure lamp for 30 hours first produces a bicyclic valence isomer which extrudes HCN to form 1-benzoyl-3-methoxypyrrole, which in turn undergoes benzoyl group migration to the 2-position to give 2-benzoyl-3-methoxypyrrole in low yield (Scheme 4) <87CPB3175>.



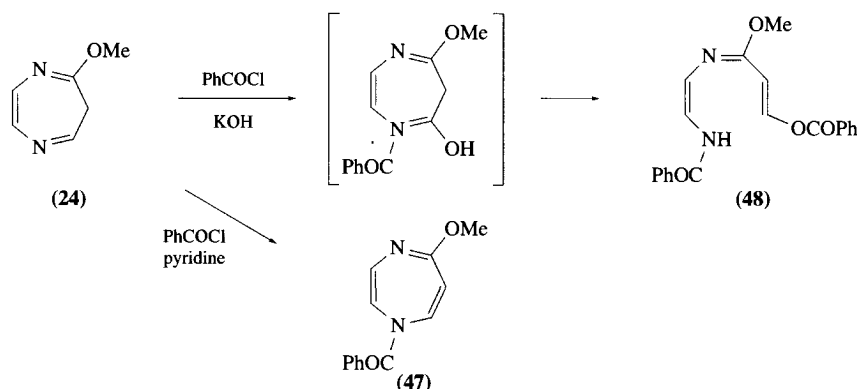
Scheme 3



Scheme 4

The products, obtained on the reaction of 5-methoxy-6*H*-1,4-diazepine (**24**) with benzoyl chloride, depend critically on the reaction conditions. Using pyridine as the base, the 6*H* isomer first tautomerized to the 1*H* isomer which was benzoylated on N-1 (**47**); there was no reaction when sodium methoxide was used as base. The use of aqueous potassium hydroxide gave a ring-opened product that had arisen from the addition of OH across the N(1)—C(7) imine bond and benzoylation of

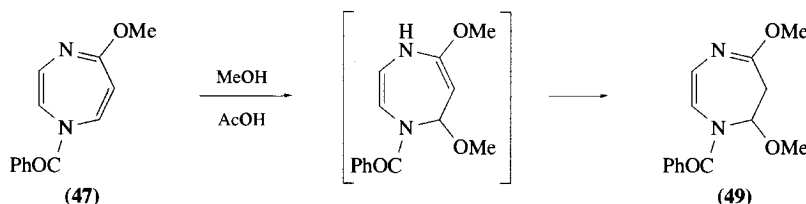
N-1 followed by N(1)—C(7) bond cleavage to give (48) (Scheme 5). If cyanide was used as the nucleophile, the corresponding ring opened nitrile was obtained <87CPB3175>.



Scheme 5

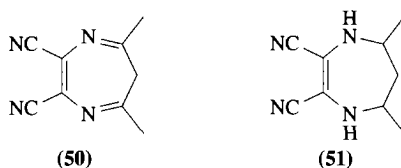
Reaction of 2-methyl-3-methoxy-2*H*-1,4-diazepine with benzoyl chloride in pyridine at 0°C resulted in ring cleavage and the methyl ester of *N*-benzoylalanine was obtained <87CPB1179>.

In methanolic acetic acid, 1-benzoyl-5-methoxy-1*H*-1,4-diazepine (47) undergoes a 1,4-addition of methanol followed by a 1,3-hydride shift to furnish 1-benzoyl-6,7-dihydro-5,7-dimethoxy-1*H*-1,4-diazepine (49) in 60% yield (Scheme 6) <87CPB3175>.



Scheme 6

From the limited reports of reduction of the monocyclic fully unsaturated 1,4-diazepines, it would appear that the 6,7-double bond is more susceptible to catalytic reduction than the 2,3-double bond <87CPB3175>. The iminoether function is stable to catalytic reduction and reduction with LAH in both the monocyclic- and benzodiazepines. Both imine groups in 2,3-dicyano-5,7-dimethyl-6*H*-1,4-diazepine (50) are reduced by sodium borohydride to the *cis*-product (51) which in turn can be oxidized with ddq to the 1*H*-6,7-dihydro analogue <74JOC2341>.



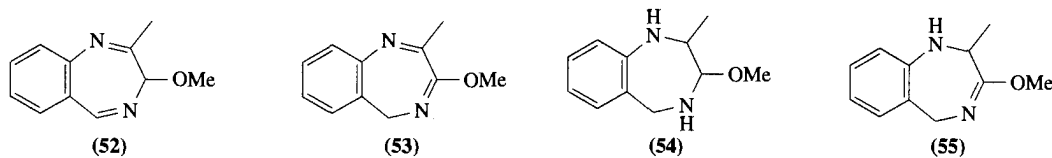
9.06.5.2 Benzodiazepines

Treatment of 5-methoxy-3*H*-1,4-benzodiazepine with acetyl chloride in pyridine gave the 1-acetyl-1*H* product; however, attempts to acetylate 5-methoxy-1*H*-1,4-benzodiazepine directly under the same conditions resulted in decomposition <87CPB3182>.

The behavior of 3-methoxy-2-methyl-3*H*-1,4-benzodiazepine (52) and its 5*H*-isomer (53) with acetyl chloride was quite different with the 3*H*-isomer (52) decomposing under the reaction conditions whereas the 5*H*-isomer (53) was recovered unchanged <87CPB4110>.

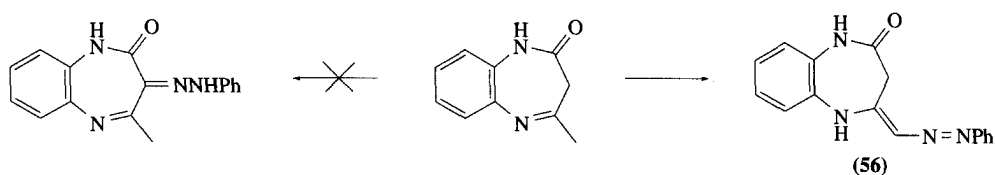
2-Amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine was oxidized by *m*-chloroperbenzoic acid in the presence of a basic ion exchange resin to the N-1 oxide <79CPB2608>.

The unsubstituted or alkyl substituted imines are readily reduced by LAH, for example, the compound (52) gives the fully reduced analogue (54) with LAH but the 5*H*-isomer (53) is reduced to an unstable iminoether (55) <87CPB3182, 87CPB4110>.



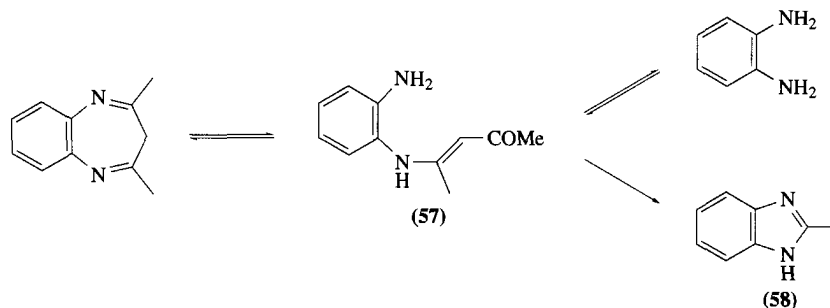
9.06.5.3 1,5-Benzodiazepines

1,5-Benzodiazepines are weak bases and are protonated by strong acids to give highly colored monocations. The 3*H* tautomer is thermodynamically more favorable but monoprotonation makes the 1*H* tautomer more favorable energetically. Bromination normally takes place at C-3 although this can also occur in the phenyl ring and at any methyl or phenyl substituents; the course of the bromination is influenced by the nature of the substituents and the conditions employed. Nitration of the seven-membered ring has not been achieved; decomposition usually occurs. The literature on diazo coupling reactions is confusing. There is one report that 2,4-diphenyl-1,5-benzodiazepine undergoes diazo coupling with 4-nitrobenzenediazonium salts in the 3-position <59JCS1132> and another report stating that the same compound does not react with diazonium salts <81JHC1341>. Also the structure assigned to the diazo coupled product from 1,3-dihydro-4-methyl-2*H*-1,5-benzodiazepin-2-one and benzenediazonium chloride <78CHE1270> has been questioned on the basis of NMR and infrared spectroscopy and is proposed to be (56) (Scheme 7) <81JHC1341>.



Scheme 7

The imine bonds of the 1,5-benzodiazepines are hydrolyzed readily in aqueous acid or alkali in a stepwise manner to give the enamine (e.g. (57)) initially which can hydrolyze further to *o*-phenylenediamine or can cyclize to the benzimidazole (58) (Scheme 8). In aqueous medium, because of this instability, 1,5-benzodiazepines often show the reactions of *o*-phenylenediamine and the 3-carbon fragment from which they are formed.



Scheme 8

1,5-Benzodiazepines can be reduced to the dihydro or tetrahydro analogues either by catalytic hydrogenation or with sodium borohydride. Both dihydro- and tetrahydro-1,5-diazepin-2-ones are reduced to the tetrahydrodiazepines with lithium aluminum hydride <B-91M1 906-01>.

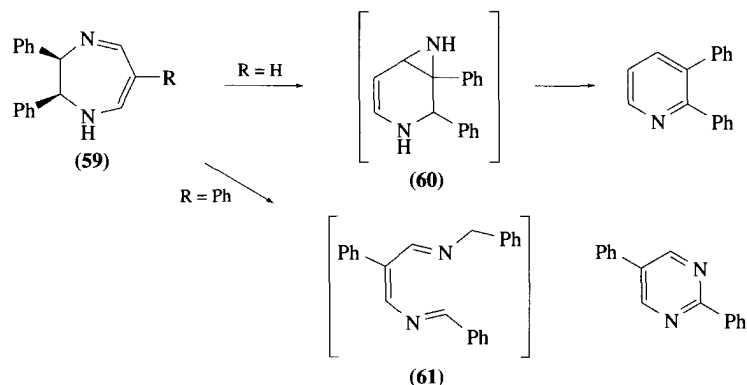
Dihydro-1,5-benzodiazepines undergo many of the reactions outlined above for the fully unsatu-

rated derivatives. A general reaction of 1,3-dihydro-2*H*-1,5-benzodiazepines is the thermal ring contraction to benzimidazoles which arises from a transannular attack of the imine N-atom on the C-2 carbonyl followed by cleavage of the C(2)—C(3) bond <B-91MI 906-01>.

9.06.6 REACTIVITY OF NONCONJUGATED RINGS

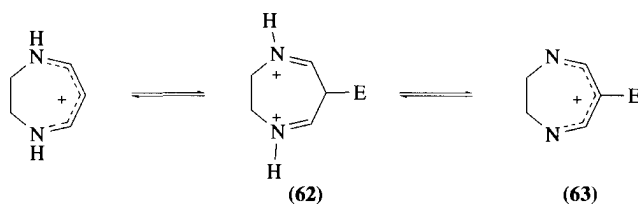
9.06.6.1 Monocyclic Dihydrodiazepines

The thermolysis of *cis*-2,3-diphenyl-2,3-dihydro-1*H*-1,4-diazepine (**59**; R = H) gave 2,3-diphenylpyridine through the loss of ammonia from an azanorcaradiene intermediate (**60**). The related 2,3,6-triphenyl analogue behaved differently and on heating at 140°C gave 2,5-diphenylpyrimidine. The intermediate proposed for this transformation was a diazatriene (**61**), which underwent electrocyclic ring closure with loss of toluene to produce the 2,5-diphenylpyrimidine (Scheme 9) <83LA1230>.



2,3-Dihydro-1,4-diazepines are strongly basic (pK_a ca. 13–14) and readily react with acids to form diazepinium salts, the chemistry of which has been studied extensively <93AHC(56)1>. *N*-Unsubstituted 2,3-dihydro-1,4-diazepinium salts are alkylated on both N atoms upon treatment with alkyl halides in DMF using potassium carbonate as base <86LA1387>. For steric reasons the presence of large substituents in the 5- and 7-positions can limit this reaction to alkyl halides with small alkyl groups.

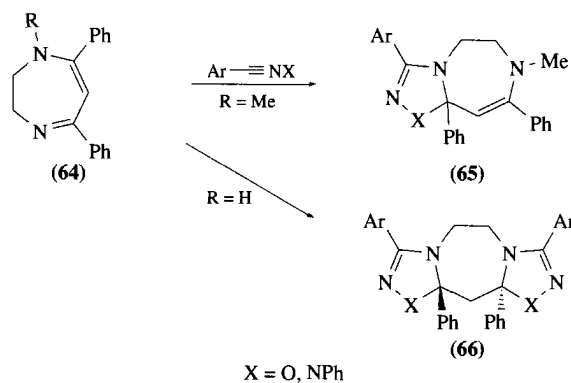
A characteristic feature of the diazepinium salts is that they undergo electrophilic substitution in the 6-position under conditions similar to those used for activated benzene derivatives. The attack of the electrophile at C-6 produces a dication intermediate (**62**) which loses a proton to regenerate the stable delocalized monocation (**63**) (Scheme 10).



Nitration can be effected by nitric acid alone or by using nitric acid–sulfuric acid mixtures and it is the position and nature of substituents in the ring that influence the strength of the reagent needed. The diazepinium salts can be brominated using either bromine in methanol or *N*-bromosuccinimide; *N*-chloro- and *N*-iodosuccinimide furnish the 6-chloro and 6-iodo derivatives, respectively. The diazepinium salts undergo diazo coupling with aryldiazonium salts but the products are readily hydrolyzed.

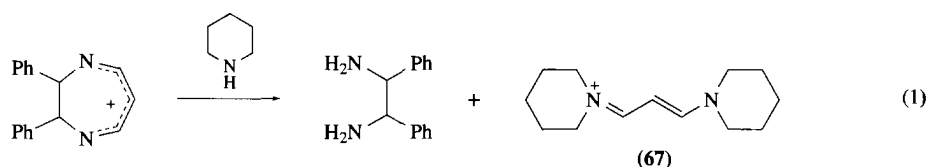
2,3-Dihydro-1,4-diazepines will perform 1,3-dipolar cycloaddition reactions with nitrile oxides and nitrile imines but it is only the imine bonds in the diazepine that react. Thus, 2,3-dihydro-5,7-diphenyl-1-methyl-1*H*-1,4-diazepine (**64**; R = Me) only gave mono adducts (**65**) with aryl nitrile

oxides and aryl nitrile imines (Scheme 11); there was no evidence of an adduct from cycloaddition to the 6,7-double bond <91JHC73>. The related 5,7-dimethyl analogue gave a bis adduct and this was attributed to a lesser steric compression between the 1-methyl and 5,7-methyl groups compared to the two phenyl groups. The *N*-desmethyl analogue (**64**; R = H) gave bis adducts (**66**) on reaction with these same dipolarophiles and it was proposed that the reactions proceeded through the bis-imine tautomer which clearly was not possible for the N-1 methyl analogue <89JHC1619>.



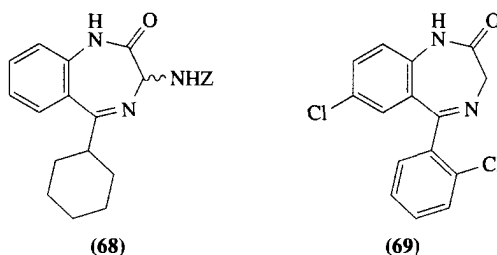
Scheme 11

Heating *cis*-2,3-diphenyl-2,3-dihydro-1*H*-1,4-diazepine (**59**; R = H) at 80°C for 1 hour in deuteriomethanol with sodium deuteriomethoxide resulted in an exchange of D for H at N-1 and C-6; whereas, prolongation of the heating to 5 hours led to complete decomposition <83LA1230>. The free base (**59**; R = H) was recovered unchanged on heating with piperidine in methanol but the perchlorate salt was readily cleaved under the same conditions to meso-1,2-diphenylethane and the vinamidinium salt (**67**) (Equation (1)). Earlier work had shown that the unsubstituted dihydrodiazepinium salt behaved similarly with piperidine but the 5,7-dimethyl analogue was quite stable <75JCS(P1)1260>.



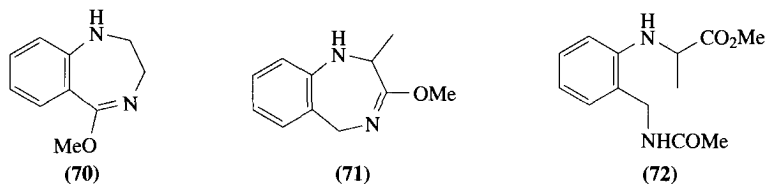
9.06.6.2 Dihydrobenzo-1,4-diazepines

Further examples of alkylation at N-1 of 2,3-dihydro-5-arylbenzo-1,4-diazepin-2-ones using sodium hydride and an alkyl halide in DMF have been reported <82CPB1141, 82CPB1477>. A mixture of DMF–dimethyl acetal in boiling toluene is reported to methylate (**68**) cleanly on N-1 in high yield <93BMC1919>. Heating (**69**) with methyl iodide in acetonitrile, however, gave the quaternary N-4 methyl compound <82CPB1141>.

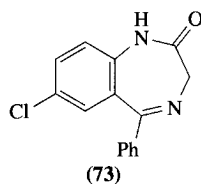


2,3-Dihydro-5-methoxy-1*H*-benzo-1,4-diazepine (**70**) was acylated on N-1 with acetic anhydride and the anion generated on deprotonation of N-1 with *n*-butyl lithium reacted normally with methyl

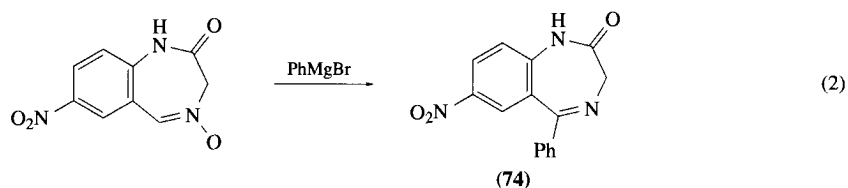
iodide and tosyl chloride <87CPB3182>. By contrast, the reaction of 3-methoxy-2-methyl-1,2-dihydro-5*H*-benzo-1,4-diazepine (**71**) with acetic anhydride resulted in ring cleavage to give (**72**) <87CPB4110>.



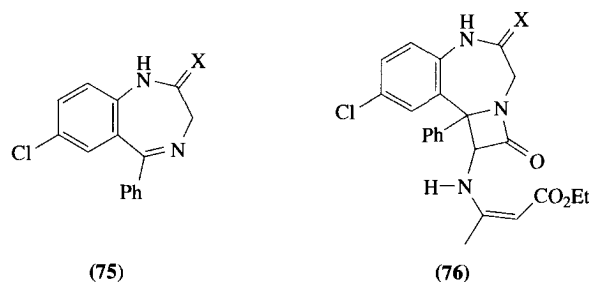
The use of trifluoroacetic acid as a catalyst in the *N*-bromosuccinimide bromination of (**73**) in dilute solution in carbon tetrachloride gave improved yields of the 3-bromo derivative <79JHC1449>.



1,4-Benzodiazepin-2-one 4-oxides undergo 1,3-addition of aryl Grignard reagents to the 4,5-nitrone moiety in pyridine solution to produce 5-aryl-1,4-benzodiazepin-2-ones (**74**) after dehydration of the intermediate *N*-OH compounds. The use of pyridine as the solvent enabled this reaction to be carried out selectively on the nitrone function in compounds containing functional groups normally reactive to Grignard reagents, for example, the nitro group (Equation (2)) <77ACS(B)701>.

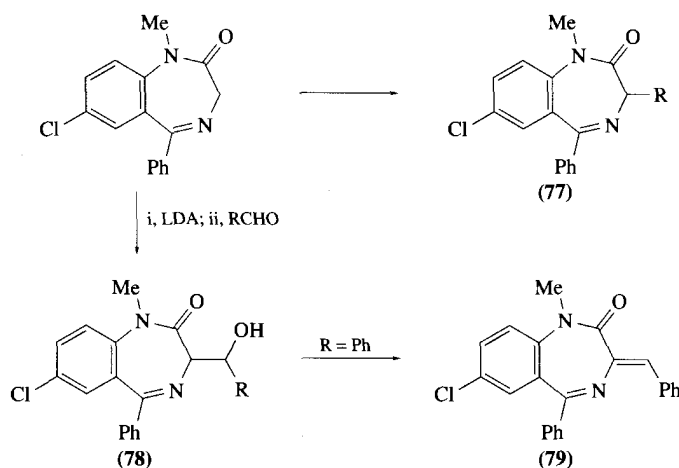


Both 7-chloro-1-methyl-2,3-dihydrobenzodiazepine (**75**; X = CH₂) and the related 2-one (**75**; X = O) react with potassium α -methyl- β -ethoxycarbonyl- γ -phenylaminoacetate in the presence of phosphorous oxychloride to give the azetidinobenzodiazepines (**76**) <83ACS(B)75>.



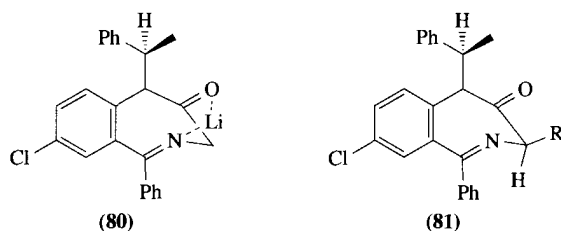
The optimum conditions for the formation of the 3-lithio derivative of diazepam involved the use of 2 equivalents of LDA in THF at 25°C. The anion so formed reacted with alkyl halides (e.g., MeI) and esters (e.g., ethyl acetate) to give the 3-alkyl and 3-acyl derivatives (Scheme 12) (**77**; R = alkyl, acyl). The reaction with aldehydes and ketones furnished carbinols and in the case of benzaldehyde the initially formed carbinol (**78**; R = Ph) dehydrated to the alkylidene derivative (**79**) on longer reaction times <81JOC3945>. A similar dehydration was noted also with cyclohexanone.

The absolute configurations of the products (**81**) from the reaction of the lithiated benzodiazepine (**80**) bearing the *S*- α -phenylethyl substituent on the N-1 atom with alkyl halides and chloroformates (*R* form) agreed with prediction based on the structure of the metallated species and its mechanism



Scheme 12

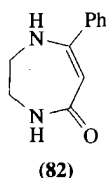
of action. The observed diastereomeric excess was low, typically 6–30%, except for the reaction with ethyl chloroformate where the value was 85% (81HCA1145).



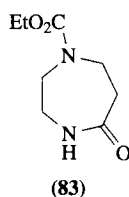
The anion of 7-deschlorodiazepam generated with potassium *t*-butoxide in toluene at -20°C reacted with isoamyl nitrite to give a 80% yield of the 3-oxime which was converted into the 3-amino derivative by hydrogenation (87JOC3232).

9.06.6.3 Monocyclic Tetrahydro- and Perhydrodiazepines

The methylation of 7-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-diazepin-5-one (82) with dimethyl sulfate under phase-transfer conditions gave the 4-methyl analogue in modest yield. Activated aryl halides (1-fluoro-2,4-dinitrobenzene) furnished the 4-aryl analogues, in neither case was there any reaction at N-1 (93BSB89). Hexahydro-1,4-diazepine is arylated on both nitrogen atoms with activated haloheterocycles such as 2-chloropyridine on reaction at 100°C under high pressure in the presence of triethylamine (90H(31)1217).

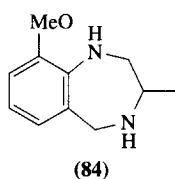


Treatment of (82) with either NBS or NCS at room temperature produced the 6-bromo and 6-chloro derivatives, respectively, and these underwent the expected nucleophilic reactions with sodium methoxide (93BSB89). Bromination of 1-ethoxycarbonyl-hexahydro-1,4-diazepin-5-one (83) with two equivalents of bromine in the presence of phosphorous pentachloride gave the 6,6'-dibromo compound, which was reduced to the monobromo analogue on hydrogenation (91TL2469).



9.06.6.4 Perhydrobenzo-1,4-diazepines

Attempts to arylate hexahydro-4-methyl-1,4-benzodiazepine at N-1 with 2,4-dinitrochlorobenzene and 2-chloropyridine were unsuccessful. Acylation with aroyl chlorides proceeded normally at N-1 and these amides were converted into the 1*N*-benzyl derivatives on reduction <84AP(317)595>. As expected the reaction of (84) with bromomethylcyclobutane under standard conditions took place at the more reactive position and gave the 4*N*-alkylated product only <91JMC3187>.

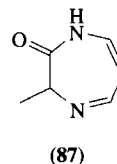
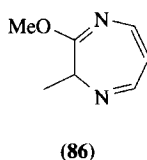
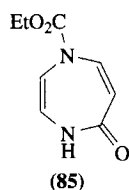


9.06.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

9.06.7.1 Monocyclic

On treatment of the 6-phenyl-2,3-dihydrodiazepinium cation with bromine at room temperature, it is the 6-phenyl substituent that is brominated in the *para* position. Analogues with substituents in the 1,2,3, or 4 positions behave similarly although the rate of bromination is reduced, however, substituents in the 5 or 7 positions or in the *ortho* position of the phenyl ring inhibit the bromination reactions totally <81JCS(P1)726, 93AHC(56)1>. 6-Phenyl-2,3-dihydrodiazepinium perchlorate is nitrated in the *para* position with cold dilute nitric acid but its 1-methyl, 2-methyl, and 1,4-dimethyl analogues are decomposed under the same conditions <81JCS(P1)726>. 6-(4-Nitrophenyl)diazepinium salts can be reduced catalytically to the 6-aminophenyl derivatives.

The lactam function in 1-ethoxycarbonyl-4,5-dihydro-1*H*-1,4-diazepin-5-one (85) reacts as expected with triethyloxonium fluoroborate to form the fully unsaturated iminoether (11) <90CPB2911>. The iminoether moiety of 2-methoxy-3-methyl-3*H*-diazepine (86) is cleaved to the lactam (87) on reaction with HCl in methanol <87CPB1179>.

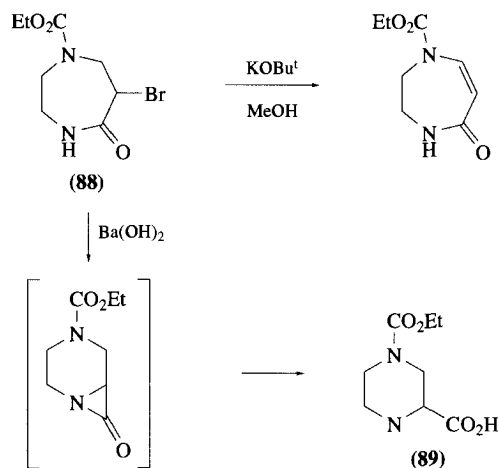


In strong acid solution 6-bromodiazepinium halides (but not perchlorates) undergo protodebromination through addition of a proton to the salt to form the dication followed by attack of bromide on the 6-bromo atom producing bromine and the monocation. Dilution of the acid mixture leads to reformation of the 6-bromo compound but addition of thiosulfate gives the debrominated product <93AHC(56)1>.

5,7-Disubstituted-6-bromo-2,3-diazepinium salts react with nucleophiles with displacement of the bromine atom and this reaction has been used to prepare 6-aryloxy, 6-alkoxy, and 6-amino derivatives <93AHC(56)1>. An explanation proposed for the nucleophilic attack at the electron-rich 6-position of the diazepinium salt is the involvement of small amounts of the bis-imine tautomer, undetectable by NMR, which would be electrophilic at C-6 because of the combined effects of the bromo atom and the two adjacent azomethine groups. In many cases, the 6-bromo-

dihydrodiazepinium salts undergo a protodebromination rather than nucleophilic substitution and the protodebromination reaction seems to be favored with increasing size of the 5 and 7 substituents <93AHC(56)1>.

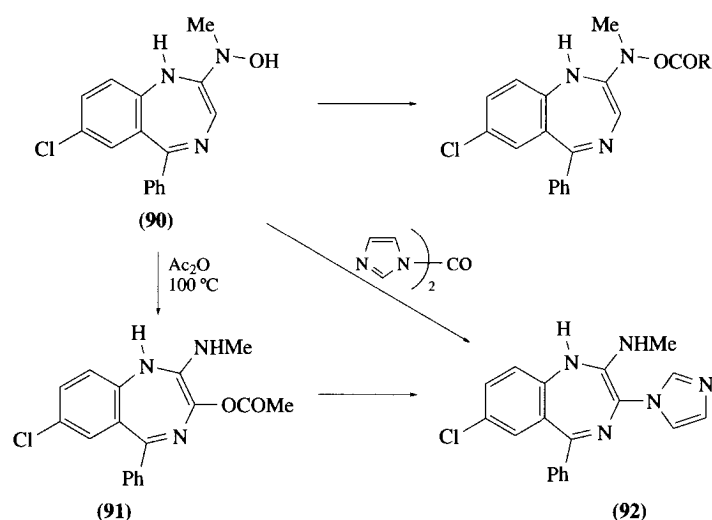
1-Ethoxycarbonyl-6-bromo-hexahydrodiazepin-5-one (**88**) eliminates HBr on treatment with potassium *t*-butoxide in methanol and undergoes a Favorskii rearrangement to the piperazine carboxylic acid (**89**) on treatment with barium hydroxide (Scheme 13) <91TL2469>.



Scheme 13

9.06.7.2 Fully Unsaturated Benzodiazepines

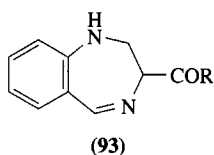
2-(Hydroxyamino)benzodiazepine (**90**) is acylated on oxygen upon reaction with acid chlorides (acetyl or benzoyl chloride) or isocyanates (methyl isocyanate) in the cold. On heating with acetic anhydride at 100°C, there is an oxido-reductive rearrangement to give the 3-acetoxy-2-methylamino derivative (**91**) (Scheme 14). This is considered to proceed by isomerization of the nitronium ion formed by cleavage of the N—O bond to the 3-carbonium ion which is trapped by the nucleophile (acetate) <80AP(313)926>. A similar mechanism is used to explain the formation of the 3-(1-imidazolyl) derivative (**92**) on reaction of (**90**) with carbonyl diimidazole.



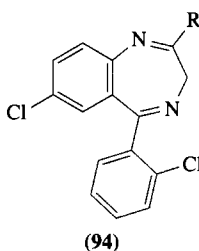
Scheme 14

Attempts to convert the 3-carboxamide (**93**; R = NH₂) and the 3-acylazide (**93**; R = N₃) into the 3-amino derivative by the Hofmann and Curtius reactions were unsuccessful; complex reaction

mixtures were obtained and the only characterizable product was the decarboxylated compound <87JOC3232>.

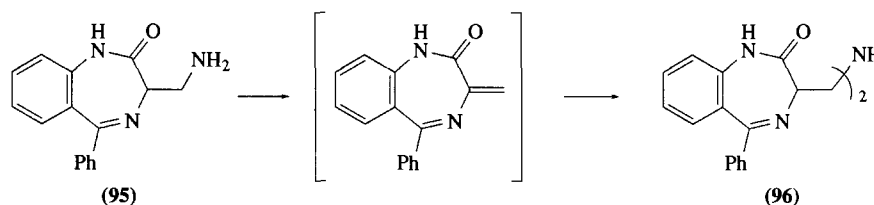


The 2-SMe group of (94; R = SMe) was readily displaced on reaction with sodium methoxide in methanol to give the 2-methoxy analogue (94; R = OMe) in high yield <82CPB1141>.



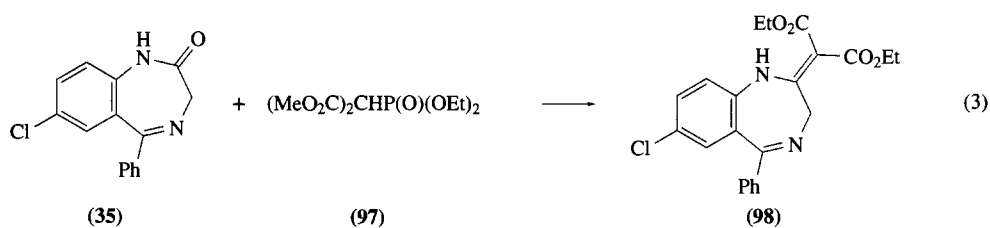
9.06.7.3 Dihydrobenzodiazepines

The amino group of 3-aminomethylbenzodiazepin-2-one (95) is acylated with acid chlorides in the presence of base. Although it is stable at room temperature, (95) eliminates ammonia on heating in isopropanol with triethylamine and the product reacts further with (95) to give the addition product (96) (Scheme 15) <90JMC450>. The 3-amino group of (95) can be acylated with amino acids <87JOC3232> and with *m*-tolyl isocyanate <94S505>.



Scheme 15

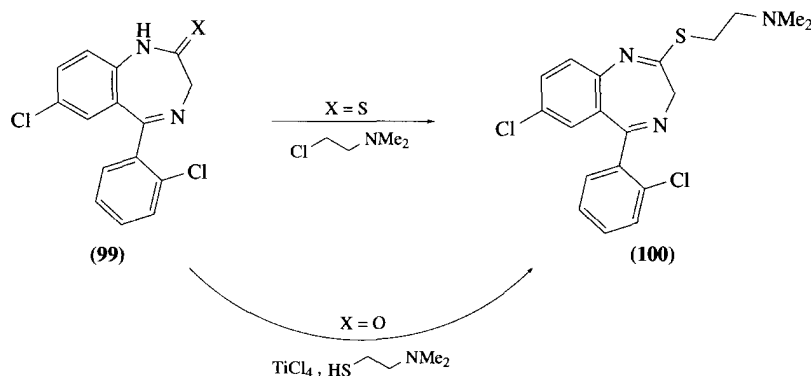
The ylide from (97) reacted with 1*N*-desmethyldiazepam (35) in a one-pot reaction to give (98) in 50% yield (Equation (3)). This is a variation on the more usual reaction in which the lactam is converted into an enol phosphate, for example, by reaction with sodium hydride and dimorpholinophosphonic chloride, which is then reacted with the anion of dimethyl malonate <93JHC945>.



The 2-carbonyl group of benzodiazepin-2-ones can be converted into the thione using traditional reagents such as phosphorous pentasulfide <82CPB1141> or Lawesson's reagent <90JMC450>. A new reagent prepared from phosphorous pentasulfide and four equivalents of an alkyl lithium smoothly converts lactams into thiolactams in THF solution. Thus, desmethyldiazepam (35) is converted into

the thione in 87% yield; however, there is no reaction if the lactam nitrogen atom is substituted <87S162>.

The thiolactams can be alkylated on sulfur by treatment with alkyl halides and base under aqueous or nonaqueous conditions, for example, (**99**; X = S) is converted into (**100**) (Scheme 16) <82CPB1141>. The thioether (**100**) can be obtained directly from the lactam (**99**, X = O) on reaction with dimethylaminoethane thiol in the presence of either titanium tetrachloride or silicon tetrachloride; other Lewis acids were ineffective <82CPB1473>.

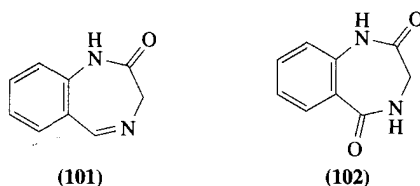


Scheme 16

The acetoxylation of desmethyldiazepam (**35**) proceeds smoothly and hydrolysis of the product under nonaqueous conditions gives the 3-hydroxy compound. This is an alternative route to the lead tetraacetate–iodine mediated acetoxylation reaction at C-3 <79JHC1449>.

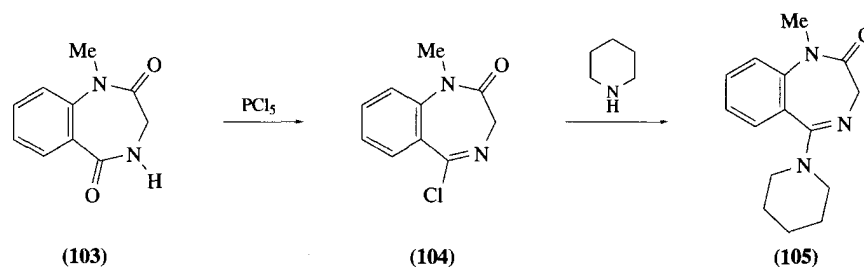
9.06.7.4 Tetrahydrobenzodiazepines

The carbonyl groups of benzodiazepin-2-ones, for example, (**101**) <84AP(317)595> and 2,5-diones, for example (**102**) <80AP595> are reduced with LAH to give the fully saturated derivatives. Conversion of the lactam to the thiolactam and reduction with Raney nickel provides an alternative procedure <90JMC450>.



The reaction of tetrahydrobenzodiazepine-2,5-dione with the reagent formed from phosphorus pentasulfide and butyllithium resulted in thiation of the 2-carbonyl group only <87S162>.

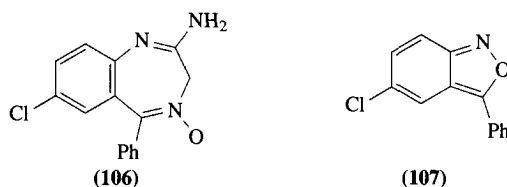
1-Methyl-2,3,4,5-tetrahydrobenzodiazepine-2,5-dione (**103**) gave the chloroimine (**104**) with PCl₅, which reacted with secondary amines with displacement of the chlorine atom to give the amidine (**105**) (Scheme 17) <94JMC719>.



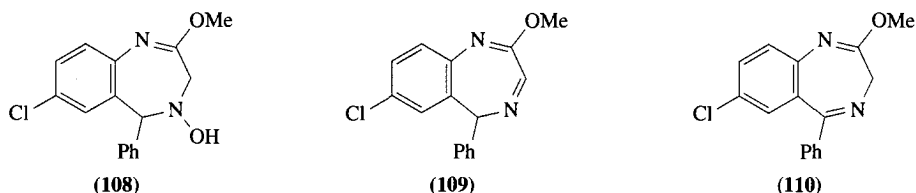
Scheme 17

9.06.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

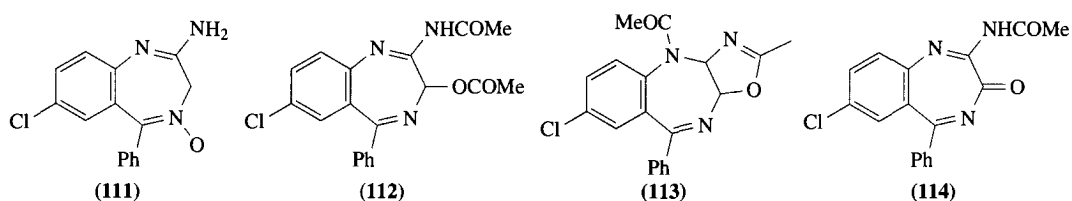
It is well known that benzodiazepin-4-oxides can be deoxygenated on treatment with phosphorous trichloride and this reaction is now reported for the 1-oxide also <79CPB2608>. On acid hydrolysis, (106) is converted into a benzisoxazole (107) <79CPB2608>.



The 4-hydroxy compound (108) formed on addition of an aryl Grignard reagent to 7-chloro-2-methoxy-3H-benzo-1,4-diazepine 4-oxide can be dehydrated by heating either with phenyl isocyanate or *N,N'*-dimethylpiperazine. Dehydration with phenyl isocyanate gave the 5*H*-isomer (109) while heating with *N,N'*-dimethylpiperazine furnished the 3*H*-isomer (110). Compound (109) could also be converted into the (110) on heating with *N,N'*-dimethylpiperazine <77ACS(B)701>.



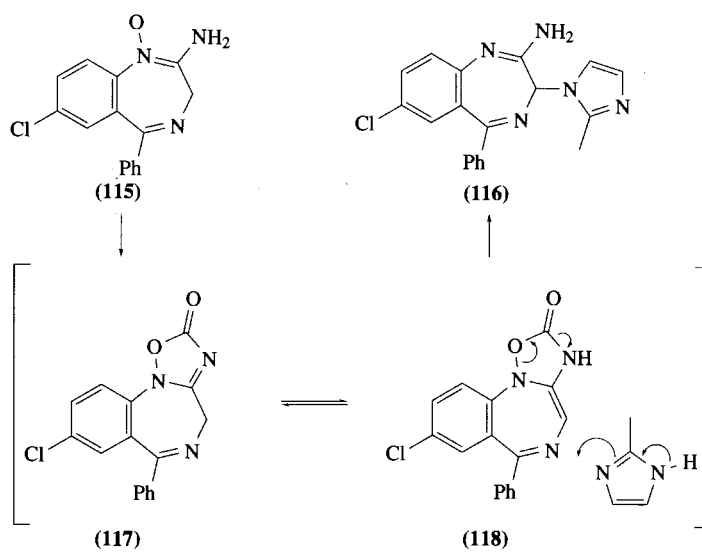
Benzodiazepine 4-oxides rearrange on treatment with acetic anhydride and acid chlorides to the corresponding 3-acetoxy (acyloxy) analogues <62JOC1691>. The reactions of 2-aminobenzodiazepine 4-oxides with acetic anhydride are more complex and (111) gave the diacetate (112), the tricyclic compound (113) and the 3-one (114) in varying proportions depending on the reaction conditions <63JOC3010>. The 3-one (114) was obtained as the sole product in low yield (37%) on heating the 1-oxide (115) in acetic anhydride <79CPB2608>.



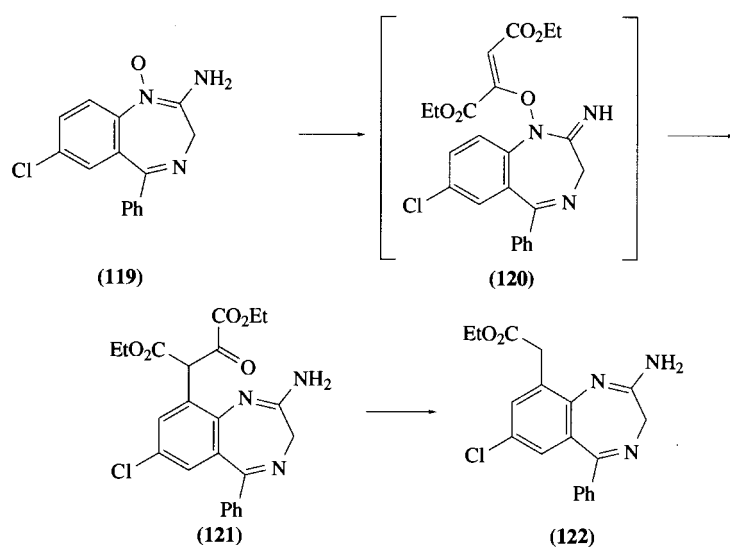
The reaction of (115) with phosgene and 2-methylimidazole did not yield the expected oxadiazolone but the 3-(2-methylimidazolyl) derivative (116). The mechanism is believed to involve the intermediacy of the oxadiazolone (117) which isomerizes to (118) which in turn is attacked at C-3 by 2-methylimidazole to produce (116) with loss of carbon dioxide (Scheme 18) <79CPB2608>.

The reaction of (119) with diethyl alkynedicarboxylate in cold methanol gave (121) which is believed to have arisen by a 3,3-sigmatropic rearrangement of the intermediate O-adduct (120) (Scheme 19). On heating in ethanol (121) is converted into the monoester (122) <79CPB2618>.

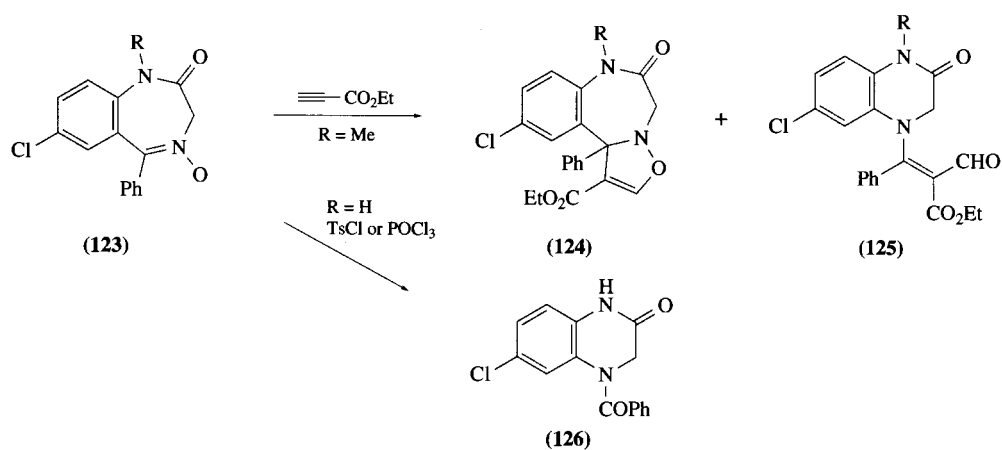
The 4-oxide (123; R = Me) undergoes a [2 + 3] cycloaddition reaction with ethyl propiolate in boiling THF to give the expected cycloadduct (124) and the quinazoline (125) which has arisen from a ring contraction reaction following cleavage of the weak N—O bond in (124) (Scheme 20) <82JA1380>. The 1-oxide (119) is recovered unchanged on reaction with ethyl propiolate <79CPB2618>. Ring contraction reactions of benzodiazepines containing N—O bonds are known, (123; R = H) rearranges to (126) on treatment with either phosphorous oxychloride or *p*-toluenesulfonyl chloride <64JOC506>.



Scheme 18



Scheme 19



Scheme 20

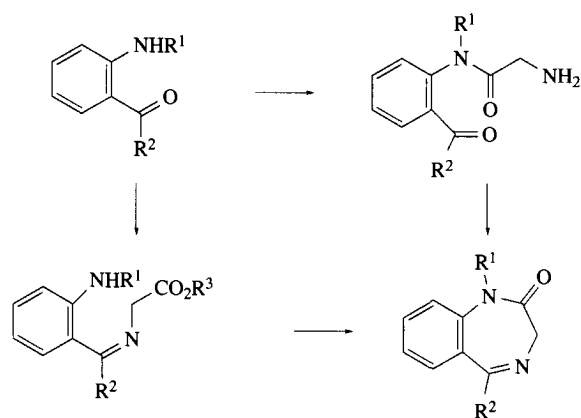
9.06.9 RING SYNTHESSES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

9.06.9.1 Monocyclic and Benzodiazepines

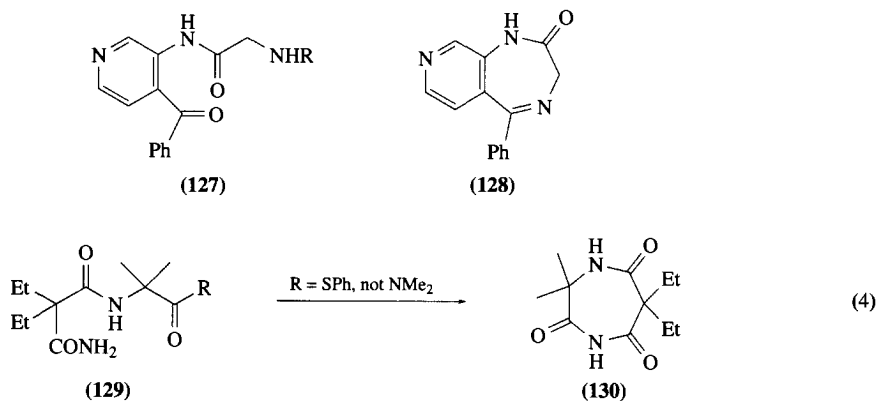
Following the system used in CHEC-I the preparative routes from nonheterocyclic precursors have been classified according to the bonds formed using the usual convention of labeling the ring bonds by lower case letters; *a* for the 1,2-bond, *b* for the 2,3, etc. Thus a type *a* synthesis involves the ring closure of a N—C—C—N—C—C—C-fragment, and the reaction of ethylenediamine with a 3-carbon fragment is an example of a *dg* type reaction. All the methods involving formation of the *a* bond are considered first in the order one-bond, two-bond types, etc. followed by a similar treatment of the *b* bond and so on. Monocyclic diazepines and benzodiazepines are discussed together under the relevant reaction type but the 1,5-benzodiazepines are considered separately.

9.06.9.1.1 Type a (N—C—C—C—N—C—C)

This reaction has been much used for the synthesis of the pharmacologically important 1,4-benzodiazepin-2-ones by one of two routes as shown in the general scheme (Scheme 21); note that if the intermediates are not isolated this is a type *ac* synthesis. In an example the *Z*-glycineamide of 3-amino-4-benzoylpyridine (**127**) was cyclized under acidic conditions to 2,3-dihydro-5-phenyl-2*H*-pyrido[3,4-*e*]-1,4-benzodiazepin-2-one (**128**) in 80% yield (87CJC1158). The linear triamide (**129**; R = NMe₂) itself could not be induced to cyclize to a diazepinetrione but on conversion into the phenylthioester (**129**; R = SPh) it underwent smooth cyclization on treatment with sodium hydride in hot toluene to hexahydro-6,6-diethyl-3,3-dimethyl-1,4-diazepine-2,5,7-trione (**130**) (Equation (4)) (85HCA465).

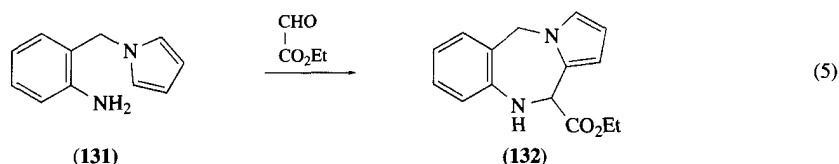


Scheme 21



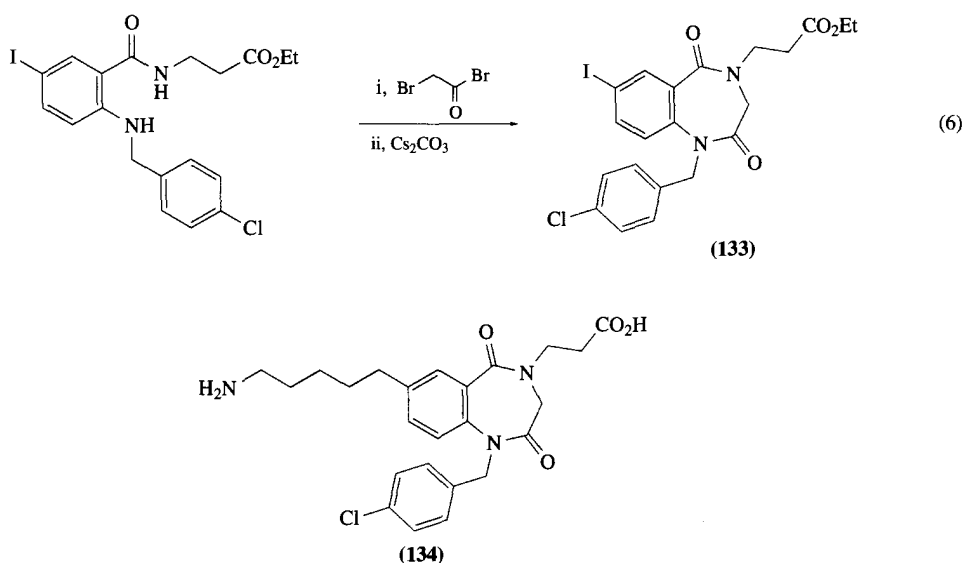
9.06.9.1.2 Type ab ($N-C-C-C-N-C+C$)

Electrophilic attack on the 2-position of pyrroles has been a fruitful route into pyrrolo-1,4-diazepines. Treatment of *o*-aminobenzylpyrrole (**131**) with methyl glyoxalate or its methoxy hemiacetal in methanol furnished methyl 10,11-dihydro-5*H*-pyrrole[2,1-*c*]-1,4-benzodiazepine-11-carboxylate (**132**) in 75% yield (Equation (5)) <84JHC833>.

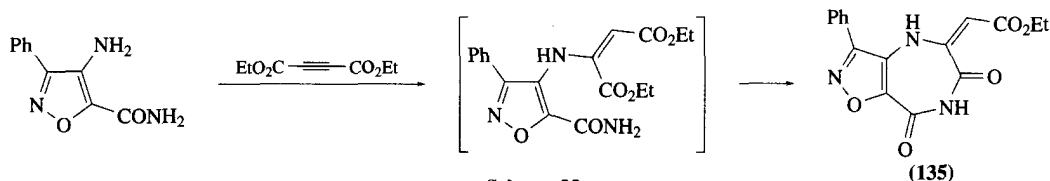


9.06.9.1.3 Type ac ($N-C-C-C-N+C-C$)

Reactions between 1,5-bisnitrogen nucleophiles and 1,2-biselectrophilic equivalents such as 1,2-dihalides, α -haloesters, and the diesters of alkyne dicarboxylic acid are useful for preparing monocyclic 1,4-diazepines and their benzo and heteroaryl analogues <84CHEC-1(7)593>. This is exemplified by the preparation of an intermediate (**133**) used in the synthesis of G5598 (**134**), a potent inhibitor of the binding of GPIIb/IIIa to fibrinogen (Equation (6)) <94TL2113>.



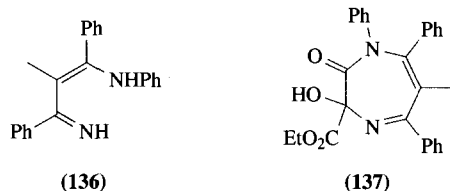
The preparation of 3-phenyl-5-carboxymethylene-5*H*-isoxazolo[4,5-*e*]-1,4-diazepine-6,8-(4*H*, 7*H*)-dione (**135**) is an example where diethyl alkynedicarboxylate is used as the biselectrophile (Scheme 22).



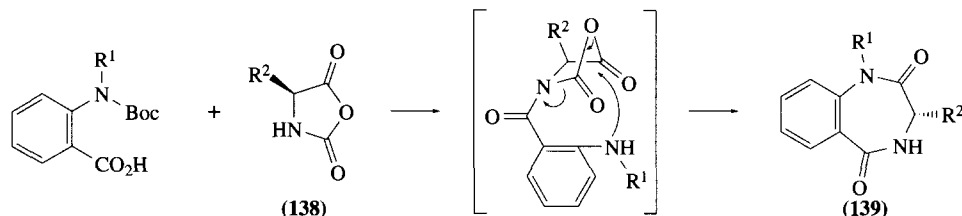
Scheme 22

Highly substituted 1,4-diazepines (**137**) can be prepared by the reaction of 3-iminopropyl-1-enylamines (**136**) successively with diethylgermanium dichloride and diethyl oxomalonate <93CC217>.

The reaction is presumed to proceed through a cyclic organogermanium analogue. A related silicon-based reaction has been reported <92S106>.



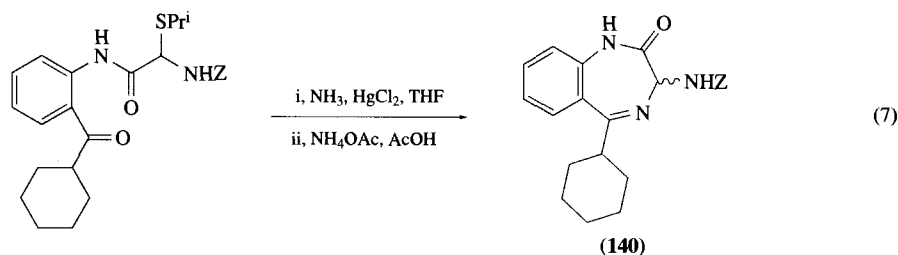
The addition products of *N*-Boc anthranilic acid and *N*-carboxy- α -amino acid anhydrides (**138**) undergo ring expansion and decarboxylation on treatment *in situ* with HCl to give 1,4-benzodiazepine-2,5-diones (**139**) (Scheme 23) <94T9051>. This reaction is interesting because no racemization was observed. However, there was considerable racemization during the cyclisation of the isolated coupling product of *N*-Boc anthranilic acid with an amino acid <93SC2265, 94T9051>.



Scheme 23

9.06.9.1.4 Type ag (C—C—N—C—C—C + N)

One of the important commercial routes to 1,4-benzodiazepines from 2-aminobenzophenones involves reaction of an *N*-acylated analogue bearing a leaving group in the acyl chain with a source of ammonia <84CHEC-I(7)593>. One example of this reaction was used to synthesize an intermediate (**140**) for a cholecystokinin type B receptor antagonist (Equation (7)) <93BMC1919>.



9.06.9.1.5 Type b (C—N—C—C—C—N—C)

The diimine prepared from 1,3-diaminopropane and benzaldehyde was reduced electrochemically using a lead cathode in an acidic medium to perhydro-*trans*-2,3-diphenyl-1,4-diazepine (**141**) in 79% yield (Equation (8)) <91JOC3063>. This reaction complements the cyclopropane diimine cyclization to *cis* products discussed below.



9.06.9.1.6 Type d (N—C—C—N—C—C—C)

CN(C)CC[N+]=[N-]
 $\xrightarrow{\text{CH}_2=\text{C}(\text{CH}_3)\text{C}(\text{O})\cdot}$
CC(=O)CN(C)CC[N+]=[N-]
 $\xrightarrow[\text{ii, LAH}]{\text{i, Ph}_3\text{P}}$
CC1(C)CN(C)CCN1

(142)

Scheme 24

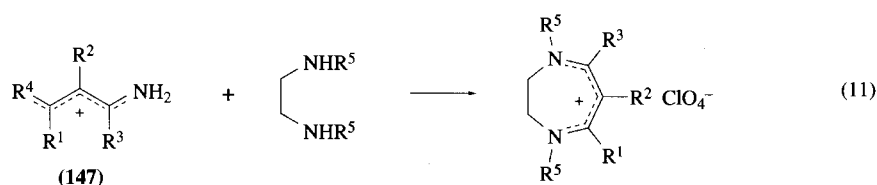
Scheme 25

(9)

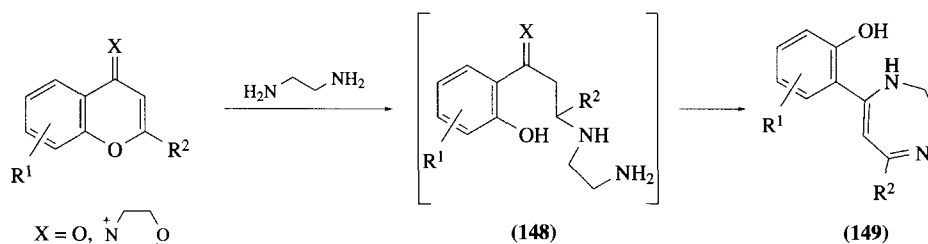
The reaction of ethylenediamine derivatives with 1,3-biselectrophilic reagents is an important route for the preparation of 2,3-dihydro-1,4-diazepines. 1,3-Dicarbonyl compounds have been used

extensively as the 1,3-biselectrophile and, indeed, the first example of this class of compound, 2,3-dihydro-5,7-dimethyl-1,4-diazepine, was prepared by the reaction of acetylacetone with ethylenediamine <40HCA1139>. The range of 1,3-dicarbonyl compounds that can be used in this reaction and the particular conditions each type requires to ensure optimum yields has been reviewed <93AHC(56)1>. A novel example of a 1,3-dicarbonyl reagent is provided by carbon suboxide which reacts with ethylenediamine in benzene at -70°C to give 1,4-diazepine-5,7-dione in high yield <87H(26)1619>.

The use of vinamidinium (**146**) and 5-aza-1-oxopentamidinium salts (**147**; $\text{R}^4 = \text{MeO}$) as 1,3-dicarbonyl equivalents in the synthesis of 1,4-diazepinium salts has been studied and these may offer advantages in that they have been used to prepare 2,3-dihydro-5,7-disubstituted-1,4-diazepines which were not readily available from the reactions of 1,3-dicarbonyl compounds themselves with ethylenediamines (Equations (10)–(11)) <93AHC(56)1>.



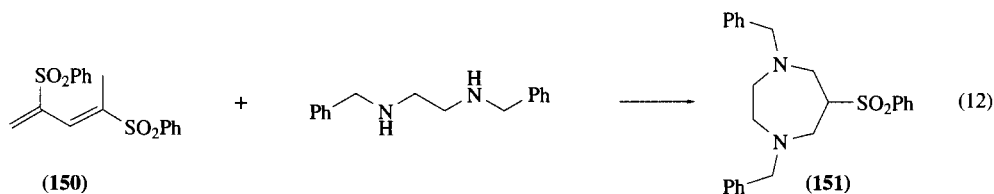
Monocyclic 1,4-diazepin-5-ones and -5,7-diones can be obtained by reacting ethylenediamines with β -ketoesters and malonic acid derivatives, respectively <84CHEC-I(7)593>. Another important synthetic route to 1,4-diazepines is the reaction of α,β -unsaturated carbonyl compounds with 1,2-diamines. An example of this is provided by the reaction of chromones or imines derived from them, with ethylenediamine (Scheme 26). The reaction proceeds by an initial Michael addition to the double bond to give the ring-opened intermediate (**148**) which cyclizes spontaneously to the 5-(2-hydroxyphenyl)-7-substituted-2,3-dihydro-1*H*-1,4-diazepines (**149**) in high yield <82PJC83, 85S339>. The influence of substituents in both the chromone and the diamine on the course of the reaction has been studied <82PJC1605, 87PJC103>.



Scheme 26

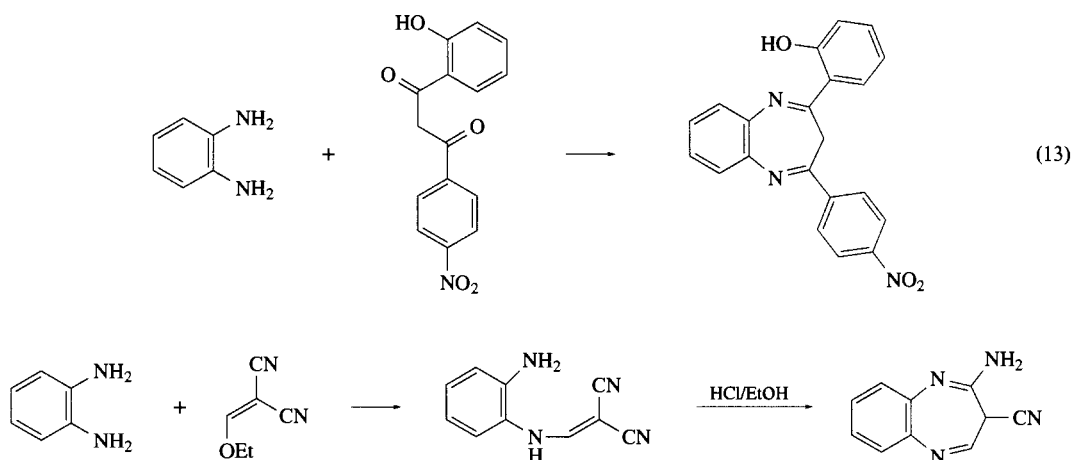
These same compounds (**149**; $\text{R} = \text{aryl}$) have also been prepared from *o*-hydroxychalcones and ethylenediamine <88MI 906-01>. 2,3-Dihydro-5,7-dimethyl-1,4-diazepine is obtained in 56% yield on heating 4-phenylsulfonyl-3-penten-2-one with ethylenediamine at 100°C in the absence of solvent <85JHC405>. This reaction provides an alternative to the vinamidinium route to 5,7-disubstituted-1,4-diazepines described above. The phenylsulfonyl groups of 2,3-bis(phenylsulfonyl)-1-propene (**150**) both activate the double bond to Michael addition and behave as a leaving group. These

properties were harnessed for the synthesis of seven-membered ring heterocycles (**151**) by reaction with tethered 1,2-bisnucleophiles, such as *N,N'*-dibenzylethylenediamine (Equation (12)) <92JOC298>.



9.06.9.2 1,5-Benzodiazepines

1,5-Benzodiazepines or [b]-fused 1,4-diazepines are most commonly prepared by the reaction of *o*-phenylenediamine with an appropriate 3-carbon fragment and thus correspond to the *dg* type synthesis or, where an intermediate is isolated and then subjected to a ring-closure reaction, a type *d* synthesis. In preparing the fully unsaturated 1,5-benzodiazepines, *o*-phenylenediamine can be reacted with 3-ketoaldehydes, 1,3-diketones, alkynic ketones, and β -chloro- α,β -unsaturated aldehydes. 2,3-Dihydrobenzodiazepines can be obtained from reaction of *o*-phenylenediamine with α,β -unsaturated carbonyl compounds, α -haloketones, β -hydroxyketones, and by partial reduction of the fully unsaturated analogues; β -ketoesters can be employed for the preparation of the 2-ones. Tetrahydro-1,5-benzodiazepines can be prepared by alkylation of *o*-phenylenediamine or by reduction of the fully unsaturated or dihydro systems. The synthesis of 1,5-benzodiazepines has been covered comprehensively <B-91MI 906-01> and examples representing a *dg* type synthesis <84AF640> and *ad* type synthesis <73CC367> are presented (Equation (13) and Scheme 27).



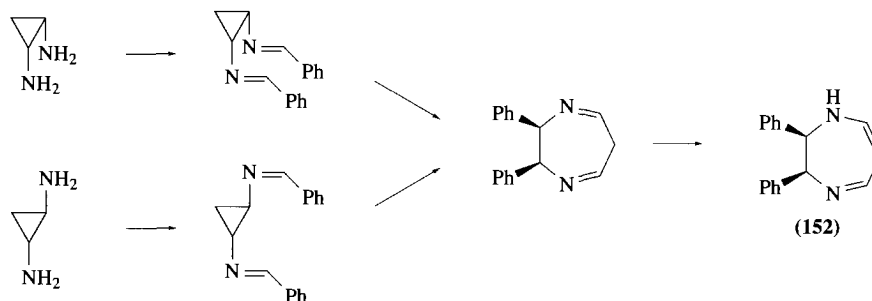
Scheme 27

9.06.10 SYNTHESIS BY RING TRANSFORMATION

9.06.10.1 Monocyclic

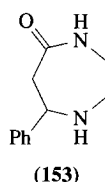
The bisimines formed from both *cis*- and *trans*-1,2-diaminocyclopropane and aryl aldehydes undergo a Cope rearrangement to the same *cis*-2,3-dihydro-1*H*-1,4-diazepines (Scheme 28) <83LA1207>. Thus, 1,2-diaminocyclopropane and benzaldehyde give *cis*-2,3-diphenyl-2,3-dihydro-1*H*-1,4-diazepine (**152**). The behavior of the *cis*- and *trans*-imines, however, is different. The *cis*-imines, in the main, cannot be isolated and rearrange spontaneously; the *trans*-imines can be isolated and undergo the Cope rearrangement on heating, either in the melt or, preferably, in a high boiling solvent. The *trans*-imines are believed to isomerize to the *cis*-imines in order to undergo the Cope

rearrangement to the 6*H*-1,4-diazepine which in turn undergoes a 1,3 sigmatropic shift to the more stable 1*H* tautomer. The imines were found to rearrange in acetate buffered methanol at 20°C and this reaction has been the subject of a mechanistic study <84CB1591>.

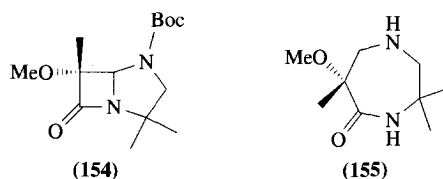


Scheme 28

The strain energy of the four-membered ring has been harnessed to prepare larger rings <83CC959>. Treatment of 2-bromoethyl-4-phenylazetidinone with liquid ammonia in a sealed tube at 45°C for 14 days furnished 7-phenyl-2,3,6,7-tetrahydro-1,4-diazepin-5-one (153) in 70% yield. The utility of this reaction is limited, however, by the long reaction times.

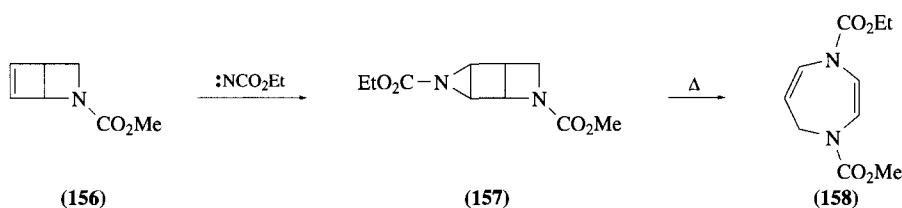


In another example, the hydrogenation of the azapenam (5*S*,6*R*)-6-methoxy-2,2,6-trimethyl-1,4-diazabicyclo[3.2.0]heptan-7-one (154), prepared by reaction of a pentacarbonyl chromium carbene complex with 1*N*-Boc-4,4-dimethylimidazoline, in the presence of 1.1 equiv. of racemic camphor sulfonic acid resulted in the cleavage of the Boc group and ring expansion of the azapenam to hexahydro-3,3,6-trimethyl-6-methoxy-5*H*-1,4-diazepin-5-one (155) in 71% yield <92JA5010>. It was pointed out that the ready availability of a variety of substituted chromium carbene complexes and imidazolines would make this a general route to this class of diazepine.



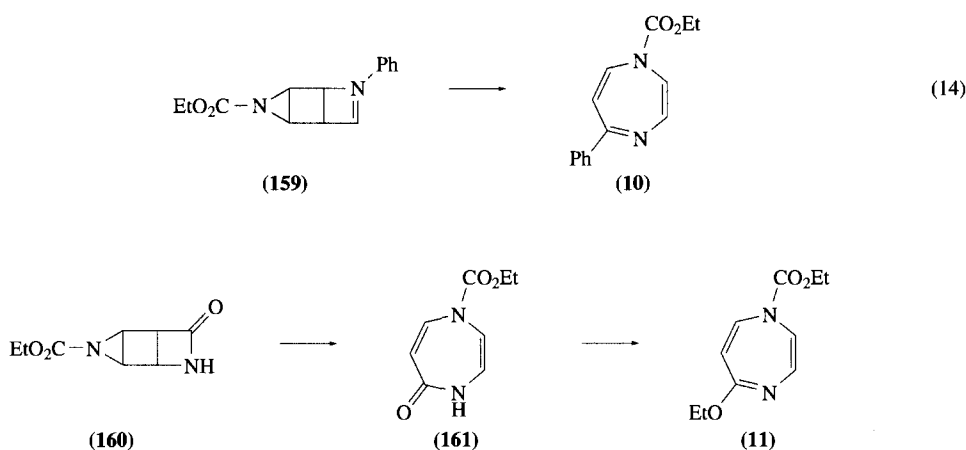
In what can be considered as a variant of the ring expansion of four-membered heterocycles, the thermal valence bond isomerization of 3,6-diazatricyclo[3.2.0.0^{2,4}]heptanes to 1,4-diazepines has been reported. The simplest example of this interesting reaction, illustrated in Scheme 29, starts with pyridine which is acylated with methyl chloroformate and reduced by sodium borohydride to the *N*-methoxycarbonyl-2-dihydropyridine, photolysis of which produces 2-azabicyclo[2.2.0]hexa-5-ene in 24% yield (156). This is reacted with ethoxycarbonylnitrene to give a 84% yield of 3-ethoxycarbonyl-3,6-diazatricyclo[3.2.0.0^{2,4}]heptane (157) which rearranges on heating under reflux in xylene for 6 hours to 4,5-dihydro-1-ethoxycarbonyl-4-methoxycarbonyl-1,4-diazepine in 84% yield (158) <85CPB4572>.

Photolysis of the related tricyclic system (159) afforded the novel fully saturated 1-ethoxycarbonyl-5-phenyl-1*H*-1,4-diazepine (10) in 84% yield (Equation (14)) <87CPB3166>. This reaction is presumed to proceed via a heteronorcaradiene intermediate analogous to that proposed in azidopyridine rearrangements. These studies were extended to pyridones as starting materials. Thermolysis of 3-ethoxycarbonyl-3,6-diaza-7-oxotricyclo[3.2.0.0^{2,4}]heptane (160), prepared from 2-pyridone in an analogous manner to that described above, in dichlorobenzene at 140°C for 1–2 hours gave 4,5-dihydro-1-ethoxycarbonyl-1*H*-1,4-diazepin-5-one (161) in high yield <87H(26)3085, 90CPB2911>, which



Scheme 29

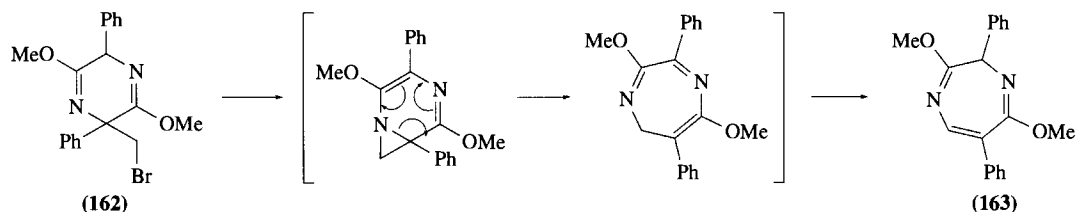
was converted into the fully unsaturated 1-ethoxycarbonyl-5-ethoxy-1*H*-1,4-diazepine (11) with triethyloxonium fluoroborate (Scheme 30).



Scheme 30

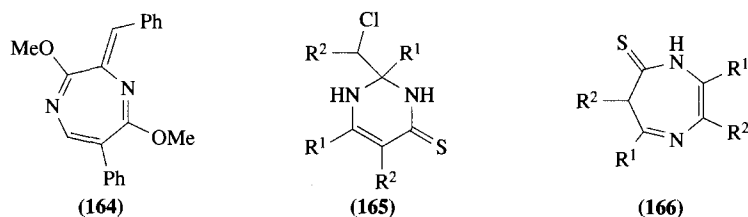
The classical ring expansion routes into diazepinones by the Schmidt or Beckmann reactions continue to be used. The Schmidt reaction on 1-ethoxycarbonyl-4-piperidone at 0°C produced the corresponding hexahydrodiazepinone derivative in 70% yield (91TL2469).

2,5-Dihydropyrazines, having a leaving group on an alkyl substituent β to a ring nitrogen atom, undergo a base-induced ring enlargement in DMSO or DMF to 2*H*-1,4-diazepines (Scheme 31) (89AG(E)613). Hence, 2-bromomethyl-3,6-dimethoxy-2,5-diphenylpyrazine (162) rearranges to 2*H*-2,6-dimethoxy-2,5-diphenyl-1,4-diazepine (163). Where the 2-phenyl group is replaced by a benzyl group, the benzyldiene derivative (164) is formed. The reaction is reported to proceed via a heteronorcaradiene which rearranges to the 5*H*-1,4-diazepine and this undergoes a rapid [1,5] sigmatropic shift to the 2*H*-1,4-diazepine. An analogous mechanism is proposed for the high yield (75–90%) conversion of 1,2-dihydropyrimidine-4(3*H*)-thiones (165; $\text{R}^1 = \text{Ph}$, *p*-tolyl; $\text{R}^2 = \text{Me}$, Et, Pr) bearing haloalkyl substituents in the 2-position, into 1*H*-1,4-diazepine-7(6*H*)-thiones (166) (93BSF566).

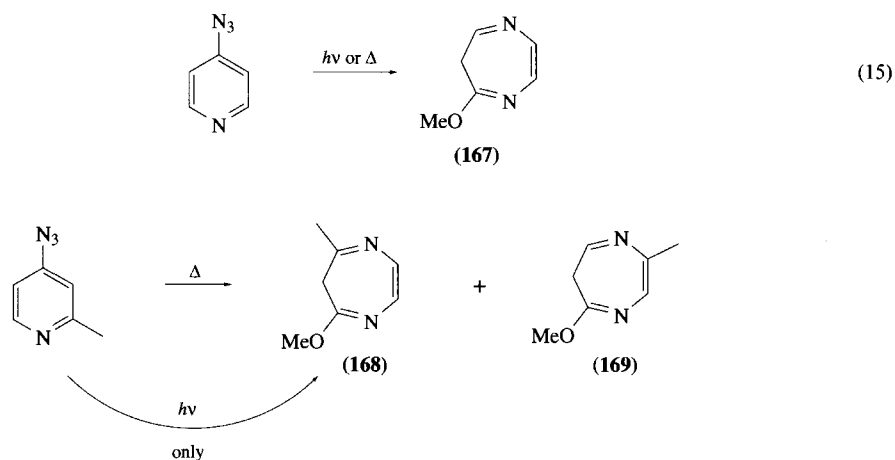


Scheme 31

The photolysis of 4-azidopyridine in a mixture of methanol and dioxane containing 1.5 equiv. of sodium methoxide gave the relatively unstable 5-methoxy-6*H*-1,4-diazepine (167), as the sole product (Scheme 32) (84CPB4694). By analogy with earlier work on the photolysis of phenyl azides, the reaction is presumed to proceed through a heteronorcaradiene intermediate. The thermolysis of 4-azidopyridine in methanol at 200°C for 8 min also yielded 5-methoxy-6*H*-1,4-diazepine (167) (50% crude yield). The reaction of the 2-methyl-4-azidopyridine under the same thermal conditions gave a 2:1 mixture of 5-methoxy-7-methyl-6*H*-1,4-diazepine (168) and 5-methoxy-2-methyl-6*H*-



1,4-diazepine (169) <85H(23)287>. 3-Methyl-4-azidopyridine behaved similarly. By contrast photolysis of 2-methyl-4-azidopyridine gave 5-methoxy-7-methyl-6*H*-1,4-diazepine (168) as the only product, although the yield was low (45%) (Equation (15) and Scheme 32) <87CPB3175>.

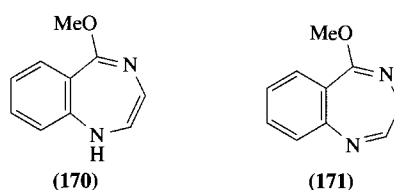


Scheme 32

1,4-Diazepines could be obtained from 3-azidopyridines only if the 2-position was substituted. For example, 4-azido-2-methylpyridine on photolysis in the presence of sodium methoxide furnished 3-methoxy-2-methyl-2*H*-1,4-diazepine. Photolysis of the unsubstituted or 2,4-disubstituted derivatives only gave 4-methoxy-5*H*-1,3-diazepines <87CPB1179>.

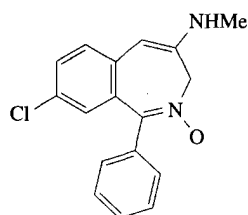
9.06.10.2 Benzodiazepines

The scope of these photolytic reactions has been extended to 4-azidoquinolines, for example, photolysis of 4-azidoquinoline in the presence of sodium methoxide, gave 5-methoxy-1*H*-1,4-benzodiazepine (170). These diazepines are reported to be unstable on standing and to chromatographic conditions <82JCS(P1)431, 87CPB3182>. However, further exposure to sodium methoxide in methanol results in a rearrangement to the relatively more stable 3*H*-analogue, for example, 5-methoxy-3*H*-1,4-diazepine (171) <87CPB3182>. The introduction of an ester or amide function *ortho* to the 1*H* nitrogen atom gives stable compounds which is attributable to the formation of a hydrogen bond between the N—H and the adjacent carbonyl oxygen atom <90CPB2919>. 3-Azidoquinolines behave similarly on photolysis <87CPB4110>.

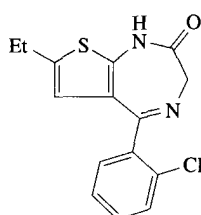
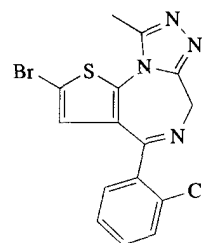


9.06.11 IMPORTANT COMPOUNDS AND APPLICATIONS

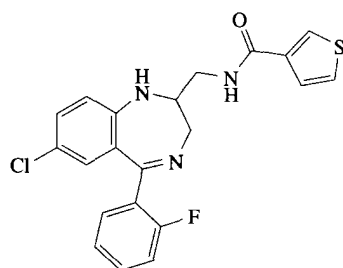
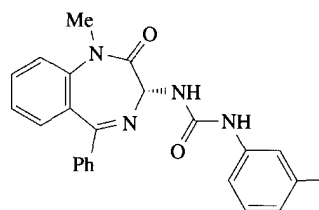
The best known of the 1,4-diazepines are undoubtedly the 1,4-benzodiazepines, a successful class of CNS drugs which are used clinically as anti-anxiety agents, hypnotics (sleep inducers), anti-convulsants, and muscle relaxants. Two members of this class, diazepam and chlordiazepoxide (**172**), are among the most widely used anti-anxiety drugs. This commercial success has led to a vast synthetic effort which has resulted in other CNS drugs based on hetero-fused diazepines (e.g., clotiazepam, (**173**)) and tricyclic diazepines (e.g., brotizolam (**174**)) along with a variety of more traditional analogues from both the 1,4- and 1,5-benzodiazepine series <B-83MI 906-01>.



(172)

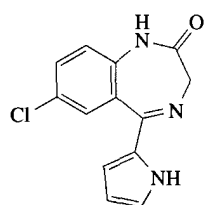
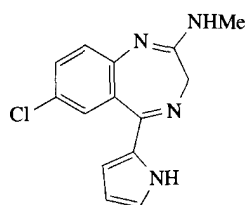
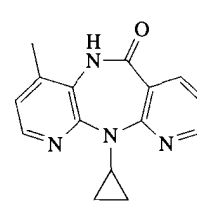
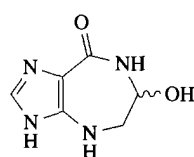
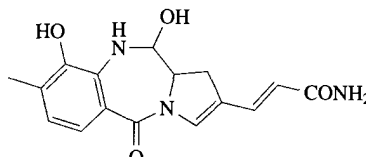
clotiazepam (**173**)brotizolam (**174**)

Benzodiazepines have been reported with novel pharmacological activities far removed from the CNS activities of the earlier generation of benzodiazepines. The natural product asperlicin was the starting point for a programme of work that led to the cholecystokin A (CCK-A) antagonist, tifluadom, (**175**) with potential for the treatment of gastric disorders <90JMC450>, and the CCK-B antagonist (**176**) for use in neuropsychiatric disorders <89JMC13>.

tifluadom (**175**)

(176)

The benzodiazepines (**177**) and (**178**) are HIV-Tat antagonists and are being evaluated as therapies for the treatment of AIDS <91SCI1799> as is the HIV-1 reverse transcriptase inhibitor nevirapine (**179**) <90SCI411>. The natural product azepinomycin (**180**) is reported to be an antibiotic with antitumour properties <88H(27)1163> and anthramycin (**181**) is an antineoplastic agent.

Ro 5-3335 (**177**)Ro 24-7429 (**178**)nevirapine (**179**)azepinomycin (**180**)anthramycin (**181**)

The benzodiazepine nucleus is now recognized as an important pharmacophore and a solid-phase synthesis of benzodiazepines which will allow the combinatorial synthesis of libraries of benzodiazepine-based compounds for pharmacological testing has been described <92JA10997>.

9.07

1,2-Oxazepines and 1,2-Thiazepines

JOHN B. BREMNER

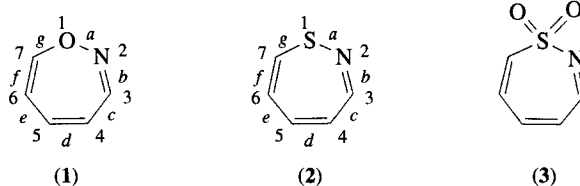
University of Wollongong, NSW, Australia

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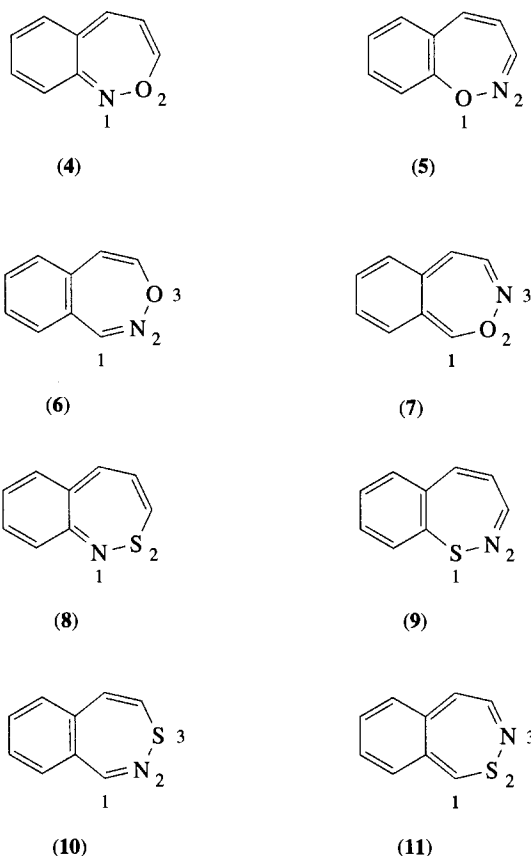
9.07.1 INTRODUCTION

There has been a steady interest in the chemistry of these systems over the past ten years since the first edition of *Comprehensive Heterocyclic Chemistry* in 1984 <84CHEC-I(5)593>. In this chapter, the 1,2-oxazepines and 1,2-thiazepines are grouped together. There have been no general reviews of these systems, apart from the treatment in CHEC-I <84CHEC-I(5)593> and that by Gagan <B-79MI 907-01>. A review of the synthesis of seven-membered heterocycles based on pericyclic reactions touches briefly on 1,2-oxazepine and 1,2-thiazepine derivatives <88S569>. The parent systems considered in this chapter are 1,2-oxazepine (**1**) and 1,2-thiazepine (**2**), and are shown below. Most of

the known compounds are reduced derivatives. Oxidized forms of the 1,2-thiazepine system are also treated, in particular derivatives of 1,2-thiazepine 1,1-dioxide (3).



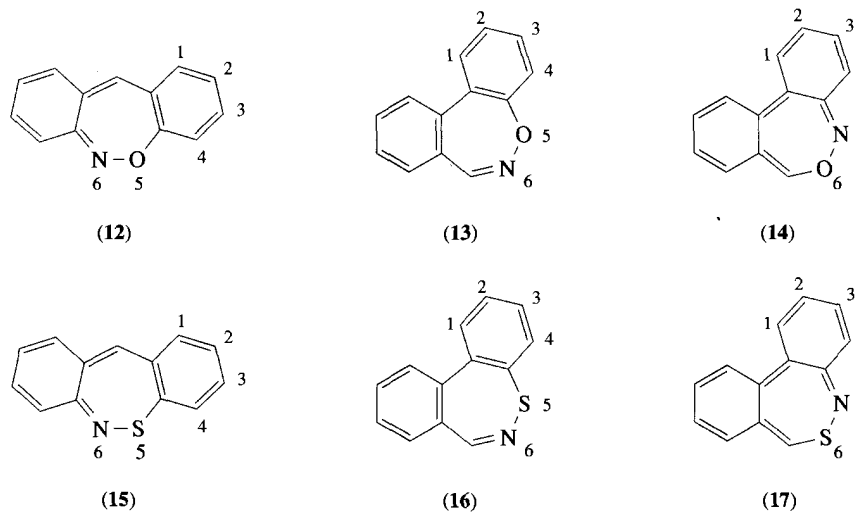
Benz-fused and dibenz-fused analogues are covered in this chapter. The possible benz-fused parent systems are the 2,1-benzoxazepine (4), 1,2-benzoxazepine (5), 3,2-benzoxazepine (6), 2,3-benzoxazepine (7), 2,1-benzothiazepine (8), 1,2-benzothiazepine (9), 3,2-benzothiazepine (10), and 2,3-benzothiazepine (11), and derivatives of some of these systems are included. There are ten possible heterocyclic skeletons in total for the benzoxazepines and ten for the benzothiazepines; skeleton numbers can be calculated on the basis of the formula given in a 1982 review on medium-sized heterocycles <82H(19)709>. The synthesis of benzothiazepines has been reviewed <86KGS1443>.



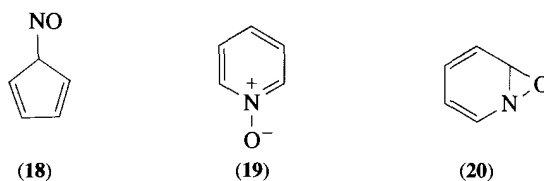
There are three possible dibenz-fused systems for each of the O,N rings and S,N rings. These are the dibenz[*c,f*][1,2]- (12), dibenz[*d,f*][1,2]- (13), dibenz[*c,e*][1,2]oxazepine (14), and dibenzo[*c,f*][1,2]- (15), dibenzo[*d,f*][1,2]- (16), and dibenzo[*c,e*][1,2]thiazepine (17) systems. Bridged systems incorporating 1,2-oxazepine or 1,2-thiazepine moieties have not been included in this chapter.

9.07.2 THEORETICAL METHODS

Minima on the potential energy surface for the valence isomerization of 5-nitroso-1,3-cyclopentadiene (18) have been calculated using the MINDO/3 method. The lowest of these minima is 1,2-oxazepine (1) (ΔH_f 13.0 kcal mol⁻¹); the other two are pyridine *N*-oxide (19) and the bicyclic



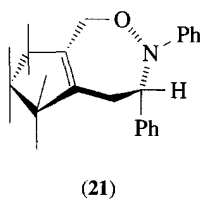
valence isomer (20). The calculations predicted planarity for (1) and carbon—carbon bond lengths indicative of an 8π -electron anti-aromatic structure $\langle 87ZOR1137 \rangle$.



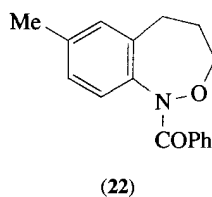
9.07.3 EXPERIMENTAL STRUCTURAL METHODS

9.07.3.1 NMR Spectra

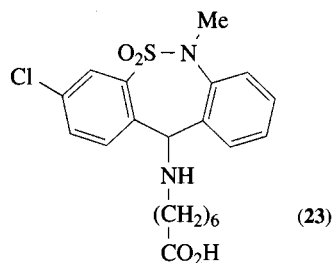
Detailed ^1H NMR studies together with calculated conformations using MMX have been reported on tetrahydro-1,2-oxazepine derivatives (e.g., (21)) formed from $[4 + 3]$ cycloadditions of *C,N*-diphenylnitronium with 1,3-dienes. The existence of two conformers with a slow rate of interconversion is indicated by the NMR data $\langle 89JOC5774 \rangle$.



Deuterium labeling experiments and NMR studies have been used to show that *N*-acyl-*N*-(3-phenylpropyloxy)nitrenium ions form the 1,3,4,5-tetrahydro-2,1-benzoxazepines through *ipso* attack on the aromatic ring, followed by 1,2-carbon migration. Furthermore, the occurrence of hydrogen migration in the sigma complex prior to aromatization was demonstrated. Also, 500 MHz ^1H NMR spectroscopy was used to confirm the position of the methyl group in the aromatic ring in (22) $\langle 90T7247 \rangle$.

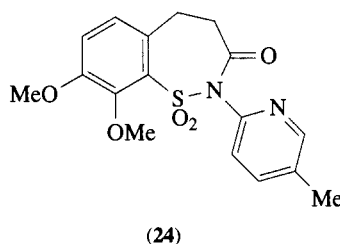


Conformational aspects of the antidepressant drug, tianeptine (**23**), which is a dibenzothiazepine derivative, have been studied by ^1H and ^{13}C NMR spectroscopy. Two separate conformations for the seven-membered ring are indicated at low to room temperature. The conformational preference for the side chain involves bending over the non-substituted aromatic ring moiety <92MRC1212>.



9.07.3.2 X-ray Methods

A single crystal x-ray structure determination has been reported on the benzothiazepinone derivative (**24**). The thiazepine ring was shown to have a boat conformation <86AX(C)1581>.



9.07.4 THERMODYNAMIC ASPECTS

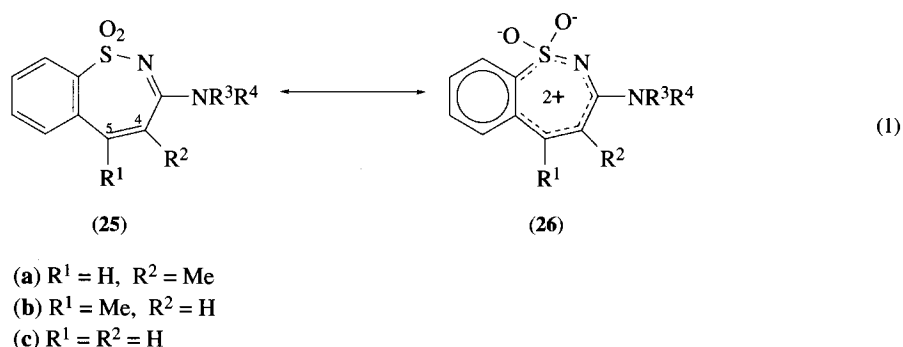
9.07.4.1 Chromatographic Behavior

Considerable attention has been focussed on the antidepressant, tianeptine (**23**), which has included the development of a reverse-phase, ion-pair, liquid chromatographic method for the determination of the drug and its major metabolites in plasma, urine, and tissues <86JC115>. Further metabolic studies in healthy volunteers involving chromatographic and mass spectral analysis have also been reported <90MI 907-01>.

Trace determination of tianeptine in plasma by gas-liquid chromatography (GLC) and the use of an electron capture detector has also been described. To increase volatility, the tianeptine was converted to the methyl ester with diazomethane and then alkylated with heptafluorobutyric anhydride to increase the sensitivity to the detector <81MI 907-01>.

9.07.4.2 Aromaticity

Amongst the benz-fused systems, the question of aromaticity in 1,2-benzothiazepine 1,1-dioxides has been addressed by Abramovitch and co-workers. The benzothiazepines are very stable chemically, but the chemical shifts for the H-4 protons in (**25b**) and (**25c**) (δ 7.1 and δ 7.2, respectively), and for the H-5 protons in (**25a**) and (**25c**) (δ 6.2 and δ 6.3), together with the relatively large size of the $J_{4,5}$ coupling constant (12.7 Hz in (**25c**)), indicates that the seven-membered ring is not aromatic, favoring structure (**25**) over (**26**) (Equation (1))) <83CC520>.



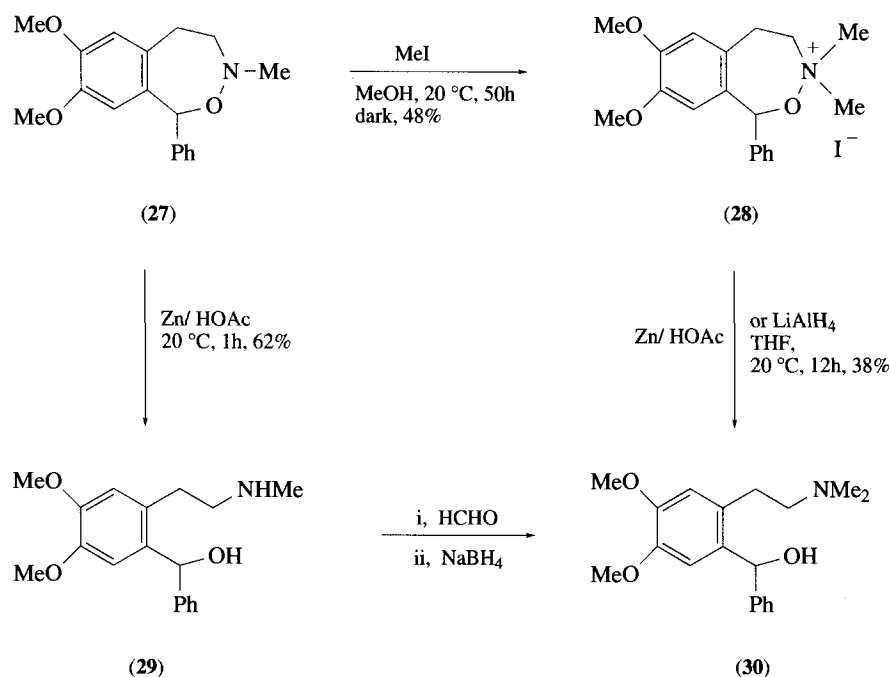
9.07.5 REACTIVITY

9.07.5.1 Reactivity of Fully Unsaturated Rings

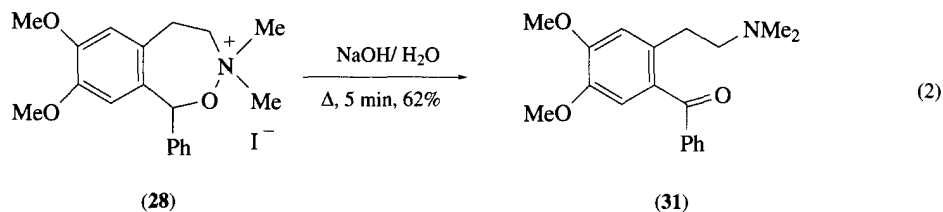
There have been no papers dealing with the reactivity of the fully unsaturated 1,2-oxazepine or 1,2-thiazepine rings or their benzo or dibenzo derivatives, apart from rearrangements of the dibenzo[*c,f*][1,2]oxazepines (**81**) as outlined in Section 9.07.7.1. The 8π -electron, 1,2-oxazepinium perchlorate salts (**61**) (see Section 9.07.7.1) are stable, consistent with the charge delocalized seven-membered ring structure proposed, and do not undergo a Diels–Alder reaction with maleic anhydride <81ZOR881>.

9.07.5.2 Reactivity of Nonconjugated Rings

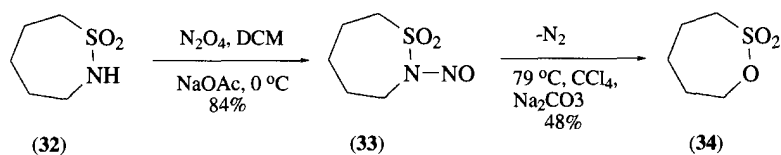
The N—O bond in the tetrahydro-2,3-benzoxazepine (**27**) can be cleaved reductively either directly using zinc in acetic acid to give (**29**) or stepwise via the methiodide salt (**28**) to give (**30**). The secondary amino alcohol (**29**) can be converted readily to (**30**) (Scheme 1). The N—O bond in (**28**) can also be broken under basic conditions in a Hofmann-like elimination to afford the amino ketone (**31**) (Equation (2)) <80AJC833>.



Scheme 1

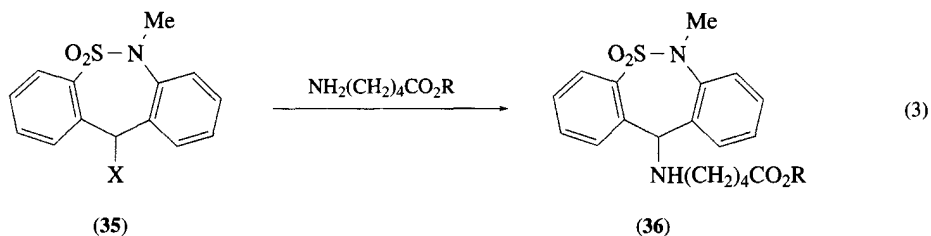


The seven-membered ring sultam (32) is nitrosated smoothly on the ring nitrogen by reaction with dinitrogen tetroxide to afford (33); the decomposition of this and other *N*-nitrososultams can then be studied, in particular the formation of the sultones (e.g., (34)) with nitrogen extrusion in the presence of base (Scheme 2) <87JOC2162>.



Scheme 2

Analogues of tianeptine have been prepared by standard nucleophilic displacement reactions involving the halide (35; X = Br, Cl), to give the amino esters (36). Subsequent saponification then gives the amino acid (36; R = H) (Equation (3)) <87FRP2594827>.



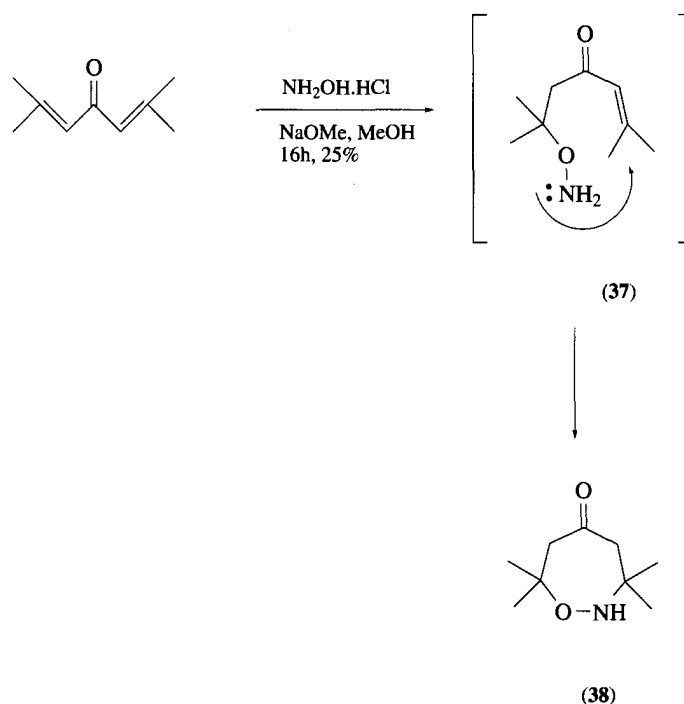
9.07.6 RING SYNTHESIS BY RING CONSTRUCTION

9.07.6.1 1,2-Oxazepines and Benz-fused Derivatives

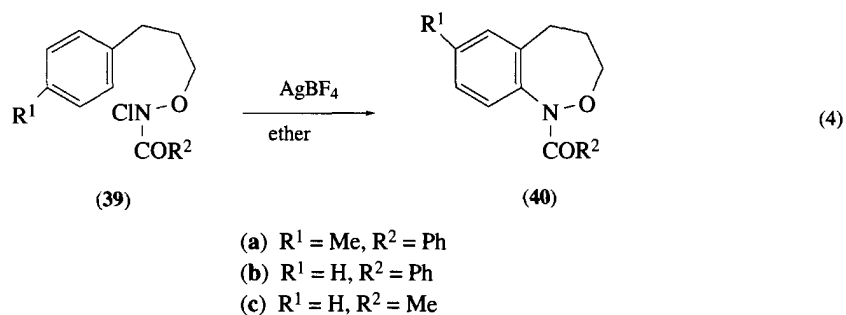
9.07.6.1.1 Type b (N—O—C—C—C—C—C)

A low yield of the solid hexahydro-3,3,7,7-tetramethyl-1,2-oxazepin-5-one (38) (m.p. 50 °C) can be obtained on reaction of phorone with hydroxylamine in the presence of base. The competing reaction is the formation of the five-membered ring compound, 3-isobutenyl-5,5-dimethyl-4,5-dihydroisoxazole by intramolecular 1,2-addition, rather than by 1,4-addition by nitrogen in the intermediate (37), followed by dehydration. Some of the oxime of (38) is also formed (Scheme 3) <81G279>.

Nitrenium ion-mediated methodology has been developed by Glover and co-workers for the synthesis of *N*-acyl-1,3,4,5-tetrahydro-2,1-benzoxazepines (40) from the *N*-chloro derivatives (39). The reaction proceeds via initial *ipso* attack followed by 1,2-carbon migration <84JCS(P1)2255, 87T2577, 90T7247>. Benzene was also used as a solvent in the case of (39b) (Equation (4)) <84JCS(P1)2255>.



Scheme 3



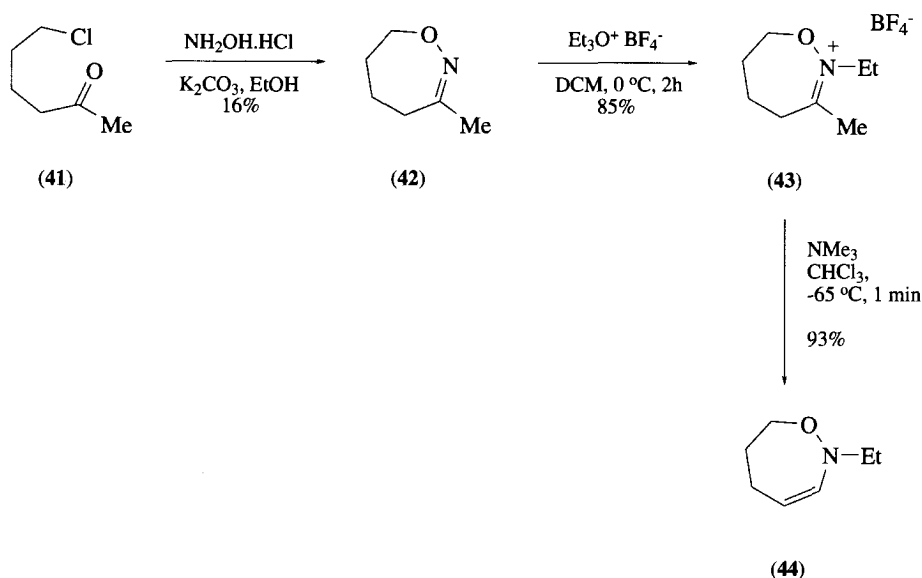
9.07.6.1.2 Type g (O—N—C—C—C—C—C)

The tetrahydro-1,2-oxazepine (**42**) can be prepared from the chloroketone (**41**) by initial formation of the oxime, followed by ring formation. The oxazepine (**42**) can be converted into the crystalline (m.p. 142–143°C) oximinium salt (**43**) on treatment with Meerwein's salt, and hence to the chemically unstable tetrahydro derivative (**44**) (Scheme 4) <83LA897>.

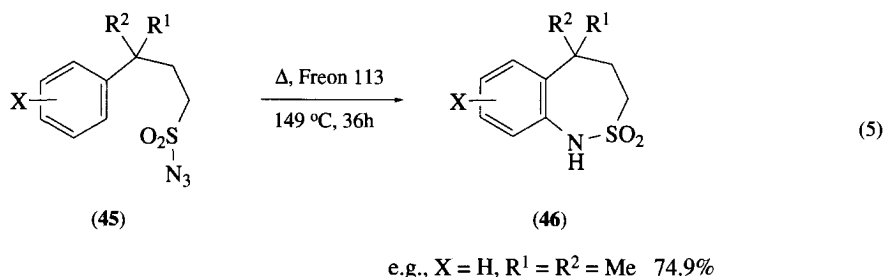
9.07.6.2 1,2-Thiazepines and Benz-fused Derivatives

9.07.6.2.1 Type b (N—S—C—C—C—C—C)

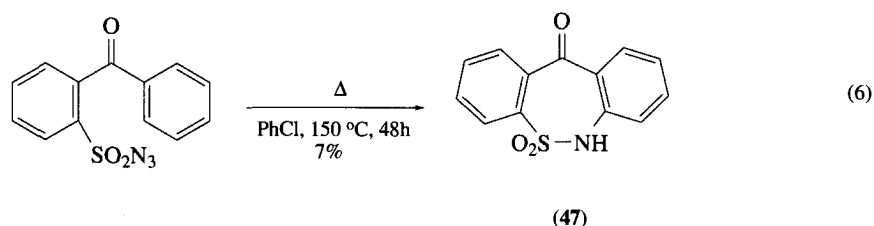
The solution and flash vacuum pyrolysis of 3-arylpropanesulfonyl azides (**45**) provides a convenient route to 2,1-benzothiazepine 2,2-dioxides (**46**) via nitrene intermediates (Equation (5)). The best yields of the seven-membered ring compounds are obtained on decomposition in solutions of Freon 113, which minimise intermolecular C—H insertion and hydrogen abstraction products <84JOC3114>.



Scheme 4



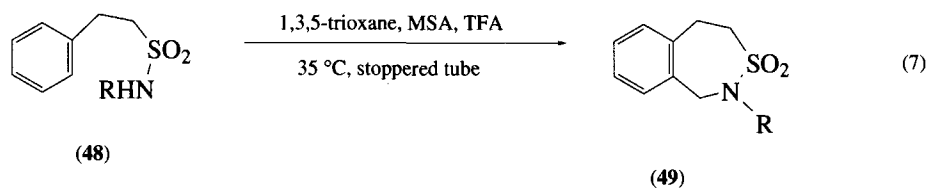
Intramolecular nitrene cyclization from thermolysis of 2-azidosulfonylbenzophenone affords the dibenzo[*c,f*][1,2]thiazepine 5,5-dioxide system (47) in low yield, together with other products. The 2-methyl and 8-methyl analogues of (47) are prepared similarly, also in low yields (<78JOC1218).



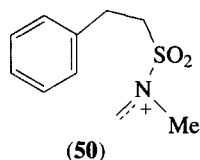
9.07.6.2.2 Type bc ($\text{N}-\text{S}-\text{C}-\text{C}-\text{C}-\text{C}+\text{C}$)

The 1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxides (49) (e.g., $\text{R} = \text{H}$, Me, Bu^iCH_2 , PhCH_2 , EtO_2CCH_2) can be obtained readily by sulfonamidomethylation of the 2-phenylethanesulfonamides (48) (Equation (7)), using 1,3,5-trioxane as the *in situ* source of the formaldehyde (92JHC859). The compounds (49) are obtained generally in high yield using a mixture of methanesulfonic acid and trifluoroacetic acid as the reaction medium: (49; $\text{R} = \text{H}$, 89%, m.p. $163-164^\circ\text{C}$); (49; $\text{R} = \text{Me}$, 78%, m.p. $175-176^\circ\text{C}$); (49; $\text{R} = \text{Bu}^i\text{CH}_2$, 80%, m.p. $119-120^\circ\text{C}$); (49; $\text{R} = \text{PhCH}_2$, 12%, m.p. $138-139^\circ\text{C}$); (49; $\text{R} = \text{EtO}_2\text{CCH}_2$, 84%, m.p. $66-67^\circ\text{C}$). The yield of (49; $\text{R} = \text{PhCH}_2$) can be increased to 73% on performing the reaction in methanesulfonic acid and acetic anhydride diluted in 1,2-dichloroethane, conditions which do not lead to cleavage of the *N*-benzyl group. The latter cyclization conditions are also used to make the 7-methoxy analogue of (49; $\text{R} = \text{PhCH}_2\text{CH}_2$, m.p. $140-$

141 °C) in 58% yield, but use dichloromethane in place of 1,2-dichloroethane and a more dilute solution. The formation of (49; R = H) by this route was noted in CHEC-I <84CHEC-I(5)593>.



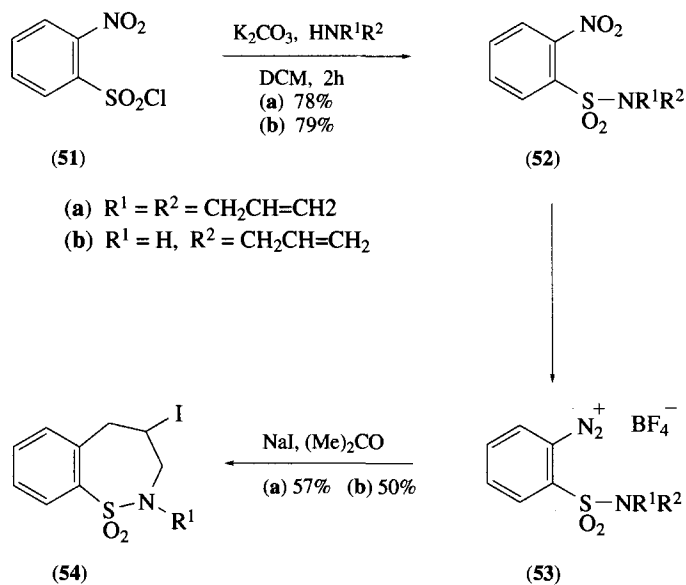
In a competition experiment, the formation of the *N*-methyl substituted derivative (49; R = Me) was shown to be favored over the unsubstituted derivative (49; R = H) by 3 to 1. This is due to the extra stabilization of the intermediate iminium ion (50) by the *N*-methyl group.



9.07.6.2.3 Type e (C—C—S—N—C—C—C)

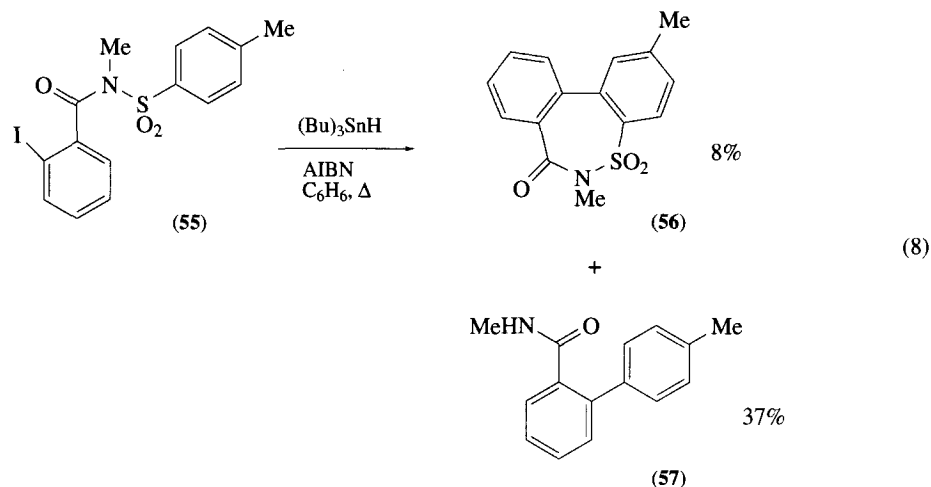
Iododediazotiation of the arenediazonium salts ((53a) and (53b)) and subsequent addition of the aryl radical to the allylic double bond leads to the 1,2-benzothiazepine 1,1-dioxide derivatives (54) by *endo* cyclization (Scheme 5) <87JOC1922>. The precursors (53) are obtained from *o*-nitrobenzenesulfonyl chloride (51) via the sulfonamides (52) and standard interconversion of the nitro group to the diazonium salt.

Direct intramolecular free radical [1,7] addition affords some of the dibenzo[*d,f*][1,2]thiazepine



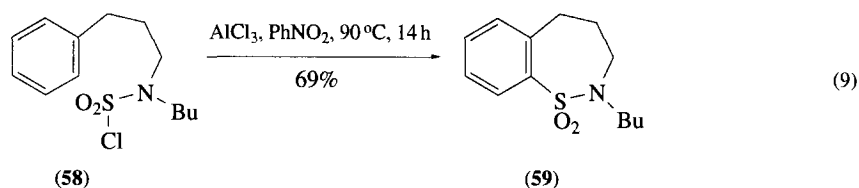
Scheme 5

5,5-dioxides (**56**), together with the *ipso*-substitution-derived product (**57**) (with loss of SO₂) on reaction of (**55**) with AIBN and tri-*n*-butyltin hydride (Equation (8)) <91CC877>.



9.07.6.2.4 Type g (S—N—C—C—C—C—C)

The 1,2-benzothiazepine 1,1-dioxide (**59**) can be made by intramolecular Friedel–Crafts cyclization of the sulfamoyl chloride (**58**), with aluminum chloride as the catalyst (Equation (9)) <92OPP463>.



9.07.7 RING SYNTHESIS BY RING TRANSFORMATION

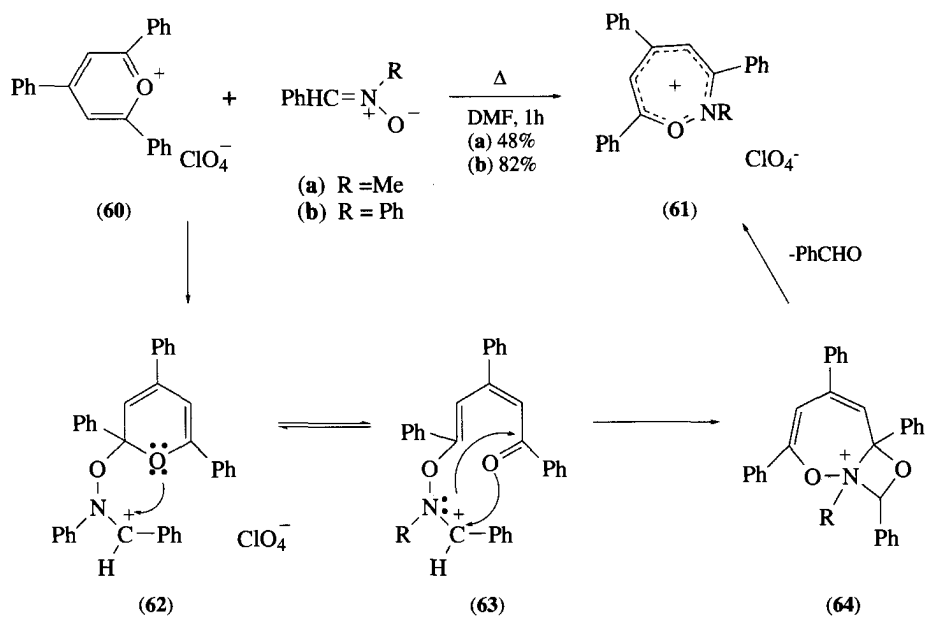
9.07.7.1 1,2-Oxazepines and Benz-fused Derivatives

A new class of seven-membered cations with 8 π -electrons, the 1,2-oxazepinium salts (**61**), has been prepared by reaction of 2,4,6-triaryl substituted pyrylium salts (e.g., **60**) with nitrones in boiling DMF. Reaction of (**60b**) with *N*-phenylhydroxylamine in DMF also gives (**61b**). The proposed intermediates in the nitrone reaction, (**62**), (**63**), and (**64**), are shown in Scheme 6 <81ZOR881>. Extension to other pyrylium salts has been described <82KG457>.

4-Hydroxy-2,3,4,5,6,7-hexahydro-1,2-oxazepine (**67**) can be accessed via intramolecular nucleophilic attack by the amide nitrogen on the epoxide intermediate (**66**). The epoxide is produced in turn, from intramolecular displacement and ring opening of the phthalimide (**65**) under basic conditions; alternatively, the epoxide may be pre-formed, but the yield of (**67**) is the same. Oxidation of (**67**) affords ketone (**68**), while hydrolysis of (**67**) gives (**69**) in high yield, isolated as the oxalate salt (1 : 1) (Scheme 7). Some 1,2-oxazine product (45% yield) is also obtained from the initial base-induced reaction, due to attack by the amide nitrogen on the substituted epoxide carbon in (**66**) <82S426>.

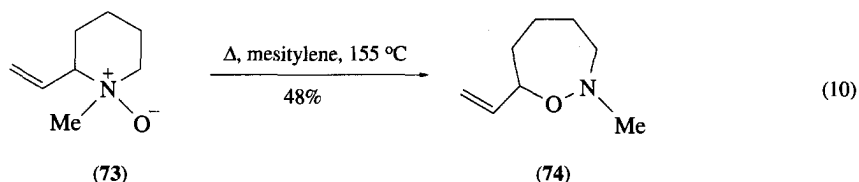
Photolysis of a benzene solution of the methyl 1-azido glucoside (**70**) gives the 1,2-oxazepine derivative (**72**) as the major product. Rearrangement is thought to proceed via the nitrene intermediate (**71**) and preferential migration of the ring oxygen atom (Scheme 8). The corresponding β -azido analogue of (**70**) gives virtually none of the 1,2-oxazepine (**72**) as indicated by NMR analysis, instead rearranging to a 1,3-oxazepine and methoxyiminolactone derivatives <94TL93>.

Thermolysis of the vinylpiperidine *N*-oxide (**73**) gives the Meisenheimer rearrangement product,

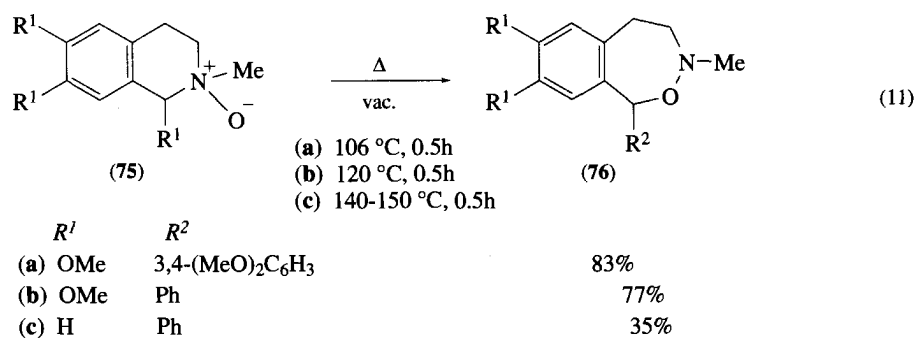


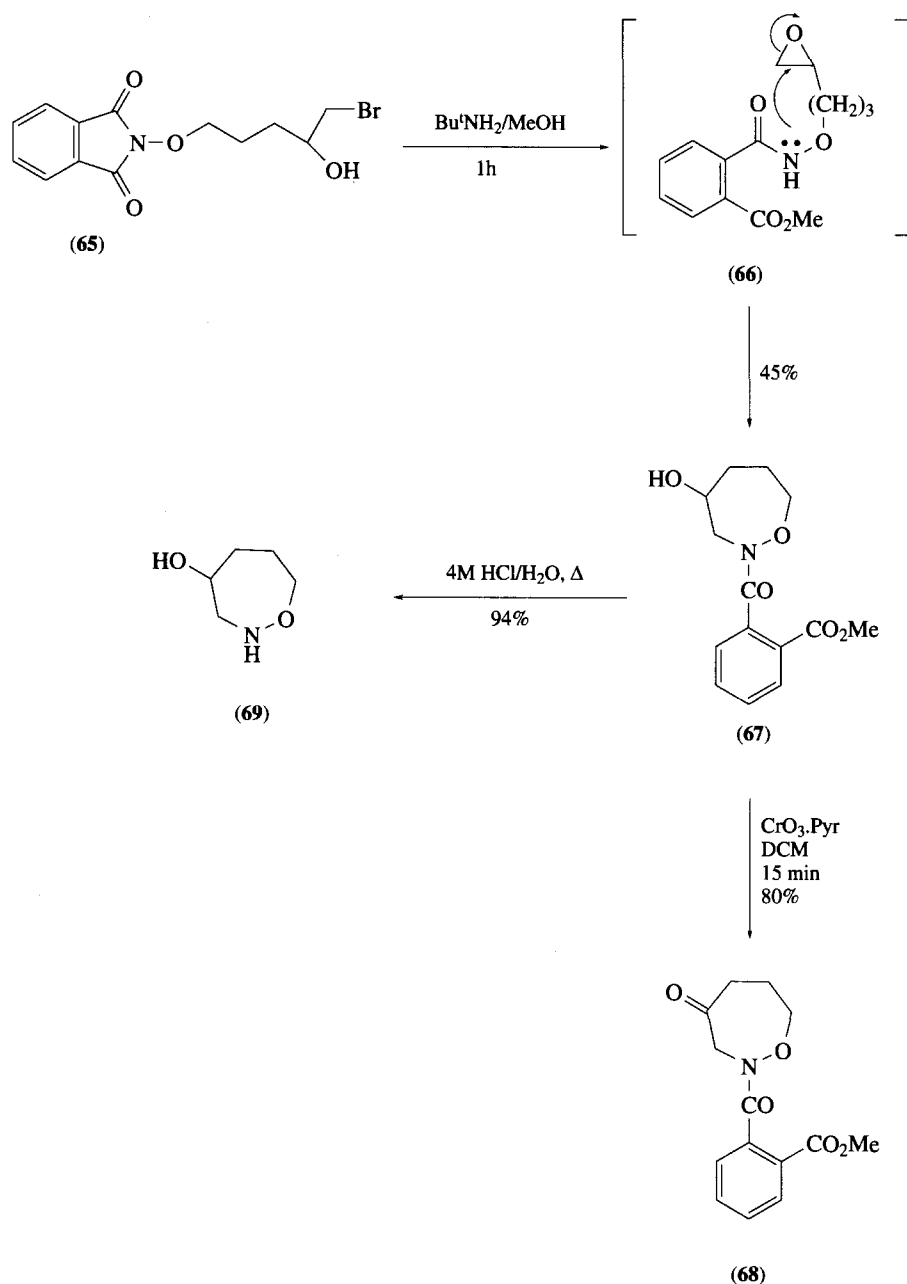
Scheme 6

hexahydro-1,2-oxazepine (74) in moderate yield; no [2,3] sigmatropic rearrangement product is observed (Equation (10)) <84CPB4117>.



Tetrahydro-2,3-benzoxazepines (76) can also be accessed in generally good yields using Meisenheimer rearrangement technology based on pyrolysis of the *N*-oxides (75). This reaction is believed to proceed via homolytic cleavage of the C(1)—N bond to give a diradical intermediate, followed by C—O bond formation. The initial cleavage is assisted by the doubly benzylic nature of the C-1 position <80AJC833>. Extension of the methodology to other heteroaromatic ring-fused [1,2]oxazepine derivatives, as well as to other 1-substituted tetrahydro-2,3-benzoxazepines, has been described (Equation (11)) <80AJC1335, 88AJC1815, 93TL3331, 94TL2409>.

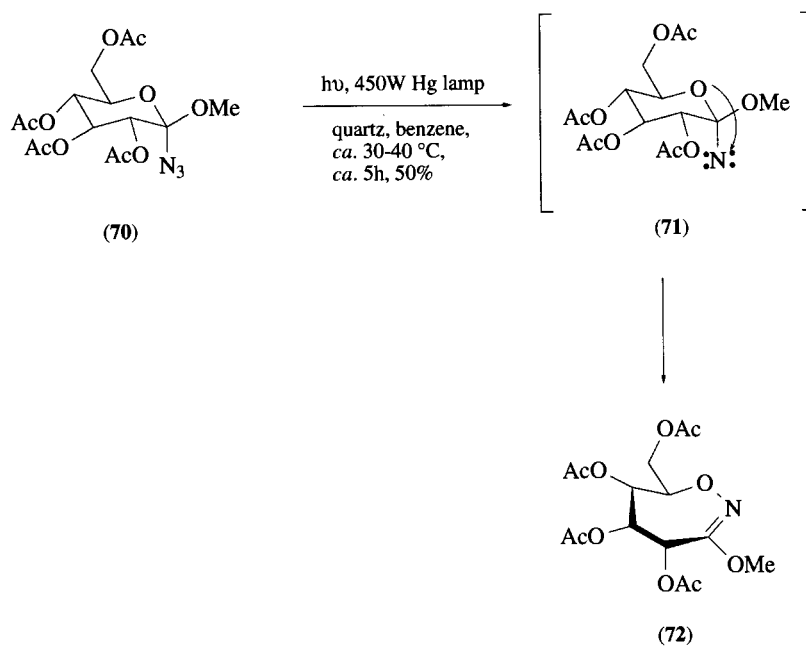




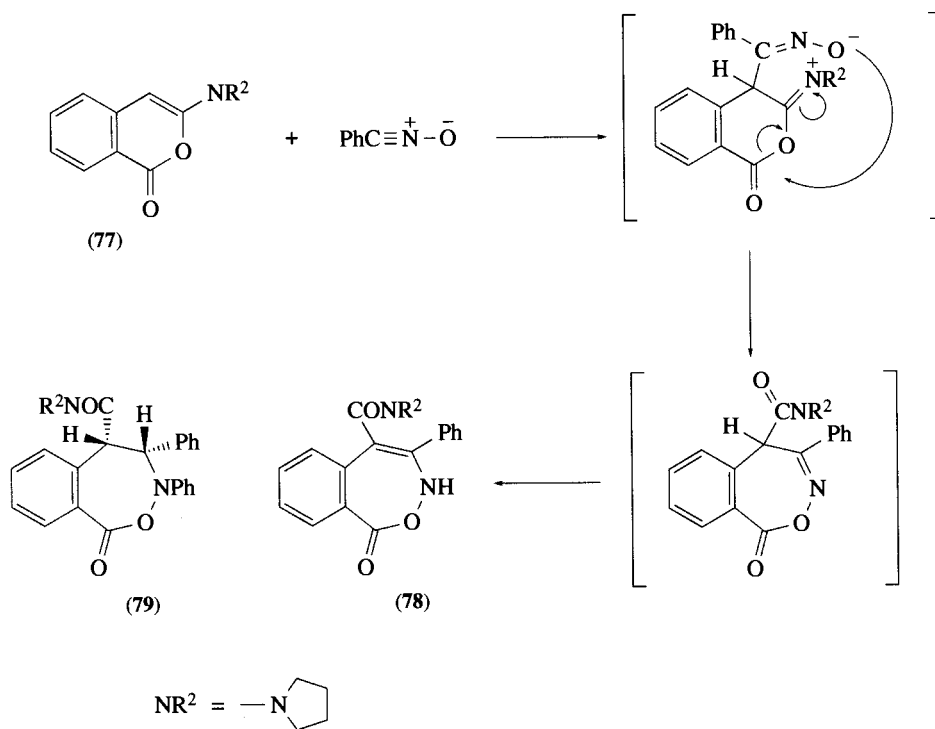
Scheme 7

An alternative ring expansion process involving the benzopyranone (**77**) and the 1,3-dipole benzonitrile oxide, generated *in situ* from *N*- α -chlorobenzylidenehydroxylamine, affords access in low yield (8.4%) to the functionalized 2,3-benzoxazepin-1-one system (**78**) (m.p. 155–156°C). An analogous reaction is demonstrated by *N*-benzylideneaniline *N*-oxide to give (**79**) (m.p. 266–267°C) in 16% yield (Scheme 9) <80JCS(P1)846>.

Dibenz[*c,f*][1,2]oxazepines (**81**) are obtained as the principal products from the photolysis of the substituted acridine *N*-oxides (**80**) in benzene. The electron-withdrawing substituents help stabilize the antiaromatic 1,2-oxazepine moiety. On refluxing in benzene, (**81b**) is converted mainly back to the starting *N*-oxide, while on heating (**81a**) in aqueous acetonitrile at 60°C, the main product is an

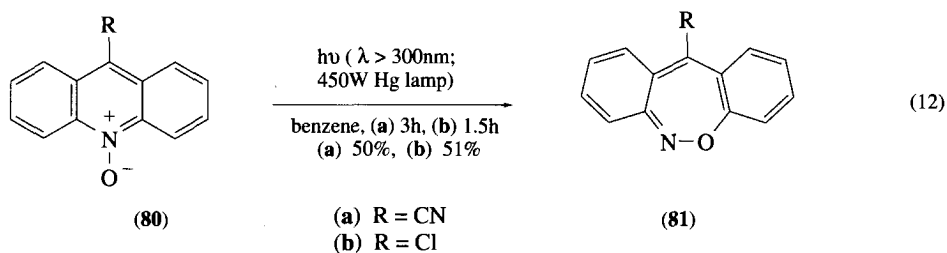


Scheme 8



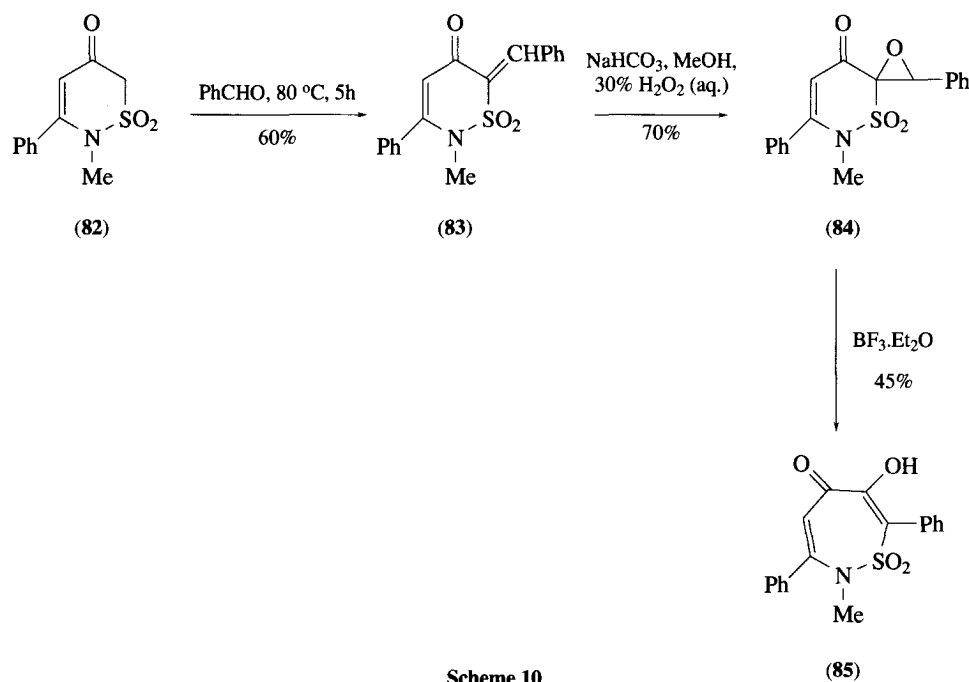
Scheme 9

oxepino-acridine derivative, with only a very small amount of the acridine *N*-oxide precursor (Equation (12)) <79T1273>.



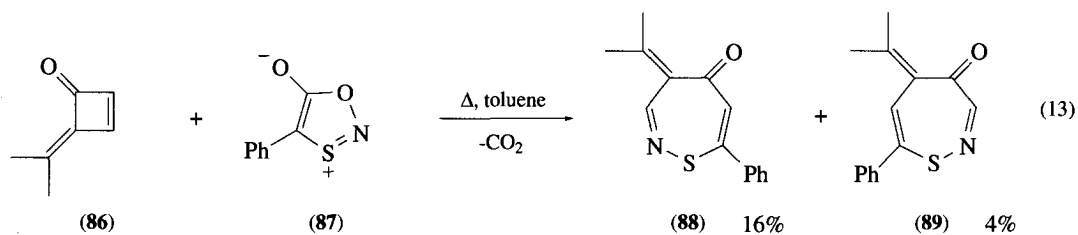
9.07.7.2 1,2-Thiazepines and Benz-fused Derivatives

Ring expansion of the β -ketosultam (82) via the alkylidene derivative (83) and epoxide (84), affords the 1,2-thiazepine 1,1-dioxide (85) (Scheme 10) <92AP(327)461>.



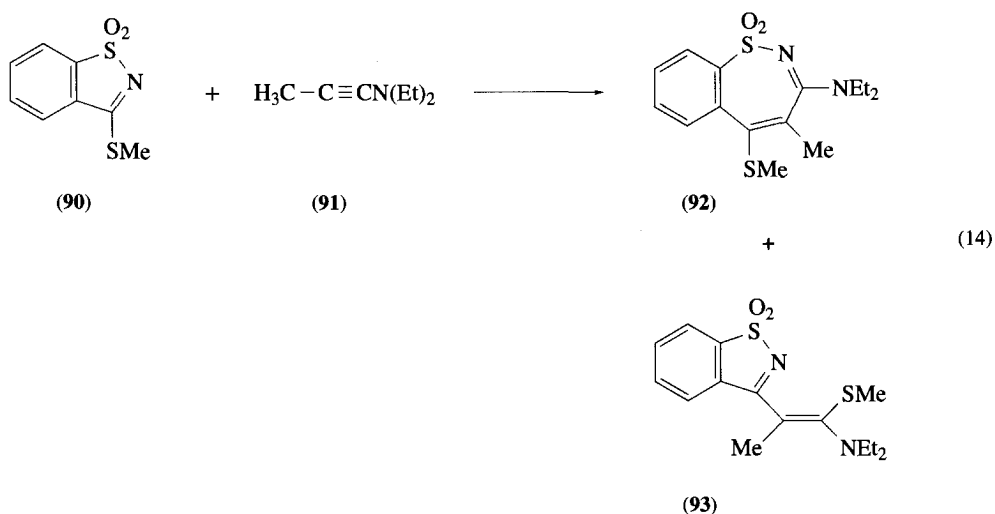
Scheme 10

Initial 1,3-dipolar cycloaddition of the mesoionic compound (87) to (86), followed by extrusion of carbon dioxide, leads to the 1,2-thiazepine derivatives (88) and (89) in low yields (Equation (13)) <85MI 907-01>.

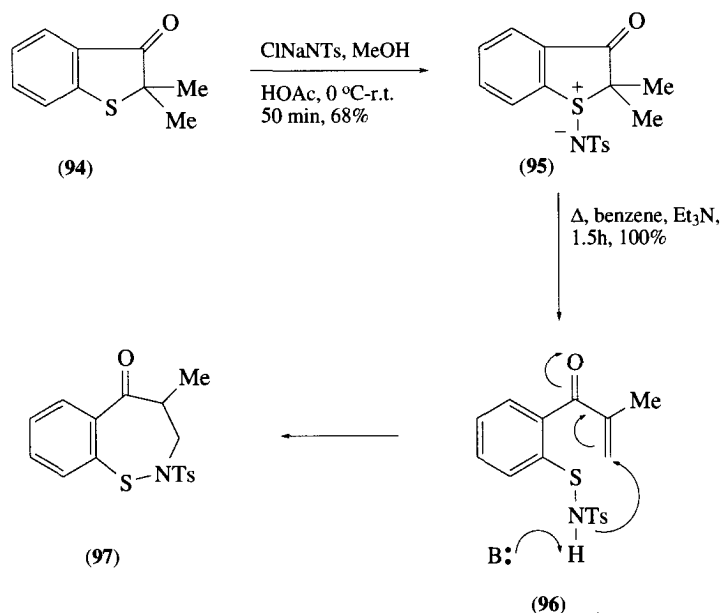


The ring-expansion product (92) is obtained in low yield from the reaction of (91) with the 3-substituted 1,2-benzisothiazole 1,1-dioxide (90), which is prepared in turn from saccharin pseudo-

chloride; the major product is the imine-vinylamine (93) (Equation (14)) <85CC845>. Other 3-dialkylamino-1,2-benzothiazepine dioxides have been synthesized by this ring-expansion route <83CC520>.



A high-yield alternative ring expansion route to 1,2-benzothiazepine derivatives, (e.g., (97)) involves treatment of sulfines with base, for example the *N*-tosylsulfinimine (95), derived from (94) (Scheme 11). When the base is omitted, isolation of the intermediate (96) is possible <80JCS(P1)2830>. The seven-membered ring derivatives 2,3-dihydro-4-phenyl (and 4-*p*-chlorophenyl)-1,2-benzothiazepin-5(4H)-one can also be made in moderate yields using a similar procedure based on reaction of analogues of (94) with *O*-mesitylenesulfonylhydroxylamine in DCM, followed by base (K_2CO_3) treatment of the crude intermediate *S*-amine salts in DMF at room temperature <80JCS(P1)2830>. Extension of this general methodology to other substituted 1,2-benzothiazepin-5-ones has been reported <83MI 907-01>.



Scheme 11

9.07.8 SYNTHETIC COMPARISONS

Routes to the fully unsaturated 1,2-oxazepines or 1,2-thiazepines and their benz-fused derivatives still remain poorly represented. From 1985 to 1995, emphasis has continued to be placed on ring

construction or ring interconversion approaches to various derivatives of the ring systems. In the former category, not surprisingly, C—O or C—N bond formation in the ring-forming step has been the most productive, although there is scope for improvement to increase yields in a number of cases. Opportunity also exists for C—C bond formation approaches. In the latter category, a number of ring-expansion methods have been developed with generally higher yields of seven-membered ring products resulting; scope for extensions also exist. Once again, however, the key intermediate step frequently involves C—O or C—N bond formation to generate the seven-membered ring.

9.07.9 IMPORTANT COMPOUNDS AND APPLICATIONS

Benzylideneisoxazepinones have been claimed as antiinflammatories, analgesics, immunomodulators, and antipyretics <90USP4892870>. The hexahydro-1,2-thiazepine 1,1-dioxide skeleton has been incorporated as a substituent in 1,3-diazine and 1,3,5-triazine herbicides <89EUP342456>. A range of hexahydro-1,2-oxazepine derivatives, for example hexahydro-2-(4-hydroxybenzoyl)-1,2-oxazepine, have been patented as agrochemical fungicides <90JAP02229175>. The dibenzo-[c,f][1,2]thiazepine dioxide derivative, tianeptine (**23**), is used clinically (as its sodium salt) as a serotonergic antidepressant. It has found use in the treatment of neurotic and reactive depressions, together with anxiety-associated depressive states <B-84MI 907-01>. Structure-activity relationships for tianeptine and its derivatives have been studied with respect to reserpine-induced ptosis reversal potency in the mouse. In contrast to the classical tricyclic antidepressants, the tianeptine series show highly specific structural requirements for activity <88MI 907-01>. Tianeptine also has anti-ulcer and anti-emetic properties <B-89MI 907-01>. Tianeptine activates neuronal uptake of serotonin <87MI 907-01, 92MI 907-01> and also affects extracellular dopamine concentrations centrally <92MI 907-02>. A further series of 11-substituted 6,11-dihydro-6-methyl-dibenzo[c,f][1,2]thiazepine 5,5-dioxides have some components which show anticonvulsant activity <94AP(327)157>. A dihydrodibenzo[c,f][1,2]thiazepine 5,5-dioxide moiety is incorporated in a new 1,3,5-triazinylpiperidine derivative series, which shows an ability to modulate multidrug resistance in DC-3F/AD and KB-A1 tumour cells *in vitro* <92JMC2481>.

9.08

1,3-Oxazepines and 1,3-Thiazepines

JOHN B. BREMNER

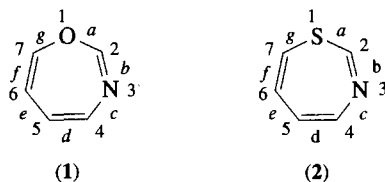
University of Wollongong, NSW, Australia

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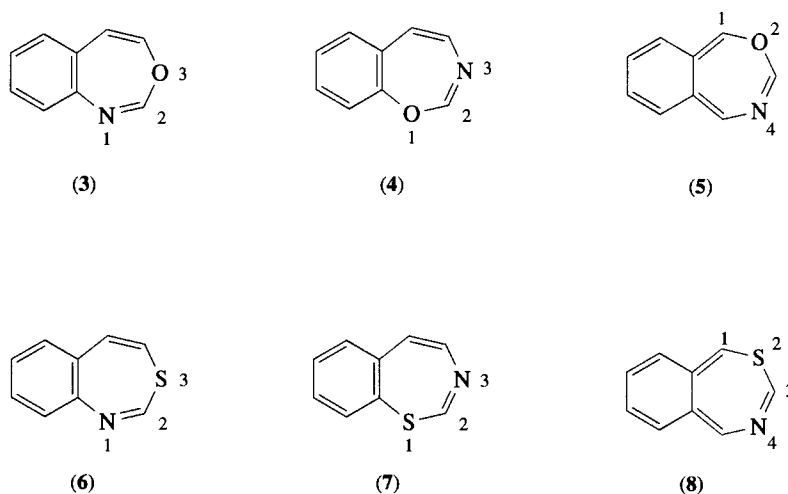
9.08.1 INTRODUCTION

The chemistry of these systems has attracted a moderate amount of attention since the publication of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I). In this chapter, the 1,3-oxazepines and 1,3-thiazepines are grouped together; also included is a treatment of some of their benz-fused and dibenz-fused analogues. There appears to have been no general reviews of these systems, apart from CHEC-I <84CHEC-I(5)593> and that by Gagan <B-79MI 908-01>. The synthesis of benzothiazepines has been reviewed <86KGS1443> and a review of the synthesis of seven-membered heterocycles based on pericyclic reactions and cyclic intermediates includes a few references to 1,3-oxazepine derivatives <88S569>. The parent systems considered, 1,3-oxazepine (1) and 1,3-thiazepine

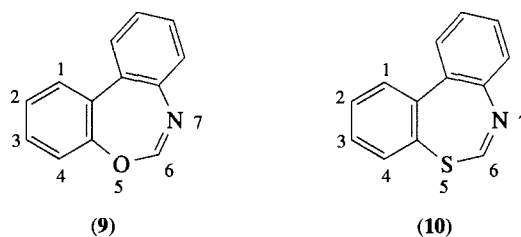
(2), are shown below. Much of the chemistry has been focused on the 1,3-oxazepine system and benz-fused derivatives. The chemistry of 1,3-thiazepines and derivatives is poorly developed.



There are three possible benz-fused skeletons each with a 1,3-relationship of the N and O atoms or N and S atoms. These are the 3,1-benzoxazepine (3), 1,3-benzoxazepine (4), 2,4-benzoxazepine (5), 3,1-benzothiazepine (6), 1,3-benzothiazepine (7), and 2,4-benzothiazepine (8).

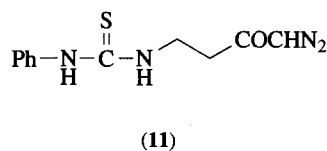


There is one possible dibenz-fused system for each of the O, N and S, N rings. These are the dibenz[*d,f*][1,3]oxazepine (9) and the dibenzo[*d,f*][1,3]thiazepine (10). Bridged systems incorporating 1,3-oxazepine or 1,3-thiazepine moieties have not been included in this chapter.

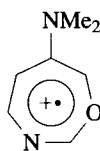


9.08.2 THEORETICAL METHODS

The molecular structure and stabilization energy of a seven-membered cyclic onium ion intermediate proposed during the anchimerically-assisted hydrolysis of the diazoketone (11) were calculated by the MNDO method <90MI 908-01>.



In a study of collisionally activated dissociation of the 1-benzyloxy-4-dimethylaminopyridinium cation, the enthalpy of formation of the 1,3-oxazepinium radical cation (**12**) has been calculated using the AM1 method and shown to be 202 kcal mol⁻¹. It is proposed that (**12**) results from rearrangement of the radical cation 4-Me₂NC₅H₄NO⁺• <90JCS(P2)1051>. The analogous rearrangement of pyridine *N*-oxides to the 1,3-oxazepine system is known photochemically <78AHC(22)367>.

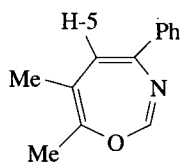


(12)

9.08.3 EXPERIMENTAL STRUCTURAL METHODS

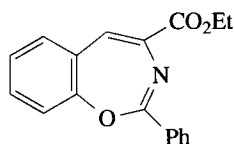
9.08.3.1 Spectroscopic Data

Infrared, ultraviolet absorption, and ¹H NMR data are given for the fully unsaturated 1,3-oxazepine derivative (**13**). In the ¹H NMR, H-5 appeared as a quartet (*J* = 1 Hz) at δ 6.16 <86CC1188>.



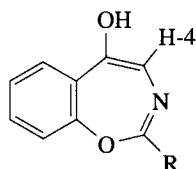
(13)

Selected spectroscopic data have also been reported for the 1,3-benzoxazepine derivative (**14**) <90HCA739>. In this case, the signal at δ 7.57 in the ¹H NMR spectrum was assigned to H-5; in the parent system, 1,3-benzoxazepine, H-5 and H-4 appeared as doublets (*J* = 8 Hz) at δ 6.57 and δ 6.25, respectively <79TL3761>.



(14)

Considerable infrared, ¹H NMR, and mass spectral data are also provided on the benz-fused compounds (**15**) by Lee *et al.* In (**15**; R = H), H-4 appeared as a singlet at δ 7.60, while H-2 was downfield as expected as a singlet at δ 7.98 <90S455>.

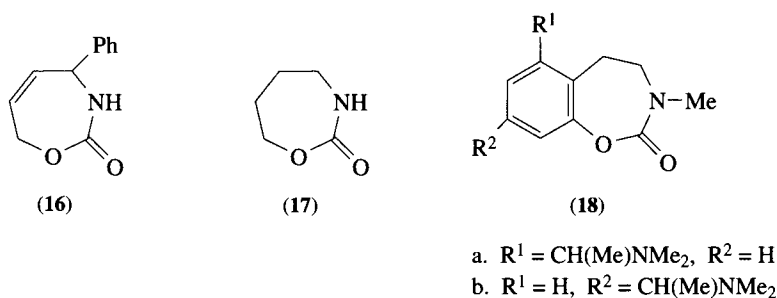


(15)

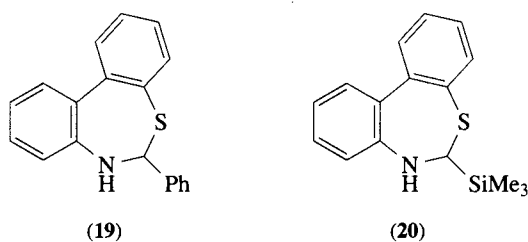
R = H, Me, cycl-Pr, Ph

Extensive spectroscopic data on substituted 1,3-benzoxazepines have been reported by Desbene and Cherton <84T3567>, while ¹H NMR and infrared absorption data on the parent isomeric system,

3,1-benzoxazepine, have been noted by Albini *et al.* In the ^1H NMR of this parent, H-4 and H-5 appeared as doublets ($J = 6$ Hz) at δ 5.78 and δ 5.58, respectively, with H-2 ascribed to the singlet at δ 6.35, while in the infrared absorption spectrum very strong and strong bands were observed at 1640 and 1680 cm^{-1} , respectively <79TL3761>. Proton NMR, infrared absorption, and mass spectra are also given for the cyclic carbamate (17) <85BCJ2855>, as well as the benz-fused analogues (18a) and (18b) <90HCA739>. In the infrared absorption spectrum of (17), the carbonyl stretching band occurred at 1710 cm^{-1} (KBr pellet). The cyclic carbamate (16) has been shown by ^1H -NMR spectroscopy to exist in a boat conformation <92CL1575>.



Proton and ^{13}C NMR, as well as infrared absorption, data are noted for the dihydrodibenzo- $[d,f][1,3]$ thiazepine (19) <91JCS(P1)1733> and the related compound (20) <91TL4359>.



9.08.3.2 X-ray Methods

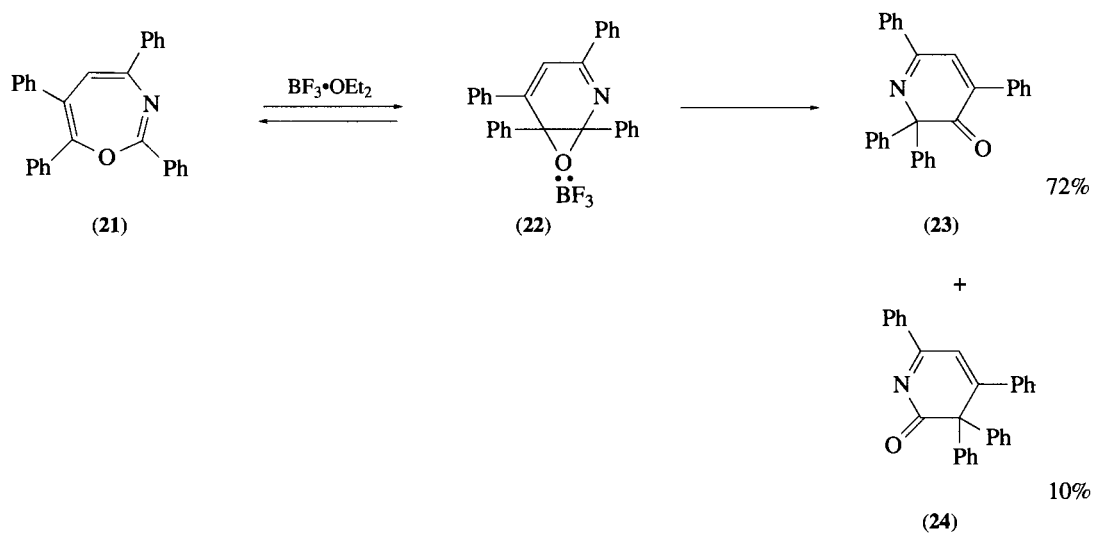
Single crystal x-ray structure determinations have been reported on the fumarate salts of the 1,3-benzoxazepin-2(3*H*)-one derivatives (18a) and (18b) <90HCA739>.

9.08.4 REACTIVITY

9.08.4.1 Reactivity of Fully Unsaturated Rings

Ring contraction of the fully conjugated ring system in 2,4,6,7-tetraphenyl-1,3-oxazepine (21) to the pyridones (23) and (24) has been observed on treatment with boron trifluoride etherate in refluxing anhydrous benzene (Scheme 1). The BF_3 -coordinated bicyclic system (22) is believed to be a key intermediate in this process <85H(23)1399>. In contrast, no reaction occurred in the case of 4-methyl-2-phenyl-1,3-benzoxazepine or 5-methyl-2-phenyl-3,1-benzoxazepine on treatment with $\text{BF}_3 \cdot \text{OEt}_2$ in refluxing anhydrous benzene. When moist benzene was used in the reaction of (21) with $\text{BF}_3 \cdot \text{OEt}_2$, hydrolytic ring opening of the seven-membered ring occurred, followed by further hydrolysis and recyclization reactions to afford substituted pyrrole and furan derivatives as well as 1,2,4-triphenyl-1,4-butanedione <85H(23)1399>. Treatment of 6,7-dimethyl-4-phenyl-1,3-oxazepine with hydrochloric acid in tetrahydrofuran resulted in its quantitative conversion to the ring-contracted product, *N*-formyl-2,3-dimethyl-5-phenylpyrrole <86CC1188>. Upon treatment with $\text{Mo}(\text{CO})_6$ or $\text{Fe}_2(\text{CO})_9$, phenyl-substituted 1,3-oxazepines are converted to substituted pyridines and pyrroles.

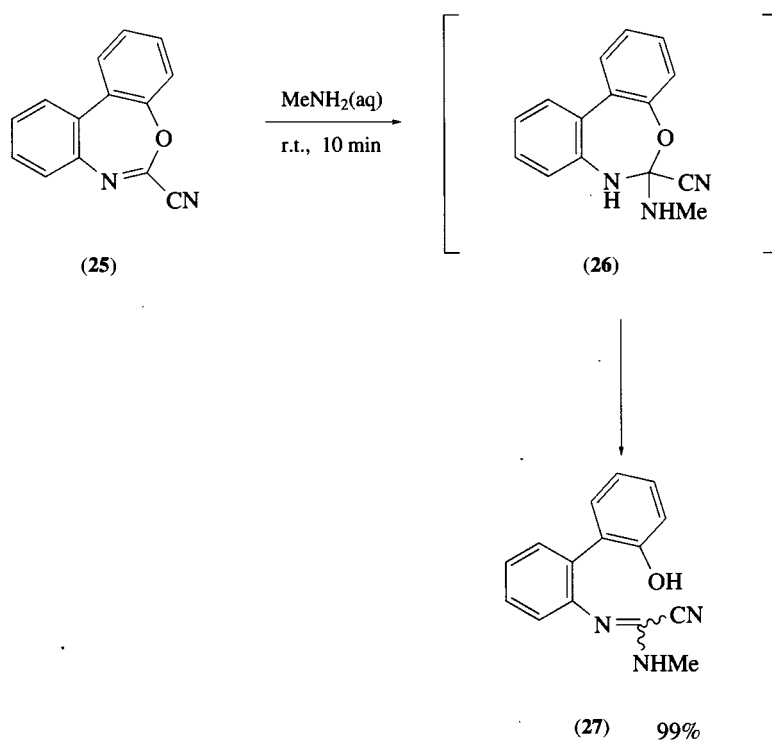
These products may arise via deoxygenation or rearrangement, respectively, of intermediate bicyclic valence isomers <85CL877>.



Scheme 1

The ring contraction of 3,1-benzoxazepines to indole derivatives was noted in CHEC-I <84CHEC-I(5)593>.

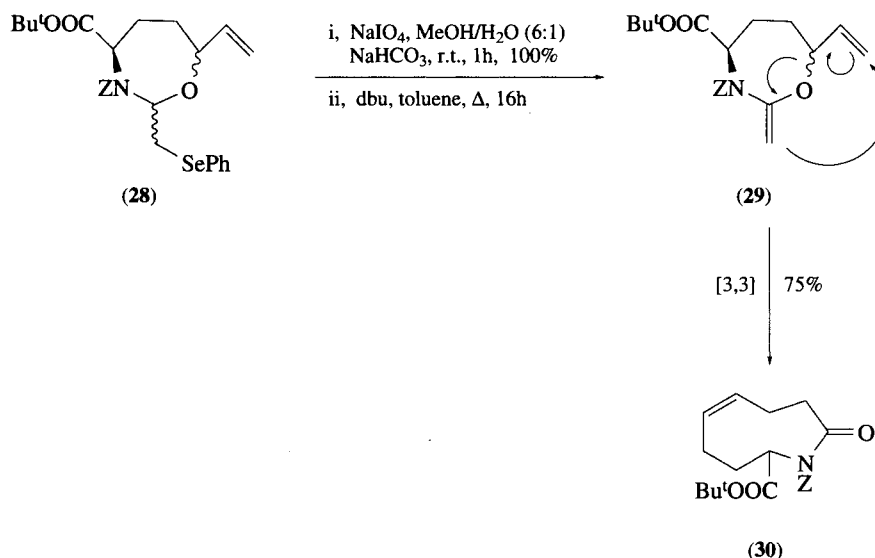
Ring opening is characteristic of the reactions of the fully conjugated systems. For example, on reaction of the dibenz[*d,f*][1,3]oxazepine (25) with methylamine, the phenolic imine (27) was obtained in near quantitative yield, most probably via the intermediate adduct (26) (Scheme 2) <78CPB2508>. Ring opening of 1,3-benzoxazepine and 3,1-benzoxazepine was also observed on treatment with piperidine, and with *N*-methylaniline in the latter case <79TL3761>.



Scheme 2

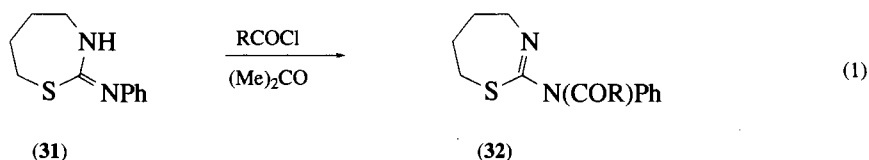
9.08.4.2 Reactivity of Nonconjugated Rings

The hexahydro-1,3-oxazepine (**28**; $Z = \text{CO}_2\text{CH}_2\text{Ph}$) could be converted in quantitative yield to the corresponding selenoxide with sodium periodate (Scheme 3). Subsequent treatment of the selenoxide with dbu in refluxing toluene was presumed to give the ketene aminal (**29**) which then gave the nine-membered ring unsaturated lactone (**30**) via an *in situ* [3,3] sigmatropic rearrangement. Analogous seven- and eight-membered ring lactones could also be made by this new and elegant methodology <92TL6857>.

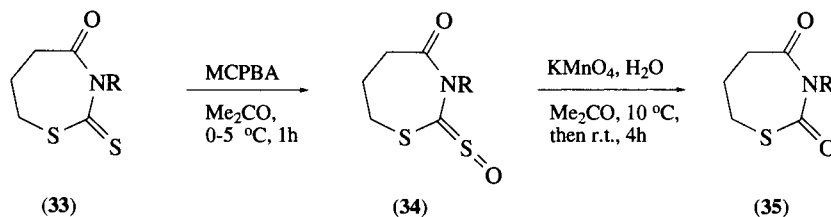


Scheme 3

The 2-phenyliminothiazepine (**31**) can be acylated on the exocyclic nitrogen to give the derivatives (**32**; $R = \text{Me}, \text{MeO}, \text{Ph}, \text{substituted Ph}$). For example, methyl chloroformate gave (**32**; $R = \text{MeO}$) in 27.5% yield, while high yields were obtained for the anilides (Equation (1)) <91MI 908-01>.



Oxidation of the exocyclic sulfur atom in the 1,3-thiazepine derivatives (**33**; $R = \text{Ph}, \text{CH}_2\text{Ph}, \text{Et}$) with MCPBA gave the thione *S*-oxides (**34**). The sulfine structure was confirmed by oxidation to the oxo derivatives (**35**) (Scheme 4). Yields and melting points for (**34**) and (**35**) are given in Table 1 <92LA337>.



Scheme 4

Table 1 Yields and melting points of the thione *S*-oxides (34) and diones (35).

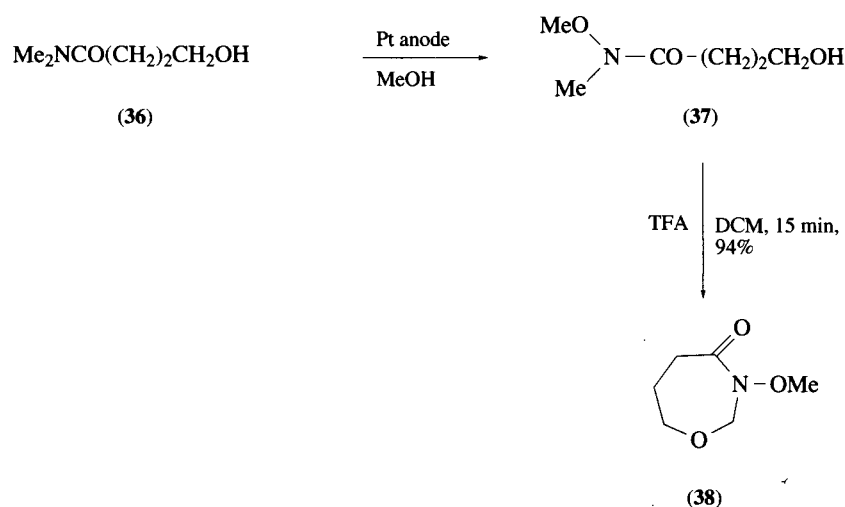
Compound	Yield (%)	Melting point (°C)
34, R = Ph	28	97
34, R = CH ₂ Ph	46	74
34, R = Et	55	20 (dec.)
35, R = Ph	39	150
35, R = CH ₂ Ph	59	58
35, R = Et	47	oil

9.08.5 RING SYNTHESIS BY RING CONSTRUCTION

9.08.5.1 1,3-Oxazepines and Benz-fused Derivatives

9.08.5.1.1 Type a (C—N—C—C—C—C—O)

Oxidation of (36) at a platinum anode gave the *N*-methoxy-*N*-methyl- ω -hydroxyamide (37), which was converted under acidic conditions to the 1,3-oxazepin-4-one (38) (Scheme 5). The carbocation precursor of (37) is not converted directly to (38) probably due to anode interaction with the terminal hydroxy group <82ACS(B)165>.

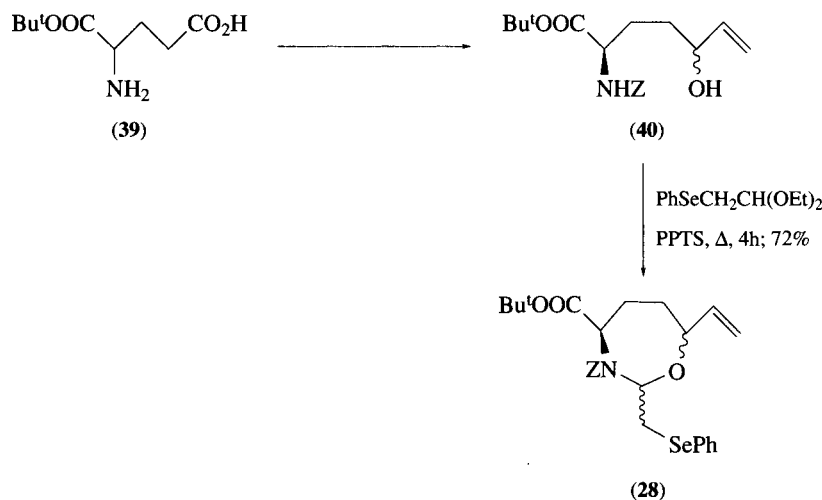
**Scheme 5**

The cyclic carbamate (17) (see Section 9.08.3.1) can be prepared in 27% yield by thermolysis (mesitylene, 160°C) of *N*-trimethylammonio-5-hydroxypentanamidate via intramolecular addition of the hydroxyl group to the isocyanate generated by loss of trimethylamine <85BCJ2855>.

9.08.5.1.2 Type ab (N—C—C—C—C—O + C)

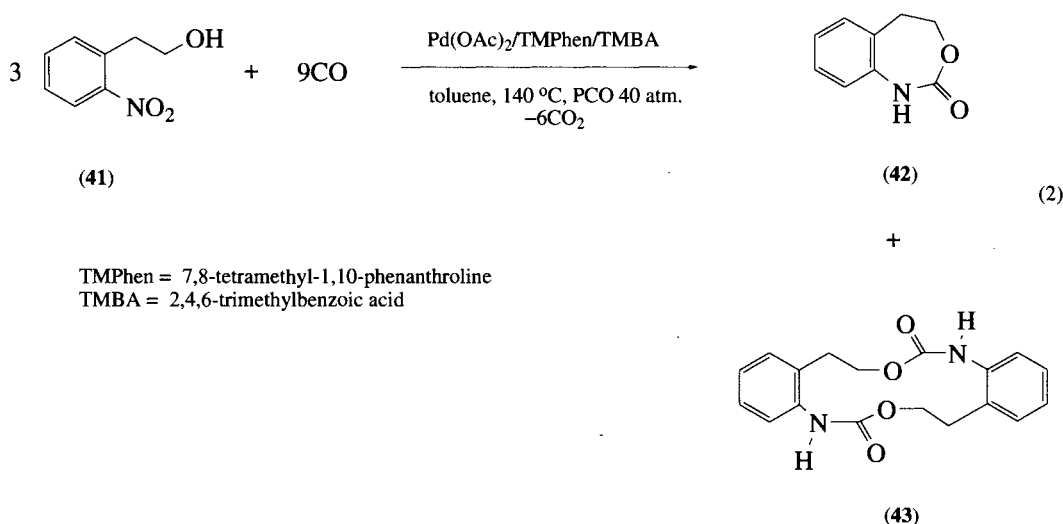
A further synthesis of the hexahydro-1,3-oxazepine system (28) has been developed by Holmes and co-workers. It is based on the cyclization of the amino alcohol (40; Z = CO₂CH₂Ph) with pyridinium *p*-toluenesulfonate and phenylselenoacetaldehyde diethylacetal using Dean–Stark con-

ditions (Scheme 6). The amino alcohol (40) was derived in turn from a protected, racemic, pyroglutamic acid-derived precursor (39) by standard methods <92TL6857>.



Scheme 6

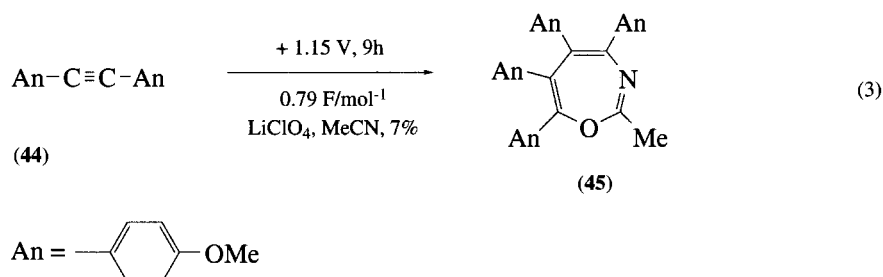
The transition metal-catalyzed reductive carbonylation of *o*-substituted nitrobenzenes is a useful method for the synthesis of nitrogen heterocycles. Application of this methodology to the preparation of 1,4-dihydro-2*H*-3,1-benzoxazin-2-one derivatives and to the synthesis of the 3,1-benzoxazepin-2-one (42) has been reported <93JOM(451)157>. Reaction of 2-(2-nitrophenyl)ethanol (41) (100% conversion) with carbon monoxide in the presence of a palladium(II) catalyst gave (42) in 60% yield, together with some of the macrocyclic dimer (43) (Equation (2)). It is suggested that a nitrene complex may not be involved with the palladium catalyst in view of the reaction path selectivity observed <93JOM(451)157>.



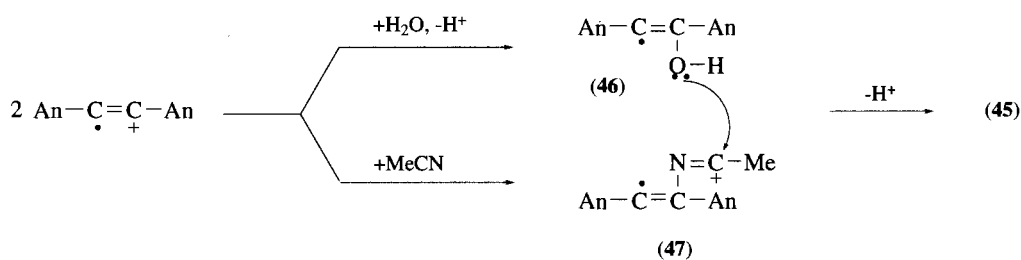
Insertion of a carbonyl group by standard technology was used in the preparation of the 4,5-dihydro-1,3-benzoxazepin-2(3*H*)-ones (18a) and (18b) (see Section 9.08.3.1). Reaction of 5-[1'-(dimethylamino)ethyl]-2-[2''-(methylamino)ethyl]phenol with 1,1'-carbonylbis[imidazole] in dichloromethane at -15°C , followed by reaction at room temperature for 14 h, then replacement of the dichloromethane with toluene and refluxing for a further 24 h gave (18b) in 60.7% yield. The isomeric compound (18a) was prepared similarly <90HCA739>.

9.08.5.1.3 Type ae ($C-C-O + C-N-C-C$)

The fully unsaturated 1,3-oxazepine (**45**) (m.p. 161–162°C) was prepared in very low yield by electro-oxidation at a graphite plate electrode of the diaryl alkyne (**44**) in acetonitrile as solvent, the latter supplying the nitrogen and one carbon to the ring (Equation (3)).



It is proposed that the radical cation formed by oxidation of (**44**) can give the radical (**46**) by reaction with adventitious water and the radical cation (**47**) by further reaction with acetonitrile, followed by coupling and cyclization to give the heterocyclic product (Scheme 7) <90CC445, 91T799>.



Scheme 7

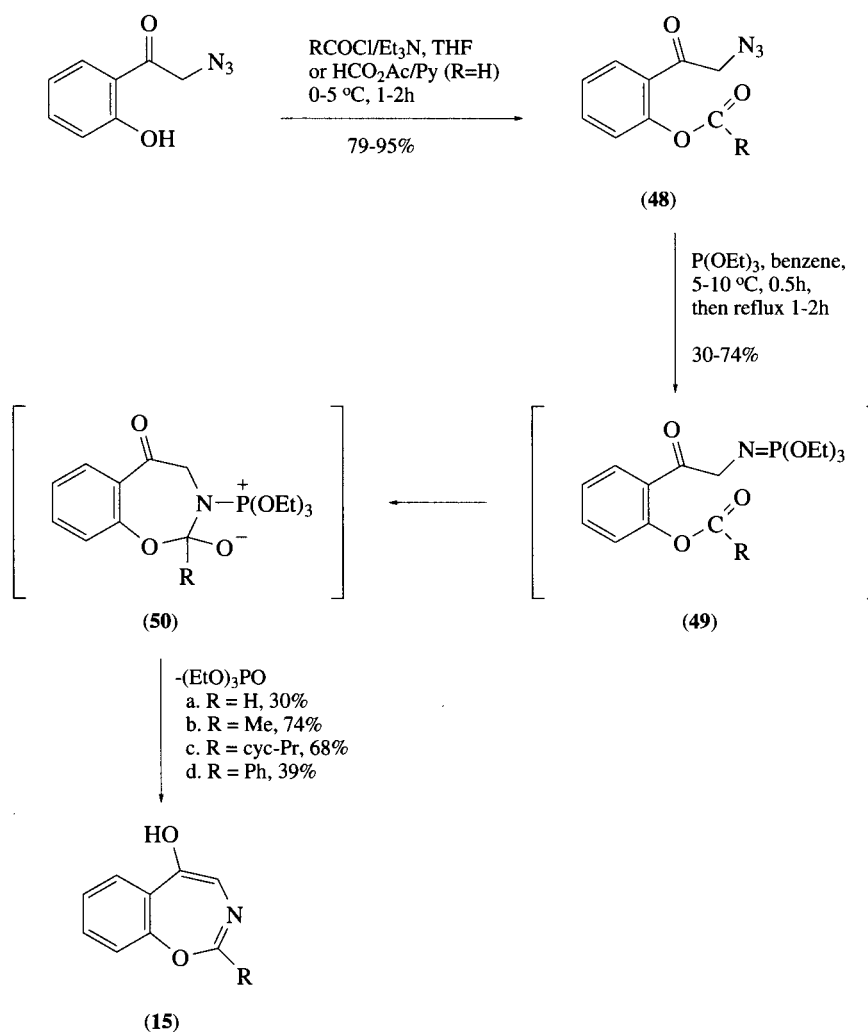
9.08.5.1.4 Type b ($N-C-C-C-C-O-C$)

An elegant route to the fully unsaturated 1,3-benzoxazepine system (**15**) has been developed by Lee *et al.* based on an intramolecular aza-Wittig reaction <90S455>. The aza-Wittig precursors (**49**) were obtained from *o*-hydroxyphenacyl azide via the esters (**48**) (Scheme 8). Treatment of (**48**) with triethyl phosphite gave the iminophosphoranes (**49**) and ultimately the benzoxazepines (**15**); with (**48**; R = Ph), competitive ring opening of the intermediate (**50**; R = Ph) occurred to also give an *N*-substituted benzamide.

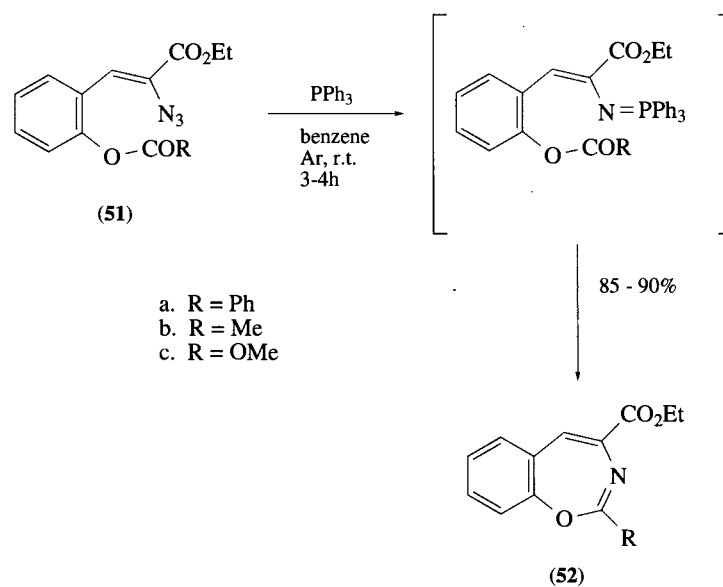
A further extension of this chemistry yielded the 1,3-benzoxazepines (**52**). The Wittig intermediates were readily obtained in this case from the azides (**51**), which were derived in turn ultimately from salicylaldehyde by standard steps (Scheme 9) <92CC81>.

9.08.5.1.5 Type g ($C-C-C-C-N-C-O$)

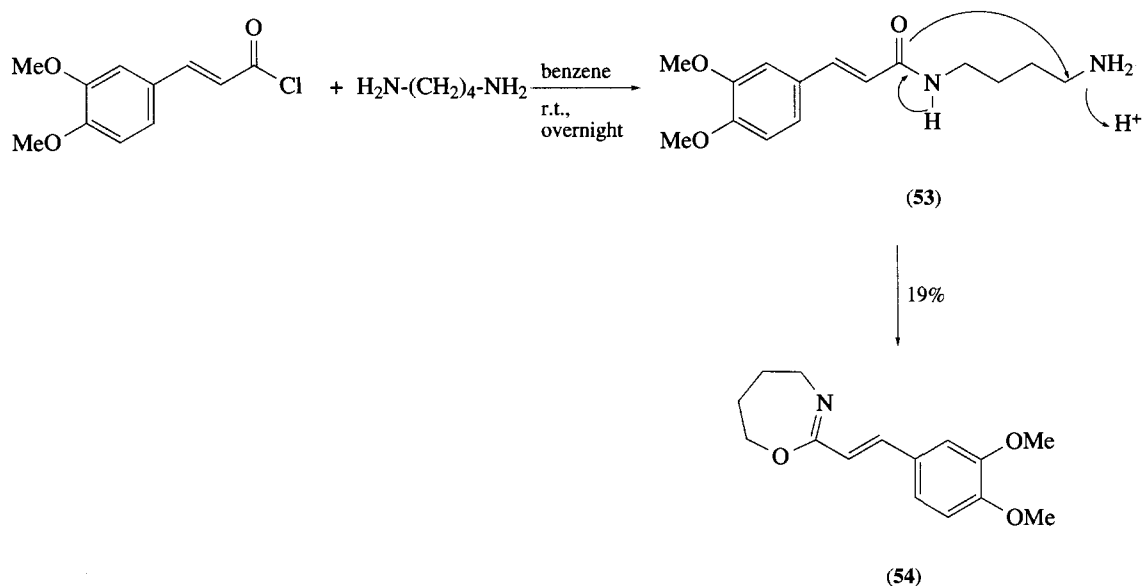
As part of the synthetic studies directed towards the natural product caracasamide, the oxazepine (**54**) (Scheme 10) was obtained in low yield during the acylation of excess butane-1,4-diamine by (*E*)-3,4-dimethoxycinnamoyl chloride, the oxazepine being formed by cyclization of the mono-acylated product (**53**); diacylation of the diamine provided the major product <92JCS(P1)3179>.



Scheme 8

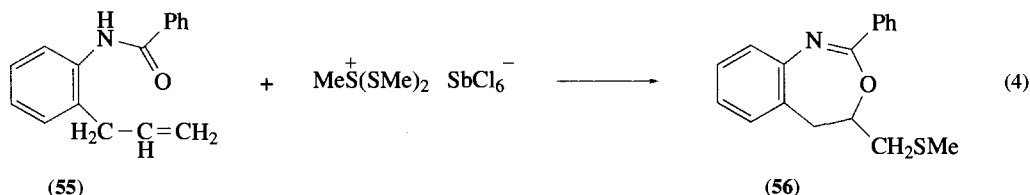


Scheme 9



Scheme 10

A ring construction approach has also been used to make the 4,5-dihydro-3,1-benzoxazepine derivative (56), utilizing electrophilic attack on the allylic double bond in (55), followed then by intramolecular nucleophilic attack by the amide oxygen on the intermediate carbocation (Equation (4)) <87H(26)39>.



9.08.5.2 1,3-Thiazepines

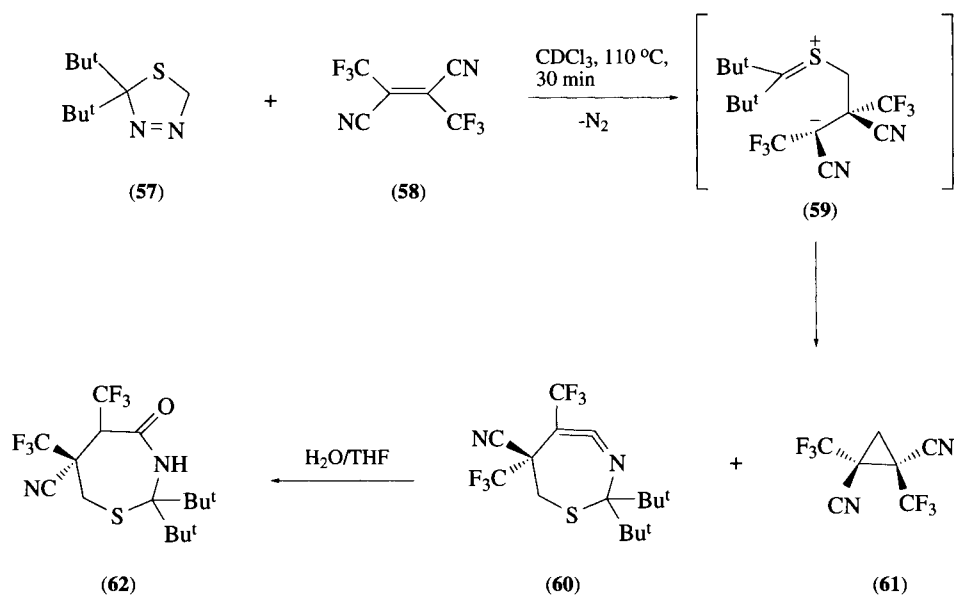
9.08.5.2.1 Type bf ($\text{C}-\text{S}-\text{C} + \text{C}-\text{C}-\text{C}-\text{N}$)

Reaction of the high π molecular orbital energy di-*t*-butyl thioketone-*S*-methylide, generated *in situ* by thermal nitrogen extrusion from the thiadiazoline (57), with the (*E*)-dipolarophile (58) gave the novel seven-membered cyclic ketene imine (60) (m.p. 81–82°C) and the cyclopropane (61) in a 78:22 ratio (Scheme 11); there was an 81% conversion of (57). Treatment of (60) with aqueous THF afforded the lactam (62) (m.p. 147–148°C). When the equivalent (*Z*)-dipolarophile was used in this cycloaddition process, the same ratio of (60) and (61) was obtained. In these reactions, a two-step process via a *gauche* zwitterionic intermediate (59) is proposed, with the bulky *t*-butyl groups hindering a 1,5-combination to give a thiolane product and thus allowing the 1,7-combination reaction to intervene <89TL7041>.

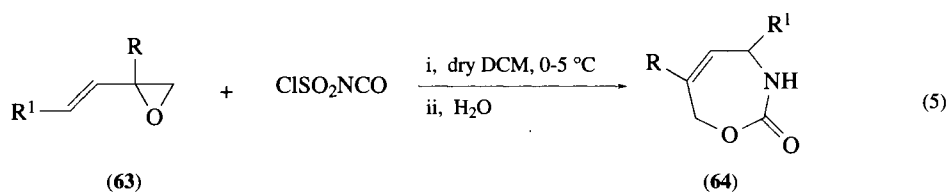
9.08.6 RING SYNTHESIS BY RING TRANSFORMATION

9.08.6.1 1,3-Oxazepines and Benz-fused Derivatives

The synthesis of 1,3-oxazepin-2-one derivatives (64) by the reaction of vinyloxiranes (63) with chlorosulfonylisocyanate has been described (Equation (5)) <92CL1575>. Yields of the seven-membered ring products were generally excellent (Table 2).



Scheme 11

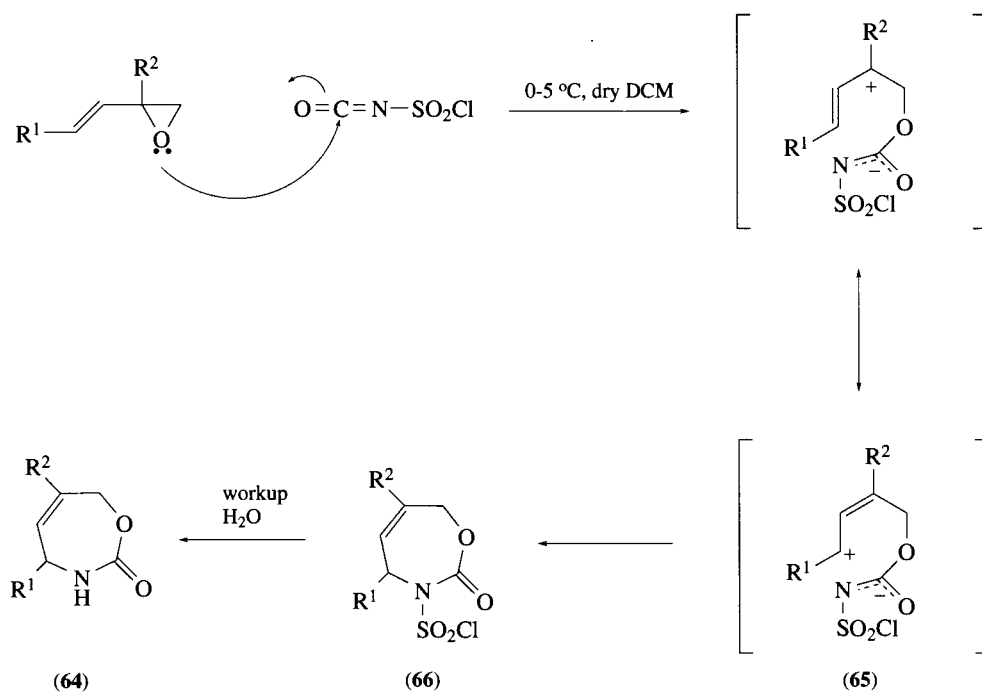
**Table 2** Yields and melting points of the 4,7-dihydro-1,3-oxazepin-2(3*H*)-ones.

(64)	<i>m.p.</i> (°C)	<i>Yield</i> (%)
a; R = H, R ¹ = Ph	99	98
b; R = H, R ¹ = Me	128	97
c; R = Ph, R ¹ = (MeO) ₂ C ₆ H ₃	60	96
d; R = Ph, R ¹ = <i>p</i> -MeOC ₆ H ₄	64	51

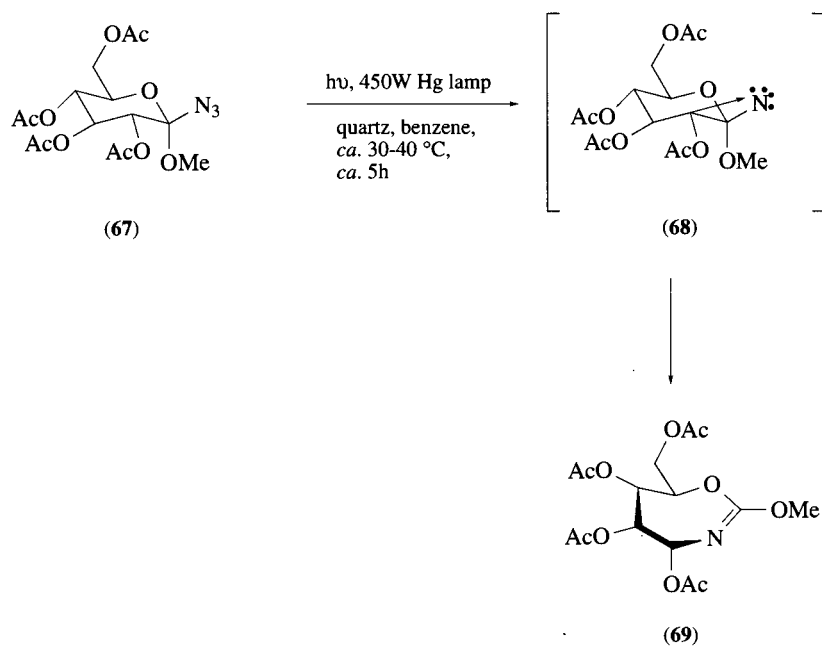
The cyclic carbamates (64) are thought to be formed via the resonance-stabilized 1,7-dipolar intermediates (65) and the chlorosulfonyl derivatives (66) (Scheme 12) <92CL1575>.

Photolysis of the azido derivative (67) in benzene afforded a mixture of products including the labile tetrahydro-1,3-oxazepine (69) in 35% yield as estimated by NMR spectroscopy (Scheme 13); (69) decomposed on silica gel during attempted purification. The formation of (69) does not proceed via a photo-Beckmann rearrangement, but appears to involve the nitrene intermediate (68) and 1,2-migration of the C-2 atom. The other major products were methoxyiminolactone derivatives. The anomer of (67) with the azido group in the α -configuration gave only 10% (NMR estimation) of (69) on photolysis, with a tetrahydro-1,2-oxazepine derivative being the major ring-expanded product, indicative of high stereocontrol in the 1,2-migration <94TL93>.

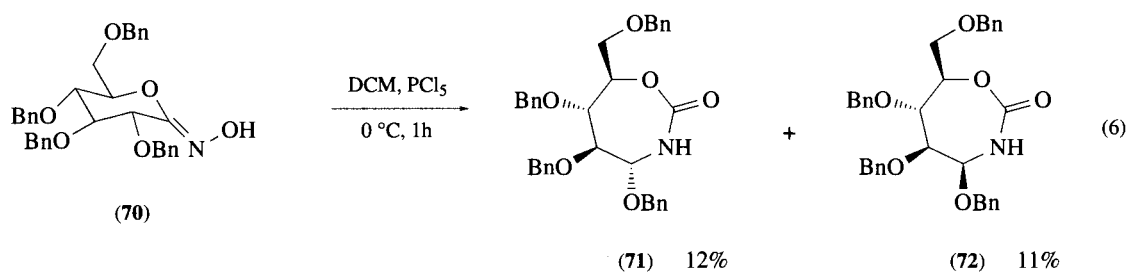
The Beckmann rearrangement of the protected lactone oxime (70) has been achieved using phosphorus pentachloride giving the 1,3-oxazepin-2-one derivatives (71) and (72) in low yields, together with 2,3,5-tri-*O*-benzyl-4-*O*-carbamoyl-D-arabinose in 16% yield (Equation (6)) <85HCA2254>.



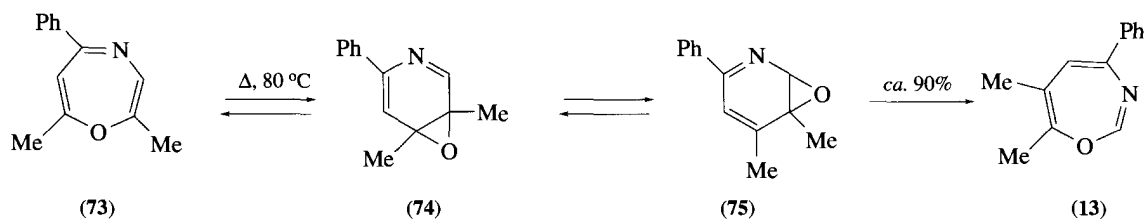
Scheme 12



Scheme 13

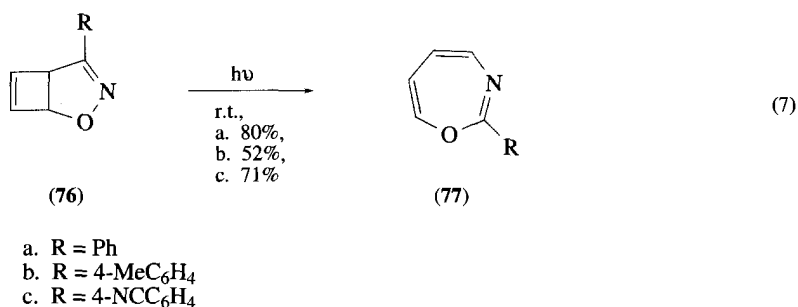


The fully unsaturated 1,3-oxazepine system (**13**) can be obtained in good yield by thermolysis of the 1,4-oxazepine derivative (**73**) (Scheme 14). This rearrangement presumably proceeds via the bicyclic systems (**74**) and (**75**) <86CC1188, 87CPB3166>. In contrast, thermolysis of related 2-unsubstituted 1,4-oxazepines in toluene at 100–120°C gave 5-hydroxypyridine derivatives in moderate to good yields <86CC1188>.

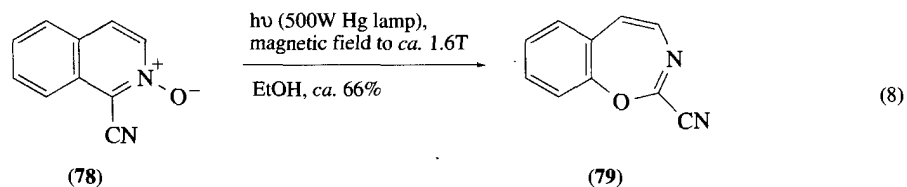


Scheme 14

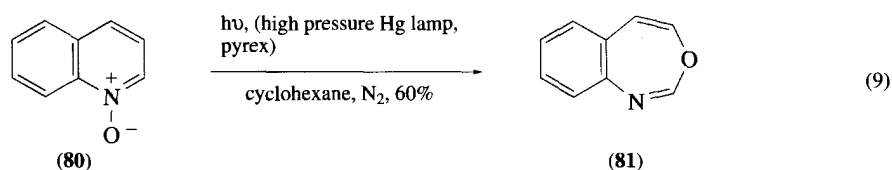
Substituted 1,3-oxazepines (**77**) with a 2-aryl substituent can be made in generally very good yields by photolysis of the bicyclic derivatives (**76**) (Equation (7)). Mechanistically, azirinypropenal derivatives appear to be involved as intermediates in the transformation <84NKK158>.



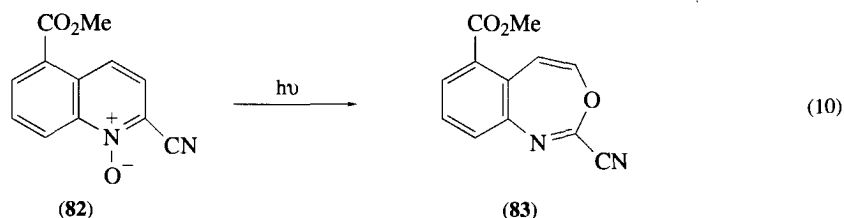
The photolysis of heteroaromatic *N*-oxides has been exploited to make 1,3-oxazepines and benz- and dibenz-fused derivatives. Photolysis of substituted pyridine *N*-oxides (e.g., 2,4,6-triphenylpyridine *N*-oxide) gives 1,3-oxazepines (e.g., 2,4,6-triphenyl-1,3-oxazepine), as discussed previously <84CHEC-I(5)593>. The parent 1,3-benzoxazepine system is prepared in solution via photolysis of isoquinoline *N*-oxide, isoquinolin-1(2*H*)-one being the other major product of the reaction. The 1,3-benzoxazepine was characterized spectroscopically in dilute solution, but it polymerized on concentration of the solution <79TL3761>. The formation of (**79**) from 1-cyanoisoquinoline *N*-oxide (**78**) (Equation (8)) does not involve a magnetic field-sensitive intermediate, consistent with the intermediacy of an S₁-derived oxaziridine intermediate in this rearrangement process <85BCJ1088>.



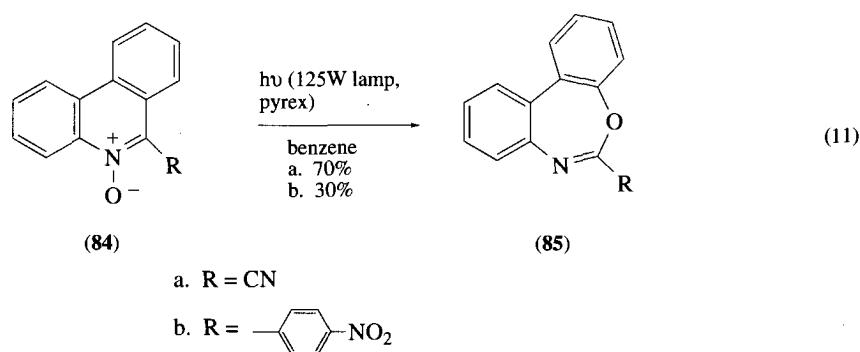
In an analogous fashion, ultraviolet irradiation of quinoline *N*-oxide (**80**) under rigorously anhydrous conditions gave rise to the hydrolytically sensitive 3,1-benzoxazepine (**81**) (b.p. 50°C, 0.1 mmHg) (Equation (9)) <79TL3761>.



Photolysis of the substituted quinoline *N*-oxide (**82**) afforded the 3,1-benzoxazepine derivative (**83**), as a stable solid (Equation (10)) <79CPB946>.

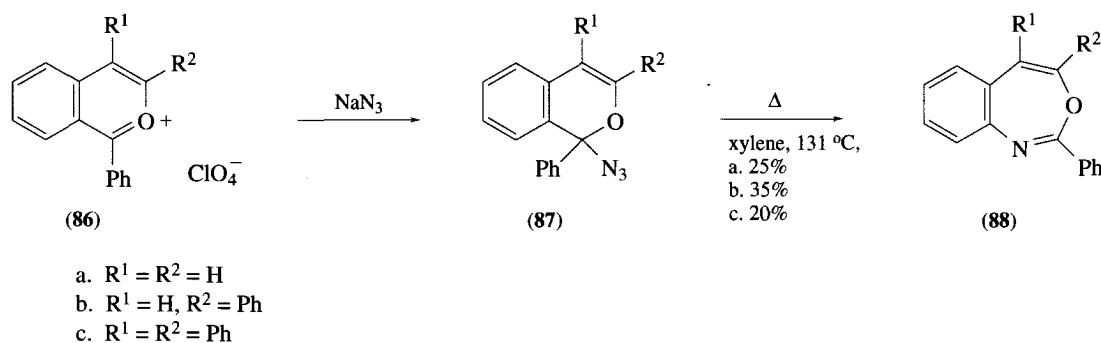


In a similar manner dibenz[*d,f*][1,3]oxazepines can be obtained from the photolysis of phenanthridine *N*-oxides, with rearrangement to phenanthridones being a competitive process, deoxygenation may also occur. The reaction path selectivity is dependent on the medium and the substituents present which change the nature of the lowest excited singlet state and intermediate stabilities. For example, on photolysis of (**84a**) in benzene, the seven-membered ring product (**85a**) was obtained in 70% yield, although with (**84b**), the yield of (**85b**) was more than halved (Equation (11)) <88JCS(P2)235>. Buchardt and co-workers also reported earlier on the rearrangement of (**84a**) to (**85a**) <82TL4849>, as did Itoh and co-workers <78CPB2508>.



A fused oxaziridine has been trapped by matrix isolation in ethanol and in 2-methyltetrahydrofuran glasses at 77 K on photolysis of (**84a**) <80JA5643>. It has been suggested that this oxaziridine cleaves homolytically to a diradical on warming and the solution phase photochemistry, leading to (**85a**), involves this diradical intermediate formed directly from the *N*-oxide <88JCS(P2)235>.

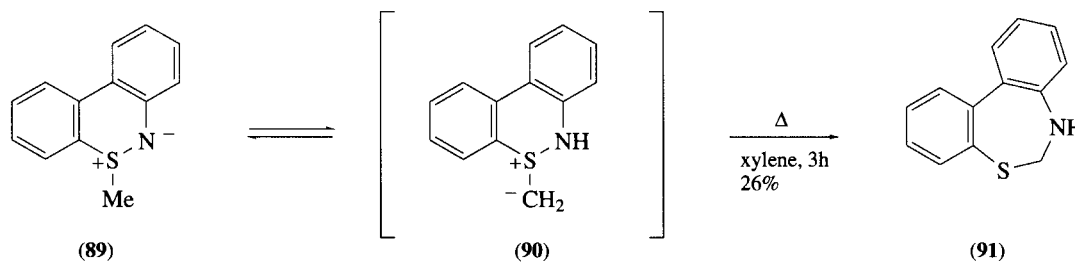
A new route to the 3,1-benzoxazepines (**88**) has been developed based on the rearrangement of the 1-azidoisochromenes (**87**) formed in turn by azide ion addition to the isochromylum salts (**86**); isolated percentage yields are noted (Scheme 15) <81JHC847>. Substituted chromylum cations also give 1,3-benzoxazepines in good yields on reaction with azide ion followed by thermolysis <84T3567>.



Scheme 15

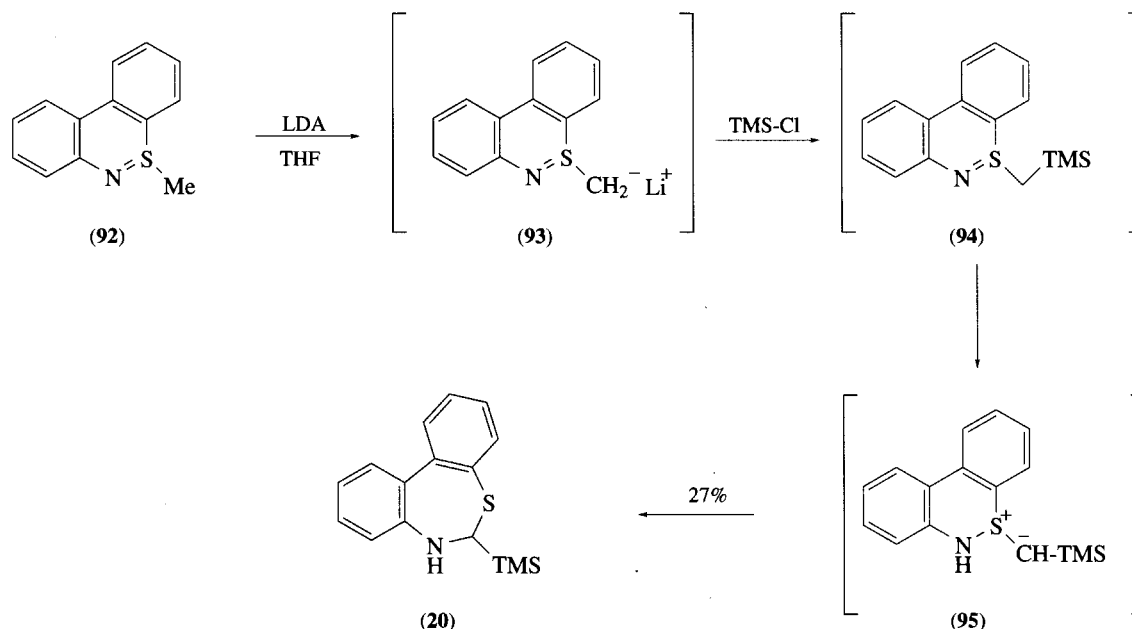
9.08.6.2 1,3-Thiazepines and Benz-fused Derivatives

Ring enlargement of the cyclic sulfilimine (**89**) has been used to make 6,7-dihydrodibenzo[*d,f*][1,3]thiazepine (**91**), by refluxing in xylene <79TL3969, 84CPB4360>. The [1,2] rearrangement, presumably via (**90**), is analogous to the Stevens rearrangement of nitrogen ylides, although an ionic intermediate is proposed in the formation of (**91**) (Scheme 16) <91JCS(P1)1733>.



Scheme 16

The ring expansion of another sulfur ylide has been utilized to prepare the substituted dihydrodibenzo[*d,f*][1,3]thiazepine (**20**). Treatment of the azathiaphenanthrene (**92**) with LDA gave the carbanion (**93**) which was then reacted with trimethylsilyl chloride, to give ultimately the thiazepine (**20**). It is presumed that a 1,3-proton shift occurred in the silylated product (**94**) to afford the ylide (**95**) and then (**20**) via a [1,2] rearrangement (Scheme 17) <91JCS(P1)1733, 91TL4359>. The derivative, 6-phenyl-6,7-dihydrodibenzo[*d,f*][1,3]thiazepine, can also be made in moderate yield by sulfur ylide rearrangement technology <91JCS(P1)1733>.



Scheme 17

9.08.7 SYNTHETIC COMPARISONS

Ring construction and ring transformation methods involving aromatic *N*-oxides provide a number of routes to 1,3-oxazepine derivatives and benz- or dibenz-fused analogues. However, extensive scope exists for the development of new ring construction approaches, for example

incorporating types (c), (d), (e), or (f) into these derivatives and for the introduction of a wider range of substituents for potential structure–property studies. There have been very few new synthetic routes developed for 1,3-thiazepine derivatives over the past decade and methods for benz-fused and dibenz-fused derivatives are also poorly represented. Sulfur ylide rearrangement chemistry has provided some advances in this area and there is potential for further development, as well as for new ring-construction methods.

9.08.8 IMPORTANT COMPOUNDS AND APPLICATIONS

A plant growth inhibitor involved in phototropism, raphanusamide, previously ascribed the structure 6-methoxy-2,3,4,5-tetrahydro-1,3-oxazepin-2-one <86MI 908-01>, was subsequently shown to be 3-(*E*)-methoxymethylene-2-pyrrolidinethione by an x-ray crystal structure determination <91TL6761>.

The cyclic carbamates (**18a**) and (**18b**) are inhibitors of acetylcholinesterase (IC_{50} (electric eel acetylcholinesterase) 0.15 and 1 μM ; IC_{50} (acetylcholinesterase from rat striatum) 0.05 and 0.3 μM respectively) <90HCA739>.

The compound hexahydro-3-tetradecyl-1,3-oxazepine is useful as a photographic material for magenta dye image stabilization <88JAP6343146>.

9.09

1,4-Oxazepines and 1,4-Thiazepines

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Kobe Pharmaceutical University, Japan

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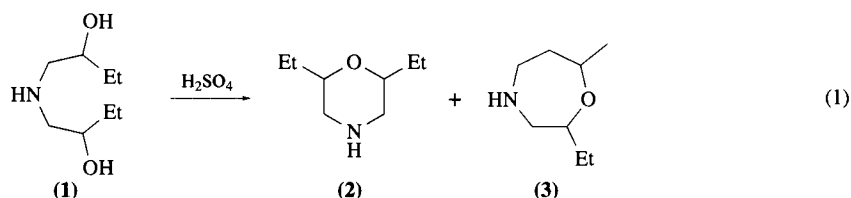
9.09.1 1,4-OXAZEPINES

1,4-Oxazepines are one of the most popular ring systems among heterocycles because of their very strong pharmacological activities and wide clinical use; therefore they have been exploited in many synthetic routes.

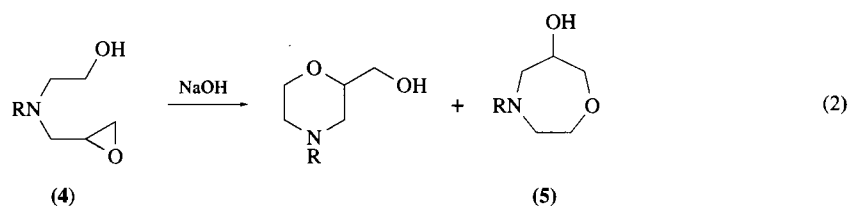
9.09.1.1 Synthesis

9.09.1.1.1 Type g (C—C—C—N—C—C—O)

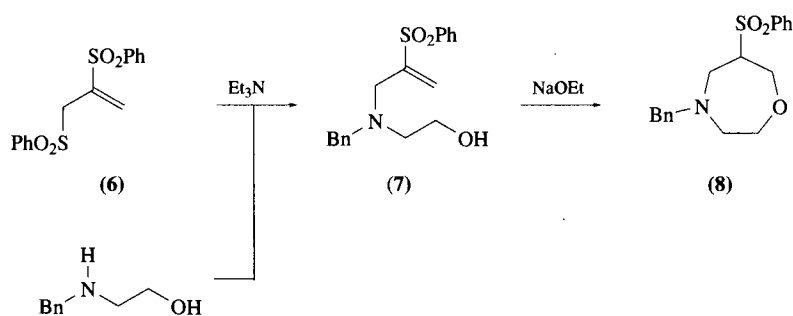
Treatment of 1,1'-iminobis-2,2-butanols (1) with 70% sulfuric acid gives rise to six-membered *cis*- and *trans*-2,6-diethylmorpholines (2) and other heterocyclic systems; whereas with 50% H₂SO₄, *cis*- and *trans*-hexahydro-1,4-oxazepines (3) are formed, along with the morpholine derivatives, as the major product (Equation (1)) <83JHC1681>.



Treatment of *N*-(3-chloropropyl)-*N*-(2-hydroxyethyl)methylamine with base affords the epoxide (4), which is further transformed into the cyclized perhydro-6-hydroxy-4-methyl-1,4-oxazepine (5), together with the piperidine derivatives (Equation (2)) <87JOC5247>. In spite of various efforts, the formation of piperidine derivatives seems unavoidable; thus the introduction of new reagents for selective formation of oxazepines was required.



Therefore the bis-sulfone, 2,3-bis(phenylsulfonyl)-1-propene (6), is introduced for the highly selective formation of oxazepines. This bis-sulfone has a three-carbon backbone structure with a vinyl and allylic sulfone, which act in concert to provide unusual reactivity. Bis-sulfone (6), when treated with *N*-benzylethanolamine in the presence of triethylamine, gave *N*-benzyl-*N*-[2-(phenylsulfonyl)-2-propyl]ethanolamine (7) in 98% yield, which is then treated with NaOEt causing cyclization and formation of oxazepine (8) in 83% yield (Scheme 1) <92JOC298>.



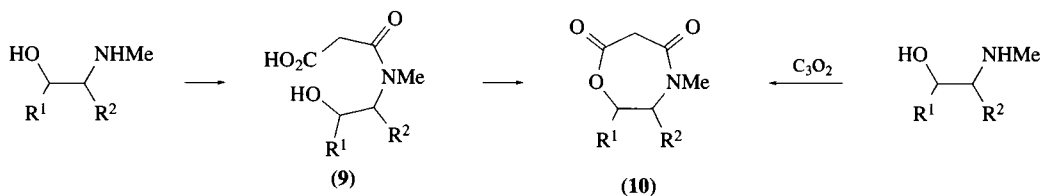
Scheme 1

9.09.1.1.2 Type dg (O—C—C—N + C—C—C)

Selective oxazepine formation is also provided by the lactonization of the hydroxy acid (9), which was prepared in 55% yield by the reaction of ephedrine with malonate, in the presence of cyanuric chloride and pyridine in acetonitrile <88SC1801>.

Carbon suboxide reacts with various bifunctional compounds including 1,2-ethanediamine, 2-aminoethanol, and glycols to give the oxazepine-5,7-diones (10) in good yield <87H(26)619>. This

provides a short effective preparation of chiral *N*,3-dimethyl-5,7-dioxo-2-phenylhexahydro-1,4-oxazepine <88SC1801> (Scheme 2).



Scheme 2

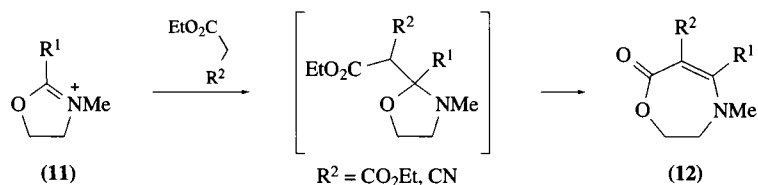
These 1,4-oxazepine-5,7-diones have been shown to be useful synthetic species equivalent to diethyl malonate <80CL163, 81CL797, 89JA6482, 90JA9022, 90TL20, 90TL2033>.

9.09.1.1.3 Synthesis from other heterocyclic systems

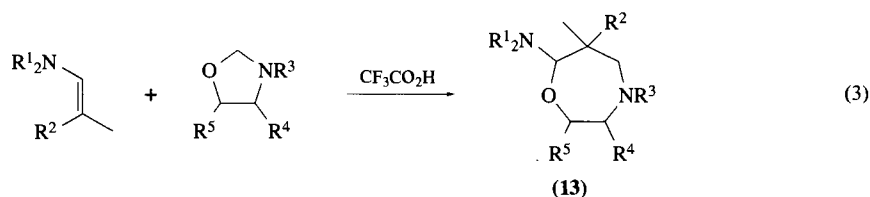
(i) From oxazolines

1,3-Oxazolium salts (**11**) are known to react with stabilized carbanions, nitrogen, oxygen, sulfur, and halogen at both the C-2 and C-5 positions. Reaction at the C-2 site results in the formation of 1,4-oxazepines (**12**), probably through an oxazolidine intermediate (Scheme 3) <82TL73, 84T349, 84T4947>.

3-Alkyl-1,3-oxazolidines react with enamines in the presence of trifluoroacetic acid to give 7-(dialkylamino)perhydro-1,4-oxazepines (**13**) (Equation (3)) <80LA1573>.

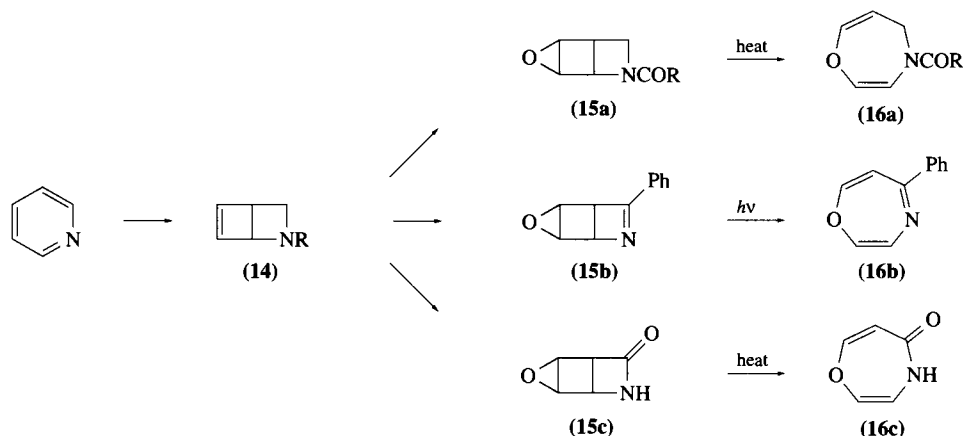


Scheme 3



(ii) From pyridines

With the successful conversion of pyridine to 2-azabicyclo[2,2,0]hex-5-enes (**14**), which can be further converted into a useful intermediate of 3-aza-7-oxatricyclo[4,1,0,0^{2,5}]hept-3-enes (**15**), irradiation of this tricycloheptene in acetonitrile was carried out to give the corresponding novel 1,4-oxazepines (**16**) in 90–95% yield after valence isomerization (Scheme 4) <85CPB4572, 86CC1188>. This type of valence isomerization has been applied to the synthesis of fully aromatized 1,4-epines with two heteroatoms, such as 1,4-oxazepines, 1,4-thiazepines, 1,4-diazepines, and azepines <85CPB4572, 86CC1188, 87H(26)3085, 87JOC5247, 90CPB2911, 90TL20>.



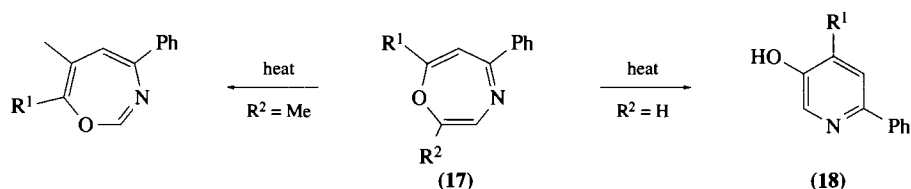
Scheme 4

9.09.1.2 Reactivities

Thermolysis of the 2-unsubstituted 1,4-oxazepines (**17**) in toluene at 100–120°C gave 2-phenyl-5-hydroxypyridines (**18**) in 65–75% yields (Scheme 5) <87CPB3166>.

Alkylation of 5,7-dioxoperhydro-1,4-oxazepine (**19**) and the Michael-type reaction of its 6-alkylidene derivatives (**20**) provided the useful synthetic methods for substituted 1,4-oxazepines (Scheme 6) <87CPB3166>.

The reaction of a chiral 5,7-dioxoperhydro-1,4-oxazepine with cyclopentene-1,2-dione dimer (**21**) in the presence of triethylamine in refluxing dichloromethane afforded one pure stereoisomer of the 2,7-*trans* Michael adduct in 60% yield <90TL20, 90TL2033>, which has been used as key intermediate for the asymmetric synthesis of virtually all monoterpenoid alkaloids and secoiridoids (Scheme 6) <80CL163, 81CL797, 87JA923, 89JA6482>.



Scheme 5

9.09.2 1,4-BENZOXAZEPINES

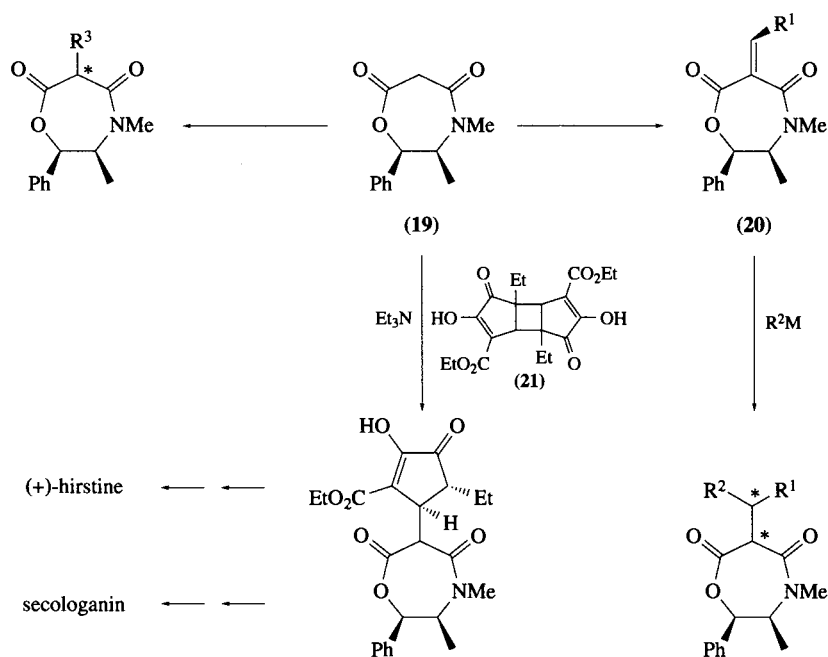
9.09.2.1 Synthesis

9.09.2.1.1 Type ac ($\text{O}-\text{C}-\text{C}-\text{C}-\text{N}+\text{C}-\text{C}$)

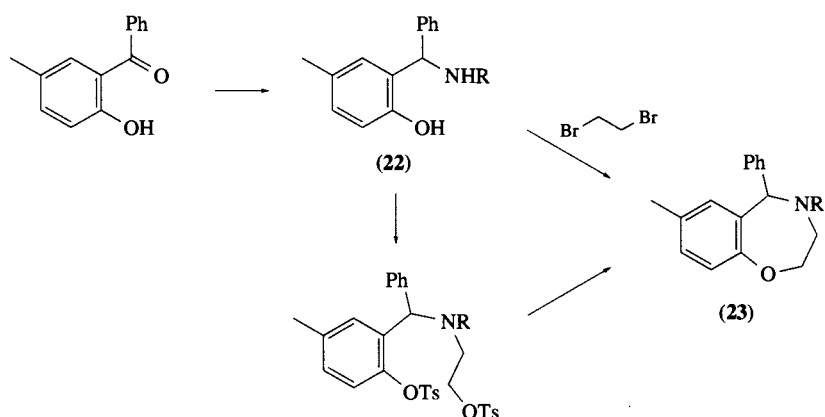
2-Hydroxy-5-methylbenzophenone was converted to the corresponding substituted diphenyl-methylamines (**22**), which on treatment with 1,2-dibromoethane and KOH gave the 1,4-benzoxazepines (**23**) in good yield. Alternatively, the amine (**22**) was also converted to the same benzoxazepines (**23**) through *O,O,N*-tritosylate, followed by cyclization with KOH and reduction with LiAlH_4 (Scheme 7) <89IJC592>.

Substituted *N*-alkylsalicylamide underwent double alkylation with 2-(tosyloxy)ethyl chloride in the presence of NaH to give the 2,3-dihydro-1,4-benzopoxazepine-5(4*H*)-one (**24**) in 25% yield <88JMC1548>, while its 2,3-dehydro derivative (**25**) was obtained by acid-catalyzed cyclization of the *N*-alkylsalicylamide derivative (Scheme 8) <88JMC1548>.

O-Alkylation of salicylamide with bromoacetaldehyde diethylacetal and subsequent thermal ring closure yielded 1,4-benzoxazepinone, which was converted to the 1,4-benzoxazepine (**26**) via simple chlorination and dehalogenation (Scheme 9) <90LA917>.



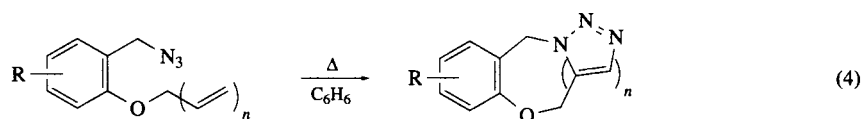
Scheme 6



Scheme 7

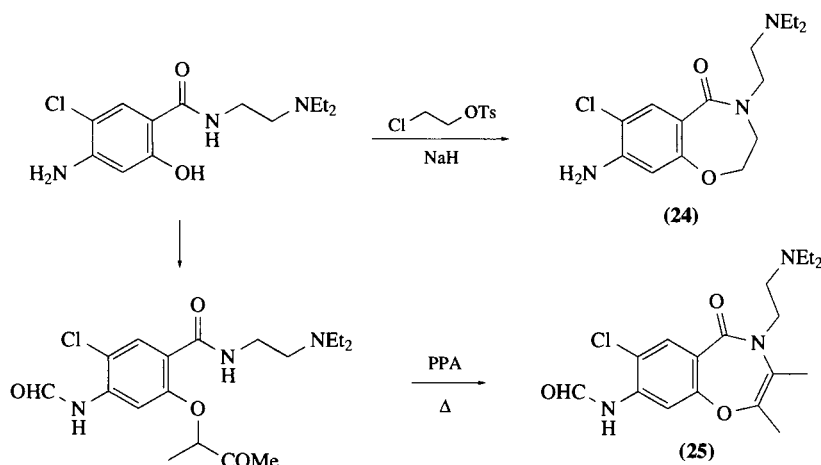
9.09.2.1.2 Type c (N—C—C—C—O—C—C)

1-Allyloxy-2-(azidomethyl)benzene plays a role as a useful synthon for oxazepine ring formation through an intramolecular azide cycloaddition <93CC607>. The cycloaddition between azide and unsaturated groups proceeded very slowly in refluxing benzene but was accelerated by bringing two groups spatially closer (Equation (4)) <93CC607>.

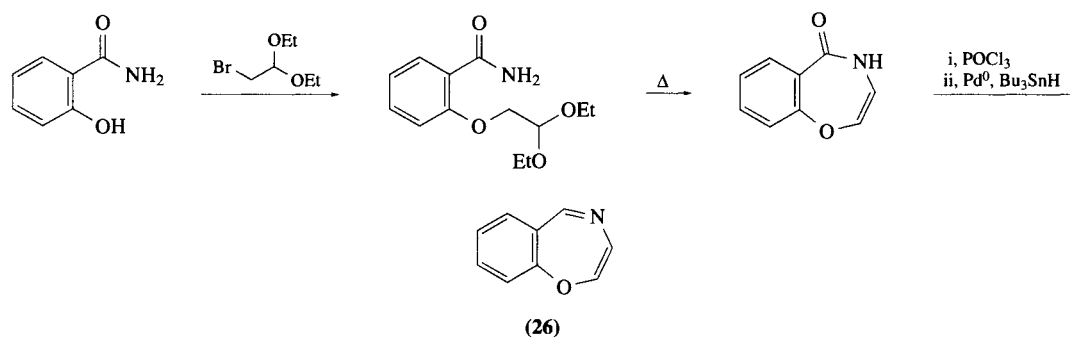


9.09.2.1.3 Type d (C—C—C—O—C—C—N) and type e (C—C—O—C—C—N—C)

When *o*-(2-aminoethyloxy)benzophenone (27) was refluxed in pyridine, the cyclic imine (28) was generated, which was then methylated and reduced with LiAlH₄ to give the 5-phenyl-tetrahydro-

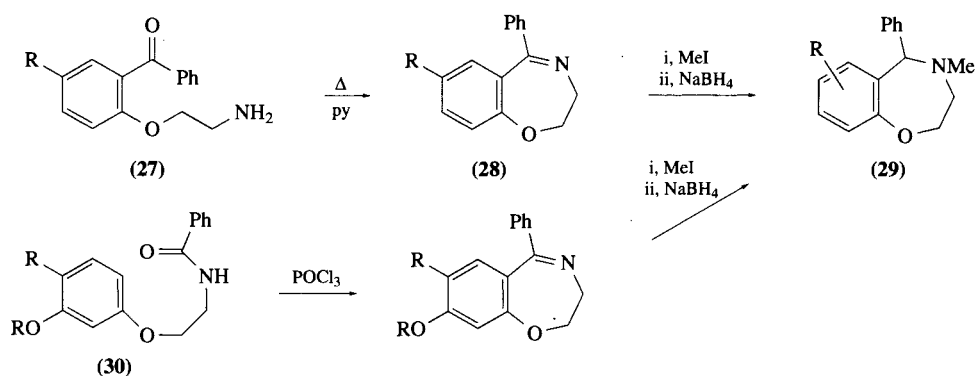


Scheme 8



Scheme 9

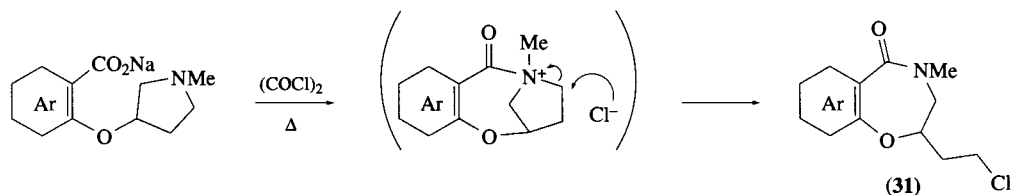
1,4-benzoxazepine (**29**), which was also prepared by the Bischler–Napieralski cyclization of the *N*-(2-aryloxyethyl)benzamide (**30**) by treatment with POCl₃ in MeCN, followed by reduction with NaBH₄ (Scheme 10) [84AJC129].



Scheme 10

9.09.2.1.4 Type d (N—C—C—O—C—C—C)

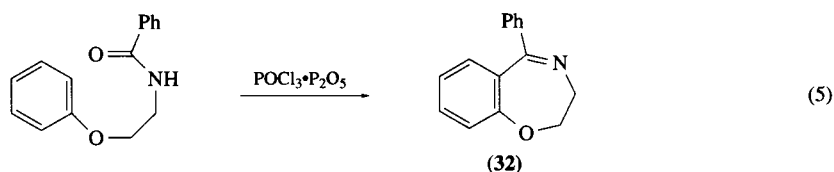
This type of ring formation, via acylation was used for the formation of fused three ring systems, which were then ring-opened for the introduction of the alkyl side chain on the oxazepine (**31**) (Scheme 11) [89JMC2178].



Scheme 11

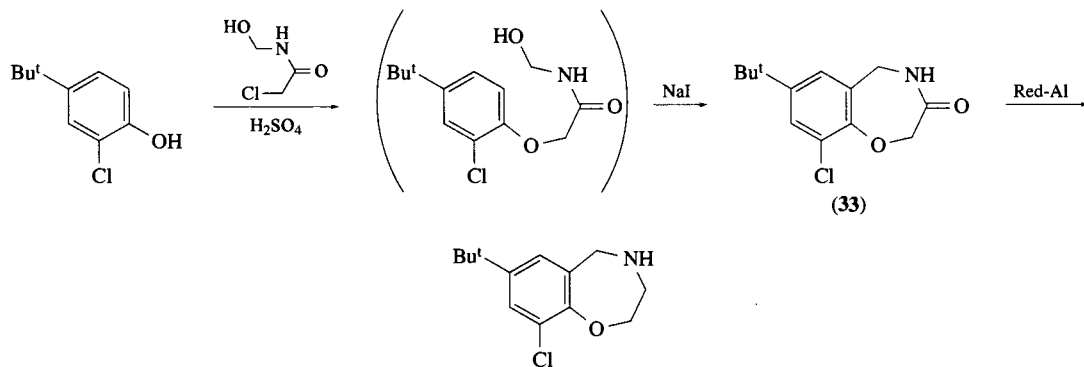
9.09.2.1.5 Type e (C—C—O—C—C—N—C)

Cyclodehydration of substituted *N*-(2-phenoxyethyl)benzamides to the corresponding benzoxazepines (32) (with $\text{POCl}_3\text{--P}_2\text{O}_5$ in xylene) has been one of the main routes for benzoxazepine synthesis (Equation (5)) <82JHC537>.



9.09.2.1.6 Type dg (O—C—C—C—N + C—C)

Substituted 2-chlorophenol was alkylated with 2-chloro-*N*-(hydroxymethyl)acetamide in the presence of H_2SO_4 to give an amide, which was then treated with NaI in boiling acetone to afford the cyclized 1,4-benzoxazepine (33). This synthesis was carried out without isolating the intermediate ether (Scheme 12) <82JMC735>.



Scheme 12

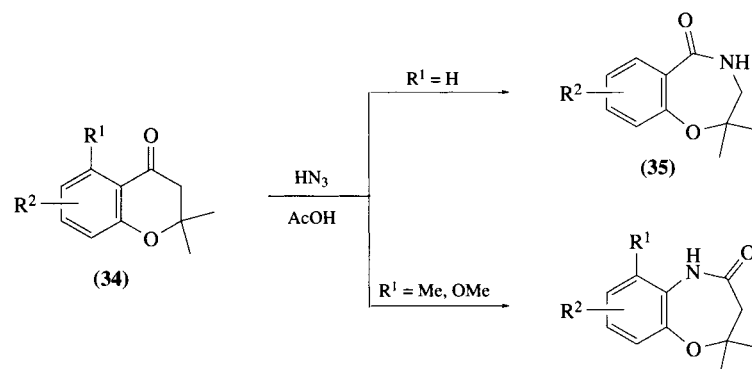
9.09.2.1.7 Synthesis from other heterocyclic systems

2,2-Dimethyl-4-chromanones (34) were treated with hydrazoic acid in acetic acid (Schmidt reaction) to afford 2,3-dihydro-2,2-dimethyl-1,4-benzoxazepines (35) in good yields (Scheme 13) <92H(34)1523>.

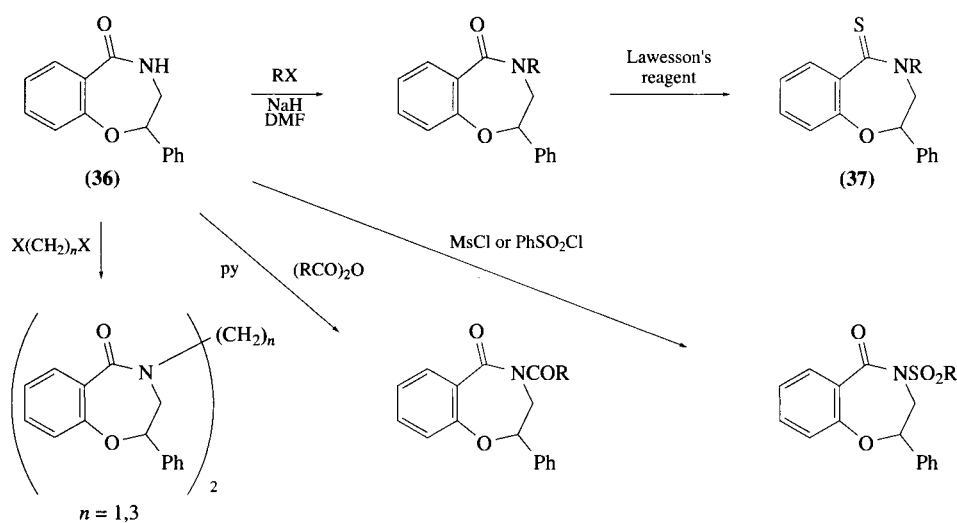
9.09.2.2 Reactivities

9.09.2.2.1 Acylation

2-Phenyl-1,4-benzoxazepin-5-one (36) was readily acylated with mesyl and benzenesulfonyl chlorides to give the corresponding *N*-acylated derivatives. Conversion of the amide to thione (37) was also carried out by the use of Lawesson's reagent (Scheme 14) <93AP(326)73>.



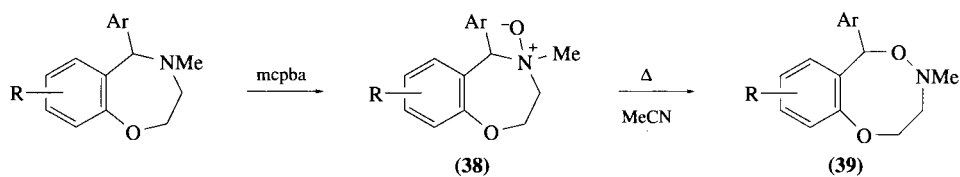
Scheme 13



Scheme 14

9.09.2.2.2 Meisenheimer rearrangement

2,3,4,5-Tetrahydro-1,4-benzoxazepine *N*-oxide (38) underwent smooth ring expansion under thermal conditions in acetonitrile to give 3,4-dihydro-2*H*,6*H*-1,5,4-benzodioxazocine (39) in yields of 60–95% (Scheme 15) [88AJC293].



Scheme 15

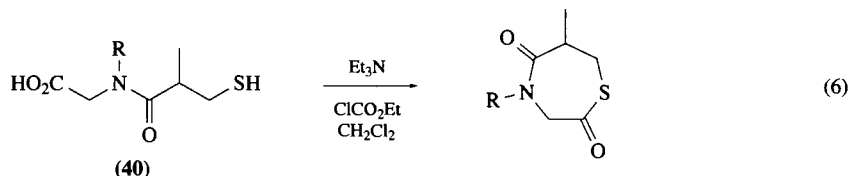
9.09.3 1,4-THIAZEPINES

9.09.3.1 Synthesis

9.09.3.1.1 Type a (S—C—C—C—N—C—C)

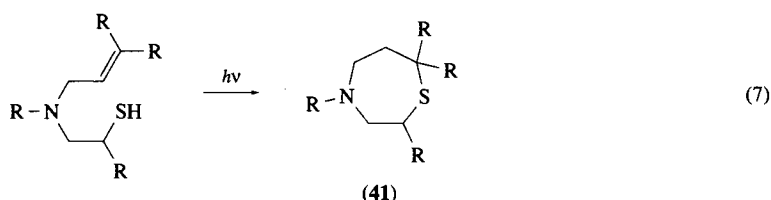
Ring closure of the β -thiolalkanoyl amino acid (40) was facilitated by treatment of 2,2'-dipyridyl disulfide in the presence of triphenylphosphine in refluxing toluene under high-dilution conditions.

Although the method provided the desired cyclized product in 30–40% yield, the disadvantage of high-dilution conditions and the necessity of purifying the product from triphenylphosphine oxide warranted further exploration of other ring-closure reactions, such as DCC in CH_2Cl_2 or neat PPA at 50°C . The most efficient method utilised ethyl chloroformate in CH_2Cl_2 in the presence of 1 equiv. of triethylamine at room temperature, which provided thiazepine formation in 30–50% yield (Equation (6)) <82CC809, 84JCS(P1)21, 93CPB1066>.



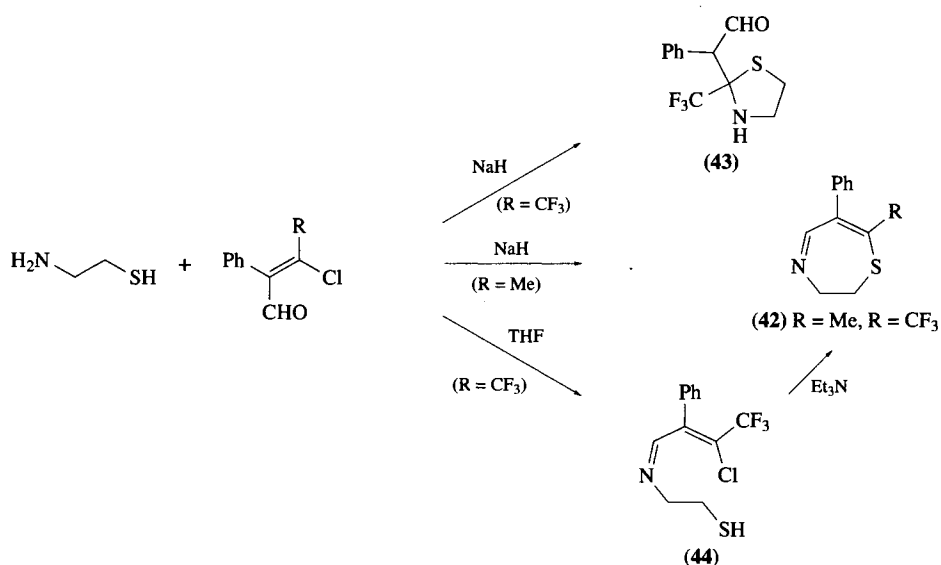
9.09.3.1.2 Type g ($\text{S}-\text{C}-\text{C}-\text{C}-\text{N}-\text{C}-\text{C}$)

Under irradiation, *N*-allyl-2-aminothiols bearing substituents on the double bond underwent a free radical initiated cyclization to give a mixture of 1,4-thiazolidine and 1,4-thiazepine (41) (Equation (7)) <84BSF(2)390, 85JBC(260)15577>.



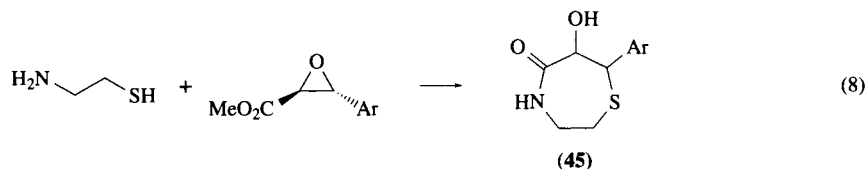
9.09.3.1.3 Type dg ($\text{C}-\text{C}-\text{C} + \text{S}-\text{C}-\text{C}-\text{N}$)

Acroleins reacted with 2-thioethylamine in a basic medium to deliver two different heterocycles. 3-Methylacrolein gave the thiazepine (42) in a quantitative yield; whereas, the 3-trifluoromethyl analogue only produced the thiazolidine (43) in good yield. When the acrolein and 2-thioethylamine reacted at 0°C for 15 min without any base, imine (44) was formed. Addition of triethylamine to a solution of this imine brought about cyclization to form the thiazepine (42) in 80% yield (Scheme 16) <83T3995, 91TL643, 93TL2483, 94BSF167>.

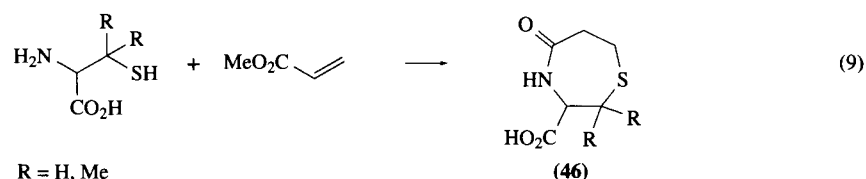


Scheme 16

Similarly, the reaction of 2-thioethylamine with *trans*-3-(*p*-methoxyphenyl)glycidate in refluxing xylene, followed by removal of the solvent and separation of products by fractional crystallography afforded a mixture of rac.-*cis*-1,4-thiazepinone (**45**) and the thiazolidine in 41% combined yield (Equation (8)) <92JHC193>.



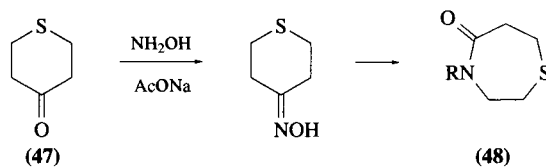
The reactions of methyl acrylate with cysteine hydrochloride and penicillamine proceeded smoothly in one step to give 5-oxo-1,4-thiazepane-3-carboxylic acid (**46**) in 42% and 29% yields, respectively (Equation (9)) <83T3995>.



9.09.3.1.4 Synthesis from other heterocyclic systems

(i) By Beckmann rearrangement

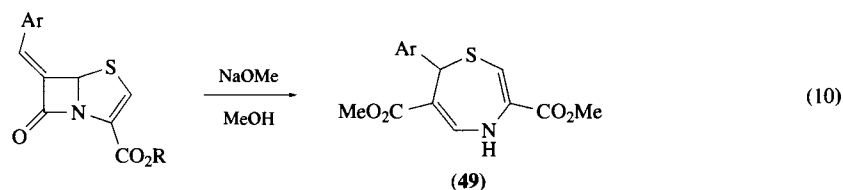
4-Oxothiane (**47**) reacted readily with hydroxylamine hydrochloride in the presence of sodium acetate to give the corresponding oxime which smoothly underwent a Beckmann rearrangement to afford 1,4-thiazepin-5-one (**48**) (Scheme 17) <81JOC1239>.



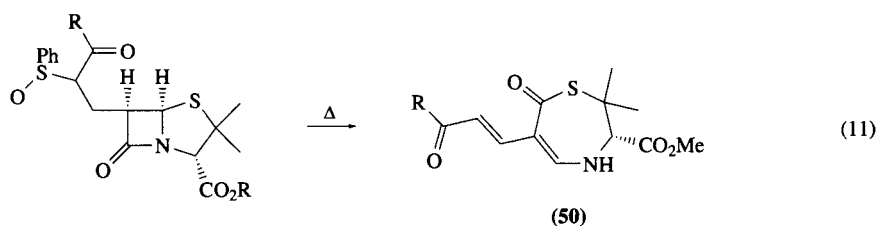
Scheme 17

(ii) From penem

Penem *p*-nitrobenzyl ester underwent rearrangement upon reaction with sodium methoxide in methanol with concomitant transesterification to yield 4,7-dihydro-1,4-thiazepines (**49**) (Equation (10)) <92CC1663>.

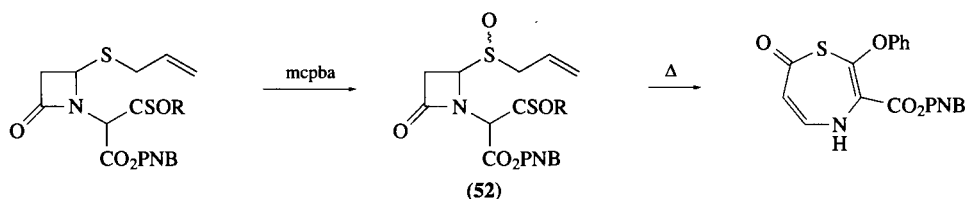
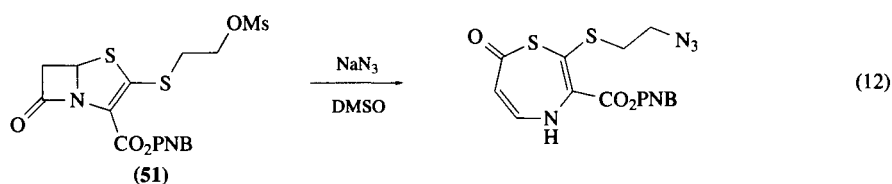


According to the process known for 6-acylpenicillanates, thermolysis of the sulfoxide of 6 β -substituted penicillanate in refluxing toluene afforded the unstable yellow thiazepinone (**50**) rather than the ester of mecillinam (Equation (11)) <84JCS(P1)21>.

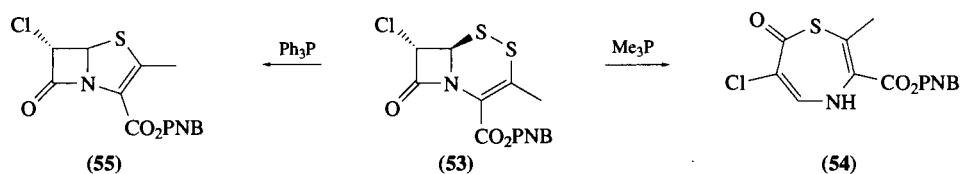


Similar ring expansion was also observed with the cephem derivative (51) and β -lactam (52) (Equation (12) and Scheme 18) <80CPB3258, 83TL3373>.

2-Thiacepham (53) was treated with trimethylphosphine to give the thiazepine (54), as a sole product, while treatment of (53) with triphenylphosphine gave the penem derivative (55) (Scheme 19) <82CC809>.



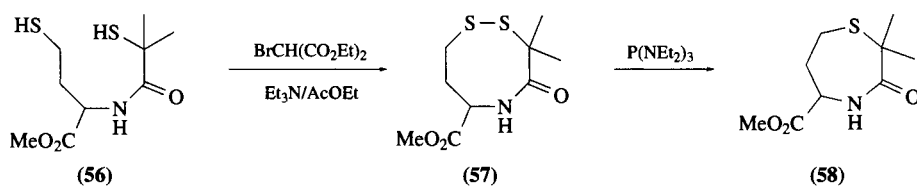
Scheme 18



Scheme 19

(iii) From cyclic disulfide

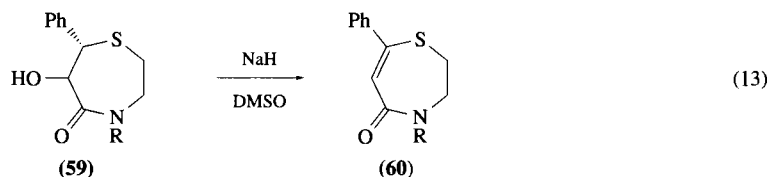
1,4-Thiazepinone (58) was obtained by oxidative cyclization of the corresponding dithiol derivative (56), by the reaction with diethyl bromomalonate in the presence of base, followed by treatment of the resulting cyclic disulfide (57) with trisdiethylaminophosphine (Scheme 20) <93CPB1066>.



Scheme 20

9.09.3.2 Reactivity

Base-promoted dehydration of *trans*-tetrahydro-6-hydroxy-1,4-thiazepin-5(2*H*)-one (**59**) with NaH in DMSO at 70°C gave the corresponding dihydrothiazepinone (**60**) in 55% yield (Equation (13)) <91JHC2051>.

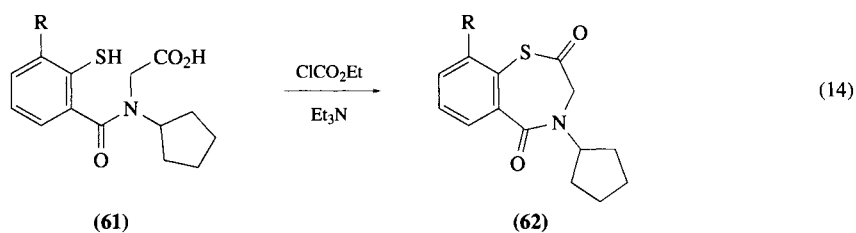


9.09.4 1,4-BENZOTHAZEPINES

9.09.4.1 Synthesis

9.09.4.1.1 Type a (S—C—C—C—N—C—C)

Thiosalicylamide was alkylated with ethyl chloroformate in CH₂Cl₂ to give the thiol acid (**61**), which underwent smooth cyclization to give the 1,4-benzothiazepine-2,5-dione (**62**) in 30–40% yield. This type of cyclization also occurred with PPA, with 2,2'-dipyridyl disulfide, and triphenylphosphine (Equation (14)) <86JMC784>.

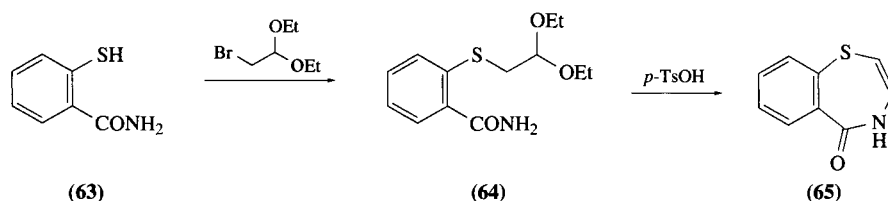


9.09.4.1.2 Type ac (N—C—C—C—S + C—C)

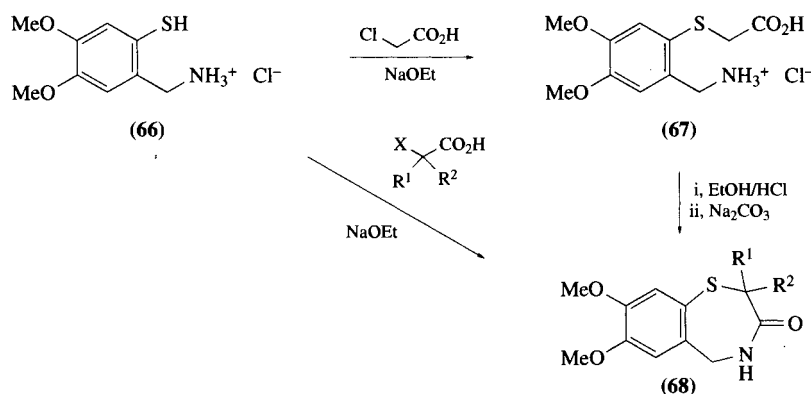
Acid-catalyzed hydrolysis of the amide acetal (**64**) of 2-thiolbenzamide (**63**) yielded the 1,4-benzothiazepin-5(4*H*)-one (**65**) (Scheme 21) <88CB2147>.

2-Thiolbenzamide (**63**) was treated with bromoacetaldehyde diethyl acetal for *S*-alkylation, which upon heating in the presence of TsOH in toluene brought about cyclization to give the 1,4-benzothiazepin-5(4*H*)-3-one (**65**) in good yield <88CB2147>, which was *N*-methylated to fix the position of the double bond.

2-Thiolbenzylammonium salt (**66**) was alkylated with chloroacetic acid in the presence of NaOEt, followed by esterification afforded the thioglycolate (**67**) which underwent cyclization by treatment with Na₂CO₃ to give the crystalline form of 1,4-benzothiazepin-3-one (**68**) in 85% yield, thus providing a generally applicable, one-step synthesis of 4,5-dihydro-1,4-benzothiazepin-3-ones (**68**) (Scheme 22) <86CB2905>.



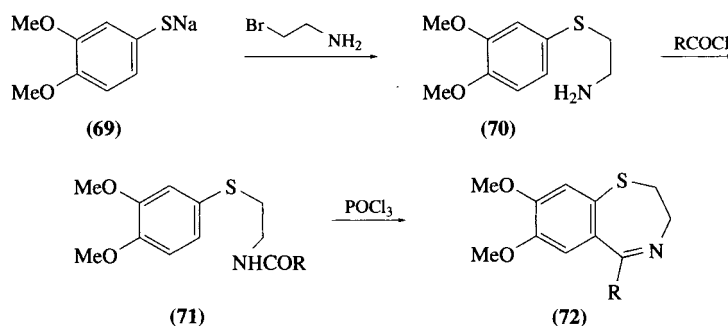
Scheme 21



Scheme 22

9.09.4.1.3 Type e (C—C—S—C—C—N—C)

The reaction of sodium thiophenoxide (**69**) with 2-bromoethylamine gave the corresponding 2'-aminoethylsulfide (**70**) which was then acylated to afford amide (**71**). Heating of the amide (**71**) with POCl_3 furnished the 2,3-dihydrobenzothiazepine (**72**) in only poor yield (Scheme 23) <87CJC175>.

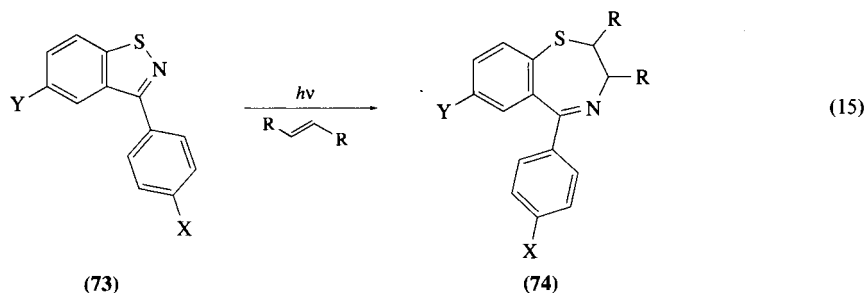


Scheme 23

9.09.4.1.4 Synthesis from other heterocyclic systems

(i) From benzisothiazole

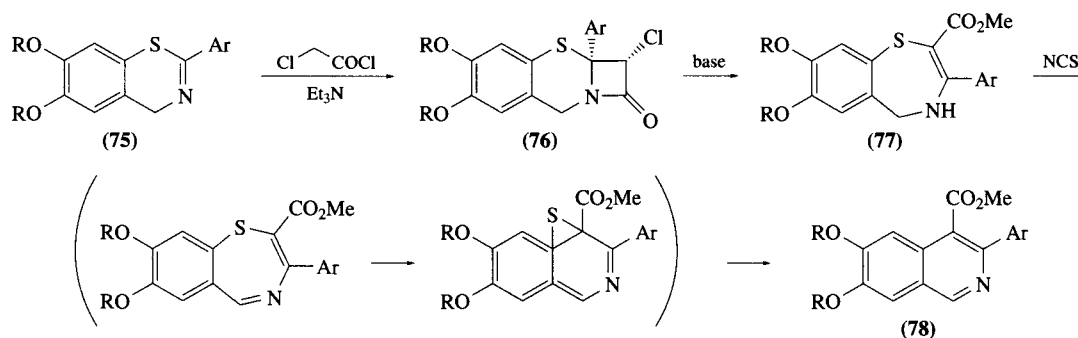
5-Phenyl-2,3-dihydro-1,4-benzothiazepines (**74**) were obtained in good yield (70–86%) by irradiation of 3-phenyl-1,2-benzothiazole (**73**) in the presence of alkenes. Irradiation was performed in Pyrex tubes with a 450 W medium-pressure mercury lamp at ca. 15°C or in Rayonet reactor at 300 nm after the reaction mixture was purged with nitrogen or degassed using several freeze–thaw cycles (Equation (15)) <81T3377, 81TL529>.



(ii) From 1,3-benzothiazine

2-Aryl-4H-1,3-benzothiazines (**75**) reacted with chloroacetyl chloride in the presence of triethylamine to form the β -lactam derivative (**76**), which underwent rearrangement in the presence

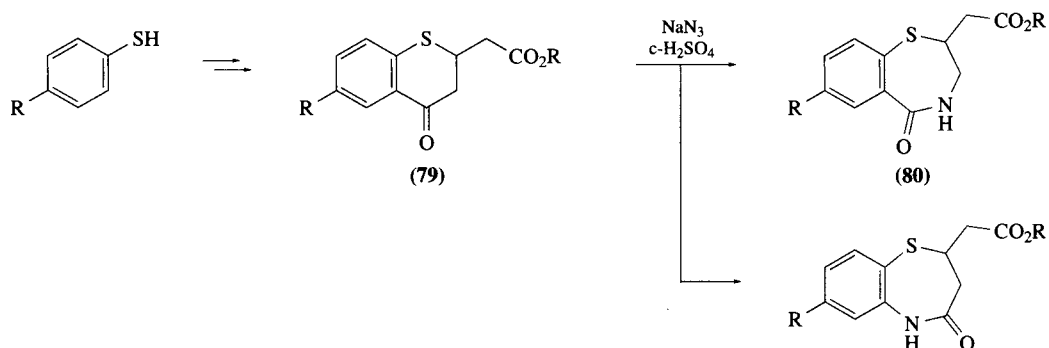
of base to form 4,5-dihydro-1,4-benzothiazepine (77) (64% yield). When it was stirred with *N*-chlorosuccinimide in ether at room temperature, further ring conversion to 3-phenylisoquinolines (78) was observed (Scheme 24) <81TL5077, 84TL4089, 87CJC18>.



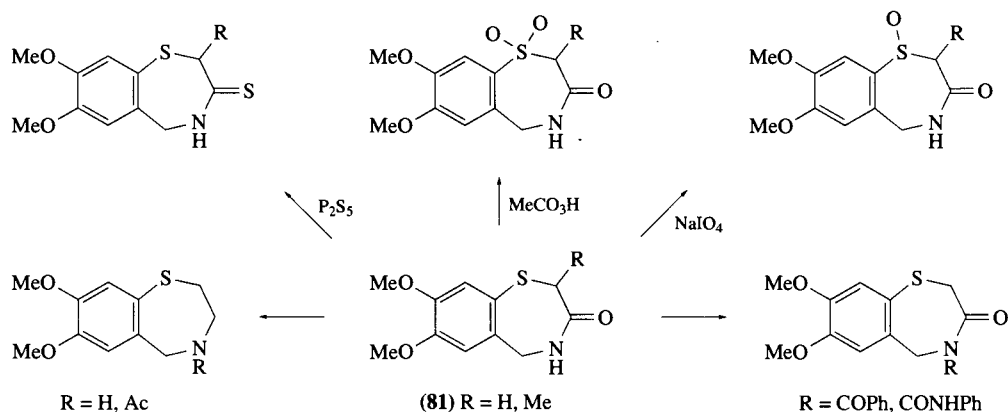
Scheme 24

(iii) From 2-thiochromanone-2-acetic acid

Thiochromanone-2-acetate (79), on treatment with NaN_3 in presence of conc. H_2SO_4 underwent a Schmidt rearrangement to give 2,3-dihydro-1,4-benzothiazepin-4(5*H*)-one-2-acetate (80) in 55–60% yield (Scheme 25) <83JC300>.



Scheme 25

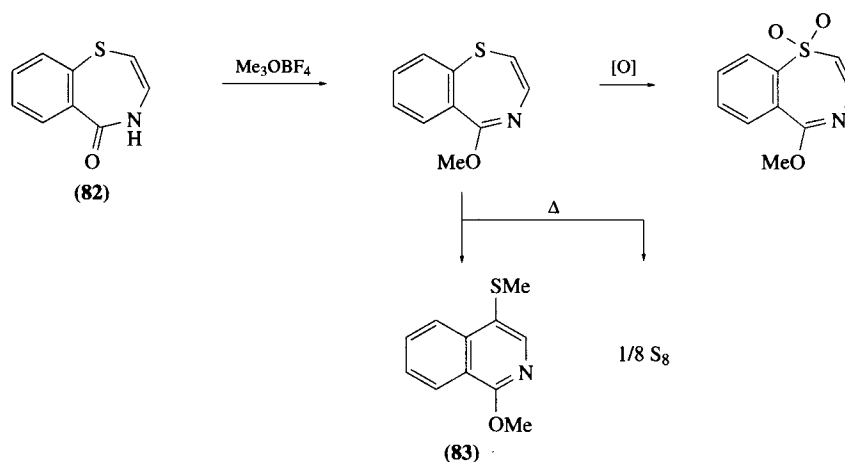


Scheme 26

9.09.4.2 Reactivity

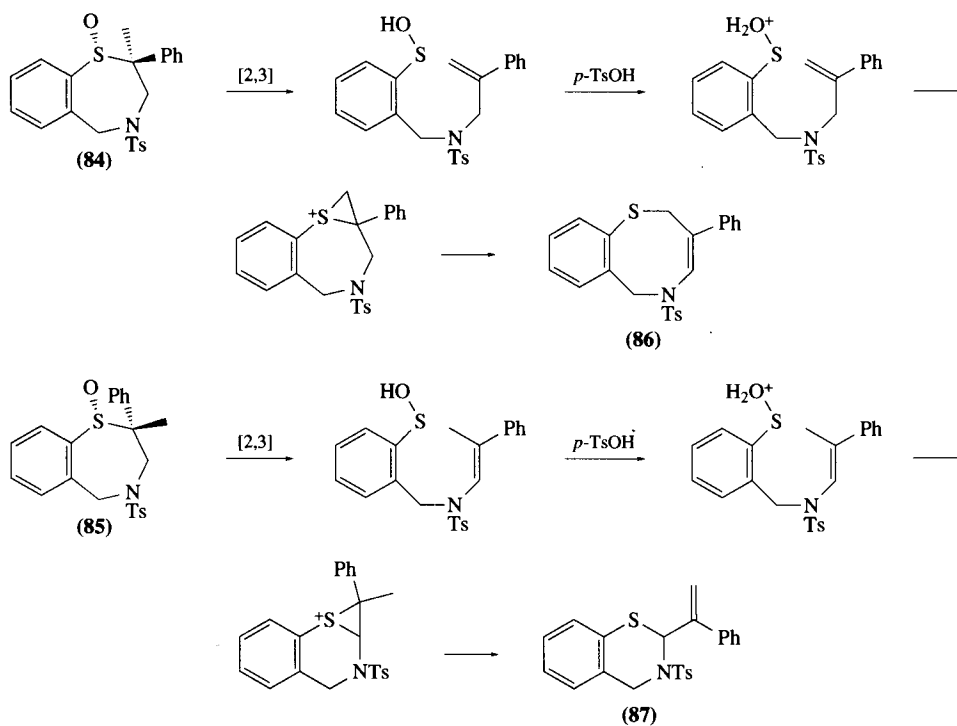
Various chemical reactions of 1,4-benzothiazepines (**81**) were investigated including oxidation (MeCO_3H , NaIO_4), reduction (LiAlH_4), acylation (ArCOCl , PhNCO), and thiolactamization to afford several types of derivatives (Scheme 26) [86CB2905, 87CJC175].

Alkylation of 1,4-benzothiazepin-5(4*H*)-one (**82**) with methyl iodide/silver tetrafluoroborate gave the sulfonium salt, which rearranged to 1-methoxy-4-(methylthio)isoquinoline (**83**) on heating in acetonitrile (Scheme 27) [88CB2147].



Scheme 27

Thermal ring transformations of *trans*- and *cis*-2-methyl-2-phenyl-1,4- and 1,5-benzothiazepine 1-oxides (**84**) and (**85**) in the presence of catalytic amount of *p*-toluenesulfonic acid occurred differently; *trans*-sulfoxides having methyl group *cis* to the sulfoxide oxygen underwent ring expansion to afford benzothiazocine derivatives (**86**); whereas, the *cis*-isomers afforded ring contraction products (**87**), indicating that the ring transformations proceeded stereospecifically (Scheme 28) [84H(22)1025].



Scheme 28

9.10

1,2-Dioxepins, 1,2-Oxathiepinines, and 1,2-Dithiepinines

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Kobe Pharmaceutical University, Japan

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9.10.1 1,2-DIOXEPINS

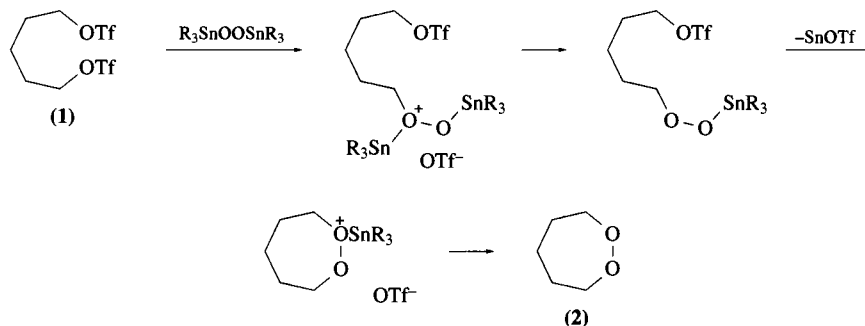
9.10.1.1 Synthesis

1,2-Dioxepane, the basic structure of 1,2-dioxepine, is actually a cyclic peroxide; therefore, often appearing in the literature as an intermediary structure for further conversion.

9.10.1.1.1 Type a ($O-C-C-C-C-C-O$)

Introduction of a triflate group (trifluoromethanesulfonate) in the synthesis facilitates a convenient synthesis of the 1,2-dioxepane ring, according to the reaction sequence, as follows; alkylation of the alkyltriflate with bis(trialkyltin)peroxide yields an oxonium intermediate. Expulsion of a

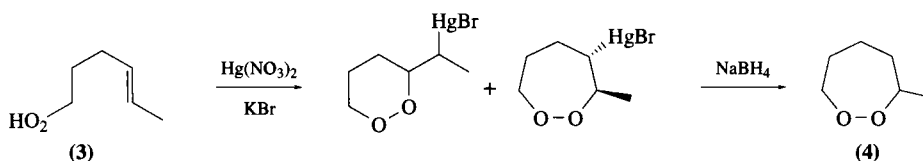
relatively stable trialkyltin cation from this intermediate gives a trialkyltin alkyl peroxide, which is then readily converted to the dialkylperoxide. This sequence can be applied to the conversion of 1,5-pentane-diol to 1,2-dioxepane (2) (37%) via 1,5-dialkyltriflate (1) (Scheme 1) <77JA3500>.



Scheme 1

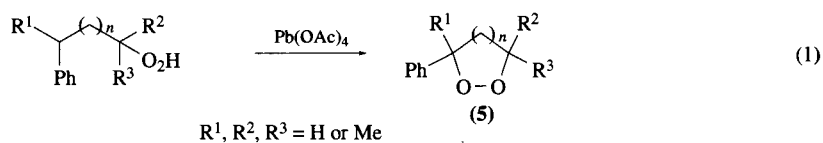
9.10.1.1.2 Type b (O—O—C—C—C—C—C)

Unsaturated hydroperoxides (3) underwent cyclization when treated with mercuric nitrate or trifluoroacetate to give the β -mercurated cyclic peroxides, which were isolated by HPLC as the alkyl mercuric bromides in ca. 40% yields, which were then reduced with borohydride to afford the cyclic peroxide, 1,2-dioxepane (4) (Scheme 2) <78JA7116, 78JOC4048>.



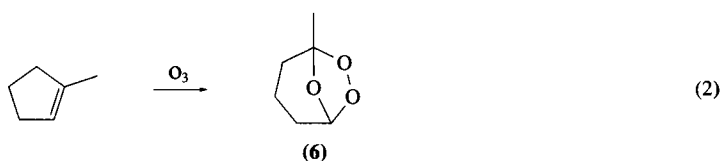
Scheme 2

Pentyl-hydroperoxide was prepared from the corresponding alcohol by oxidation with 50% H_2O_2 in the presence of 85% H_3PO_4 at 60°C for 6 h to give the hydroperoxide in 48% yield, which was then treated with $Pb(OAc)_4$ in pentane under reflux for 18–45 h to generate 1,2-dioxepane (5) in 10–14% yield (Equation (1)) <81S633>.

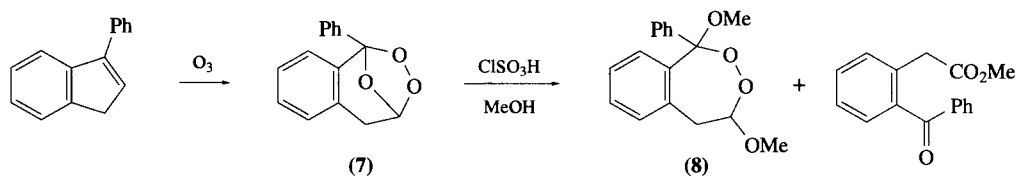


9.10.1.1.3 Type bg (C—C—C—C—C + O—O)

Ozonolysis of 1-methylcyclopentene in methanol at $-78^\circ C$ provided the simplest route to the 1,2-dioxepanes (6) though the yield is variable. For example, a mixture of *cis*- and *trans*-7-methoxy-7-methyl-1,2-dioxepan-3-ol in 84% yield and a mixture of *cis*- and *trans*-7-methyl-3-methyl-1,2-dioxepan-3-ol in 4% yield was obtained (Equation (2)) <89CB145>.



The ozonide (7), prepared from indene containing a dioxepine moiety in the molecule, was treated with methanol in the presence of chlorosulfonic acid to give the dioxepine (8) (Scheme 3) <80JCS(P1)2909>.



Scheme 3

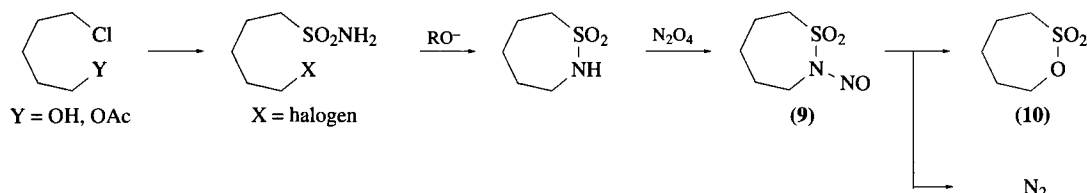
9.10.2 1,2-OXATHIEPINES

9.10.2.1 Synthesis

The presence of sulfur and adjacent oxygen in the seven-membered ring, 1,2-oxathiepine, makes these compounds unstable; therefore, most of the known ring systems possessing this moiety are obtained in the form of the *S*-oxide (sulfonate) or *S,S*-dioxide (sulfonate).

9.10.2.1.1 Type a (*S*—C—C—C—C—C—O)

1,5-Pentanesultam (9) is a good precursor for the formation of 1,2-oxathiepine ring and can be prepared by treatment of its precursor with dinitrogen tetroxide <87JOC2162>. The conversion proceeded first by the formation of *N*-nitroso sultam, which underwent thermal decomposition in an acidic medium to release nitrogen, giving the cyclic ester, oxathiepine (10) (Scheme 4) <87JOC2162>.



Scheme 4

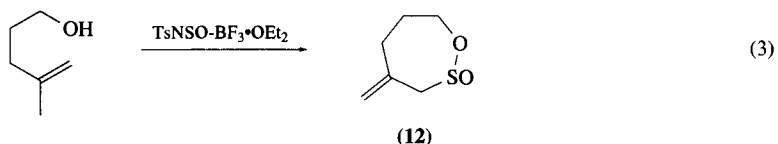
5-Hydroxypentanethiol was treated with chlorine gas in CH_2Cl_2 at -78°C , followed by alkaline hydrolysis to afford the sultine in only 10% yield; however, a one-pot, two-stage chlorination process gave good yields of six- and seven-membered sultines (11) (90%) (Scheme 5) <89TL2763>.



Scheme 5

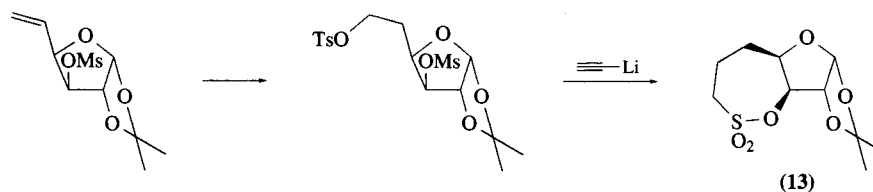
9.10.2.1.2 Type ab (*O*—C—C—C—C—C + *S*)

A variety of unsaturated alcohols reacted with $\text{TsNSO}\cdot\text{BF}_3\cdot\text{OEt}_2$ to give the seven-membered sultine (12) (Equation (3)) <93CC1195>.



9.10.2.1.3 Type ce (C—C—C—C—O—S—C)

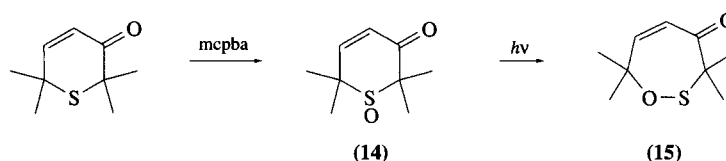
The mesylate–tosylate in the framework of the pyranose derivative reacted with lithium acetylide–ethylenediamine complex to give the seven-membered sultone (**13**) in 98% yield, as a result of displacement of a tosylate coupled with deprotonation at the mesylate producing a nucleophile and then ring formation (Scheme 6) <81CJC260>.



Scheme 6

9.10.2.1.4 Synthesis from other heterocyclic systems

On irradiation, cyclic sulfoxides (**14**) underwent C—S bond homolysis (α -cleavage) to give the sulfinyl–alkyl radical, which would further undergo recombination to form ring-expanded heterocyclic sulfenates (**15**). Thus, photoisomerization of 2*H*,6*H*-thiin-3-ones occurred in MeCN or benzene to form seven-membered cyclic sulfenates, oxathiepinones, which are also obtained by treatment with MCPBA. These oxathiepinones underwent thermal [2,3] sigmatropic rearrangement to the intermediate thietan-3-one 1-oxides, followed by the Pummerer reaction to afford thietan-3-one or 2-acylthiophene depending on the substituent (Scheme 7) <93HCA1251>.



Scheme 7

9.10.3 1,2-DITHIEPINES

9.10.3.1 Synthesis

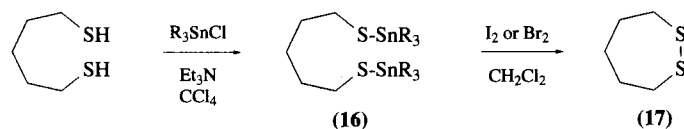
Synthetic methodology of this ring system has been limited only to a few routes, either type a or type bg.

9.10.3.1.1 Type a (S—C—C—C—C—C—S)

The most conventional route to 1,2-dithiepane system was by an oxidative cyclization of pentane-1,5-dithiol or its equivalent, including pentanes with a 1,5-di-(*S*-bearing) substituent such as a thiol or dithiolate salts <71JOC322, 81JA159, 84JA5271, 86TL441, 88JOC396, 89T91, 92JOC2013>. The procedure for cyclization of long chain compounds has been limited, in general, to high-dilution and titrimetric methods <70JOC749>. In order to suppress the formation of intermolecularly formed dimeric and polymeric disulfides, while yet enhancing the formation of intramolecular disulfide, some routes utilized a solid support for fixing the molecule in a favored form to enhance cyclization <92TL7709>.

A tin-directed cyclization technique was introduced for a selective formation of the monomer. This mild, template-driven ring closure gave a good yield of the desired monomer <86TL441>. Thus, high yield preparations of cyclic disulfides, including 1,2-dithiolanes, 1,2-dithiane, 1,2-dithiepane, and up to 1,2-dithiacyclodecane, by this oxidative cyclization with bromine or iodine from the

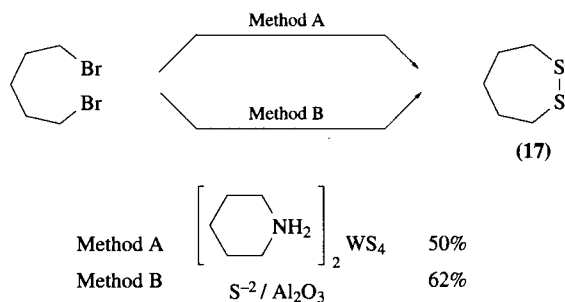
corresponding bis(tri-*n*-butyltin)thiolates (**16**) were achieved. This method permitted a rapid synthesis of cyclic disulfides (**17**) in good to excellent yields and has the advantage over high dilution and titrimetric techniques (Scheme 8) <86TL441>.



Scheme 8

9.10.3.1.2 Type *bg* ($C-C-C-C-C+S-S$)

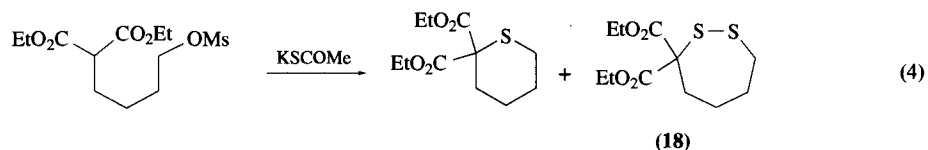
For the direct formation of 1,2-dithiepanes, the use of tetrathiol metalates (MS_4^{2-}) of molybdenum and tungsten was effective; thus, the reaction of tetrathiotungstate with 1,5-dibromopentane afforded 1,2-dithiepane (**17**) in 50% yield (Scheme 9) <92JOC1899>.



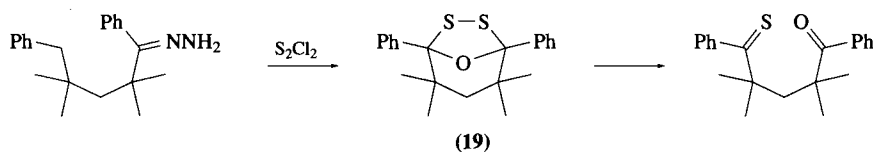
Scheme 9

An alternative method for the formation of cyclic disulfide was invented by the reaction of S^{2-} on alumina in two steps by making good use of solid support (Scheme 9) <92JOC2013>.

There are various methods for the synthesis of 1,2-dithiepins. Reaction of diethyl 2-(4-mesyloxybutyl)malonate with $KSCOMe$ in DMF in the presence of air at room temperature gave a mixture of thiacyclohexane (50%) and dithiacycloheptane (**18**) (30%) (Equation (4)) <80TL2119>.



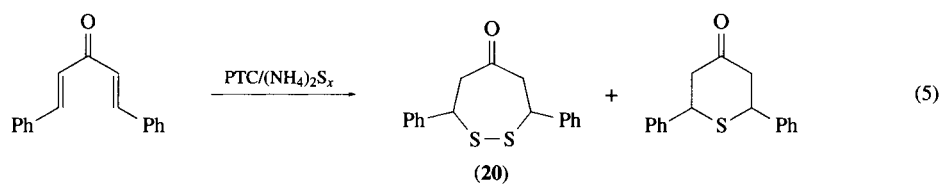
The monohydrazone of 2,2,4,4-tetramethyl-1,5-diphenylpentane-1,5-dione, which was prepared by treatment of the corresponding diketone with hydrazine, reacted with S_2Cl_2 in benzene to afford the fused 1,2-dithiepine (**19**) <92CC7, 93BCJ1714>. The product was subjected to desulfurization with hexamethylphosphorus triamide $[P(NMe_2)_3]$ to form 5-thioxo-1-pentanone (Scheme 10) <92CC7, 93BCJ1714>.



Scheme 10

1,4-Dien-3-one reacted with ammonium polysulfides under the condition of phase transfer catalysis (PTC) to give two diastereomers of 1,2-dithiepanone, 3,7-diphenyl-1,2-dithiepan-5-ones (**20**),

together with six-membered thianones; while with PTC/ Na_2S_x , polymerization and cyclization were competitive (Equation (5)) <93JOC6103>.



9.11

1,3-Dioxepanes, 1,3-Oxathiepanes, and 1,3-Dithiepanes

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Universität GH Kassel, Germany

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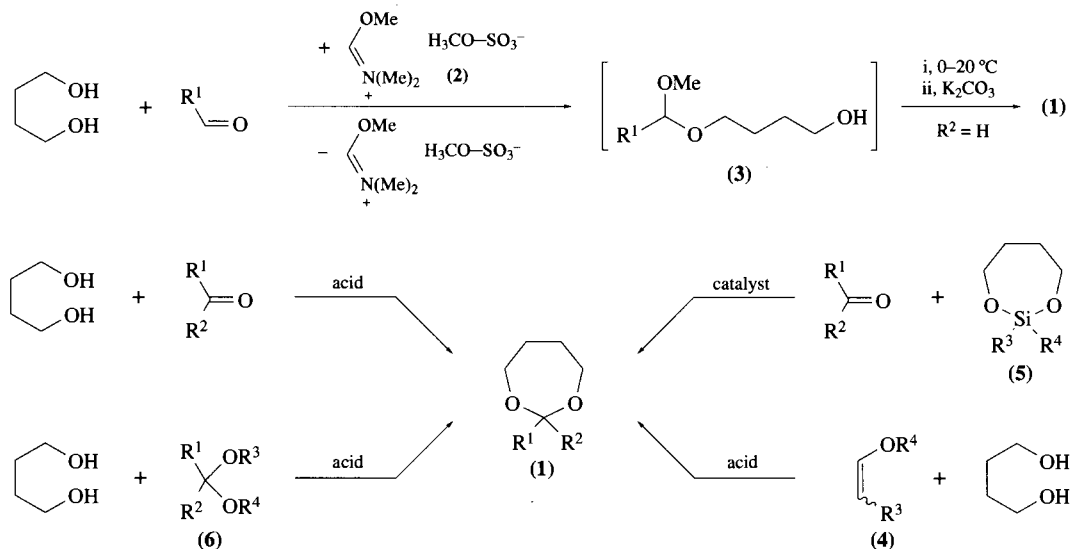
9.11.1 1,3-DIOXEPANES AND 1,3-DIOXEPINS

9.11.1.1 1,3-Dioxepanes

9.11.1.1.1 Synthesis

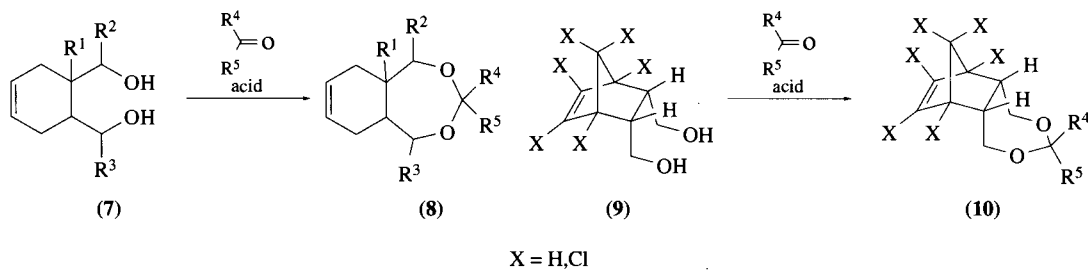
1,3-Dioxepanes (**1**) have usually been prepared by direct acetalization of aldehydes or ketones with 1,4-diols in the presence of an acid (<72GEP(O)2059704, 83CC705, 85JCS(P1)2093, 92GEP(O)4104411,

92MI 911-01), a cation exchange resin (79BSF264, 81ZPK949) or clay minerals (79BSF264); however, direct acetalization of ketones gives poor yields in general. The reaction of aliphatic aldehydes with 1,4-butanediol and DMF-dimethylsulfate adduct (2) yields 1,3-dioxepanes under very mild conditions (Scheme 1) (79S975). This reaction is believed to proceed via mixed acetals (3), which immediately cyclize under the reaction conditions to give (1) (79S975). 1,3-Dioxepanes have also been obtained by treatment of 1,3-dioxo-2-silepanes (5) with aldehydes or ketones (87MI 911-01).

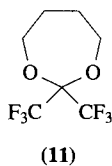


Scheme 1

Bicyclic 1,3-dioxepanes (8) and (10) were prepared in a stereoselective manner by direct acetalization of aldehydes and ketones with diols (7) and (9; X = H), or chlorendic diol (9; X = Cl) (Scheme 2) (75BSF1763, 76USP3984438). For another approach to dioxepane (10) by [4 + 2] cycloaddition of 2-ethyl- or 2-isobutyryl-4,7-dihydro-1,3-dioxepin with cyclopentadiene dimers see Section 9.11.1.2.2. Acetalization of hexafluoroacetone with 1,4-butanediol to 1,3-dioxepane (11) has been effected with dicyclohexyl carbodiimide as condensating agent (87MI 911-01).

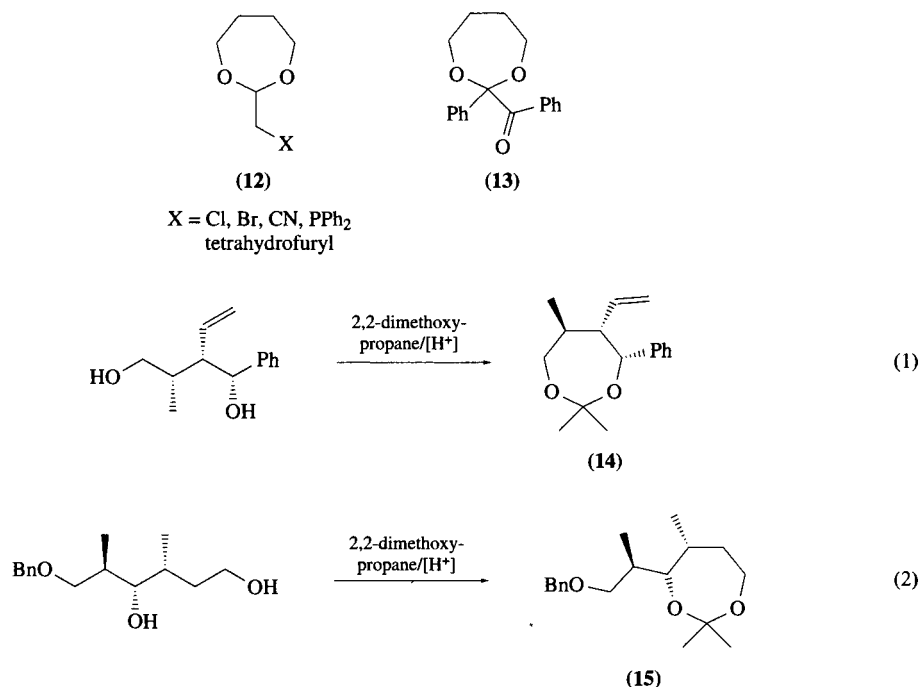


Scheme 2

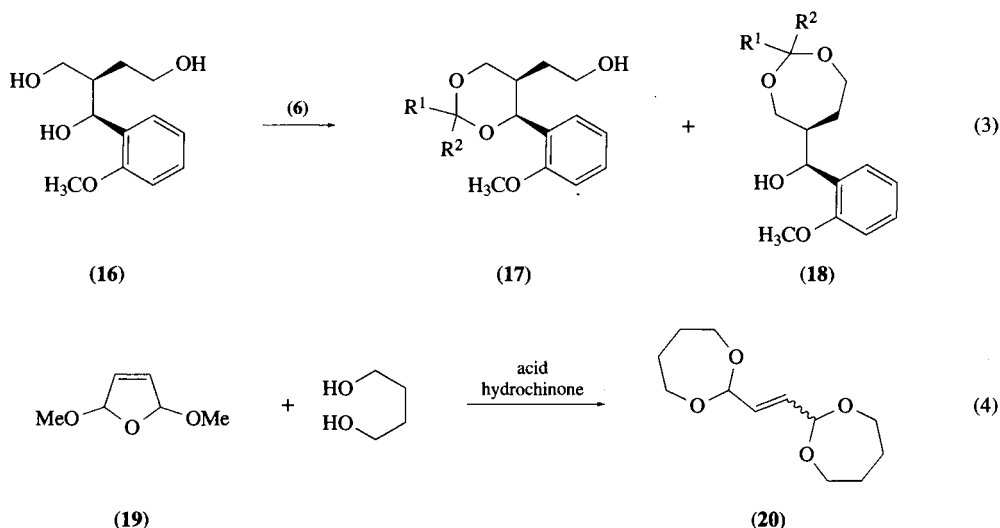


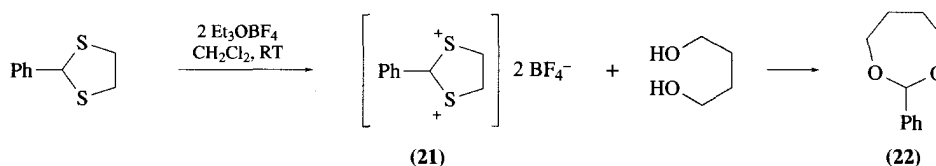
The second general route to 1,3-dioxepanes (1) involves acid-catalyzed alcohol exchange of an acyclic acetal (6) with a 1,4-diol (transacetalization) (81JOC2981), as demonstrated by the synthesis of (12; X = Cl, Br) by reaction of 2-halo-1,1-dialkoxyethane with 1,4-butanediol (79MI 911-01, 95JOC5729) or the preparation of (13) from benzil dimethyl acetal (90UKZ1116). Transacetalization is preferred for the synthesis of 1,3-dioxepanes derived from ketones (61JOC4762) and the stereo-

selective construction of highly substituted 1,3-dioxepanes, e.g. (14) (Equation (1)) <91JA4218> and (15), an intermediate in the total synthesis of ionophore antibiotic routiennocin (Equation (2)) <92SL395, 92SL399, 92T7899>.



In the reaction of triol (16) with (6) the ring size of the products depends on the nature of the acetal. Thus, treatment of (16) with 2,2-dimethoxypropane affords a nearly 1 : 1 mixture of the six- and seven-membered ring; whereas the reaction with 1,1-diethoxyethane gives only dioxane (17) (Equation (3)) <86TL2539>. Methylene acetals have been prepared by transacetalization from dimethoxymethane in the presence of an acid and lithium bromide <85CR(B)379>, and (20) was obtained from 2,5-dimethoxy-2,5-dihydrofuran (19) and 1,4-butanediol (Equation (4)) <76MI 911-01>. Vinyl ethers (4) can be used as synthetic equivalents for acyclic acetals <77ZOR467, 79BSF264, 92MI 911-02>. In the Hg(SO₄)₂/acid-catalyzed reaction of ethyne with 1,4-butanediol, the vinyl ether is formed as an intermediate, which immediately reacts further to give 2-methyl-1,3-dioxepane <23JA3115, 48GEP800398>. Benzalation of 1,4-diols under nonacidic conditions was achieved by treatment of benzaldehyde ethylenedithioacetal with triethyloxonium tetrafluoroborate via disulfonium salt (21) (Scheme 3) <75TL4543>.

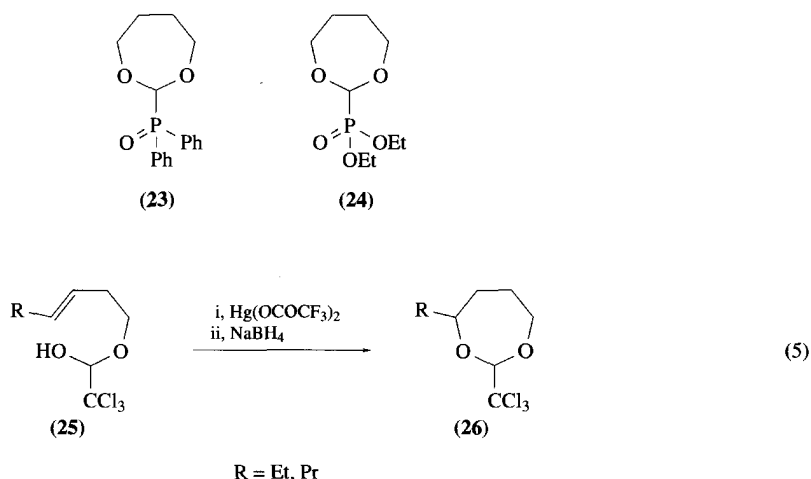




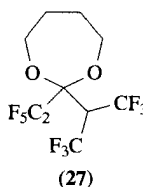
Scheme 3

Functional groups in position 2 or the side chain of substituents in position 2 of a 1,3-dioxepane have been introduced by several methods. Thus, chlorosubstituted acetal (**12**) has been used as precursor for the introduction of the diphenylphosphano group by reaction with LiPPh_2 to give (**12**; $\text{X} = \text{PPh}_2$) <91ZN(B)1519>. 2-Tetrahydrofuryl-1,3-dioxepane (**12**; $\text{X} = \text{tetrahydrofuryl}$) was prepared by hydrogenation of the corresponding furyl derivative (obtained by acetalization of furfural with 1,4-butanediol) <77IZV2132, 77MI 911-01>.

Quaternization of the corresponding 2-dimethylamino-1,3-dioxepanes with methyl iodide and phosphorylation or phosphonylation, respectively, of the intermediate iodoacetals leads to (**23**) and (**24**) <77JPR8>. Mercury(II)-mediated cyclization of hemiacetals of chloral and homoallylic alcohols (**25**) followed by reductive workup affords 2-trichloromethyl-substituted 1,3-dioxepanes (**26**) (Equation (5)) <74JOC1474>. Reaction of diphenyldiazomethane with 1,4-butanediol in the presence of 2,3-dichloro-5,6-dicyanobenzoquinone gives 2,2-diphenyl-1,3-dioxepane <80TL3919, 84JOC4060>.

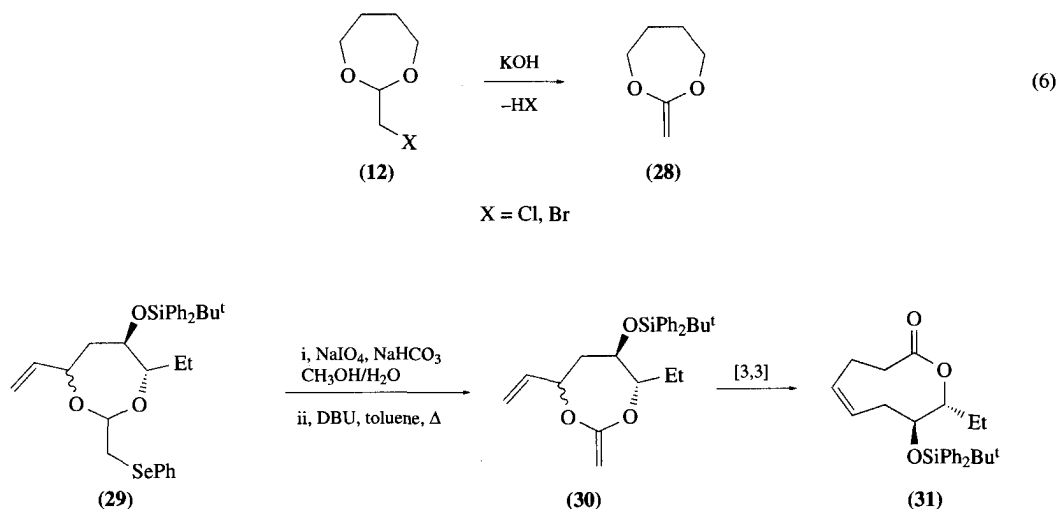


1,3-Dioxepanes have been manufactured by treatment of alkenes in the liquid phase with oxygen and carbon monoxide with $\text{PdCl}_2/\text{CuCl}$ as a catalyst, for example synthesis of (**12**; $\text{X} = \text{CN}$) from acrylonitrile <94JAP06087781>, or by oxidation of alkenes with Th(III) -acetate in 1,4-diols <76BCJ3285>. Treatment of perfluoro(2-methyl-2-pentene) with 1,4-butanediol and triethylamine leads to (**27**) <85NKK1974>.

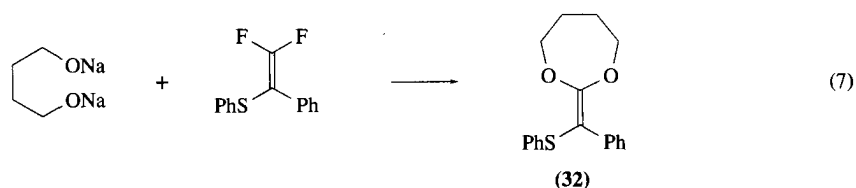


Among 1,3-dioxepanes with an exocyclic double bond, 2-methylene-1,3-dioxepanes (**28**) have been the subject of most interest. They have usually been prepared by dehydrohalogenation of (**12**) (Equation (6)) <92MIP9214722, 92MIP9214723> or phenylselenenoxide elimination, for example preparation of Claisen substrate (**30**) from (**29**) (Scheme 4) <91T7171>. Several improvements for the dehydrohalogenation step have been proposed, for example PTC catalysis <93GEP(O)4231193>, ultrasound irradiation <92SL893> or use of aliquat 336 <95JOC5729>. PTC catalysis seems to be of particular advantage in the synthesis of enantiomerically pure cyclic ketene acetals, as this procedure avoids racemization <93SC1935>. Cyclic ketene acetal (**28**) has also been prepared from acetonitrile

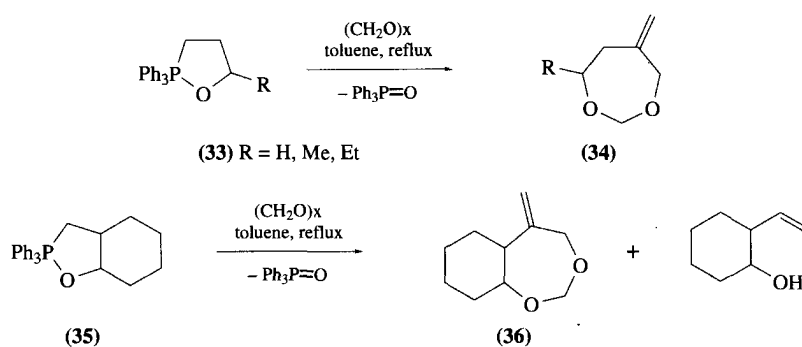
via a Pinner reaction approach <93SC1979>. Exocyclization of β,β -difluoro- α -phenyl vinylsulfide with bidentate heteroatom nucleophiles affords (32) (Equation (7)) <95H(41)641>.



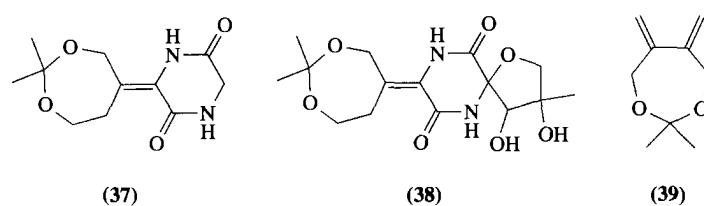
Scheme 4



5-Methylene-1,3-dioxepanes (34) and (36) were prepared by reaction of oxaphosphoranes (33) and (35) with paraformaldehyde (Scheme 5) <93TL4233>. Geometric isomers of compounds (37) and (38) (only (*Z*)-isomer depicted) have found interest in the chemistry of the antibiotic bicyclomycin <78JA6786, 92JOC3662>. Diene (39) was studied in the Diels–Alder reaction with buckminster fullerene <95JOC8330>.



Scheme 5

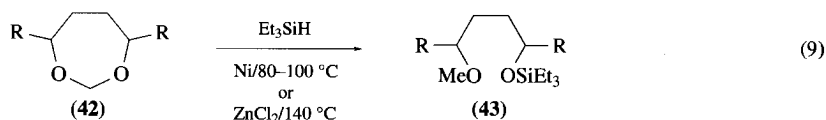
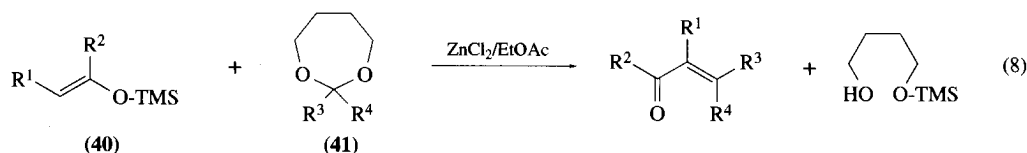


9.11.1.1.2 Reactivity

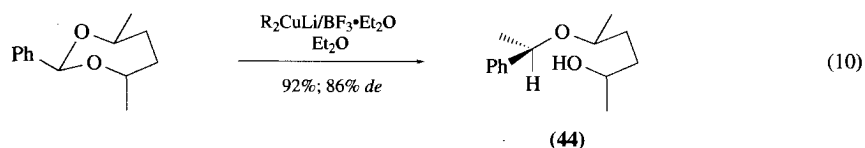
Ring-cleavage reactions are the most typical reactions for 1,3-dioxepanes. They give glycol monoesters on treatment with *t*-butyl hydroperoxide and a ruthenium <92CL2237, 92JAP04283540> or palladium catalyst <83CC1245>, with iodoxy radical and iodine oxide (generated by irradiation of iodine oxide; formed *in situ* with red mercury(II) oxide and iodine) <90JCS(P1)2825>, or by oxidation with hydrogen peroxide and a metal salt <82ZOR1050, 83MI 911-01>. However, orthoesters are formed by anodic oxidation of 1,3-dioxepanyl derivatives of β -ketocarboxylates <81T3131>. Ring opening of 1,3-dioxepanes was also effected with TiCl_4 <83CC705, 85JCS(P1)2093> and dichloro- and trichloroborane <81JCS(P1)1807>.

Treatment with phosphorus pentachloride results in the formation of 4-chlorobutyl acetate <73JOC1173>. 4-Bromobutyl esters are also produced by bromination of 1,3-dioxepane and 2-mono-substituted 1,3-dioxepanes with *N*-bromosuccinimide at 70 °C. Bromination in the side chain occurs only at lower temperatures, or when both 2-positions are substituted <81KGS174>. Use of dioxane-dibromide in dioxane as brominating agent at ambient temperatures predominantly leads to α -bromoalkyl derivatives <77DOK(237)338, 78KGS131>.

Iodomethoxy-iodoalkanes are obtained in the reaction of 2-unsubstituted 1,3-dioxepanes with trimethylsilyl iodide at 80 °C <90ZOB1355>. Reaction of 1,3-dioxepanes (41) with trimethylsilylenol ethers (40) affords α,β -unsaturated ketones and 4-trimethylsilyloxybutanol-1 (Equation (8)) <93ZOB663>, and triethylsiloxy ethers (43) are formed by hydrosilylation of 1,3-dioxepanes (42) in the presence of colloidal nickel or ZnCl_2 (Equation (9)) <82ZOB2284, 84ZOB372>.



1,3-Dioxepanes can be reductively cleaved either by hydrogenation <81GEP(O)2945918>, or with Grignard reagents <87DOK(292)1390>, diisobutylaluminum hydride <83CL1593, 87DOK(293)1133>, and organocopper reagents or cuprate derivatives promoted by boron trifluoride-etherate in ether <84TL3083, 89T507>. In the latter case, hydroxybutyl ether (44) was obtained with 86% *de* probably via an *anti* nucleophilic attack of the reagent from the *si* face with concomitant cleavage of the C—O bond next to the axial methyl group (Equation (10)).

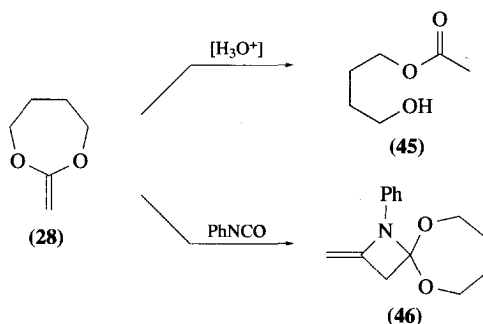


Treatment of 2,2-dimethyl-1,3-dioxepane with carboxylic acids results in the formation of tetrahydrofuran and acetone <61JOC4762>. Acid-catalyzed hydrolysis of methyl-substituted 2,2-diphenyl-1,3-dioxepanes in 80% dioxane-water <95H(40)607> as well as alcoholysis <75ZPK1410> and thiolysis <75MI 911-01, 75ZPK677> of 1,3-dioxepane have been studied. Acetolysis of 2-unsubstituted 1,3-dioxepanes gives hemiacetal acetate products <84JOC4958>.

Besides ring cleavage reactions, 1,3-dioxepanes with a hydrogen in the 2-position undergo dichlorocarbene insertion to give 2-dichloromethyl derivatives <92ZOR1301>. Radical addition to 1-octene gave 1-dodecyl formate, 4-octyl-1,3-dioxepane and 5-octyl-1,3-dioxepane <74CR(C)701>.

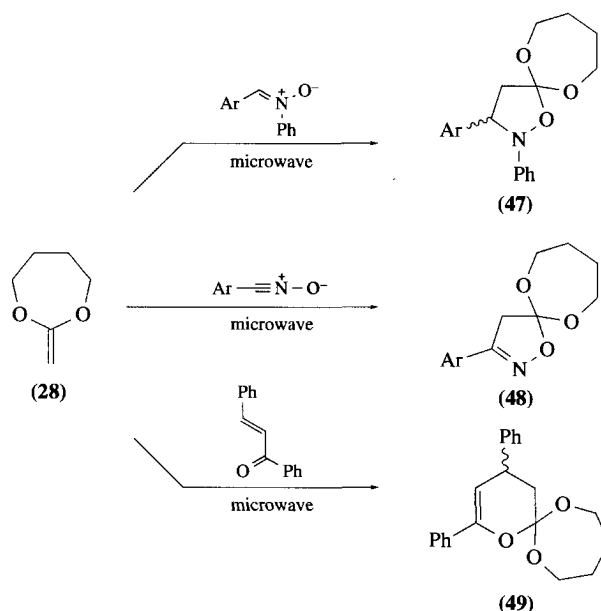
Acid-induced ring opening of 2-methylene-1,3-dioxepanes leads to monoacetylated diols (45) with virtually quantitative monoacetylation selectivity (Scheme 6) <95JOC5729>. Acid-catalyzed addition of methanol gives cyclic orthoacetates <86TL1587>.

2-Methylene-1,3-dioxepane (28) has also found application in 1,3-dipolar and hetero-Diels–Alder cycloadditions in solvent-free conditions under microwave irradiation to give products (47), (48), and (49) (Scheme 7) <94JCS(P1)3595>. Treatment with phenyl isocyanate gives spiro compound (46)



Scheme 6

in quantitative yield (Scheme 6) <88TL2327>. Claisen rearrangement of cyclic ketene acetal (30) affords the nine-membered lactone (31), a key intermediate in the synthesis of naturally occurring obtusenyne (Scheme 4) <91T7171>.



Scheme 7

9.11.1.1.3 Applications

1,3-Dioxepanes have found wide applications in polymerization reactions, for example (only selected examples cited) in cationic copolymerizations with 1,3-dioxacycloalkanes <78MAC959, 88MM870, 89MAC435, 90MM59, 94MI 911-01> and trioxacycloalkanes <79IEC259>. They have been studied in the copolymerization with polyethyleneglycol <89MI 911-01> and siloxanes <83JAP(K)58174412>, and in the synthesis of polyacetals <72MIP903271> and polyformals derived from nitro- and fluorodiols <87JPS(A)805>. 2-Methylene-1,3-dioxepane (28) was copolymerized with acrylic monomers <95JAP07033824>. It gives hydrolyzable polyesters for decomposable plastics in the radical polymerization with styrene <90JAP02214719>. Ring-opening polymerizations of (28) have also been studied <82MI 911-01, 82MM711, 84MI 911-01>. A photosensitive resin composition was obtained from epoxy-diacrylate resin (28), and benzoin isopropyl ether <83EUP95182>. Compound (10; X = Cl) was used as a flameproofing agent for plastics <76USP3984438>.

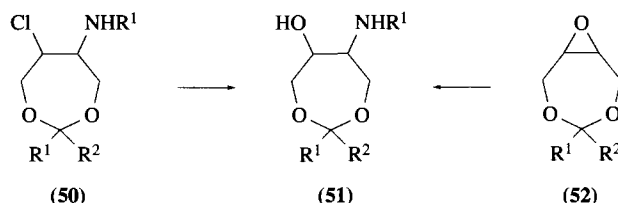
1,3-Dioxepanes have also found applications as herbicides <74GEP(O)2405510, 76USP3940259, 76USP3942972, 76USP3948950, 78USP4110101, 82EUP54278, 83EUP89313, 85GEP(O)3340265, 87GEP(O)3536117, 91EUP434965>, fungicides <84EUP122410, 84GEP(O)3231347, 84GEP(O)3232737, 88JAP(K)63215608>, insecticides and acaricides <76USP3984438, 80USP4230720, 86EUP196524>, pesticides <81PJC2315>, bactericides

<87GEP(O)3542002>, and as a plant sugar enhancer <86GEP(O)3428457>. They have also been used as perfume components <87GEP(O)3539468, 87GEP(O)3603661, 92GEP(O)4104411, 92MI 911-01> and cosmetics <75GEP(O)2331821>, as well as antiinflammatory agents and analgesics <82ZOR1050, 85JAP(K)60097927>. 1,3-Dioxepane was used as component for stabilizers of methyl chloroform <74CP943141, 76USP3935287>.

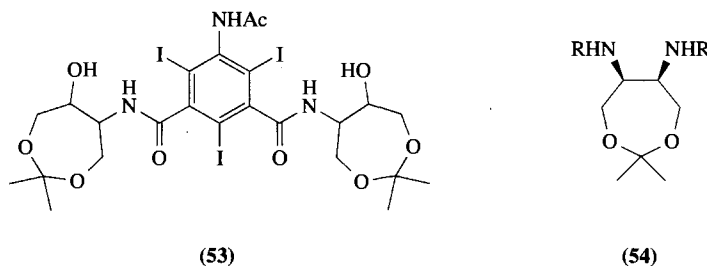
1,3-Dioxepanes have often been used as precursors or intermediates in natural product synthesis, for example in the synthesis of forskolin <88CC167>, (+)-croomine <89JA1923>, diarylbutane lignans <88AJC305>, of analogues of the antiviral acyclonucleoside 9-[4-hydroxy-(3-hydroxymethyl)-butyl]guanine <88JCS(P1)2767> and ribavirin <88MI 911-01>, of carbocycline analogues <87JA7495>, in the synthesis of macrolide antibiotics <86IZV2571>, prostaglandin derivatives <82JA1621>, vitamin B₆ <79LA1657> and pyrimidine compounds <76USP3939181>, multistriatin enantiomers <79MI 911-02>, maytansinoids <76JOC2469>, and nephromopsic acid <91JA4218>.

Diphenylphosphane-substituted 1,3-dioxepane (**12**; X = PPh₂) has been applied in the synthesis of fluxional transition metal complexes with mixed oxygen-phosphane ligands <92ICA237, 93CB1317, 93IC1266, 94ICA165>.

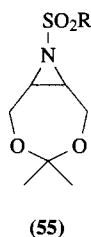
Among 1,3-dioxepanes with hetero substituents in positions 5 and 6, aminoalcohols (**51**; R = alkyl, acyl, sulfonyl) play an important role as precursors for intermediates of nonionic x-ray contrast media <82USP4341756, 87MIP8700757, 91EUP406992, 93EUP573289, 93MIP2037605, 94MIP9422810>, as well as NMR imaging and diagnostic agents <85GEP(O)3328365, 89GEP(O)3809671, 90EUP368429, 93EUP545511, 94USP5284647, 94USP5334371>. Compounds (**51**) can be prepared from chloro precursors (**50**) or 5,6-epoxy-1,3-dioxepanes (**52**) (Scheme 8), which in turn have been synthesized from 4,7-dihydro-1,3-dioxepins (cf. Section 9.11.1.2.2). Structure (**53**) is a representative example for an intermediate of such contrast media <81EUP33426>. Diamino derivatives (**54**; R = H, sulfonyl) have also found application in the preparation of diagnostics <91EUP438206> and for the synthesis of catalysts for asymmetric epoxidation <94MIP9403271>.



Scheme 8



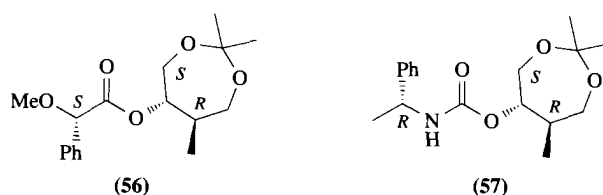
Furthermore, derivatives of (**51**) were used as intermediates for drugs <82EUP56575, 93JAP(K)05058995> and bactericides <87GEP(O)3542002>, and they have been used as intermediates for the synthesis of (+)-biotin <83IJC(B)419>. *cis*-Platin complexes with (**54**; R = H) as a ligand exhibit significant antitumor activity <89JMC742>, and azidirinyldioxepanes (**55**) have been tested for hypoglycemic activity <93MIP9304067, 93TL3639>.



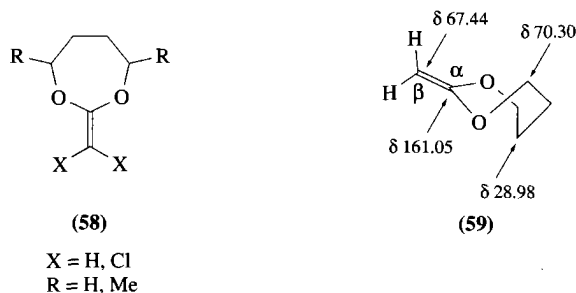
9.11.1.1.4 Stereochemistry and physical properties

The conformational analysis of diastereomers of 2,4- and 4,7-disubstituted 1,3-dioxepanes <73JOC3971> and of bicyclic derivative (**9**; X = H) <76BSF307> by ^1H and ^{13}C NMR spectroscopy, and the conformational analysis of 2,4,7-trisubstituted 1,3-dioxepanes have been described <81JA936>. It has been shown that 1,3-dioxepanes can adopt a large number of conformations from which the four twist-chair conformations are preferred. For the 2,4,7-trisubstituted 1,3-dioxepanes qualitative evidence about the nature of the major conformations can be obtained from the ^{13}C NMR spectra. It has been shown that due to the 1,3- and 4,7-diaxial steric interactions (Me-H or Me-Me) the most stable twist-chair conformations depend on the largest number of equatorial substituents <81JA936>. The suggestion was made that 1,3- and 4,7-diaxial steric interactions should be more severe for the 1,3-dioxepanes than for the corresponding carbocyclic compounds <73JOC3971>.

The absolute configuration of (5*R*,6*S*)-2,2,5-trimethyl-6-hydroxy-1,3-dioxepane was determined by x-ray crystallography and NMR spectroscopy of its *O*-methylmandelate ester (**56**) <86JOC2370> or (1-phenylethyl) carbamic ester (**57**) <79MI 911-02>.



The relative configuration of the diastereomers of 4,7-dimethyl-2-methylene-1,3-dioxepane (**58**; R = Me, X = H) has been determined <92JOC3662, 92MIP9214722>. From ^{13}C NMR chemical shifts in comparison to other acyclic and cyclic ketene acetals, a twist-chair conformation was delineated for 2-methylene-1,3-dioxepane (**59**), though the O—C—O end of this compound is probably more flattened than the corresponding hydrocarbon <78T2365>. Dipole moment measurements of (**59**) and the dichloro derivative (**58**; X = Cl, R = H) support these suggestions <79T547>.

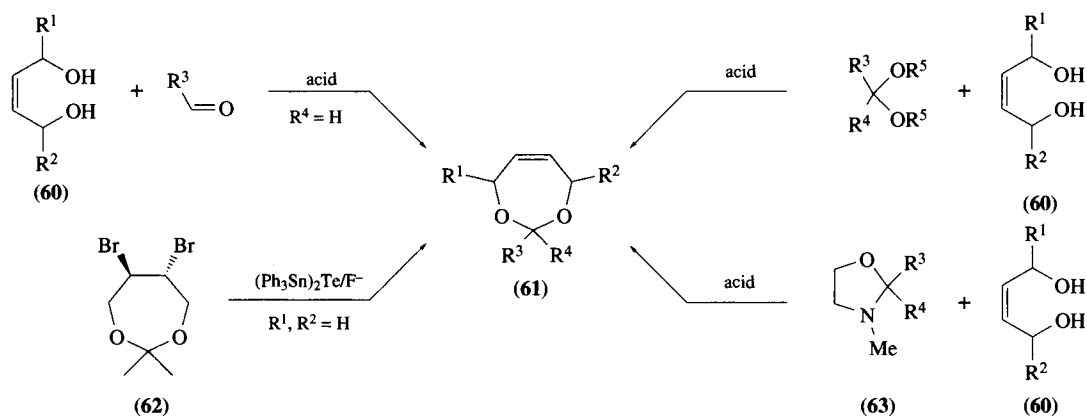


9.11.1.2 4,7-Dihydro-1,3-dioxepins

9.11.1.2.1 Synthesis

Similar to the synthesis of 1,3-dioxepanes (**1**), 4,7-dihydro-1,3-dioxepins (**61**) are readily prepared by acetalization of carbonyl compounds and (*Z*)-2-buten-1,4-diol (**60**) in the presence of an acid <56JOC1366, 70USP3410871, 72USP3635958, 72USP3652594, 72USP3658846>, a cation exchange resin <80CB1472>, clay minerals <75BSF2558> or boron trifluoride etherate <85JOC2004> (Scheme 9).

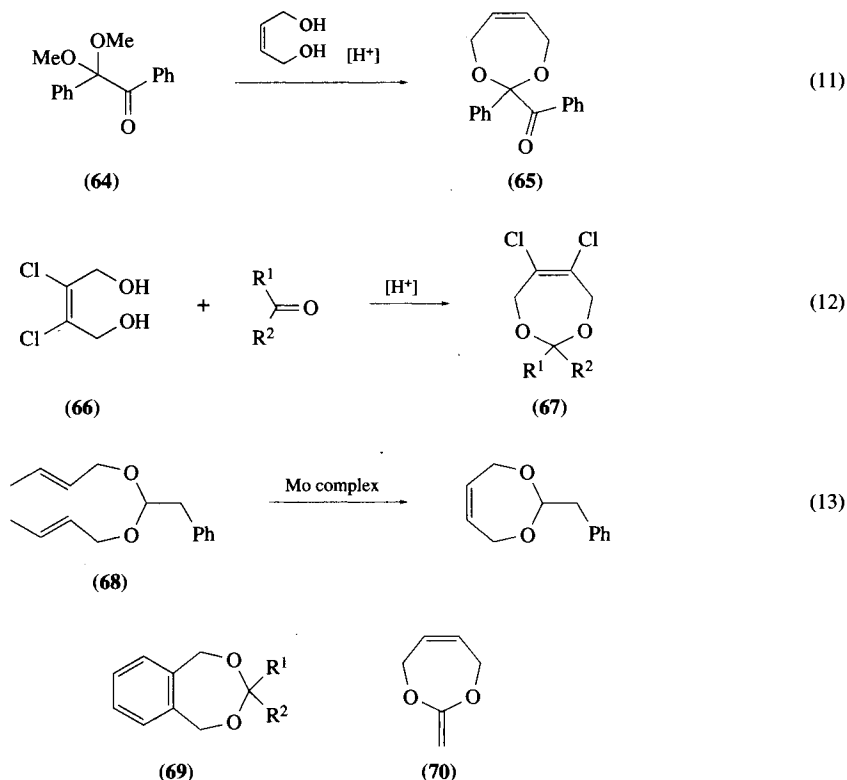
Due to the (*Z*)-geometry of the diol, aldehydes give generally high yields; however, for ketones the transacetalization procedure between (**60**) and an acyclic acetal is superior with respect to the reaction rate and yield <73USP3738997, 83JAP(K)58134087, 84JOC1985>. *In situ* transacetalization by reaction of a ketone, an unsaturated 1,4-diol and orthoformate together with an acidic catalyst is particularly advantageous <75BSF2558>. Aldehydes can also be reacted with 1,4-diols, an acid and simple alcohols. This procedure primarily leads to mixed acetals, which dismute on heating to give dioxepanes <74S23, 74USP3769303>. *N,O*-Acetal (**63**) has been used for transacetalization instead of an acyclic acetal <80URP771099>. Bis(triphenylstannyl)telluride coupled with fluoride has proved to



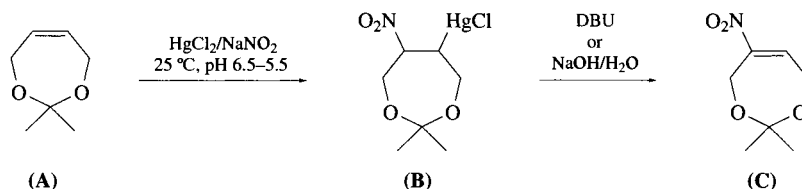
Scheme 9

be a mild debromination reagent, which converts *trans*-5,6-dibromo-1,3-dioxepane (62) to (61; $R^1, R^2 = H$) in high yield (90TL6291).

2-Benzoyl-2-phenyl-4,7-dihydro-1,3-dioxepin (65) was prepared by treatment of a slurry of benzil mono-dimethyl acetal (64) in (Z)-2-buten-1,4-diol with *p*-toluenesulfonic acid at 50–70°C under continuous removal of methanol *in vacuo* (Equation (11)) (84GEP(O)3226617). 5,6-Dichloro-4,7-dihydro-1,3-dioxepins (67) have been obtained from diol (66) and aldehydes or ketones (Equation (12)). The synthesis of the starting diol (66) was achieved by reduction of dichloromaleic anhydride with LAH (80KGS19). A more extraordinary route to 4,7-dihydro-1,3-dioxepins is the ring-closing metathesis of diene (68) with $Mo(CHCMe_2Ph)(NAr)(OCMe(CF_3)_2)_2$ ($Ar = 2,6-(Pr^i)_2C_6H_3$) as the metathesis catalyst (Equation (13)) (92JA5426). Benzodioxepins (69) were obtained by acetalization of 1,2-bis(hydroxymethyl)benzene (78JA4055). 2-Methylene-4,7-dihydro-1,3-dioxepin (70) was prepared in the usual manner by dehydrohalogenation of the corresponding 2-bromomethyl derivative with potassium *t*-butoxide and aliquat 336 (91TL1539) or the chloro derivative with alkali (83JAP(K)58154575).



5-Nitro-4,7-dihydro-1,3-dioxepins (C) are available by a two-step reaction sequence, i.e. nitromercuration with mercuric chloride and sodium nitrite in aqueous solution of pH 6.5 to 5.5 (phosphate buffer), followed by base-catalyzed conversion of the nitromercurials to nitro alkenes with aqueous sodium hydroxide or DBU (Scheme 10) <78JA6294>.

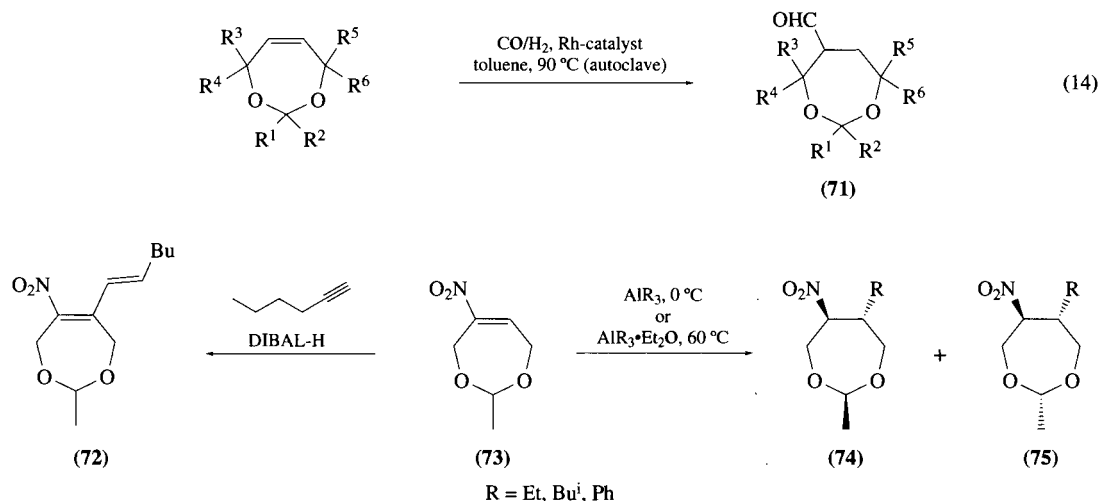


Scheme 10

5-Nitro-4,7-dihydro-1,3-dioxepins have also been obtained by treatment of the corresponding 4,7-dihydro-1,3-dioxepins with NO_2Cl and dehydrochlorination of the 5-chloro-6-nitro intermediates <78CCA259>.

9.11.1.2.2 Reactivity

Typically, 4,7-dihydro-1,3-dioxepins undergo addition reactions, for example addition of bromine or chlorine to give (62) or the corresponding dichloro compound <57JOC662, 84CCA281>. Hydroformylation of 4,7-dihydro-1,3-dioxepins yielded 5-formyl-1,3-dioxepanes (71) (Equation (14)) <87GEP(O)3539468>, and reaction of nitrodioxepins (73) with triorganoalanes or the corresponding etherate gave a diastereomeric mixture of (74) and (75) (Scheme 11) <88JOC45>. In the reaction of diisobutylalkenylalanes, prepared *in situ* from terminal alkynes and dibal, with nitrodioxepins (72), only the unsaturated group is transferred to the double bond to give (72) <87T5411>.

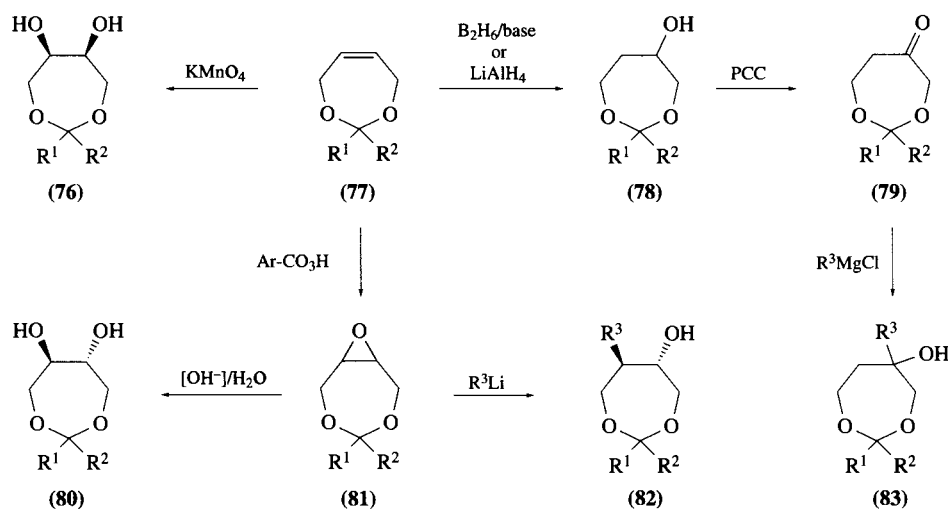


Scheme 11

The *cis*-diols (76) have been obtained stereoselectively by permanganate oxidation of (77) at pH 7 (Scheme 12). Alternatively, *trans*-diols (80) are available by base-catalyzed ring opening of the epoxide (81) <75CR(280)681>. Treatment of epoxide (81) with lithium dimethylcuprate <75TL2643, 76JOC2469> gave alcohols (82) with substituents in position 6 of the dioxepane ring. The 6-unsubstituted alcohols (78) were prepared by reaction of (77) with diborane and a base <75CR(280)681> or LAH <92JOC3662>. Pyridinium dichromate <92JOC3662> or pyridinium chlorochromate oxidation <75CR(280)681> of the latter alcohol and Grignard reaction of the cyclic ketone (79) then gave alcohol (83).

The epoxides (81) themselves have been synthesized by treatment of 4,7-dihydro-1,3-dioxepins (77) with *p*-nitro- <75BSF1763> or *m*-chloroperbenzoic acid <75TL2643> or $\text{HOCl}/\text{H}_2\text{O}_2$ <81EUP33426>. Alternatively, hexafluoroacetone/hydrogen peroxide in disodium hydrogen phosphate buffered

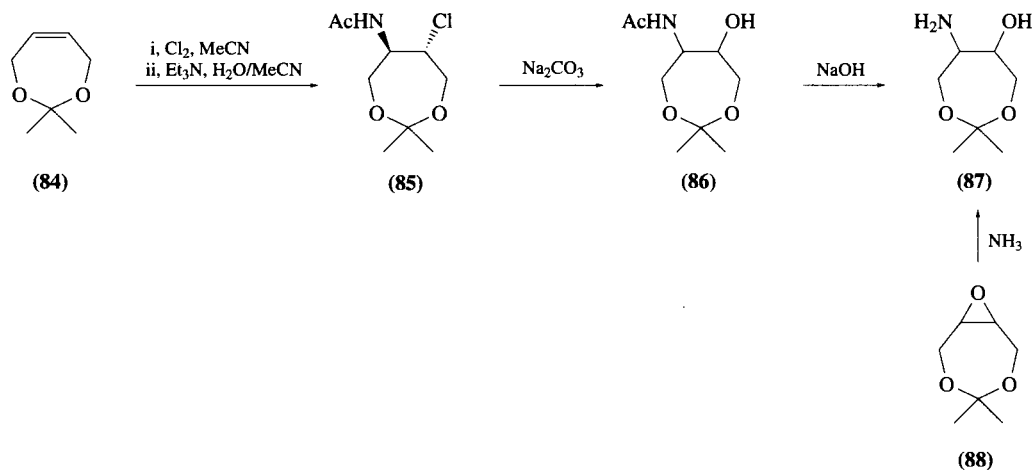
1,3-Dioxepanes, 1,3-Oxathiepanes, and 1,3-Dithiepanes



Scheme 12

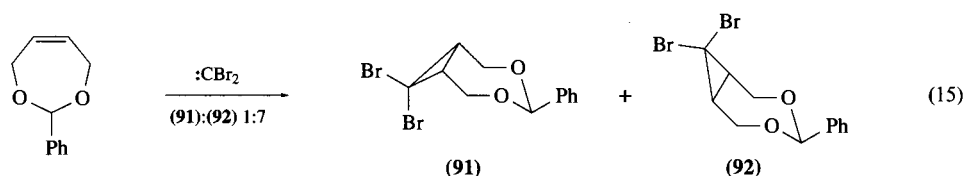
solution was proposed as a catalytic epoxidation system for 4,7-dihydro-1,3-dioxepins <80S810>; however, use of 90% H_2O_2 makes this variation problematic.

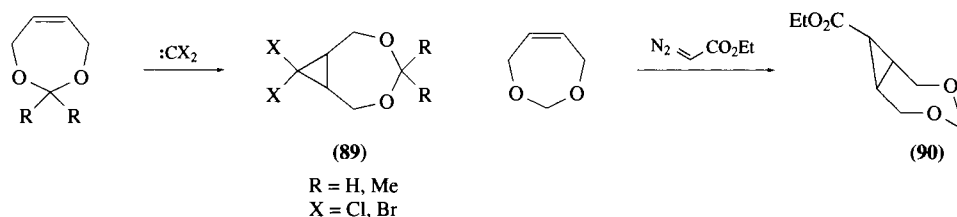
Aminoalcohols (**87**), important intermediates in the synthesis of x-ray contrast media, can be prepared either by reaction of 4,7-dihydro-1,3-dioxepins with chlorine in acetonitrile and treatment of the *N*-acyl derivative (**85**) with Na_2CO_3 and 50% NaOH <83USP4389526> (cf. also <92OPP536>) or by ring opening of epoxides (**88**) with NH_3 , amines or azides <81EUP33426> (Scheme 13). For the phenylselenofluorination of 4,7-dihydro-1,3-dioxepins <90TL663>.



Scheme 13

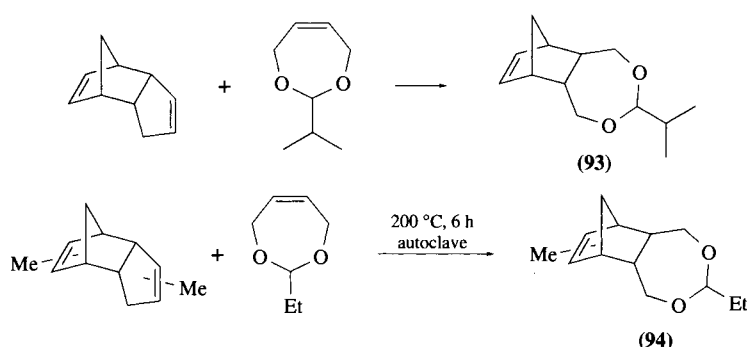
4,7-Dihydro-1,3-dioxepins undergo [2 + 1] cycloaddition reactions with dihalogencarbene <75BSF1763, 76JA4158, 94CB1137> and ethyl diazoacetate <82CB201> to give cyclopropanes (**89**) and (**90**), respectively (Scheme 14). Reaction of 2-phenyl-4,7-dihydro-1,3-dioxepin with dibromocarbene affords a 7 : 1 diastereomeric ratio of the *endo* and *exo* cycloadducts (**91**) and (**92**) (Equation (15)) <93ZOR1885>.





Scheme 14

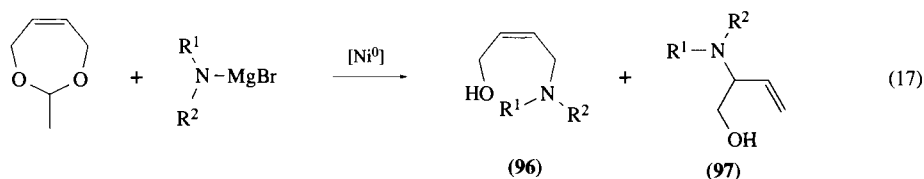
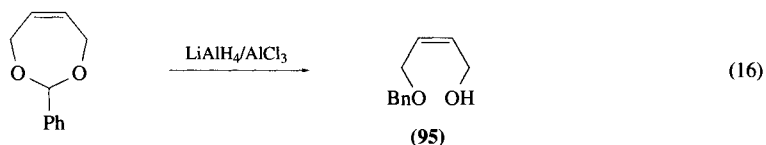
Diels–Alder reaction of 4,7-dihydro-1,3-dioxepins with cyclopentadiene dimers leads to bicyclic 1,3-dioxepanes, for example formation of (93) and (94) (Scheme 15) <80GEP(O)2918168, 83GEP(O)3204627>.



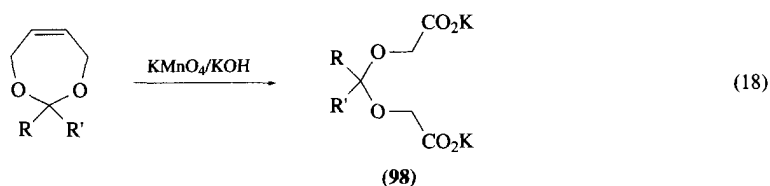
Scheme 15

The [2 + 2] and 1,3-dipolar cycloaddition reactions with several heterocycles and ketene insertion reactions have also been studied <72LA(755)177, 75MI 911-02, 77JHC81, 84MI 911-02, 84TL2731, 85CCCC1982, 87MI 911-02, 91MI 911-01>.

Reductive ring cleavage, for example, the synthesis of monoprotected diol (95) from 2-phenyl-4,7-dihydro-1,3-dioxepin, has been effected with LAH in the presence of aluminum trichloride (Equation (16)) <81TL3919, 90JCS(P1)1375> or with LAH in CH₂Cl₂/ether <95JOC6937>. Secondary halogen magnesioamides react with dioxepins in the presence of catalytic amounts of Ni⁰ to give a mixture of allylaminoalcohols (96) and homoallylaminoalcohols (97), which arise either from α- or γ-substitution (Equation (17)) <94T12953>. Similarly, 2-methyl-4,7-dihydro-1,3-dioxepin gives α- and γ-alkylation products on treatment with Grignard reagents and catalytic amounts of NiDppeCl₂ <89G69, 92G45>. Fragmentation of 2-monosubstituted 4,7-dihydro-1,3-dioxepins with BuLi gave crotonaldehyde enolate, which could be trapped with TBDMS-Cl or benzyl bromide <84TL4647>.

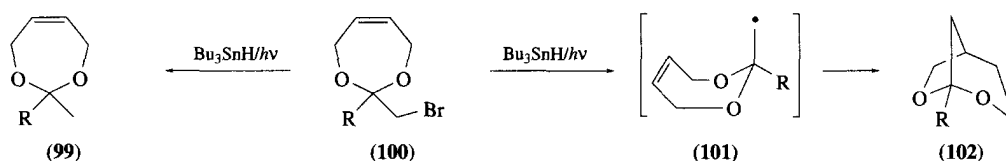


The double bond of 4,7-dihydro-1,3-dioxepins has been cleaved by permanganate oxidation in aqueous potassium hydroxide solution at 0 °C to give the potassium bis(carboxymethyl) acetals (98), which can be used as substitutes for phosphate in detergent formulation <81S612>.



2-Halomethyl-4,7-dihydro-1,3-dioxepins undergo transannular cyclization on treatment with tributyltin hydride; however, the reaction pathway strongly depends on the substitution pattern of the substrate. Simple reduction to **(99)** occurs for **(100; R = H)**, probably because of the inaccessibility of the axial boat conformation **(101)** (Scheme 16). For **(100; R = Me, Ph)** the dioxabicyclo-[3.2.1]octanes **(102)** were obtained in 46–48% yield together with 12% of the dioxepin **(99)** <93JCS(P2)871>.

Other typical reactions are double-bond isomerization and Heck reaction, which lead to 4,5-dihydro-1,3-dioxepins (cf. Section 9.11.1.3).



Scheme 16

9.11.1.2.3 Applications

4,7-Dihydro-1,3-dioxepins have found wide application in polymerization reactions. They gave polyacetals on copolymerization with trioxane <88MI 911-02, 89EUP337755, 90MAC99>. The bulk polymerization of 4,7-dihydro-1,3-dioxepin was initiated with borontrifluoride etherate <81MAC585>. The free-radical polymerization of 4,7-dihydro-1,3-dioxepin and derivatives thereof with maleic anhydride affords a 1 : 1 alternating copolymer, whereas the cationic copolymerization with maleic anhydride gave oligomers <81MM471, 82MI 911-02>. Copolymerization of 2,2-dimethyl-4,7-dihydro-1,3-dioxepin with maleic anhydride and/or maleimides gave polymers that are useful as curing agents for epoxy resins <83USP4384093>. Copolymers of 2-isopropyl- <93PJC433> and particularly 2-cyclohexyl-4,7-dihydro-1,3-dioxepins with maleic anhydride exhibit antitumor activities <82MI 911-03, 90PP464, 91MI 911-02>. In contradiction to the traditional mechanism, the radical ring-opening polymerization of 2-methylene-4,7-dihydro-1,3-dioxepin proceeds exclusively via the 1,2-addition mechanism <88PP410>. 2-Benzoyl-2-phenyl-4,7-dihydro-1,3-dioxepin **(65)** has found application as a nonyellowing initiator of photochemical curing and polymerizations <84GEP(O)3226617>. 4,7-Dihydro-1,3-dioxepin was used as a stabilizing agent for 1,1,1-trichloroethane <69GEP(O)1817488>.

4,7-Dihydro-1,3-dioxepins were applied as herbicides <72USP3635958, 72USP3652594, 76USP3966768> and fungicides <84GEP(O)3232737>. 2-Mono- <74USP3822291, 75USP3905919, 76MI 911-02, 76USP3953614>, 2,2-di- <74GEP2407863, 74USP3822290, 76USP3936398> and 4,7-di- and tetrasubstituted 4,7-dihydro-1,3-dioxepins <87GEP(O)3539467> have found interest as perfumes and fragrances as well as emollients <80EUP12543>. They played an important role in the synthesis of vitamin B₆ and related compounds <70JAP45011906, 70USP3525749, 73GEP(O)2143989, 75MI 911-02>.

9.11.1.2.4 Stereochemistry

In comparison to the fully saturated 1,3-dioxepane system, the number of possible conformations for 4,7-dihydro-1,3-dioxepins is reduced because of the *sp*² hybridization at carbons 5 and 6 <76BSF307>. There are two chair, two twist and two boat conformations. NMR spectroscopic data indicate a rapid equilibrium between the chair and the twist conformations. It has also been shown that the conformational ratio strongly depends on the substitution pattern in positions 2, 4, and 7 <65MI 911-01, 75JOC450, 86ZOB144, 95HCA2148>. The most stable conformation of benzodioxepins was determined by low-temperature NMR measurements <81CJC2283>. Evidence for a twist–chair con-

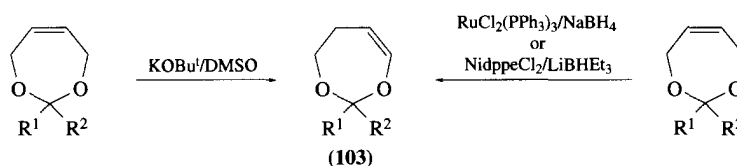
formation was also obtained from dipole moment measurements as well as IR and Raman spectra <80IZV1794, 81IZV1030>.

For 2-*p*-nitrophenyl-5,6-dichloro-4,7-dihydro-1,3-dioxepin, a twist-chair conformation in the crystalline state was obtained by x-ray crystallography <83ZOB132>.

9.11.1.3 4,5-Dihydro-1,3-dioxepins

9.11.1.3.1 Synthesis

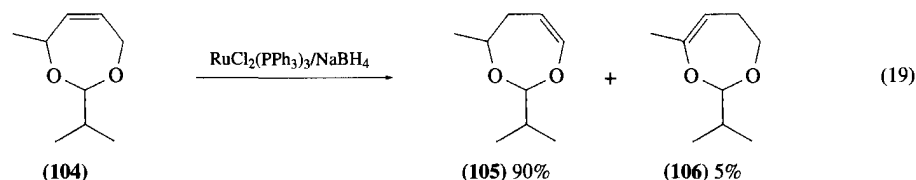
Two major routes for the synthesis of 4,5-dihydro-1,3-dioxepins (**103**) from 4,7-dihydro-1,3-dioxepins as substrates are available, i.e. double-bond isomerization and the Heck reaction (Scheme 17).



Scheme 17

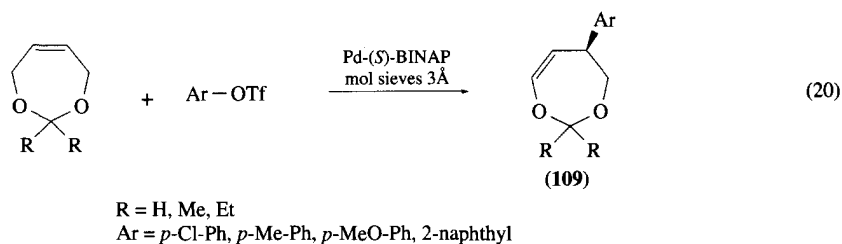
The double-bond isomerization can be effected either under basic conditions with potassium *t*-butoxide in DMSO <71CR(C)1655, 80CB1472> or with transition metal complexes, particularly rhodium and hydridic ruthenium complexes, generated *in situ* by treatment of the corresponding dichloro precursors $\text{RuCl}_2(\text{PPh}_3)_3$ <85LA1951> or $\text{RuCl}_2(\text{PPh}_3)_4$ <86USP4574158> with sodium borohydride. The $\text{RuCl}_2(\text{PPh}_3)_3/\text{NaBH}_4$ system has proved to proceed under milder conditions.

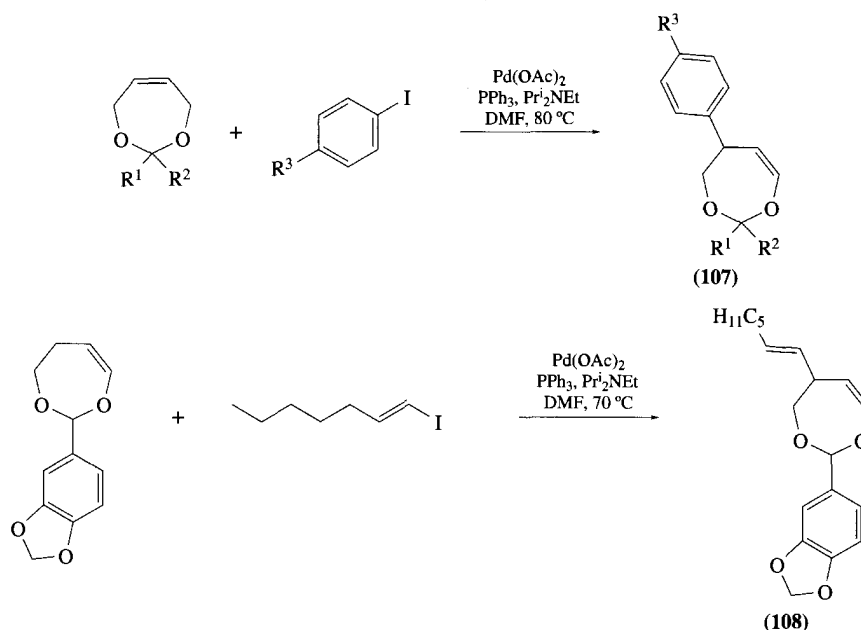
High regioselectivity has been observed in the double-bond isomerization of diastereomers of 2,4-substituted 4,7-dihydro-1,3-dioxepins with ruthenium complexes. Thus, isomerization of 4,7-dihydro-1,3-dioxepin (**104**) afforded mainly 4,5-dihydro-1,3-dioxepin (**105**), whereas the the regioisomer (**106**) is only formed to a small extent (Equation (19)) <87JOC2707>.



A nickel complex was used for the flash isomerization of 4,7-dihydro-1,3-dioxepins <95TL1133>. This method is limited to 2-monosubstituted 4,7-dihydro-1,3-dioxepins. The Pd-catalyzed double-bond isomerization has also been reported <84CCA405>, and the asymmetric double-bond isomerization with $\text{Ru}_2\text{Cl}_4(\text{diop})_3$ and $[\text{Rh}(\text{cod})\text{Cl}]_2/\text{diop}$, respectively, as a catalyst has been investigated, which leads to enantiomerically enriched 4,5-dihydro-1,3-dioxepins <86AG261>. However, the *ee* values obtained are poor (3–25% *ee*).

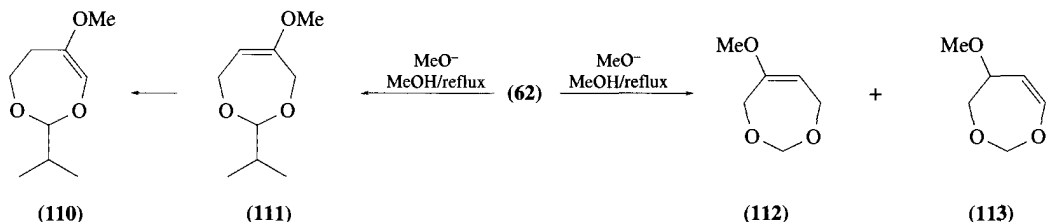
The Heck reaction with palladium acetate, as a catalyst, gave arylated and vinyated products (**107**) and (**108**), respectively (Scheme 18) <93H(36)2437, 93SL785, 94TL7989>. The asymmetric variation of this method using Pd-(*S*)-BINAP, as a catalyst, afforded enantiomerically enriched 5-aryl-4,5-dihydro-1,3-dioxepins (**109**) (Equation (20)) <94TL1227>. Use of molecular sieves has proved to be important for the enantiomeric excess.



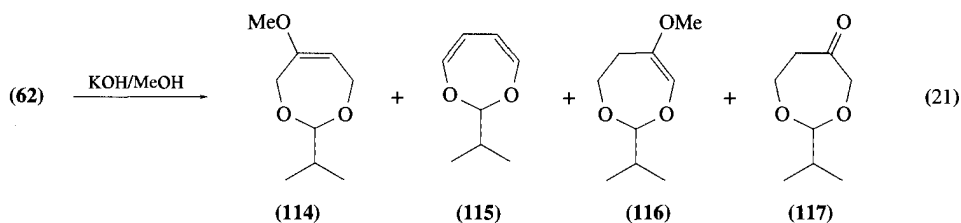


Scheme 18

Other routes to 4,5-dihydro-1,3-dioxepins involve dehydrobromination of bromo-substituted dioxepanes, but discrepancies arose for these reactions with respect to the product formation. Thus, it has been reported that reaction of *trans*-5,6-dibromo-4,7-dihydro-1,3-dioxepin (**62**) with sodium methoxide affords a mixture of bromodioxepin (**112**) and 5-methoxy-4,5-dihydro-1,3-dioxepin (**113**) (Scheme 19) <56JOC1366>. Alternatively, the same reaction led to methoxydioxepin (**111**), which spontaneously isomerized to give 6-methoxy-4,5-dihydro-1,3-dioxepin (**110**) <84CCA281>. Reaction of (**62**) with KOH in methanol yielded a mixture of (**114**) as the main product together with diene (**115**) and smaller amounts of products (**116**) and (**117**) (Equation (21)) <84CCA281>.

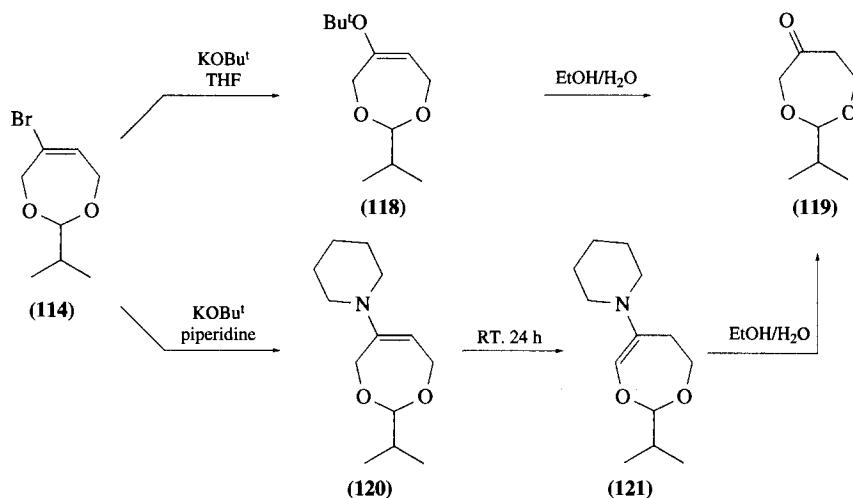


Scheme 19

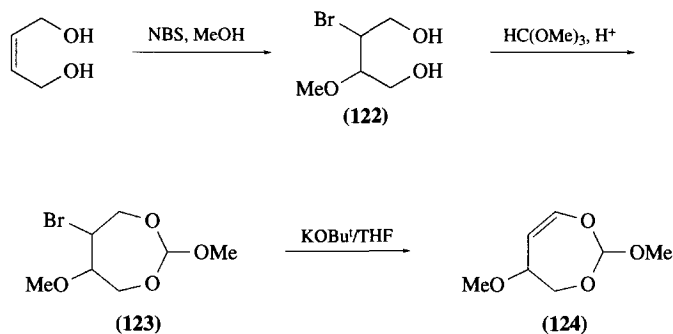


Treatment of 5-bromo-4,7-dihydro-1,3-dioxepin (**114**) with stronger bases, for example potassium *t*-butoxide, gave substitution product (**118**), but when the reaction with potassium *t*-butoxide was carried out in the presence of piperidine, the piperidinyl derivative (**120**) was obtained, which isomerized on standing at room temperature to give (**121**) (Scheme 20) <84CCA281>. Dehydrobromination of bromodioxepane (**20**) with potassium *t*-butoxide in THF afforded regioselectively 5-methoxy-4,5-dihydro-1,3-dioxepin (**124**) (Scheme 21) <95SL175>.

4,5-Dihydro-1,3-dioxepins (**125**), (**126**), and (**128**) have been obtained by cross-coupling of 1,3-



Scheme 20



Scheme 21

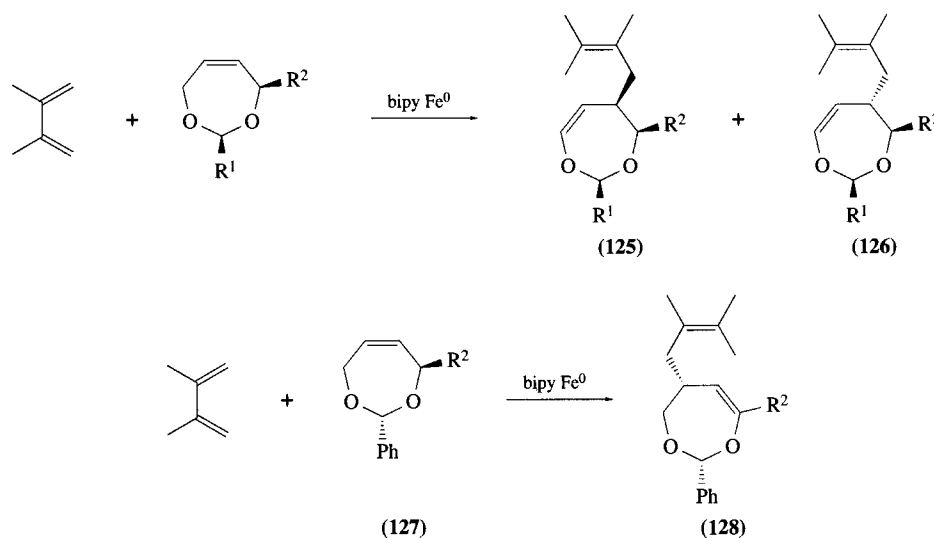
alkadienes with 2,4-substituted 4,7-dihydro-1,3-dioxepins via a formal iron(0)-catalyzed [4 + 4]ene reaction (Scheme 22) <87JA2542>. These reactions proceed with high diastereoselectivities yielding predominantly the *cis* products (125). The regiochemistry depends on the relative configuration of the substrates. Homochiral 2,4-disubstituted 4,7-dihydro-1,3-dioxepins have also been used for these cross-coupling reactions. The ligands as well as the substituents in the 2-position of the acetal are critical for these reactions.

9.11.1.3.2 Reactivity, stereochemistry, and applications

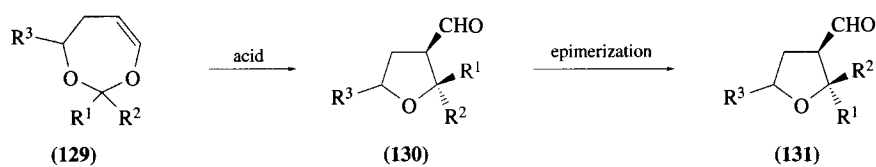
The dihydro-1,3-dioxepin-tetrahydrofurancarbaldehyde rearrangement is the most typical reaction for 4,5-dihydro-1,3-dioxepins. The rearrangement has been induced by a Brønsted <80CB1472, 80GEP(O)2901644> or Lewis acid <82CB2728, 85LA1951, 86USP4574158, 87JOC2707>. Rearrangement with Lewis acids under kinetically controlled conditions leads primarily to tetrahydrofuran-3-carbaldehydes (130; R² = H) with a 2,3-*cis* relationship, which can be epimerized to give the *trans* derivatives (131; R² = H) (Scheme 23). Rearrangement of 2,4-dimethoxy-4,5-dihydro-1,3-dioxepin (124) with silica gel in refluxing benzene gave dihydrofurans (132) and (133), which both have been transferred to 3-formylfuran (134) (Scheme 24) <95SL175>. The rearrangement of 4,5-dihydro-1,3-dioxepins has found wide application in natural product synthesis, for example the synthesis of racemic quercus lactones <85LA1951>, eldanolide <86T1135>, and γ -butyrolactones <93H(36)2437>.

Rearrangement of 4,5-dihydro-1,3-dioxepins with triisobutyl aluminum or dibal gave 3-hydroxymethyltetrahydrofurans, for example formation of (135) and (136) (Scheme 25) <91G17, 93SL785>. In this case, the *trans*-diastereomers predominate, and even at -78°C a 1 : 1 mixture was obtained <93SL785>.

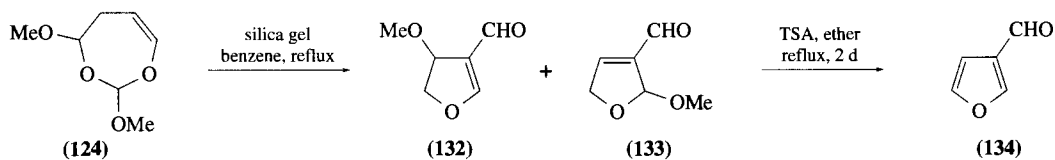
Hydrogenolytic cleavage of 4,5-dihydro-1,3-dioxepin (107) with sodium metal in liquid ammonia



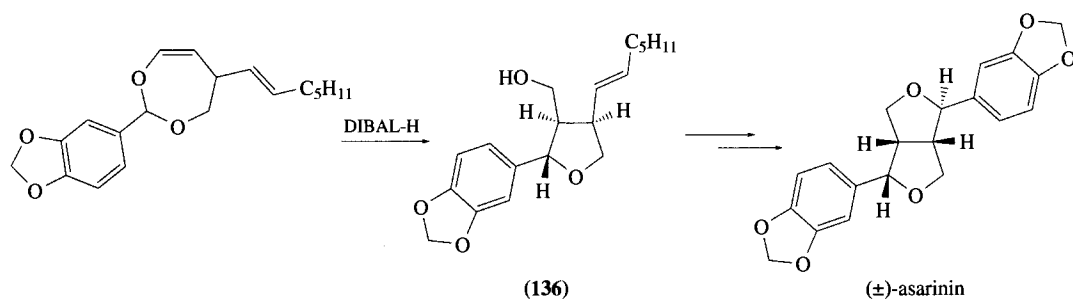
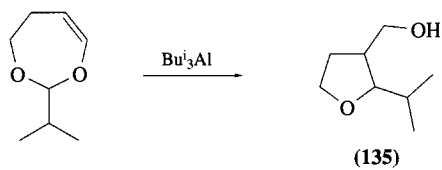
Scheme 22



Scheme 23

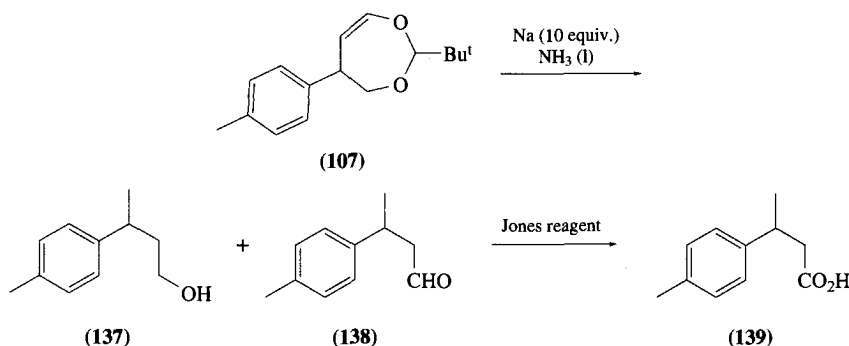


Scheme 24

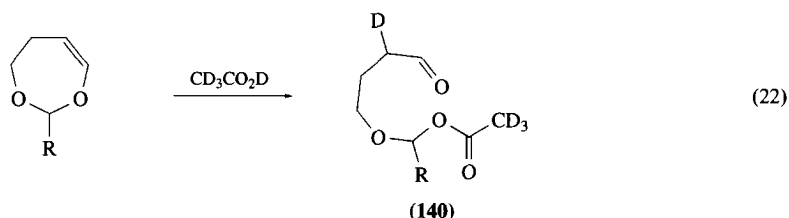


Scheme 25

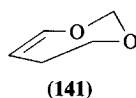
yielded a mixture of alcohol (**137**) and aldehyde (**138**), which both have been transformed to Rupe's acid (**139**) by oxidation with Jones reagent (Scheme 26) <93SL393, 94TL7989>. Acetolysis of 4,5-dihydro-1,3-dioxepins with $\text{CD}_3\text{CO}_2\text{D}$ gave ring-opened products (**140**) (Equation (22)) <82CB2728>.



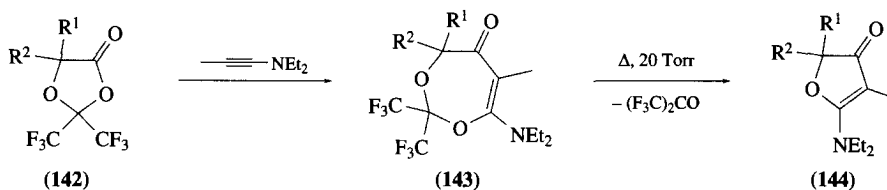
Scheme 26



From NMR spectroscopic data and theoretical calculations, the chair conformation (**141**) has been deduced as the preferred conformation of 4,5-dihydro-1,3-dioxepins <94ZN(A)714>.



4,5-Dihydro-1,3-dioxepin-5-ones (**143**), which have been prepared from (**142**) by ring enlargement with ynamines, undergo thermolytic cycloelimination of hexafluoroacetone to give furanones (**144**) (Scheme 27) <75TL3223, 78LA1037, 78LA1052>. 4,5-Dihydro-1,3-dioxepins have found interest in the copolymerization with maleic anhydride <83USP4384093>.



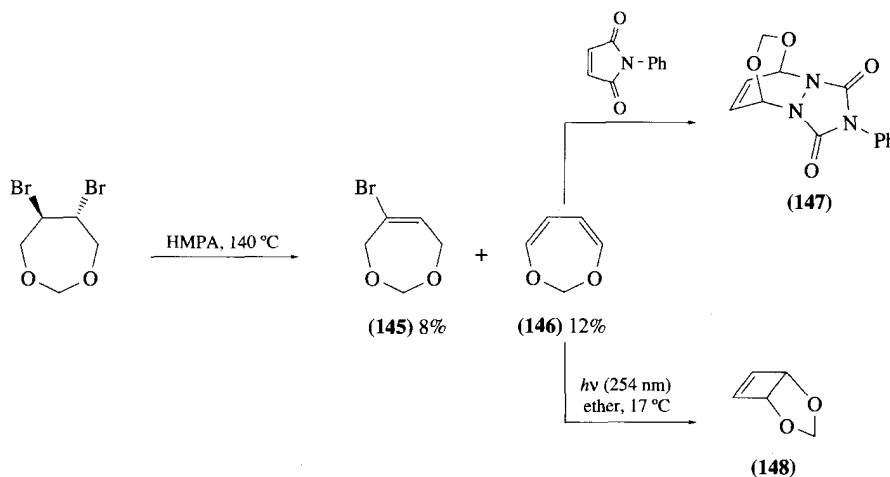
Scheme 27

9.11.1.4 1,3-Dioxepins

9.11.1.4.1 Synthesis and reactivity

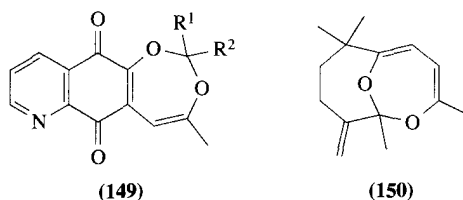
Less is known about 1,3-dioxepins. The 2-isopropyl derivative (**115**) was isolated as a by-product in the dehydrobromination of *trans*-5,6-dibromo-1,3-dioxepanes with potassium hydroxide in meth-

anol <84CCA281>. The parent member of this class of compounds, 1,3-dioxepin (**146**), was obtained by treatment of *trans*-5,6-dibromo-1,3-dioxepane with HMPA at 140°C for 4 h (Scheme 28) <76TL2113>. It gave a Diels–Alder adduct (**147**) with 4-phenyl 1,2,4-triazoline-3,5-dione, and irradiation led to cyclobutene derivative (**148**).



Scheme 28

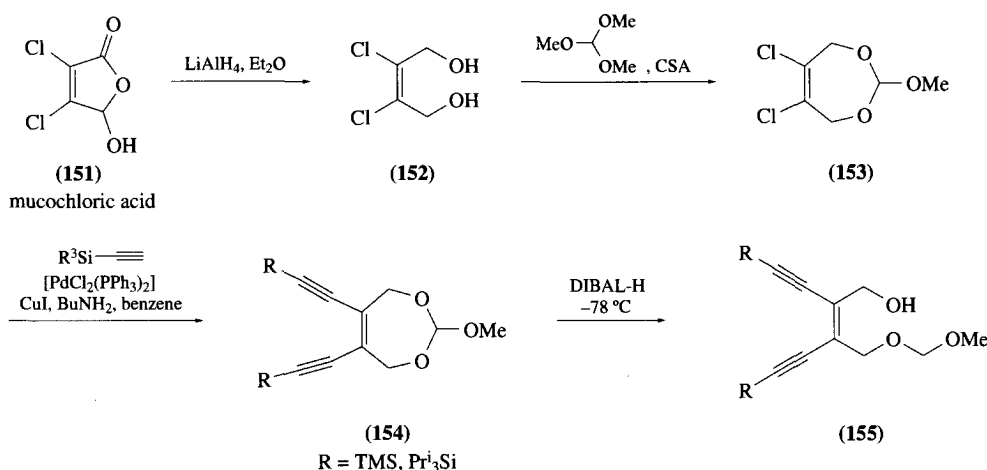
Moreover, dioxepin (**149**) has been prepared by a photochemical reaction of 6-alkoxy-7-(2-oxoalkyl)quinoline-5,8-quinone via intramolecular hydrogen abstraction <93H(36)1477>, and bicyclic 1,3-dioxepin (**150**) was prepared, and its PE spectra have been studied <95HCA2148>.



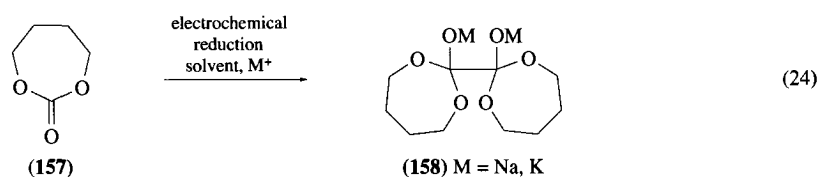
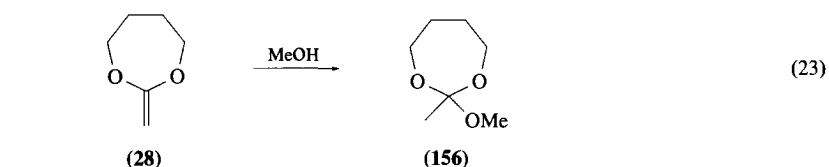
9.11.1.5 Seven-membered Cyclic Orthoesters and Carbonates

The methods of preparation and the reactivity of 2-alkoxy-, 2,2-dialkoxy-1,3-dioxepanes and 1,3-dioxepan-2-ones as orthoester and carbonate derivatives may differ from those of the cyclic acetals already described. 2-Alkoxy-1,3-dioxepanes and dioxepins (cyclic orthoester derivatives) have been prepared by transacetalization of acyclic orthoesters with 1,4-diols <72USP3652594, 73USP3738997, 74CL741, 75GEP(O)2461525, 76USP3966768, 93AG437, 95HCA13, 95SL175>, for example the synthesis of methoxydioxepane (**123**) <95SL175>. Similarly, 5,6-dichloro-2-methoxy-4,7-dihydro-1,3-dioxepin (**153**) was prepared by acid-catalyzed reaction of diol (**152**) with trimethyl orthoformate (Scheme 29) <93AG437, 95HCA13>. The starting diol (**152**) could be obtained from mucochloric acid. Methoxydioxepin (**153**) has been further transformed to 5,6-dialkynyl-2-methoxy-4,7-dihydro-1,3-dioxepins (**154**), which upon ring cleavage with diisobutylaluminum hydride gave (**155**), precursors for the synthesis of tetraethynylethenes. 2-Alkoxy-4,7-dihydro-1,3-dioxepins exhibits significant herbicidal activity <72USP3652594, 73USP3738997, 76USP3966768>.

Addition of methanol to 2-methylene-1,3-dioxepane (**28**) leads to the corresponding seven-membered cyclic orthoacetate (**156**) (Equation (23)) <86TL1587>, and electrochemical reduction of 1,3-dioxepan-2-one (**157**) in an electrolyte containing alkali metal ions affords orthoester derivatives (**158**), useful for stabilizing *n*-doped polyacetylene as the anode-active material of a battery (Equation (24)) <85JAP(K)60126281>.



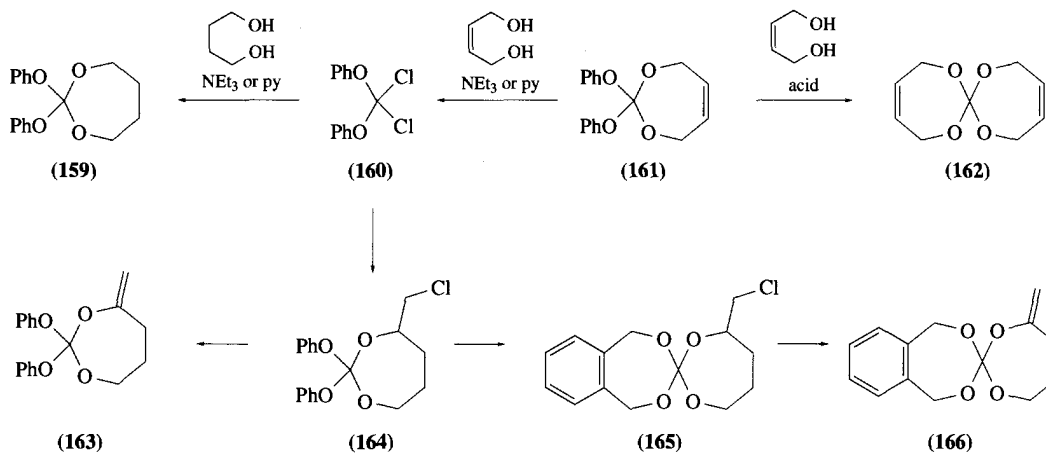
Scheme 29



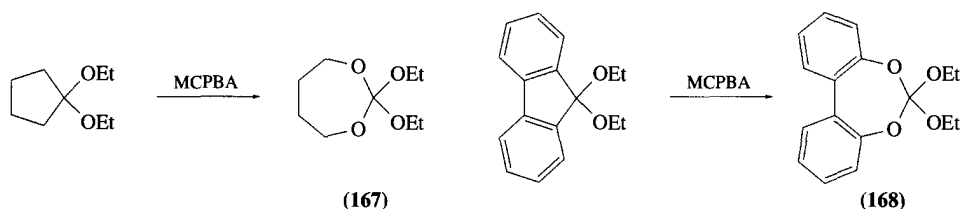
The major route to seven-membered cyclic orthocarbonate and spiro orthocarbonate derivatives consists in the alcohol exchange of the chloro substituents of dichlorodiphenoxymethane (**160**) with 1,4-diols (Scheme 30). The starting material (**160**) is readily available by treatment of diphenylcarbonate with phosphorus pentachloride, and it can be used in a crude form. Thus, treatment of (**160**) with 1,4-butanediol or but-2-en-1,4-diol in the presence of triethyl amine or pyridine affords orthocarbonate derivatives (**159**) and (**161**), respectively, in virtually quantitative yield. Acid-catalyzed alcohol exchange of the phenoxy groups with a diol then leads to spiro orthocarbonates, for example (**162**) <86GEP(O)3502106, 90S249>. Similarly, spiro orthocarbonate (**166**) was prepared from (**160**) by successive reactions with two different 1,4-diols followed by dehydrohalogenation, and the radical polymerizations of (**163**) and (**166**) have been studied <92EUP503896, 93MM737, 94JPS(A)323>.

Seven-membered cyclic orthocarbonates are also available via a formal “double Baeyer–Villiger” reaction by oxidation of a cyclopentanone diethyl acetal with *m*-chloroperbenzoic acid, for example the synthesis of orthocarbonates (**167**) and (**168**) (Scheme 31) <82JA1769>. However, only moderate yields (15–37%) of pure seven-membered cyclic orthocarbonates have been obtained, as complications arise with the separation of the complex reaction mixture. Moreover, precautions should be taken, because these reactions become very violent after an induction period. However, this procedure provides a simple method for the oxidative removal of the carbonyl group from a ketone via the intermediacy of an orthocarbonate. This is accomplished by treatment of the crude reaction mixture with LAH in ethereal solution to give the corresponding diols, thereby avoiding the crucial product separation.

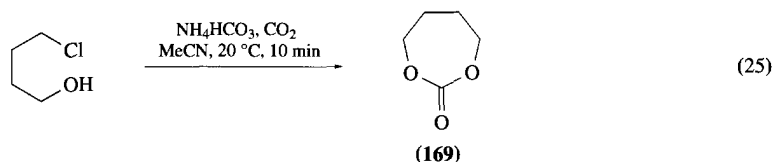
The parent member of this class of compounds, 1,3-dioxepan-2-one (**169**) has been synthesized either by treating 4-chloro-1-butanol with ammonium bicarbonate in acetonitrile under a CO₂ atmosphere <80MIP479522> or by reaction of butylene oxide and solid CO₂ in the presence of MnBr₂ <72JAP47026786> (Equation (25)), and (**169**) has been used as a solvent for the halogenation of ketene <73GEP(O)2247764>.



Scheme 30



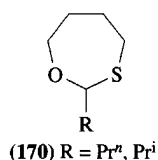
Scheme 31

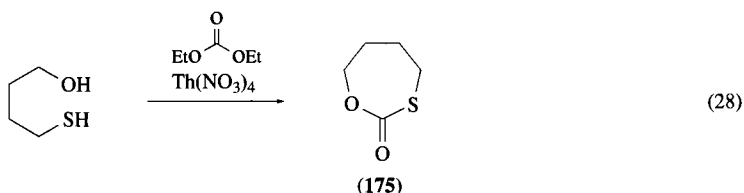
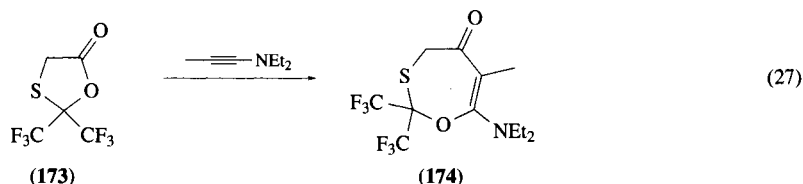
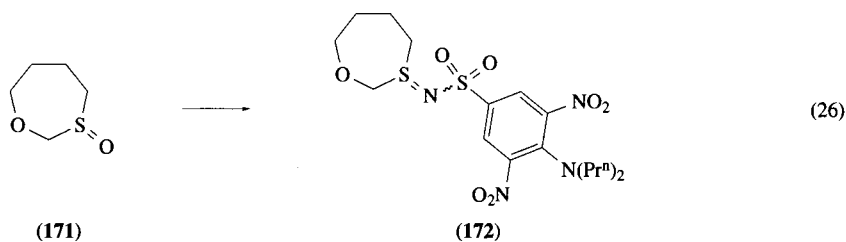


9.11.2 1,3-OXATHIEPANES AND 1,3-OXATHIEPINS

9.11.2.1 Synthesis, Reactivity, and Applications

Only a few reports in the literature deal with the synthesis and reactivity of 1,3-oxathiepanes and 1,3-oxathiepins. Thus, 1,3-oxathiepanes (170) have been prepared, and their radical isomerization to acyclic thioesters has been studied <84ZOR287>. Sulfoxide (171) was reacted with the corresponding sulfanilamide to give sulfimine (172) (Equation (26)), which exhibits herbicidal activity <74USP3786048>. According to the preparation of the analogous dioxo compound (143) (cf. Section 9.11.1.3.2), 4,7-dihydro-1,3-oxathiepinone (174) could be obtained by ring enlargement of substrate (173) (Equation (27)) <75TL3223>, and the synthesis of 1,3-oxathiepan-2-one (175) was achieved by the reaction of diethyl carbonate with 4-thio-1-butanol (Equation (28)) <66FRP1445849>.

(170) R = Prⁿ, Prⁱ

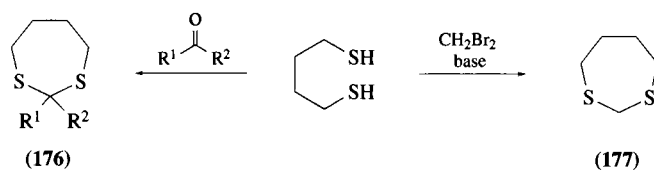


9.11.3 1,3-DITHIEPANES AND 1,3-DITHIEPINS

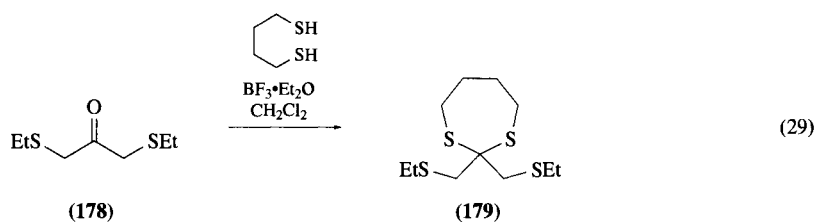
9.11.3.1 1,3-Dithiepanes

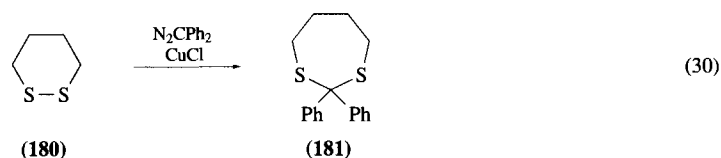
9.11.3.1.1 Synthesis

1,3-Dithiepanes (**176**) can be prepared by condensation of a carbonyl compound with a 1,4-dithiol <49ZOB84, 75CR(C)1529> or by the reaction of a 1,4-dihaloalkane with sodium thiosulfate followed by reaction with a carbonyl compound <49ZOB849> (Scheme 32). Alternatively, a 1,4-butanedithiol can be reacted with dibromomethane in the presence of a base, for example, the synthesis of (**177**) <64T427, 64T437, 76JA2005>. The mercaptalization of (**178**) with 1,4-butanedithiol was catalyzed with boron trifluoride etherate (Equation (29)) <81LA1899>. It has also been reported that treatment of a 1,3-dioxepane with sulfur at 120–280 °C in an aromatic hydrocarbon and in the presence of CaCO₃, as a catalyst, gave the corresponding 1,3-dithiepane <77URP586174>, and 2,2-diphenyl-1,3-dithiepane (**181**) could be obtained by diphenylcarbene insertion into disulfide (**180**) (Equation (30)) <85TL5187>.

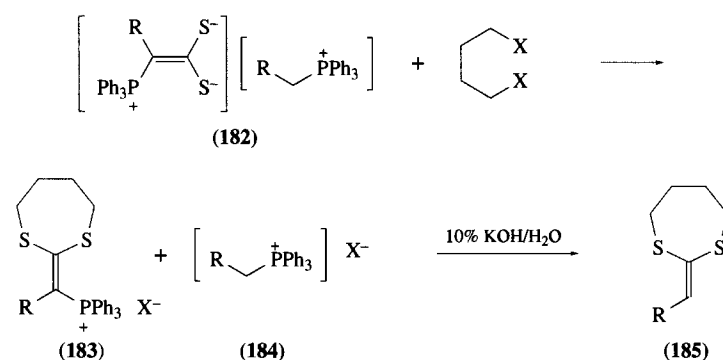


Scheme 32

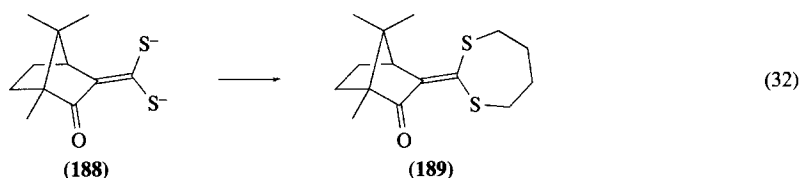
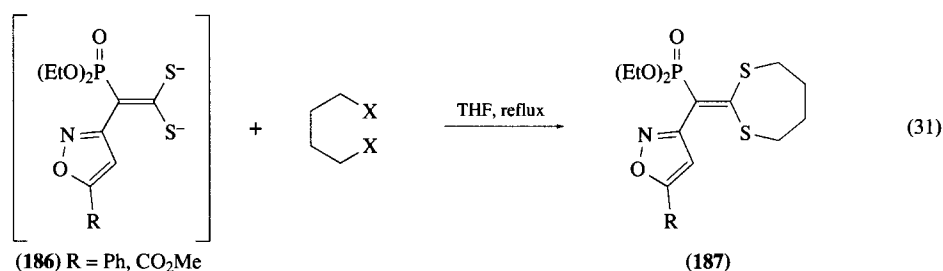




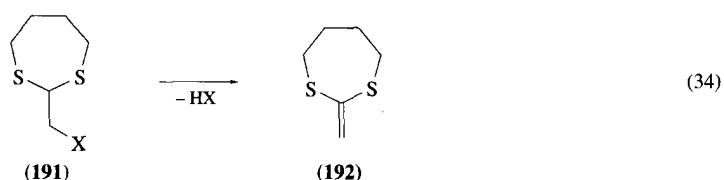
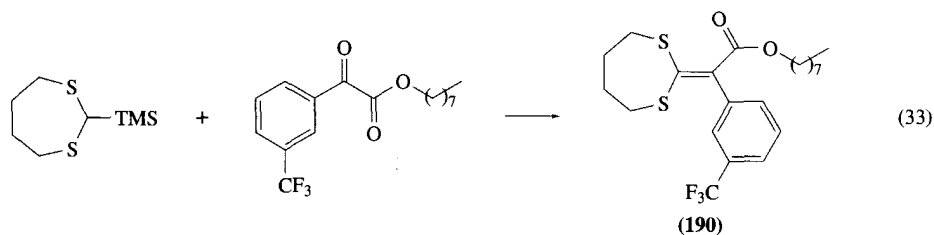
A general route to 2-alkylidene-1,3-dithiepanes starts with the reaction of the triphenylphosphonium salts **(182)** with a 1,4-dihaloalkane, which affords a mixture of **(183)** and **(184)** (Scheme 33). As the separation of **(183)** from the salt mixture is troublesome, 2-alkylidene-1,3-dithiepanes are preferentially liberated from the salts by refluxing the crude salt mixture in 10% aqueous potassium hydroxide solution. The starting phosphonium salts **(182)** are readily prepared by treatment of alkylidenetriphenylphosphoranes with CS₂ in a 2:1 molar ratio under lithium salt free conditions <79CB28>. In a similar manner, quenching of dianions **(186)**, obtained by treatment of the corresponding isoxazolephosphonate with sodium hydride in THF and addition of the carbanion intermediate to CS₂, with a 1,4-dihaloalkane yields ketene thials **(187)** (Equation (31)) <92JPR432>. α -(1,3-Dithiacyclohept-2-ylidene)camphor **(189)** was prepared from α -(dithiomethylene)camphor di-Na salt **(188)** and 1,4-butanedithiol (Equation (32)) <69CR(C)186>.



Scheme 33

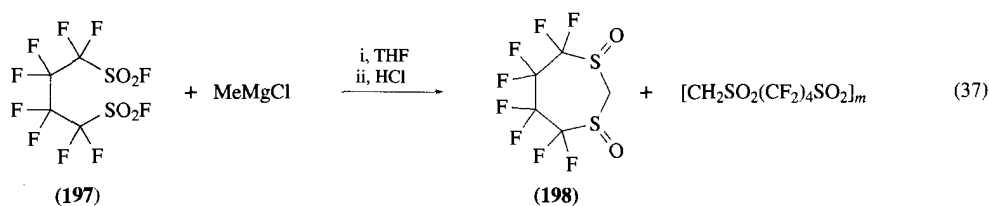
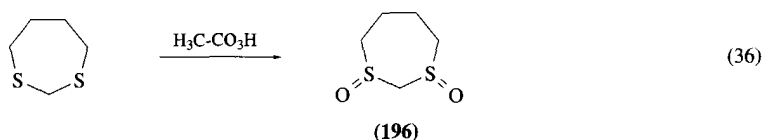
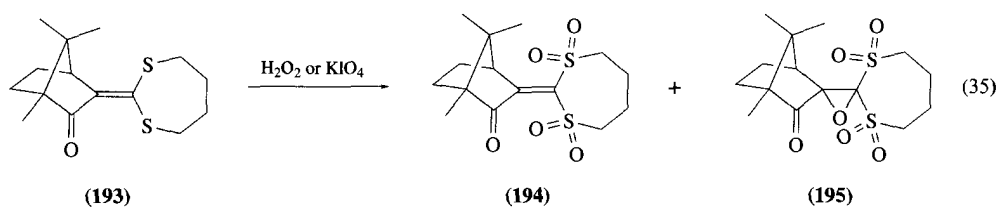


Another method for the preparation of 2-alkylidene-1,3-dithiepanes is the reaction of 2-trimethylsilyl-1,3-dithiepane with carbonyl compounds, for example the synthesis of **(190)** (Equation (33)) <83EUP810266>, and ketene thials **(192)** can also be obtained in the usual manner by dehydrohalogenation of 2-haloalkyl-substituted 1,3-dithiepanes **(191)** (Equation (34)) <75RTC83>.

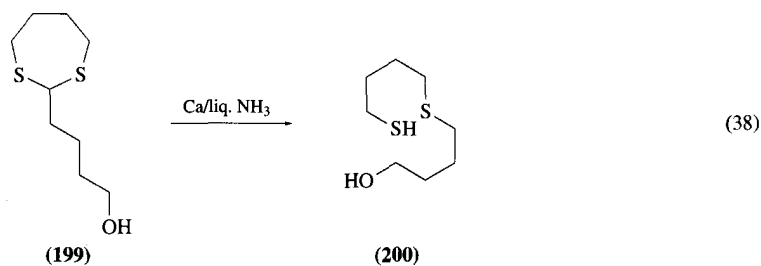


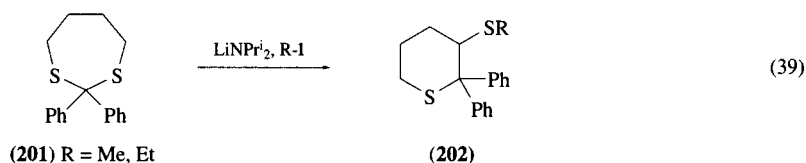
9.11.3.1.2 Reactivity and applications

Oxidation of camphor-derived 1,3-dithiepane (**193**) with hydrogen peroxide or potassium periodate affords a 1 : 1 mixture of disulfone (**194**) and epoxy-disulfone (**195**) (Equation (35)) <84T2951>. The oxidation of 1,3-dithiepane to disulfone (**196**) was effected with peroxyacetic acid (Equation (36)) <77USP4032538>. 1,1,3,3-Tetraoxopolyfluoro-1,3-dithiacycloalkanes, for example (**198**), have been synthesized by the reaction of α,ω -bis(fluorosulfonyl)perfluoroalkanes (**197**) with methylmagnesium chloride or bromide (Equation (37)) <95IC792>.

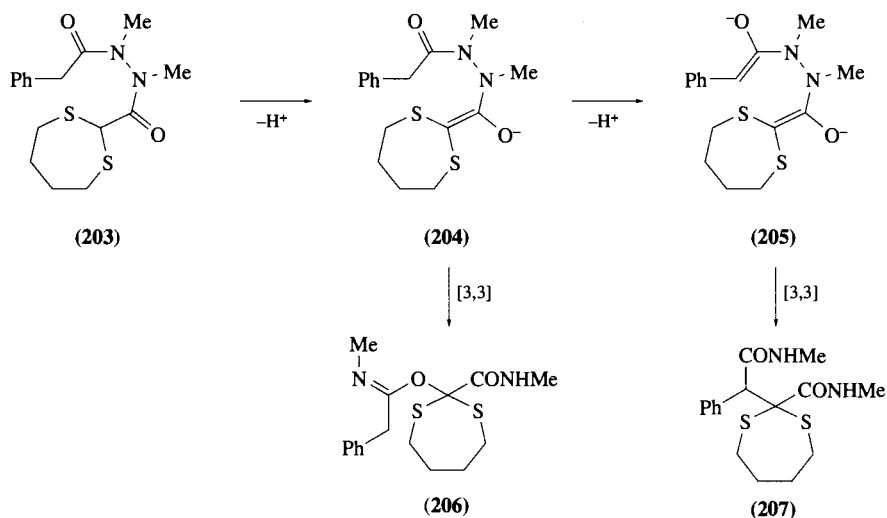


Reduction of 1,3-dithiepane (**199**) gave ring-opened product (**200**) (Equation (38)) <75CR(C)1529>, and a Wittig-type rearrangement of 2,2-diphenyl-1,3-dithiepanes (**201**) has been reported, which affords ring-contraction products (**202**) (Equation (39)) <78MI 911-01>.



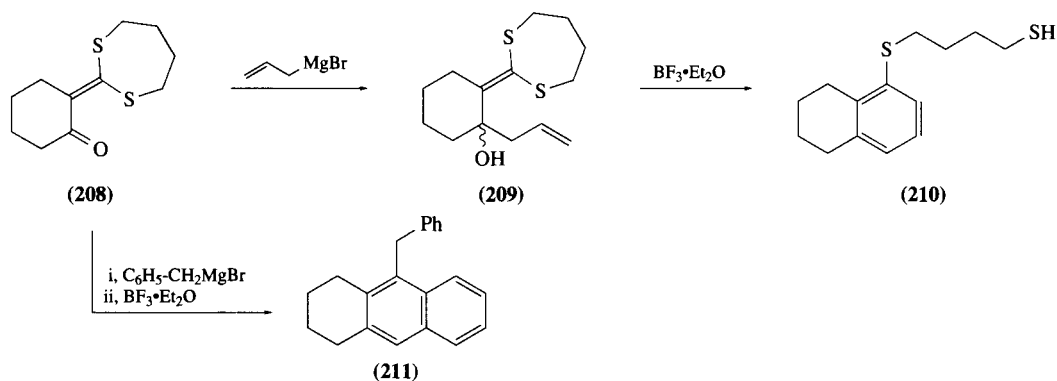


2-Substituted 1,3-dithiepane (**203**) has found interest in the anionic 3,4-diaza[3,3]sigmatropic rearrangement of *N,N'*-diacylhydrazines <91TL4517>. Thus, enolization of (**203**) with five equivalents of LDA at -78°C and 5 h at 0°C followed by workup, gave a mixture of the C—O product (**206**) in 10% yield and the C—C product (**207**) in 51% yield via [3,3]sigmatropic shift monodeprotonation intermediate (**204**) and biscalboxamide enolate (**205**) (Scheme 34).



Scheme 34

Reaction of a β,β -(1,4-butylenedithio)- α,β -unsaturated ketone with allylmagnesium bromide followed by treatment of the intermediate carbinol with boron trifluoride etherate leads to aromatization products, for example formation of (**210**) (Scheme 35) <94MI 911-02>. The reaction of (**208**) with benzylmagnesium bromide under the same conditions gave product (**211**).

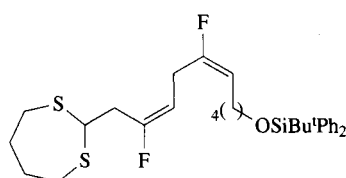


Scheme 35

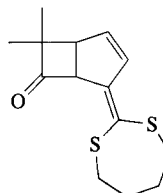
The triethanolamine-catalyzed decarboxylation of 1,3-dithiepane-2-carboxylic acid in DMSO <68T5271> as well as the acid- and base-catalyzed hydrolysis of the 1,3-dithiepane-2-carboxylic acid ethyl ester have been studied <68T5293>.

1,3-Dithiepanes have found wide interest as herbicides <74GEP(O)2405510, 75USP3901902, 76USP3940259, 76USP3942972, 76USP3948950, 76USP3951640>, fungicides <82EUP200267>, analgesics <73MI 911-01>, anti-parasitic compounds <75JMC158>, and flavors <78JAP53025514, 78JAP53025542>. Compound (**212**) has been used as an intermediate for the preparation of fluorinated arachidonic acid derivatives, which

are useful as 5-lipoxygenase inhibitors and antiallergic, antiasthmatic, and antiinflammatory agents <90EUP396841>. 2-Alkylidene-1,3-dithiepane (**213**) has found interest in the synthesis of ($\pm$)-filifolone <84HCA1854>. The polymerization of 2-methylene-1,3-dithiepane has been studied, but it failed under radical conditions <91MI 911-03>.



(212)

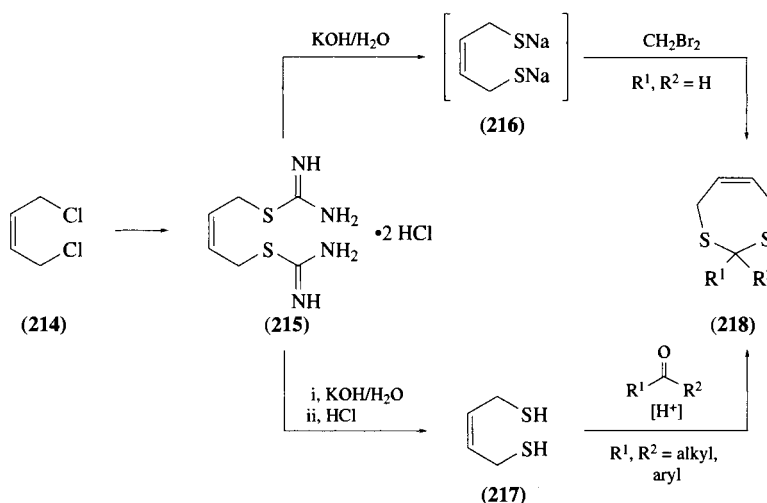


(213)

9.11.3.2 4,7-Dihydro-1,3-dithiepins

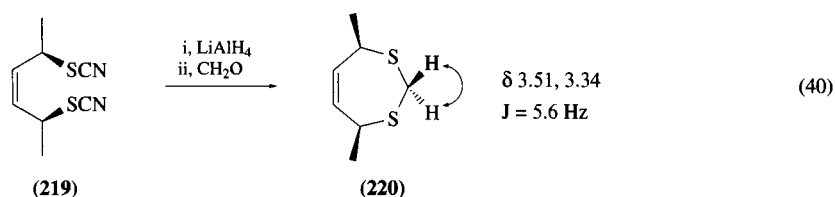
9.11.3.2.1 Synthesis

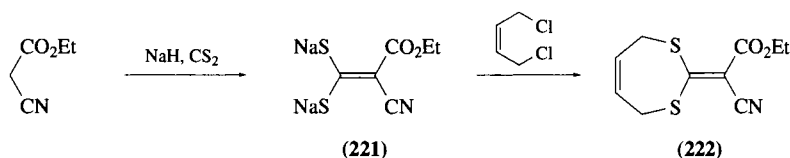
4,7-Dihydro-1,3-dithiepins (**218**) have usually been obtained from (*Z*)-1,4-dichloro-2-butene (**214**) via the isothiuronium salt (**215**) (Scheme 36). For the preparation of the 2-unsubstituted 4,7-dihydro-1,3-dithiepin, the isothiuronium salt can be reacted directly with dibromomethane and potassium hydroxide in methanol <76TL1251, 78OPP133>, but isolation of the dithiol (**217**) and acid-catalyzed reaction with an aldehyde or ketone in a second step is preferred for the preparation of 2-substituted 4,7-dihydro-1,3-dithiepins <93JCS(P2)871>.



Scheme 36

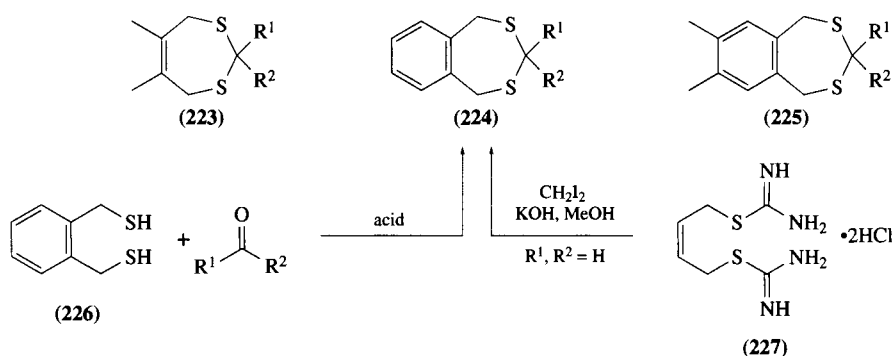
The 4,7-dimethyl-substituted 4,7-dihydro-1,3-dithiepin (**220**) could be obtained by LAH reduction of *meso*-hex-3-en-2,5-diyl dithiocyanate (**219**) and treatment with paraformaldehyde (Equation (40)) <93CC246>, and 2-alkylidene-4,7-dihydro-1,3-dithiepins, for example (**222**), which are useful as pharmaceutical intermediates, have been synthesized by reaction of C—H acidic substrates with sodium hydride, followed by condensation with CS₂ and cyclization of intermediate (**221**) with (*Z*)-1,4-dichloro-2-butene (Scheme 37) <85GEP228255, 86JPR215>.





Scheme 37

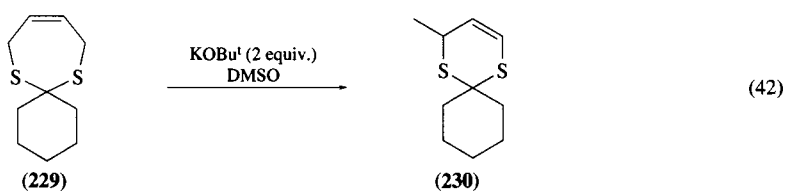
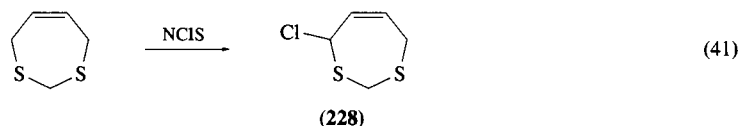
The NMR spectra of 4,7-dihydro-1,3-dithiepins (**218**) and (**223**) as well as their benzoannellated derivatives (**224**) and (**225**) have been studied <64TL1929, 65MI 911-01, 89IZV1696, 91ZOR1065>. This data reveals an equilibrium between the chair and the twist-boat conformation, in which the chair conformation clearly predominates, particularly in the case of the benzoannellated derivatives. The energy barriers for the ring inversion have also been determined. Benzoannellated 1,3-dithiepins of type (**224**) and (**225**), respectively, are readily prepared either by acid-catalyzed treatment of dithiol (**226**) with a carbonyl compound or by reaction of the corresponding bis-isothiuronium salt (**227**) with diiodomethane (Scheme 38) <72TL1837>.

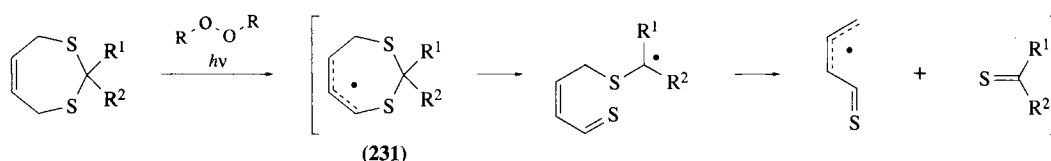


Scheme 38

9.11.3.2.2 Reactivity and applications

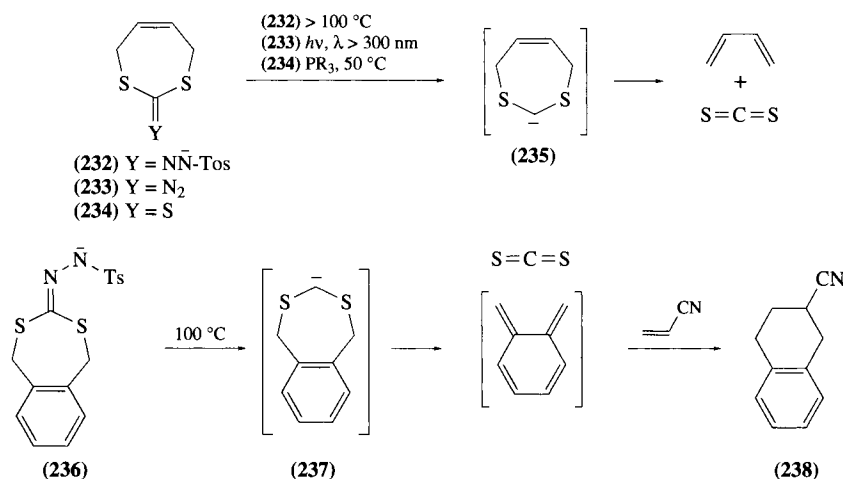
4,7-Dihydro-1,3-dithiepin has been chlorinated with *N*-chlorosuccinimide to give compound (**228**) (Equation (41)) <76TL1251>. An attempted double-bond isomerization with potassium *t*-butoxide in DMSO of 4,7-dihydro-1,3-dithiepin (**229**) was unsuccessful, but reaction with two equivalents potassium of *t*-butoxide in DMSO gave an unexpected ring-contraction product, whose structure was tentatively assigned to (**230**) (Equation (42)). The EPR spectra of the photolysis with light from a 500 W super pressure mercury arc of a mixture of 2-substituted 4,7-dihydro-1,3-dithiepins and di-*t*-butyl peroxide in *t*-butylbenzene or cyclopropene as a solvent indicated a fragmentation via radical (**231**) (Scheme 39) <93JCS(P2)871>.





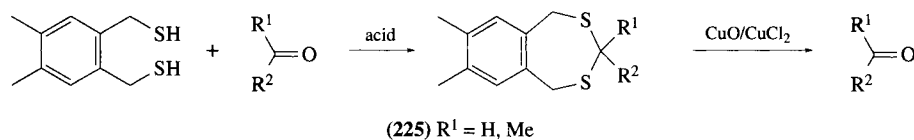
Scheme 39

The fragmentation of 2-heterosubstituted 4,7-dihydro-1,3-dithiepins (**232**)–(**234**) via carbene (**235**) gave 1,3-butadiene and carbon disulfide. The tosylhydrazone (**232**) was synthesized by cyclization of 1,4-dichlorobut-2-ene with the *S,S'*-sodium-potassium salt of dithiocarbonic acid-tosylhydrazone, the diazo compound (**233**) was synthesized by careful pyrolyzation of the dry Na salt of (**232**), and the trithiocarbonate (**234**) was synthesized from 1,4-dichlorobut-2-ene and potassium trithiocarbonate in DMSO. Similarly, pyrolysis of the sodium salt of benzoannulated dithiepin (**236**), obtained in a one-pot synthesis from α,α' -dichloro-*o*-xylene, carbon disulfide, potassium hydroxide, and tosylhydrazide gave *o*-quinodimethane, which could be trapped by dienophiles, such as acrylonitrile, to give Diels–Alder product (**238**) (Scheme 40) (92SCI711).



Scheme 40

Benzoannulated 1,3-dithiepins (**225**; R^1 and/or $R^2 = H$) are readily alkylated via generation of the anion with butyllithium (Scheme 41) (75S720). Chlorination of (**225**; $R^1, R^2 = H$) gave the 2-chloro derivative (**239**), which can be reacted with Grignard reagents to give the 2-aryl- or the 2-alkyl-substituted derivatives and with triethylphosphite to give the corresponding phosphonate (**240**) (78JPR255), which was used in Wadsworth–Emmons-type alkenylation reactions for the synthesis of ketene dithioacetal (**241**) (78T3081) (Scheme 42). Cleavage of compounds (**225**) is performed with $CuO/CuCl_2$ (75S720).



Scheme 41

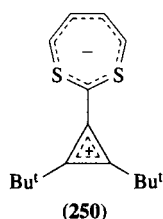
9.11.3.3 1,3-Dithiepins

9.11.3.3.1 Synthesis and reactivity

1,3-Dithiepin (**242**), the parent member of this class of compounds, was prepared by dehydrochlorination of 4-chloro-4,7-dihydro-1,3-dithiepin (**228**) with potassium *t*-butoxide in ether



Scheme 43



Reaction of the anion (**243**) with trimethylsilyl chloride, D₂O and benzophenone, respectively, gave compounds (**245**), (**246**), and (**247**). Acid-treatment of (**247**) afforded ring-enlarged heterocycle (**249**) rather than the ketene dithioacetal (**248**), but (**248**) could be obtained by deprotonation of the trimethylsilyl derivative (**245**) with butyllithium and reaction with benzophenone <76TL1251>.

Fulvalenoids of type (**250**) were prepared by treating the anion of trimethylsilyl-1,3-dithiepin (**245**) with either di-*t*-butylcyclopropenone or 2,6,6,7-dibenzotroponone, and fluorenone, respectively, for example the synthesis of compounds (**250**), (**251**), and (**253**) <80CL1427>. Based on the ¹H NMR spectra, the electron-accepting ability and hence the aromatic character of these compounds as well as that of (**252**) has been studied (Figure 1) <88PS(39)221>.

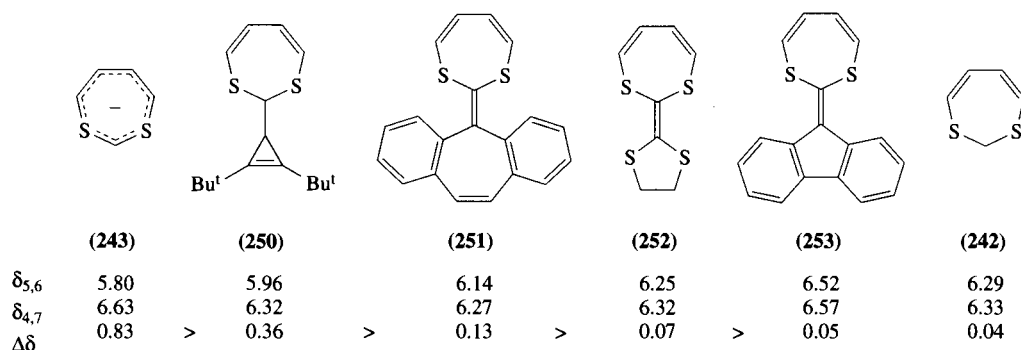
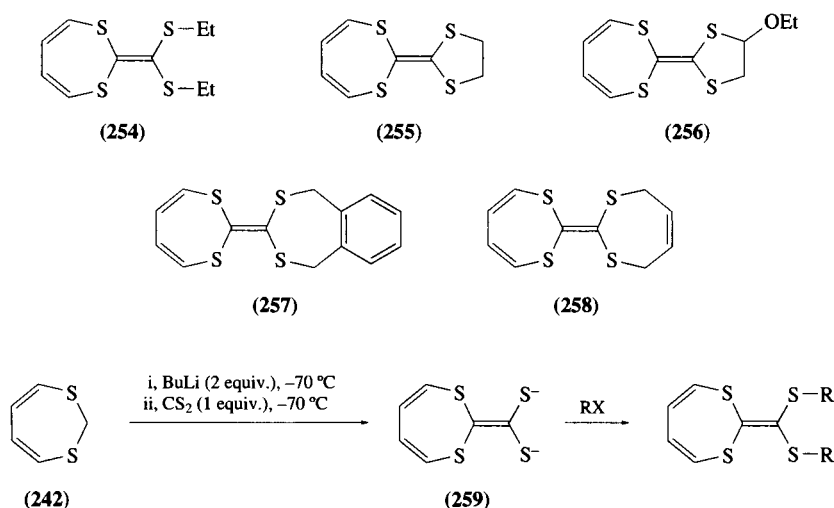


Figure 1 The aromatic character of selected 1,3-dithiepins.

The synthesis of ketene dithioacetal (**252**) and (**254**)–(**258**) possessing a tetrathioethene unit was achieved by alkylation of 1,3-dithiepin-2-carbodithiolate <88PS(39)221>. These compounds have found interest in the chemistry of metal complexes <88ICA295, 88PS(39)221>. The synthesis of palladium(II), copper(II) and lithium complexes containing 1,3-dithiepin-2-carbodithiolate (**259**) as a ligand has been reported (Scheme 44) <91ICA169>.



Scheme 44

9.12

1,4-Dioxepanes, 1,4-Oxathiepanes, and 1,4-Dithiepanes

HERBERT FRAUENRATH
Universität GH Kassel, Germany

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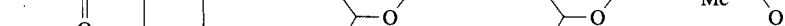
9.12.1 1,4-DIOXEPANES AND 1,4-DIOXEPINS

9.12.1.1 Ethers

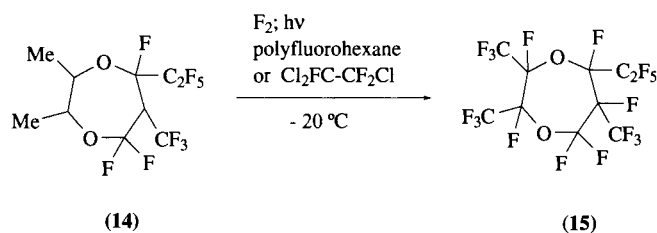
Early syntheses of the parent member of this class of compounds, 1,4-dioxepane (**6**), and simple derivatives of (**6**) by etherification were usually complicated by side reactions, even in highly diluted solutions <34CB146, 37LA(528)155, 53JA2373, 62T289, 65JOC2988, 67JA7017, 68ZC220>. The fragmentation of ω,ω',ω'' -tribromopivalophenone although afforded methylene derivative (**1**) in only 18% yield in a mixture of products, but (**1**) could be degraded to 1,4-dioxepane (**6**) via 1,4-dioxepan-6-one (**2**) and 1,4-dioxepan-6-ol (**3**), and hydrogenolysis of (**1**) gave the 6-methyl derivative (**5**) <70LA(736)75>.

In the mid-1980s, several alternative methods for the synthesis of the fully saturated 1,4-dioxacycloheptane rings were developed. Thus, CuCl-catalyzed reactions of 3,4-dichloro-1-butene with trimethyleneglycol gave cyclic ether (**7**) (Equation (1)) <86MI 912-01>. Vinylidenedioxepanes (**9**) have also been obtained by the reaction of substrate (**8**) with aldehydes in the presence of catalytic amounts of TiCl_4 <88JOM(349)43>.

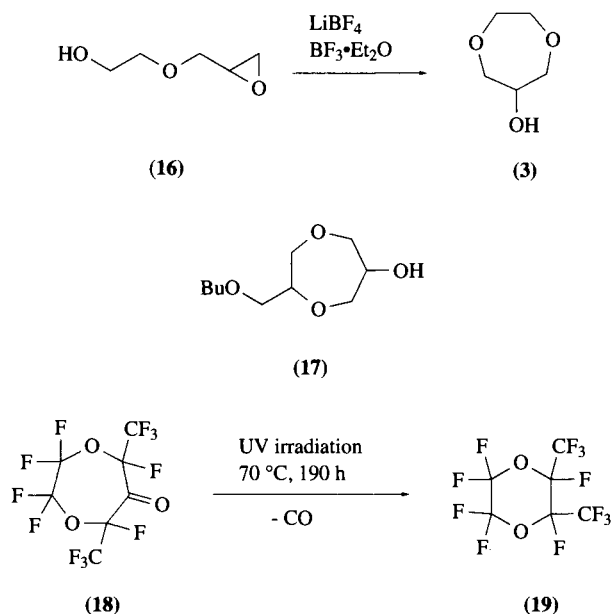




(10) **(11)** **(12)** **(13)**

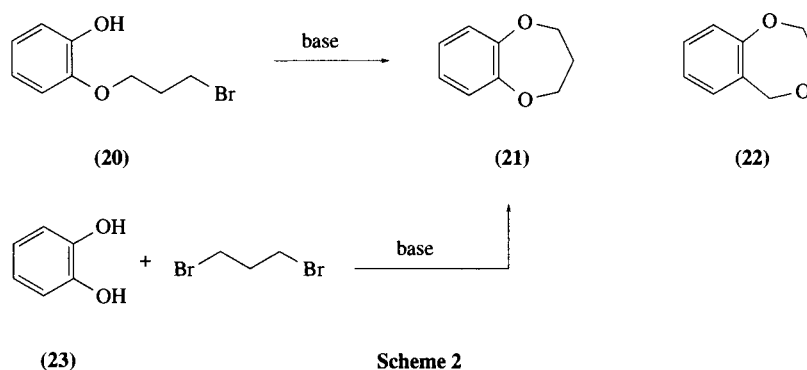


The synthesis of 6-hydroxy-1,4-dioxepane (**3**) was also achieved by treatment of epoxide (**16**), prepared from epichlorohydrin and ethyleneglycol, with lithium tetrafluoroborate and boron-trifluoride etherate <87ZOR284>. Similarly, cyclization of bis(2,3-epoxypropyl) ether with butanol catalyzed by sodium butoxide in chlorobenzene at 55–80 °C gave 6-hydroxy-1,4-dioxepane derivative (**17**) in 26–28% yield in a mixture of products <74ZOR1603>. Perfluorinated 1,4-dioxepan-5-one (**18**), prepared from perfluoro-2,7-dimethyl-3,6-dioxasuberic difluoride <92JAP(K)04316576>, was photochemically decarbonylated by irradiation with UV light to give perfluorinated ether (**19**), useful as solvent, heating medium or insulating liquid <92JAP(K)04316577>.

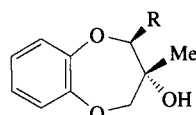
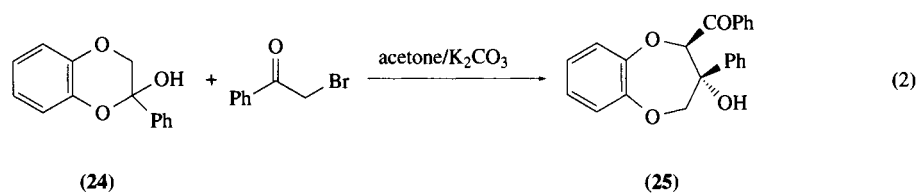


9.12.1.2 Benzoannelated Ethers

Two types of benzoannelated ethers containing a 1,4-dioxepane moiety are known: 3,4-dihydro-2*H*-1,5-benzodioxepin (**21**), and 2,3-dihydro-5*H*-1,4-dioxepin (**22**). 3,4-Dihydro-2*H*-1,5-benzodioxepin (**21**) can be prepared either from (**20**) or (**23**). Derivative (**25**) has been obtained by the reaction of 2-hydroxy-2,3-dihydro-2-phenyl-1,4-benzodioxin (**24**) with phenacylbromide <87UKZ614>, and compounds (**26**) were isolated as by-products together with isomeric 2-substituted 2,3-dihydro-2-hydroxymethyl-1,4-benzodioxins from the reaction of α -(2-hydroxyphenoxy)-alkylketones and dimethylsulfoxonium methylide <88JHC943>.

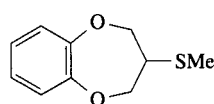


Scheme 2

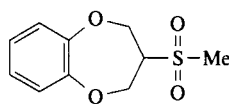


(26)
R = H, Me

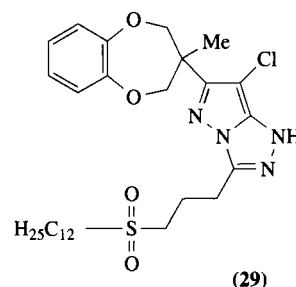
Benzodioxepins (27) and (28) have been synthesized, and their conformations as well as steric and electronic factors have been studied (90CJC513). Compound (29) has been used as a photographic magenta coupler (95JAP(K)06347958). *N*-(Aminocarbonyl)-3,4-dihydro-2*H*-1,5-benzodioxepin-2-acetamide (30) has found interest as a 5-lipoxygenase inhibitor (92USP5120758).



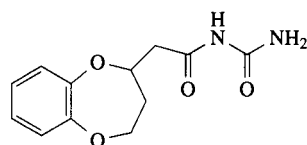
(27)



(28)

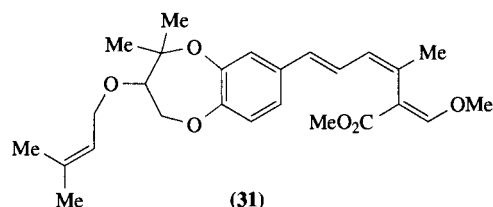


(29)



(30)

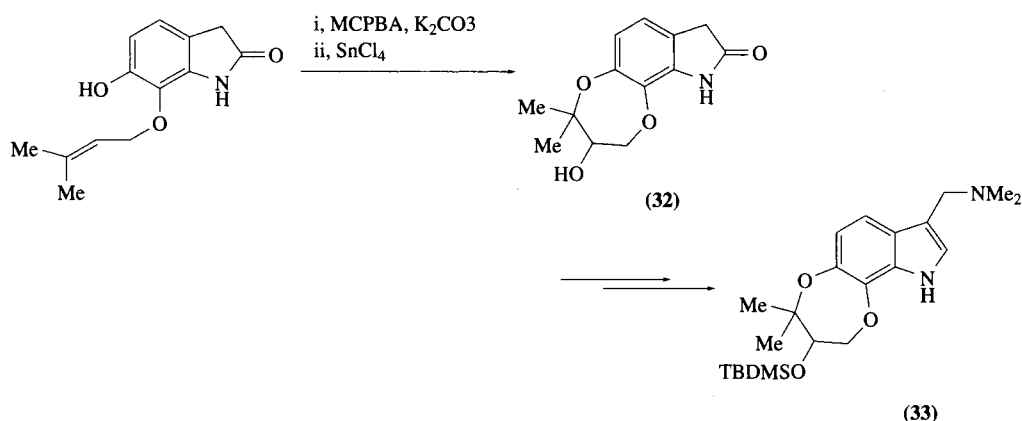
Natural products with a *gem*-dimethyl benzodioxepin ring have been detected, for example, the antifungal natural product strobilurin (31) (90JAN661), and several benzodioxepin derivatives, i.e., compounds (32) and (33), with a similar structural feature have been synthesized in the total synthesis of (+)-paraherquamide B (90TL6325, 96JA557).



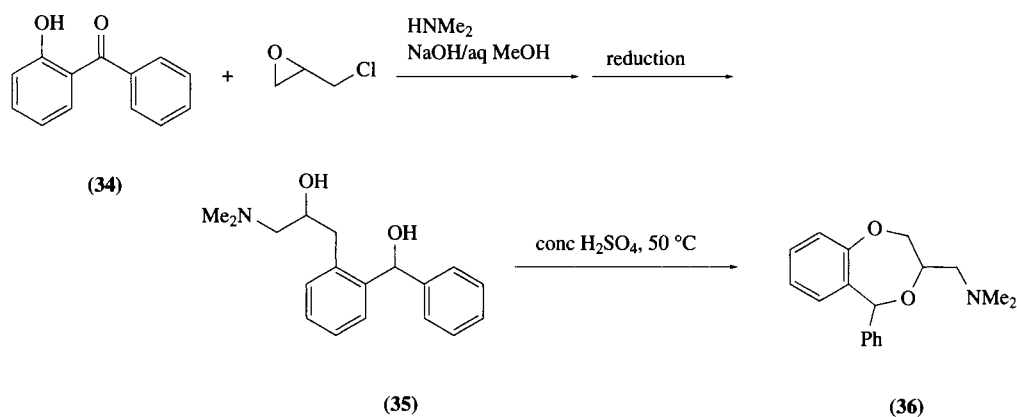
(31)

2,3-Dihydro-5*H*-1,4-dioxepins are usually prepared by cyclization. Thus, a number of compounds of type (36), (37), and (38) (isolated as oxalates or hydrochlorides), which have found interest as sedatives, antiepileptics, and antidepressants, were prepared by cyclization of the respective carbinols (35) with concentrated sulfuric acid. The starting carbinols have been synthesized from the corresponding benzophenones (34) (Scheme 4) (79JAP(K)53077081).

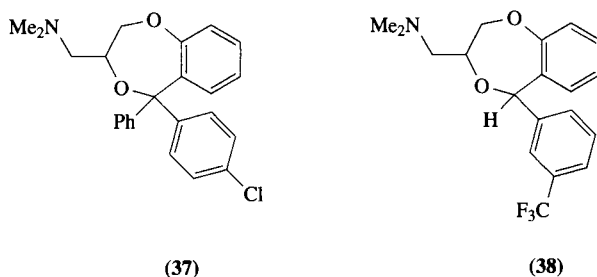
Similarly, the reaction of epoxypropanes (39) (prepared from the respective salicylaldehyde and epichlorohydrine) with amines afforded epoxybenzoxacines (41). The intermediate anils could be isolated, but distillation *in vacuo* gave (41) with loss of amine (76SC175). Furthermore, a large number of spirobenzodioxepinpiperidines (44) have been synthesized by cyclization of precursors



Scheme 3



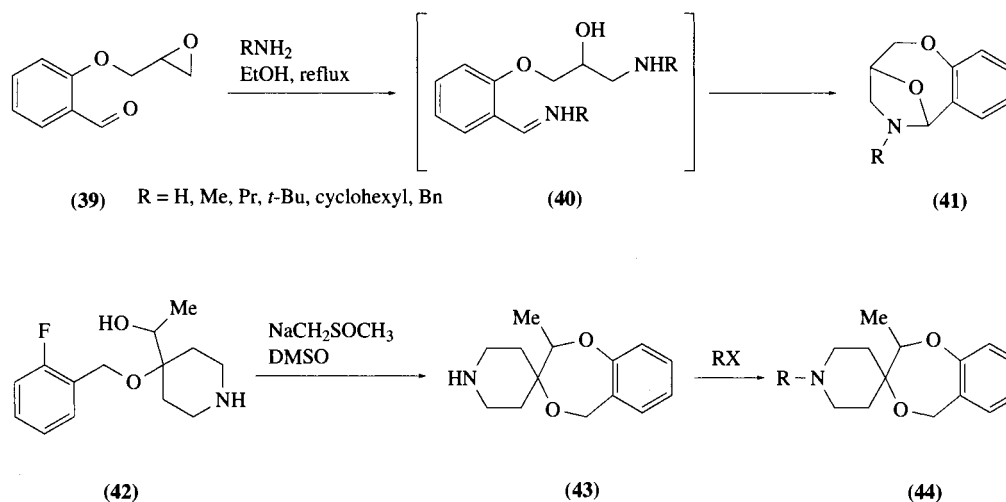
Scheme 4



(42) with sodium dimslyate in DMSO and *N*-alkylation. Compounds (44) have found interest as antihypertensives <84USP4405631, 86USP4521537>. The stereoelectronic stabilization in non-chair conformations of substituted 2,3-dihydro-5*H*-1,4-benzodioxepins has also been studied <88T5033>.

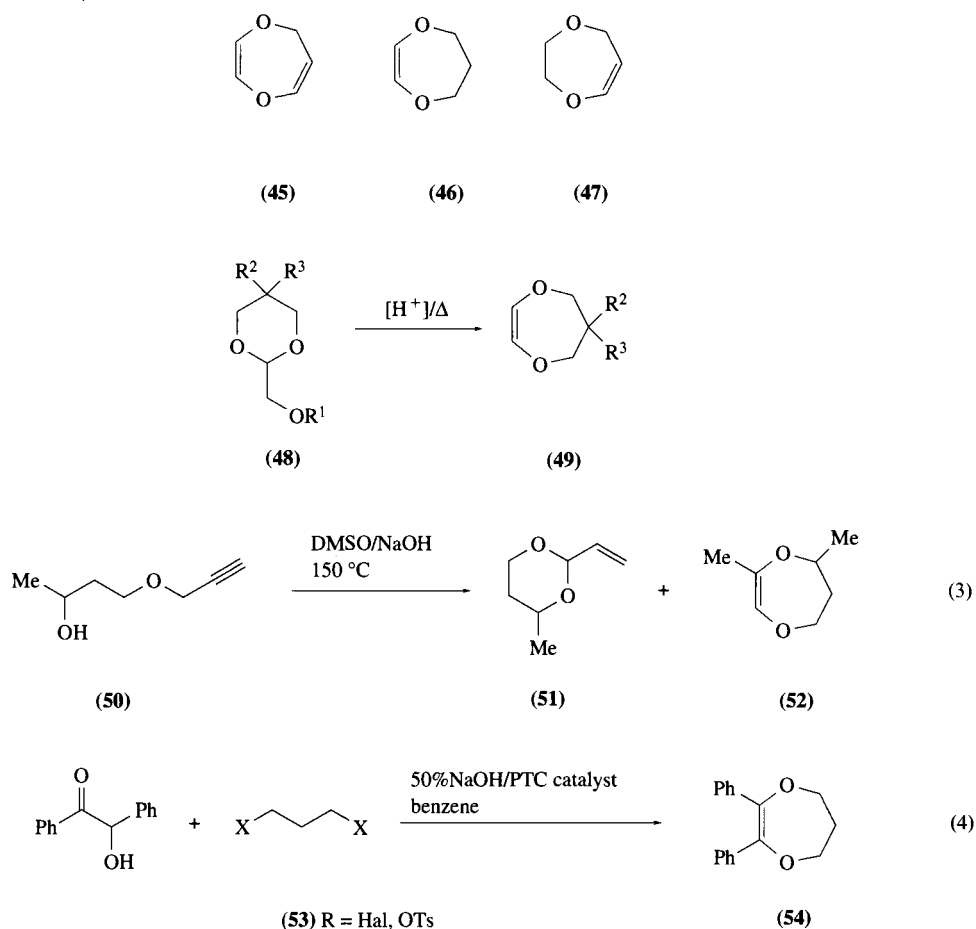
9.12.1.3 Enol Ethers and Enediol Ethers

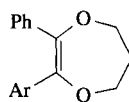
Besides the fully unsaturated 5*H*-1,4-dioxepin (45), the unsaturated 1,4-dioxepins, 6,7-dihydro-5*H*-1,4-dioxepin (46), and 2,3-dihydro-5*H*-1,4-dioxepin (47), incorporate either the structural feature of an enediol ether or an enol ether. One general method for the preparation of seven-membered rings of type (46) involves ring expansion; thus, treatment of 2-(methoxymethyl)-1,3-dioxane with dodecylbenzenesulfonic acid in vacuum gas oil at 250 °C and simultaneous distillation gave (46) with 69% conversion and 84% selectivity. Several 6,6-disubstituted derivatives (49), which have found interest as intermediates for agrochemicals, drugs, and plastics, have analogously been



Scheme 5

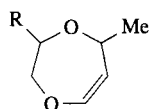
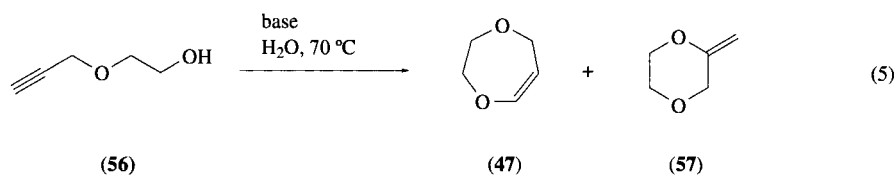
prepared from substituted precursors (48) <90GEP(O)3823603>. Dioxepin (52) was isolated as a by-product in the base-catalyzed cyclization of 1,3-butanediol monopropargyl ether (Equation (3)) <85MI 912-01>, and 2,3-diphenyl-6,7-dihydro-5*H*-1,4-dioxepin (54) could be obtained from stilbenediol dianion and a bifunctional alkylating agent (Equation (4)) <77JCR(S)273>. The synthesis of 1-aryl-2-phenyl-substituted 6,7-dihydro-5*H*-1,4-dioxepins (55) has also been reported <84CHEC-I(7)621>.



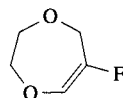


(55)

The base-catalyzed cyclization of propargyloxyethanol in water gave 2,3-dihydro-5*H*-1,4-dioxepin (**47**) and 2-methylene-1,4-dioxane (**57**) in nearly equal amounts (Equation (5)) <68ZC220>, and methyl-substituted dioxepins (**58**) were obtained as by-products by this protocol in the base-induced cyclizations of substituted propargyloxyethanols <73JOC1455>. The fluoro derivative (**59**) was observed as a by-product in the reduction of 7-halo-7-fluoro-2,5-dioxabicyclo[4.1.0]heptanes <72CL921>.

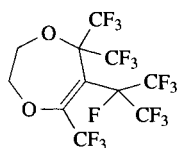


(58) R = H, Me

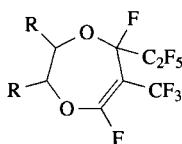


(59)

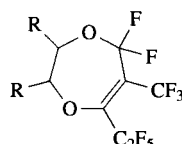
Several reports deal with the synthesis of perfluorinated 2,3-dihydro-5*H*-1,4-dioxepins, for example, the synthesis of (**60**), which has found industrial interest as refrigerator oil and magnetic recording medium lubricant <95MIP9417023>, and the synthesis of (**61**), (**62**), and (**63**) (R = H, Me) <79JCS(P1)214, 85NKK1974, 87EUP190393>. As a typical example for their preparation, stirring of perfluoro-2-methyl-2-pentene with ethylene glycol in THF in the presence of triethylamine with cooling for 8 hours gave (**64**) (42% yield) (Equation (6)) <85IZV2066, 87JAP(K)61200983>.



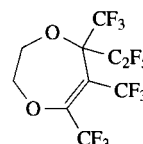
(60)



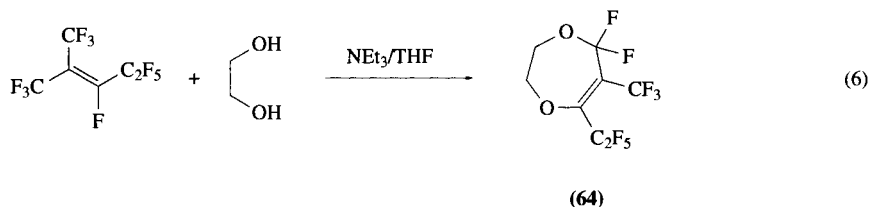
(61)



(62)

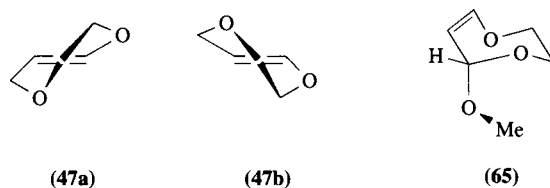


(63)

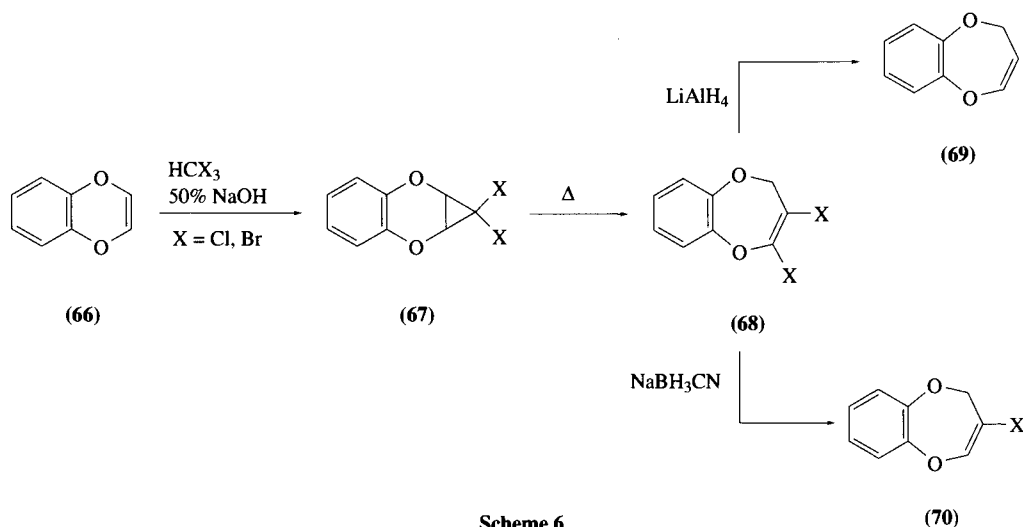


(64)

The conformational analysis by MM2 calculations indicates a preference for the twist-boat conformation in 2,3-dihydro-5*H*-1,4-dioxepin (**47**) and for a chair in 6,7-dihydro-5*H*-1,4-dioxepin (**46**) as well as in the methoxy derivative (**65**). It has been suggested that the stability of the different conformations should be governed by the conjugation of the oxygen atoms with the π system, in (**46**) and (**47**), by this conjugation and the anomeric effect in (**65**). The barrier for the chair-twist boat interconversion has been calculated to be 2.50 kcal mol⁻¹ in (**47**) and 3.78 kcal mol⁻¹ in (**65**) <89JOC6034>.

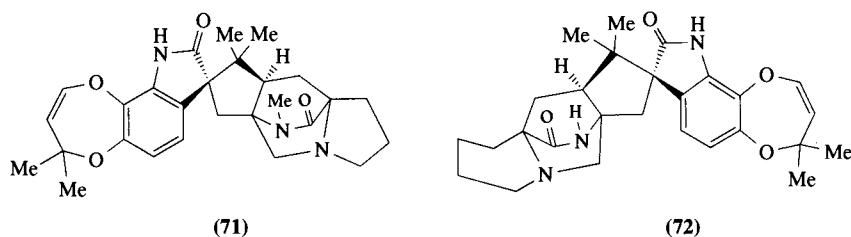


Less is known about 2,3-dihydro-5*H*-1,4-benzodioxepins. The parent member of this class of compounds (**69**) and its halogenated derivatives (**68**) and (**70**) could be obtained from 1,4-benzodioxin (**66**) by dihalogencarbene addition, thermolysis, and reduction (Scheme 6) <83AG(E)64>.



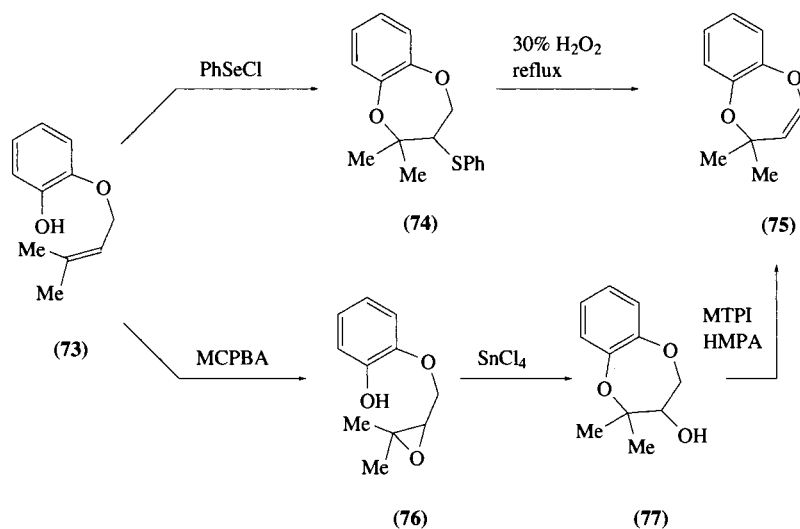
Scheme 6

The *gem*-dimethyl 2,3-dihydro-5*H*-1,4-benzodioxepin moiety occurs in several natural products, for example, in the paraherquamides, which exhibit potent anthelmintic and antinematodal activity, and in the marcfortines (**72**; marcfortine B). In the course of the total synthesis of (+)-paraherquamide B (**71**), the synthesis of the benzodioxepin unit by phenylselenoetherification and by epoxidation followed by a Lewis acid-mediated ring closure was explored, but the phenylselenoetherification only gave poor yields of (**74**). The dehydration of the secondary alcohol (**77**) was effected with methyltriphenoxyposphonium iodide (MTPI) in HMPA (Scheme 7) <90TL6325, 96JA557>.

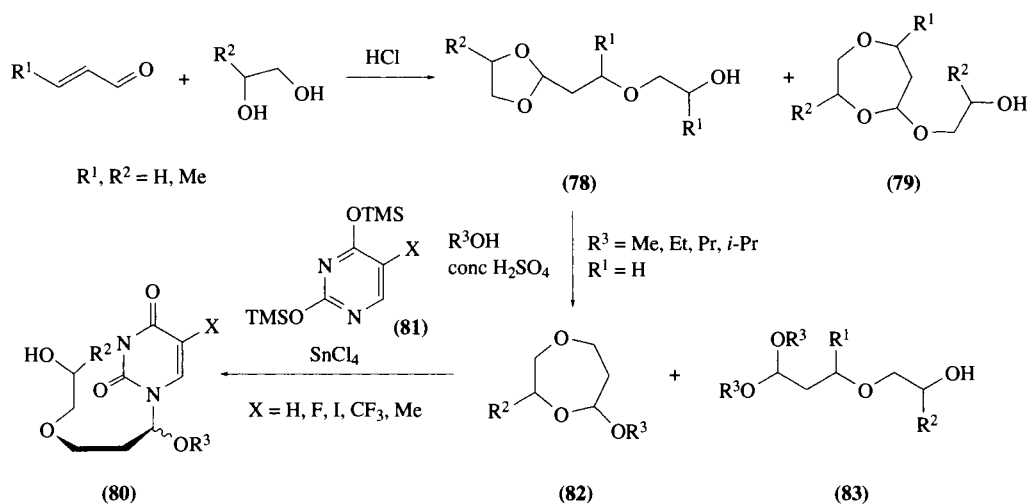


9.12.1.4 Acetals and Hemiacetals

Several reports deal with the isolation of 1,4-dioxepane acetals (**79**) as by-products from a complex mixture of the reaction of acrolein or 2-butenal with ethylene glycol or propylene glycol together with 1,3-dioxolanes (**78**) as the main products <83AQ270, 84T4893, 87JPR579>. The by-products probably arise via intramolecular transacetalization of (**78**), and the transacetalization of the 1,3-dioxolanes to give 1,4-dioxepanes (**82**) and open-chain derivatives (**83**) could be made to the main process by treatment of (**78**) with simple alcohols and concentrated H₂SO₄ <83AQ210>. Ring opening of (**82**) with SnCl₄ and several silylated 5-substituted pyrimidine bases (**81**) gave acyclonucleoside analogues (**80**) (Scheme 8), which have found interest because of their antitumor activity, and because they are structurally related to the selective antih herpes virus agent acyclovir <92MIP9117147, 93SL389>.

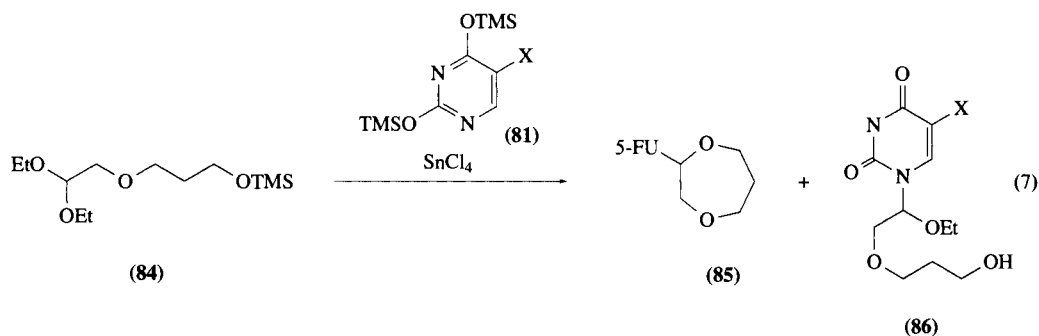


Scheme 7

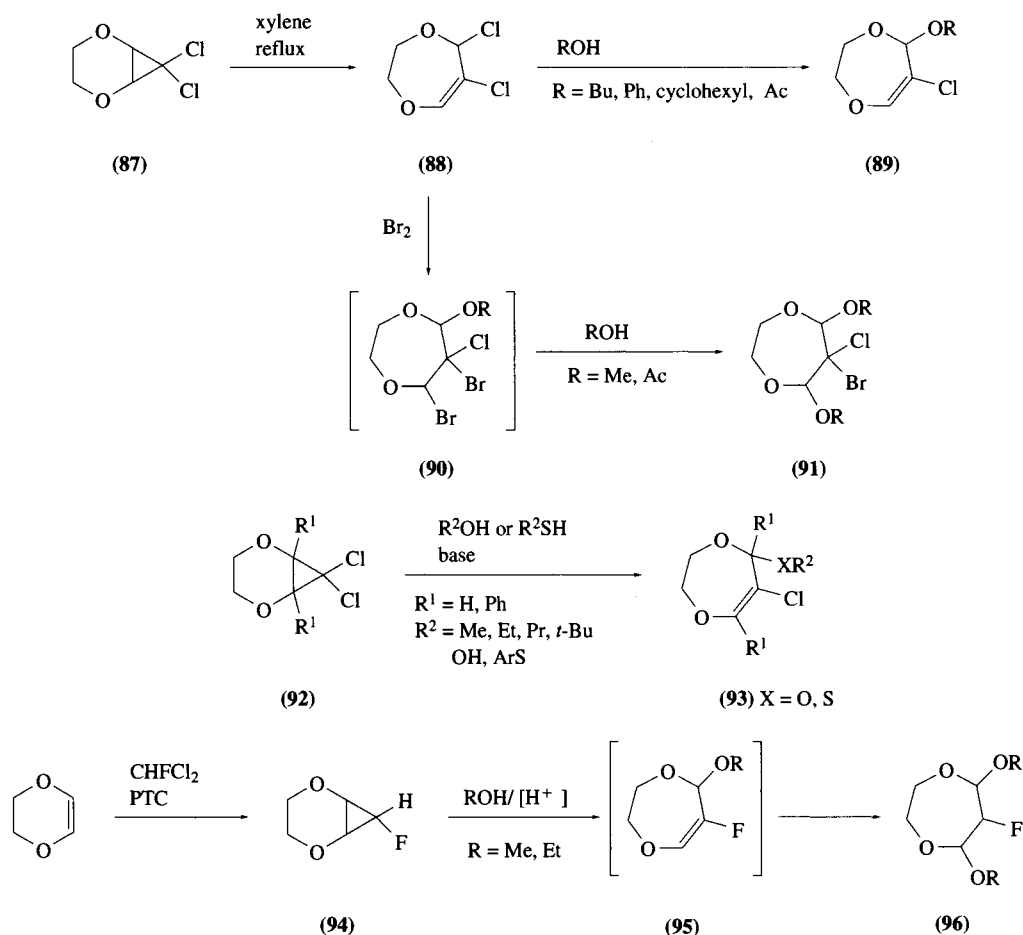


Scheme 8

Several 5-fluorouracil derivatives having oxacycloalkane moieties also exhibit significant anti-tumor activity. Thus, fluorouracil derivative (85) has been prepared by the reaction of trimethylsilyloxy acetal (84) with SnCl₄ and 5-fluoro-substituted pyrimidine base (81), but this reaction gave only 28% of (85) together with 45% of acyclic product (86) (80JAP55130975, 81TL1029).



Similar to the ring enlargement of 1,4-benzodioxins (see Section 9.12.1.3), by the reaction with carbenes, a number of unsaturated acetal derivatives (**89**), (**91**), or (**93**), could be obtained by ring expansion of 1,4-dioxene-dihalogen carbene adducts (**88**) and (**92**) followed by exchange of the allylic chlorine atom by alcoholysis, acetolysis, or thiolysis either under neutral or basic conditions [76UKZ968, 77ZC331]. Acetal (**96**), which has found interest as an acetal-protected fluoro-malondialdehyde building-block, was prepared from 1,4-dioxin and dichlorofluoromethane [89JOC5618].



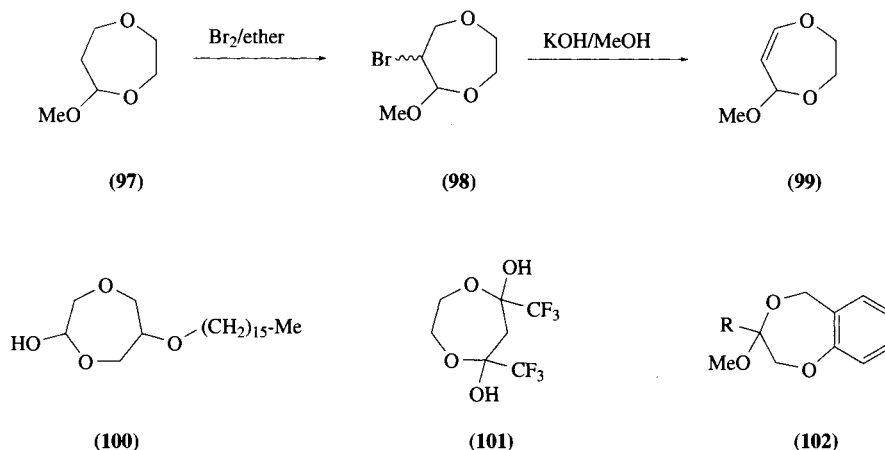
Scheme 9

Bromination of acetal (**98**) and dehydrobromination gave unsaturated acetal (**99**) [83AQ210]. Hemiacetals, (e.g., (**100**)), have been synthesized for use as covalent carriers and for the preparation of liposomes containing dicetyl phosphate, cholesterol, and trypsin [87GEP(O)3619883]. Bis-hemiacetal (**101**) could be obtained by the reaction of hexafluoroacetylacetone and glycol, but this compound decomposes on standing [67NKZ470].

NMR Spectroscopic studies of the benzoannulated acetals (**102**) indicated that the predominant conformation of these compounds is that of twist-boat [88TS033].

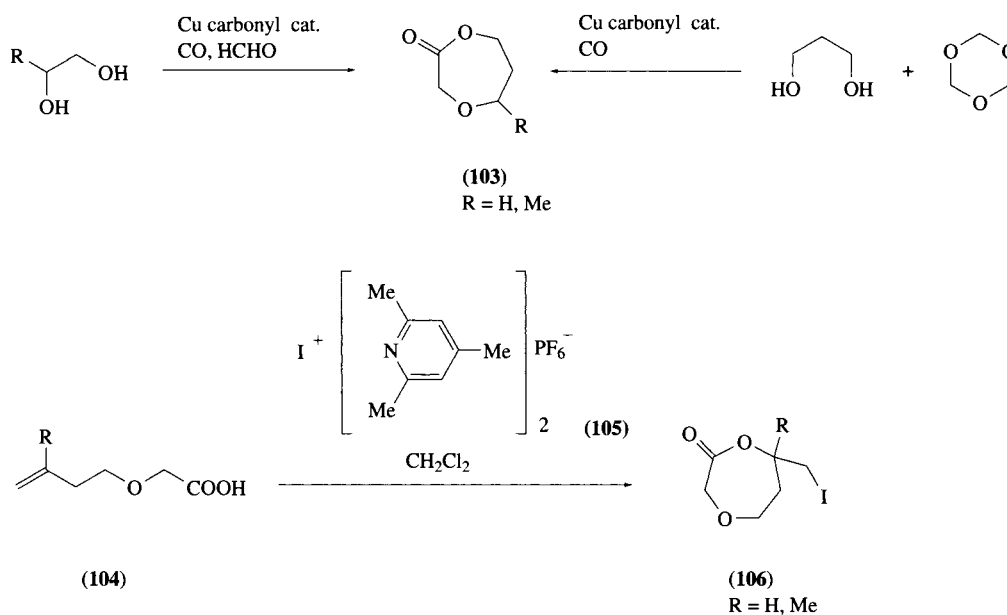
9.12.1.5 Lactones

1,4-Dioxepan-2-ones (**103**) have been manufactured from diols, paraformaldehyde, and carbon monoxide in the presence of a copper(I) or silver carbonyl catalyst (Scheme 10). Thus, treatment of Cu_2O with 98% H_2SO_4 and CO and reaction with paraformaldehyde and 1,2-propanediol under CO atmosphere gave 5-methyl-1,4-dioxepan-2-one in high yield [89JAP01093581]. By the same protocol, 1,4-dioxepan-2-one could be obtained by cyclocondensation of trioxane with CO and



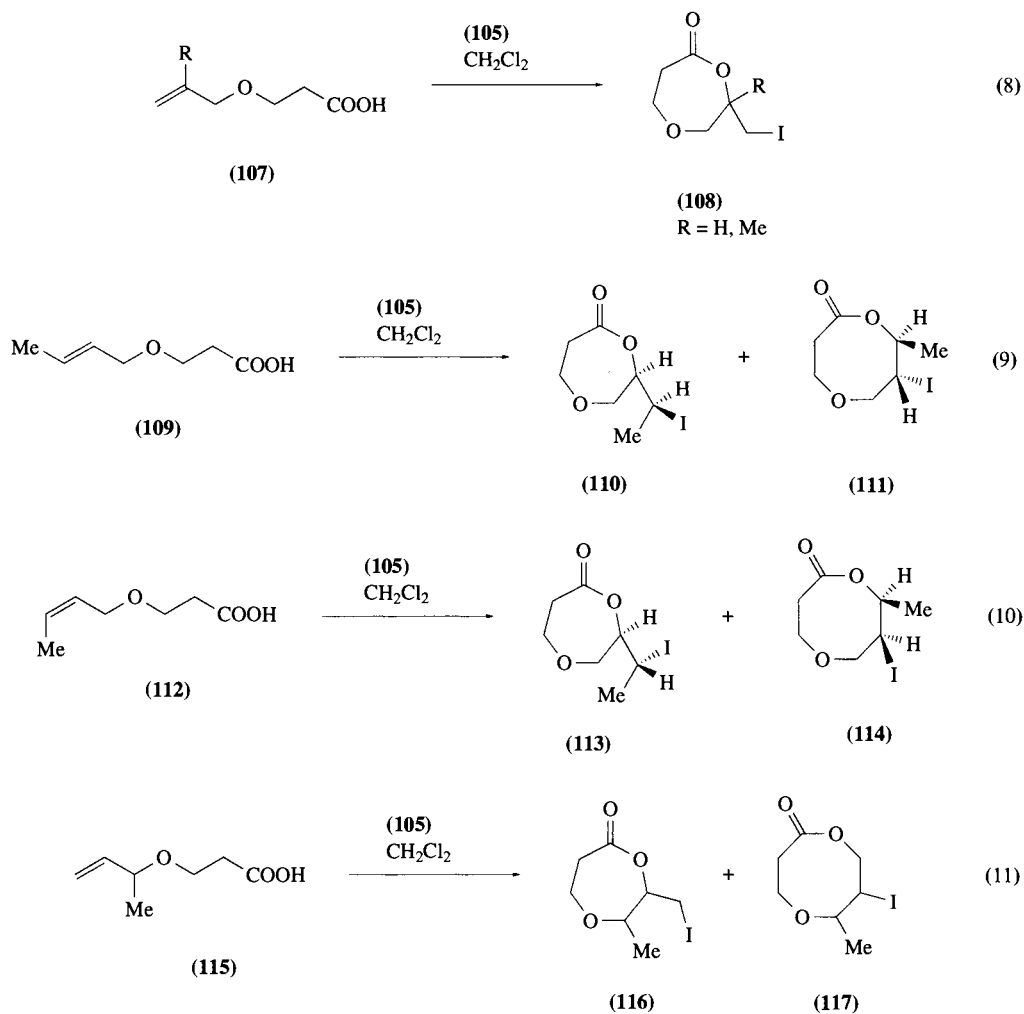
trimethyleneglycol <91USP4990629>, and reaction of 1,3-dioxane with CO in the presence of a copper(I) carbonyl catalyst also gave 1,4-dioxepan-2-one <89JAP01299285>. The dioxepan-2-ones have found interest as intermediates for *in vivo* absorbable sutures or wound-healing agents, and copolymers of 1,4-dioxepan-2-one with 1,5,8,12-tetraoxacyclotetradecane 7,14-dione were used in the fabrication of absorbable surgical devices such as sutures and as coatings for medical devices <95USP5442032>.

7-Iodomethyl-substituted 1,4-dioxepan-2-ones (**106**) were obtained by iodolactonization of 3-oxa-6-heptenoic acids (**104**) with bis(*sym*-collidine)iodine(I) hexafluorophosphate (**105**), as the I^+ transfer reagent. This reaction occurs regioselectively via an *exo*-mode cyclization <94JOC5912>.

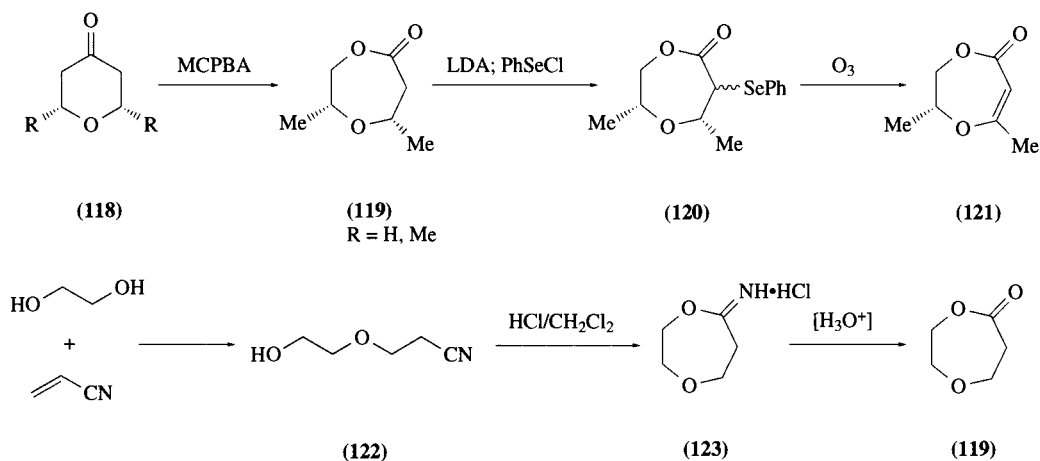


Scheme 10

1,4-Dioxepan-5-ones (**108**) have been obtained by iodolactonization of 4-oxa-6-heptenoic acids. The cyclization of (**108**) occurs regioselectively via the *exo*-mode as long as the 7-position of the starting alkenoic acids is unsubstituted. However, in the case of seven-substituted substrates, for example (**109**) and (**112**), the *endo*-mode cyclization can successfully compete with the *exo*-mode cyclization to give a 1:1 mixture of the seven- and eight-membered lactones (**110**) and (**111**), or (**113**) and (**114**), respectively. Probably for steric reasons, the iodolactonization of substrate (**115**) gave predominantly the *endo*-mode cyclization product (**117**), (**116**):(**117**) = 22:78 <88S862, 93JOC4, 94JOC5912>.

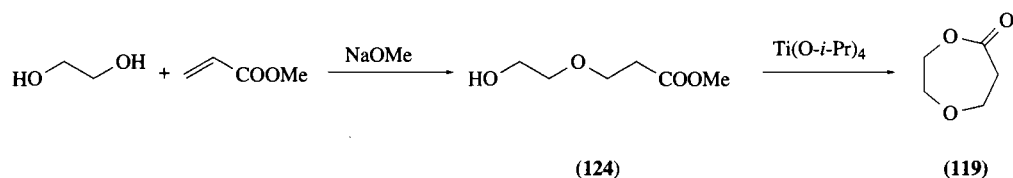


The parent member of this class of compounds, 1,4-dioxepan-5-one, and its methyl derivatives (**119**) have been prepared by Baeyer–Villiger oxidation, and the methyl derivative has been transformed to the dioxepinone (**121**) [89MM3838, 94CC687]. 1,4-Dioxepan-5-one could also be obtained by cyclization of (**122**) and hydrolysis of the intermediate iminoether hydrochloride (**123**) (Scheme 11) [89MM3838].

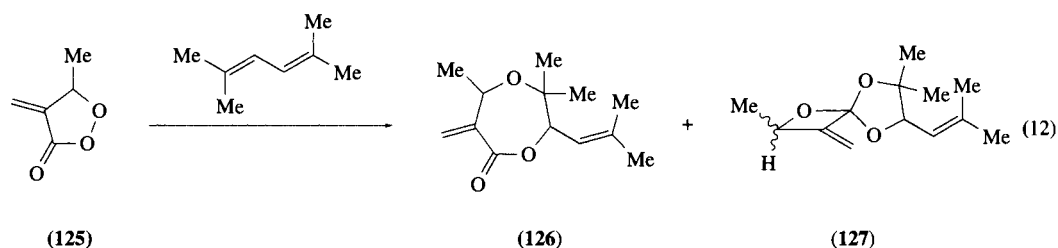


Scheme 11

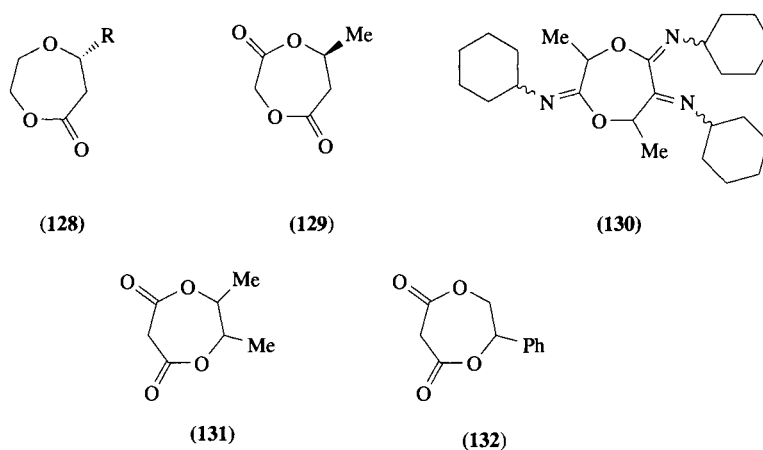
The synthesis of 1,4-dioxepan-5-one was also achieved by $\text{Ti}(\text{O-}i\text{-Pr})_4$ -catalyzed cyclization of methyl 3-(2-hydroxyethoxy)propionate (**124**) (Scheme 12) <87JPS(A)2629>. Dioxepanone (**126**) was formed by addition 2,5-dimethyl-2,5-hexadiene to methyleneperoxyketone (**125**) together with spiro derivative (**127**) <86JOC4479>.



Scheme 12

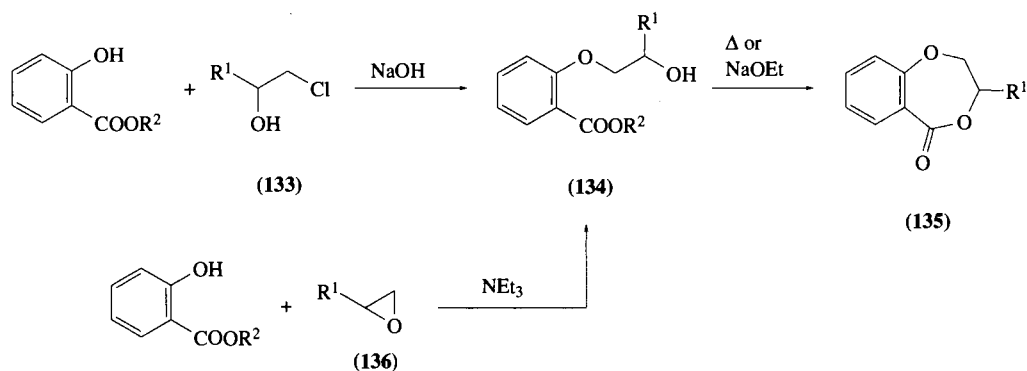


Dioxepanones have found wide interest in polymerization reactions. Thus, the polymerization of 1,4-dioxepan-5-one with 4–20% cross-linking agent gave biodegradable elastomers <94MI 912-01>. The ring-opening polymerization initiated by aluminum triisopropoxide, stannous 2-ethylhexanoate, or dibutyltin oxide, respectively, has been studied <90MI 912-01, 93MI 912-01, 95MI 912-01>. The copolymerization of 1,4-dioxepan-5-one with L- or D,L-lactide, 1,3-dioxan-2-one, oxepan-2,7-dione, and oxepan-2-one with stannous 2-ethylhexanoate as initiator, have also been investigated <92MAC221, 93MAC127, 95MI 912-02>. Copolymers from 1,4-dioxepan-5-one and lactide and/or glycolide were prepared for use in surgical sutures and suture lubricants <84USP4470416>. Biodegradable homopolymers and block copolymers with ϵ -caprolactone and aluminum triisopropoxide, as initiator, have also been prepared <94MM5556>. The ring-opening polymerization of optically active (7*R*)-(–)-7-methyl-1,4-dioxepan-5-one or the respective 7-ethyl derivative (**128**) with dibutyltin oxide <92JAP04316575> and of (7*S*)-methyl-1,4-dioxepan-2,5-dione (**129**) has been reported <92PP461>. Cyclic co-oligomer (**130**) was isolated in the copolymerization of acetaldehyde with cyclohexylisocyanide <67MI 912-01>, and diones (**131**) and (**132**) have been prepared by the reaction of carbon suboxide with bifunctional aliphatic compounds <87H(26)1619>.

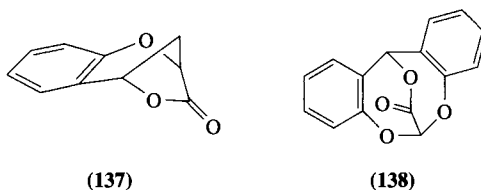


9.12.1.6 Benzoannelated Lactones

The major route to 2,3-dihydro-5*H*-1,4-benzodioxepin-5-ones (**135**) is applicable to a wide range of compounds. This route involves the reaction of a salicylate with a glycerol monochlorohydrin (**133**), or epichlorohydrin, and lactonization of the resulting salicylic ether (**134**) either by distillation *in vacuo* with a trace of alkali or treatment with sodium ethoxide (Scheme 13) <69CR(C)867, 69FRP1526823, 70FRP92526, 75BSF277>. Instead of halohydrins, epoxides (**136**) can be added to salicylic acid or its esters in the presence of a catalyst to generate intermediate (**134**) <73MI 912-01, 78USP4096119>.

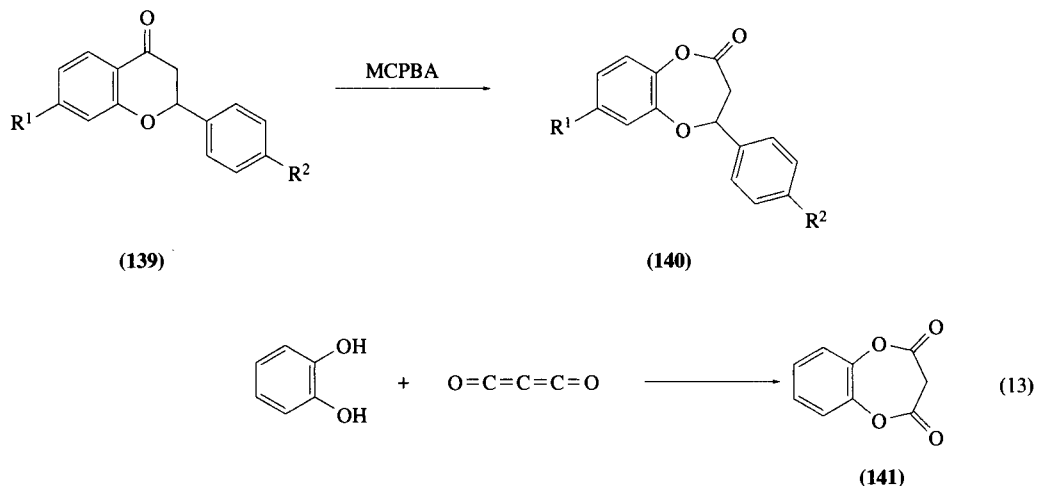


Scheme 13



The polymerization of 2,3-dihydro-5*H*-1,4-benzodioxepin-5-ones (**135**) <75GEP(O)2502154, 81USP4255152, 92USP5082925> and the sodium borohydride reduction of (**137**) have been studied <82NJC149>. The latter compounds have been used for the synthesis of benzoquinoylnaphthalenes and -chromans, which are of interest for treatment of cerebral diseases <90EUP322248>. Lactones (**138**) were of interest for agricultural use <91USP4976770>.

The major pathway to 3,4-dihydro-2*H*-1,5-benzodioxepin-2-ones (**140**) is the Baeyer-Villiger oxidation of flavanones (**139**) <91SC2263>. Reaction of catechol with carbon suboxide gave benzo-dioxepindione (**141**) <90MI 912-02>.

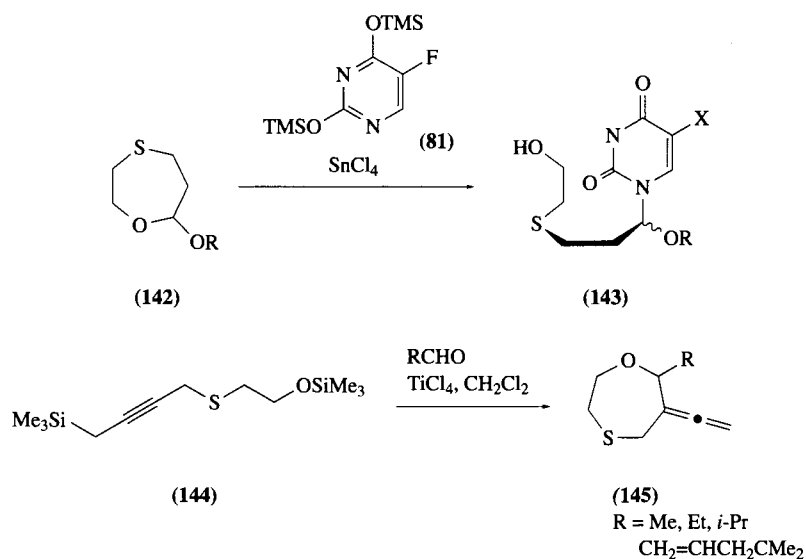


Compounds (**141**) have been tested for antimicrobial activity. 4-Phenyl-3,4-dihydro-1,5-dioxepin-2-one undergoes ring fission on treatment with LDA to afford catechol monocinnamate <94MI 912-02>.

9.12.2 1,4-OXATHIEPANES AND 1,4-OXATHIEPINS

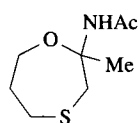
9.12.2.1 Saturated Ethers, Acetals, and Lactones

Information about 1,4-oxathiepanes is sparse. According to the synthesis of the respective dioxo derivatives, acetals (**142**) have been prepared and reacted with the pyrimidine base (**81**) to give ring-opened product (**143**) <93MIP9117147, 93SL389>, and titanium tetrachloride-catalyzed reaction of alkyne (**144**) with aldehydes gave vinylideneoxathiepanes (**145**) <88JOM43>.

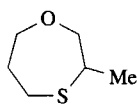


Oxathiepane (**146**) has been prepared <73RTC890>. Oxathiepanes (**147**) and (**148**) were isolated as by-products from the reaction of diallylether with hydrogen sulfide <94ZOR849> and the radical-initiated cyclization of aminothiols, respectively <82TL5039>. The synthesis of oxathiepane (**149**) has also been described <67G1770>, and (**150**) has found interest as a long-acting thiamine derivative <68JAP43011897>.

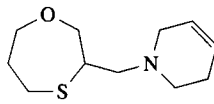
Dihydro-5*H*-1,4-oxathiepin-2(3*H*)-one (**152**) was obtained by free radical addition of thioglycolic



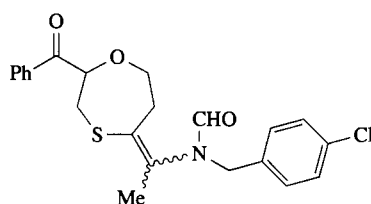
(146)



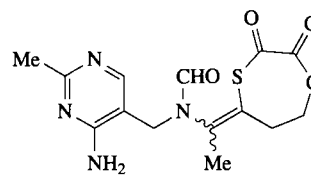
(147)



(148)

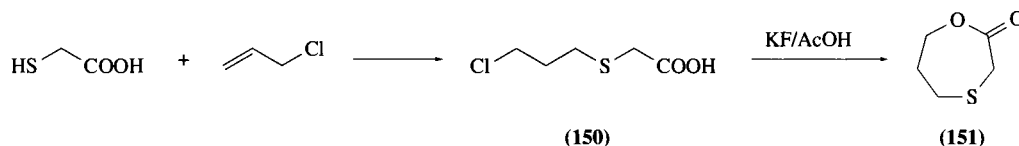


(149)

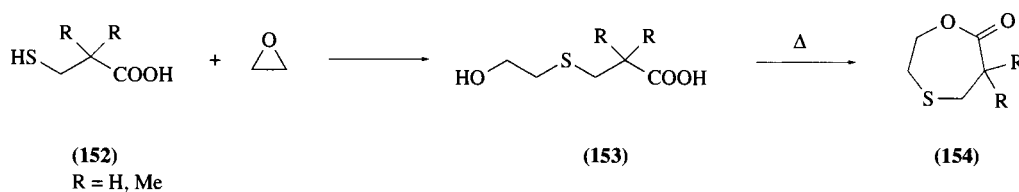


(150)

acid to allylchloride and cyclodehydration of intermediate **(150)** with potassium fluoride in AcOH <77JCS(P1)2476>. Similarly, tetrahydro-7*H*-1,4-oxathiepin-7-ones **(154)** could be prepared from β -thiopropionic acid **(152)** and oxiranes via intermediates **(153)** <71BAP661>.



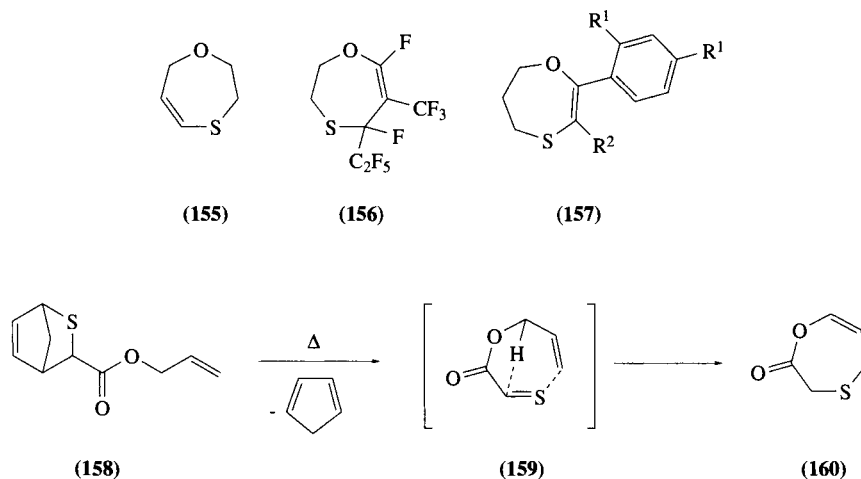
Scheme 14



Scheme 15

9.12.2.2 Oxathiepins and Benzoannelated Derivatives

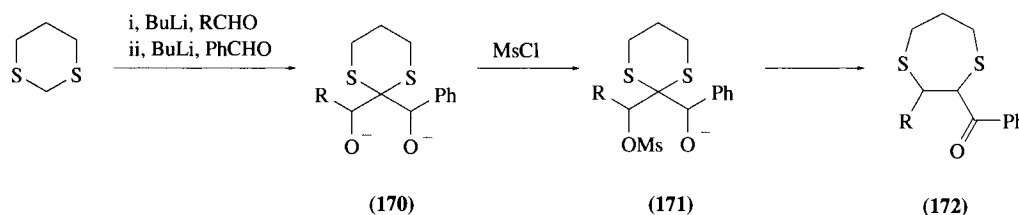
2,3-Dihydro-7*H*-1,4-dioxepin **(155)** was isolated from photolytic <80BSF361> and cyclization <80BSF353> reactions. Polyfluorinated oxathiepin **(156)**, which does not effect the ozone layer, and which is useful in the preparation of drugs and agrochemicals, was readily prepared by cyclization of perfluorinated 2-methyl-2-pentene with thioethanol in the presence of potassium carbonate <85IZV2066, 89NKK1772, 90JAP(K)01265087>. 6,7-Dihydro-5*H*-1,4-oxathiepins **(157)** have found interest in the synthesis of antifungal compounds <90CPB1258>. 5*H*-1,4-Oxathiepin-2(3*H*)-one **(160)** could be obtained by thermolysis of **(158)** and intramolecular ene reaction of the intermediate allyl thioacetate **(159)** (Scheme 16) <90CC138, 92JCS(P1)191>. Lactone **(161)** was observed as a by-product in the total synthesis of ($\pm$)-diplodialide-A <79JCS(P1)323>. Reaction of polyfluoro-2-alkynoic acids with thioethanol gave polyfluorinated oxathiepins **(162)** and **(163)**, respectively <92JFC(57)177>.



Scheme 16

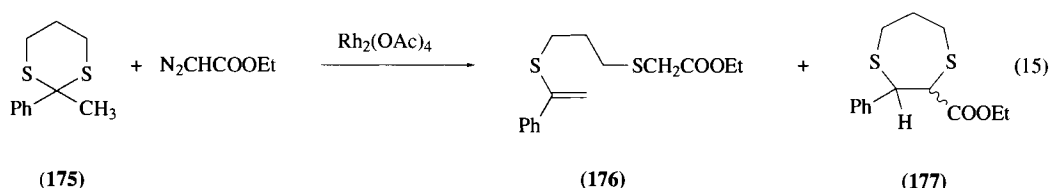
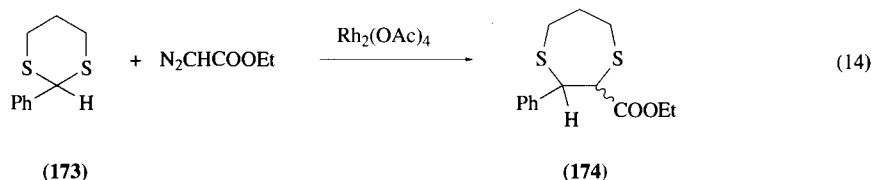
Analogous to the synthesis of 1,4-benzodioxepin-5-ones, the benzoxathiepinones **(166)** were prepared by the reaction of ethyl 2-thiobenzoates with chlorohydrin and glycerol chlorohydrin and cyclization of intermediate **(165)** (Scheme 17) <75BSF277>. The sodium borohydride reduction of benzoxathiepinone **(167)** has also been studied <82NJC149>.

ment reactions of a 1,3-dithian moiety to give 1,4-dithianes have also been observed in the reactions of carbohydrate derivatives <74CC811, 77T393>.

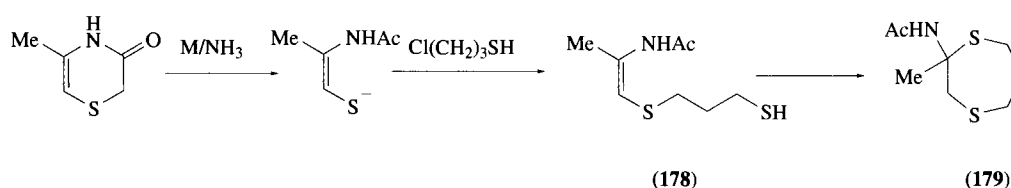


Scheme 19

Sulfur ylides have been generated by the rhodium(II)-catalyzed decomposition of diazo esters in the presence of 1,3-dithianes (173) and (175). The intermediate sulfur ylides undergo [1,2]rearrangement to give 1,3-dithiepanes (174) and (177); however in the case of substrate (175), the elimination product (176) predominates <84JOC1917>. 6-Benzoyl-1,4-dithiepane has been prepared by the reaction of ethane-1,2-dithiol with acetophenone and formaldehyde, but similar reactions with other ketones gave mostly polymeric products <79ZOR1709>. Several 2-substituted 1,4-dithiepanes have been isolated, as by-products, in the macrocyclization of alkynes with 1,3-propane-dithiol <93MI 912-02>.



2-Methyl-1,4-dithiepane was obtained from diallyl sulfide and hydrogen sulfide in HMPA <90IZV2669>. UV Irradiation of hexane solutions of the corresponding allylic thiols gave 2,5-diethyl- and 2-ethyl-5-methyl-1,4-dithiepanes as dimers <73NKK1366>. 2-Acylamino-substituted 1,4-dithiepanes were prepared from (178) by the reaction sequence shown in Scheme 20 <73RTC890>.

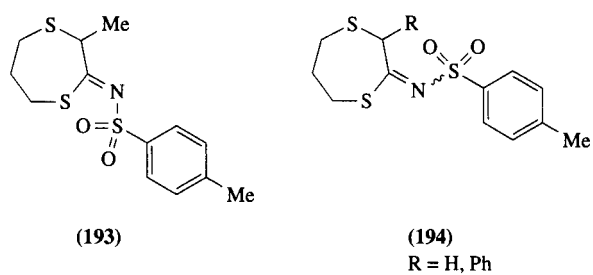
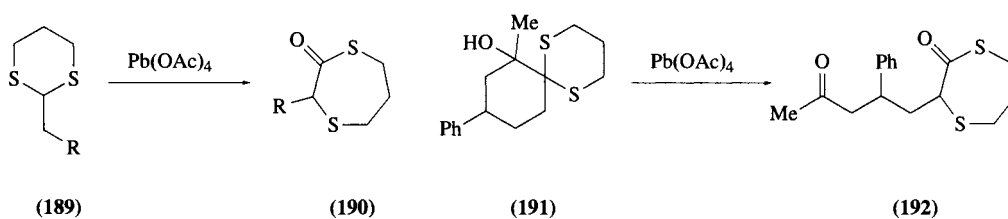
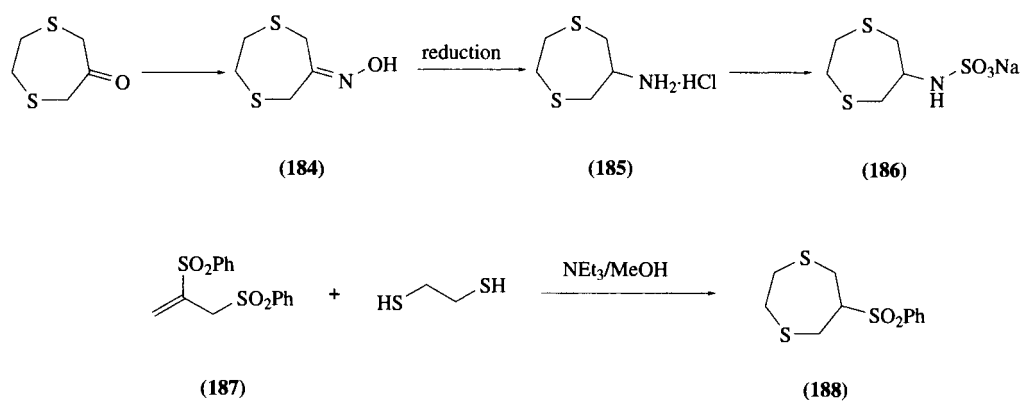
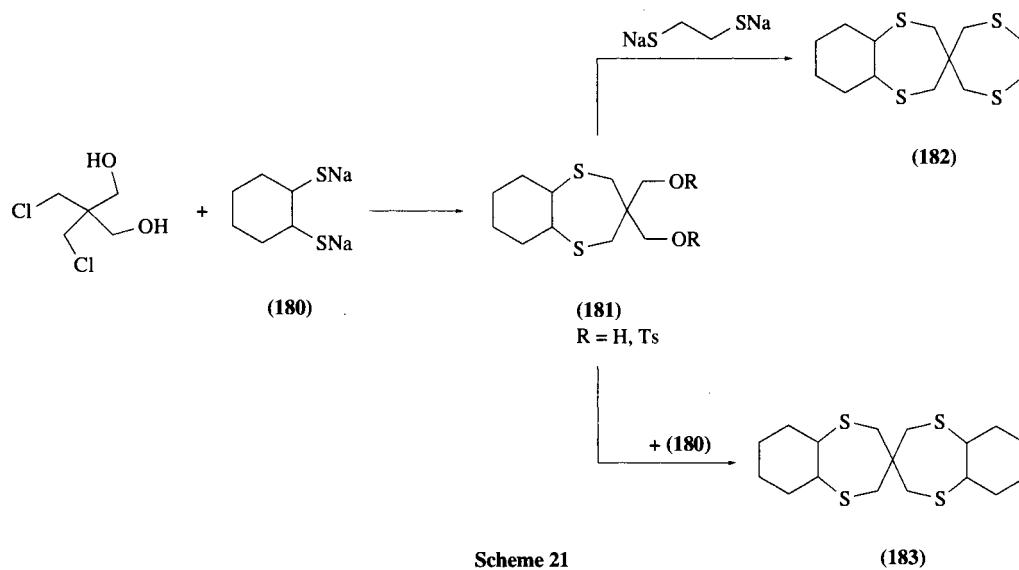


Scheme 20

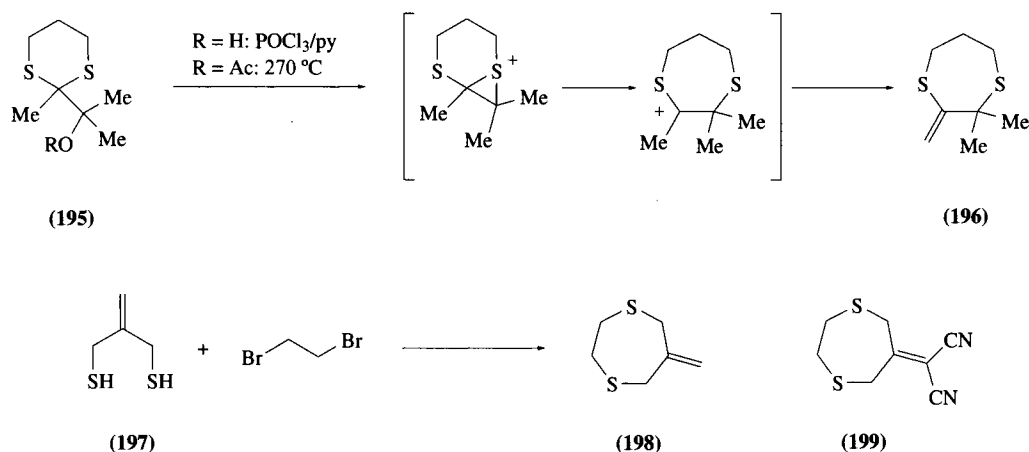
Several seven-membered thiaspiranes have been synthesized by the reaction of tosylate (181) with 1,2-dithiolates (Scheme 21) <77M885, 78MI 912-02>, and spirocyclic heterocycles incorporating a 1,4-dithiepanering have also been synthesized from 1,4-dithiepan-6-one <76IJC(B)777>.

The thiocyclamate analog (186) was prepared from 1,4-dithiepan-6-one via oxime (184) and amine (185) <90AP(323)317>. Coupling of 2,3-bis(phenyl-sulfonyl)-1-propene (187) with ethanedithiol gave phenylsulfonyl derivative (188) <92JOC298>.

Oxidative cleavage of 1,3-dithianes (189) with Pb(OAc)₄ is the major route to thiolactones (190) <80CPB558>. Oxidative *seco*-rearrangement of hydroxy-1,3-dithianes gave 3-substituted 1,4-dithiepan-2-ones (e.g., (192) from (191)) <80JOC1839; 78HCA3087, 76JA4313>. The preparation of benzene-sulfonamides (193) and (194) has also been described <88TL6475>.



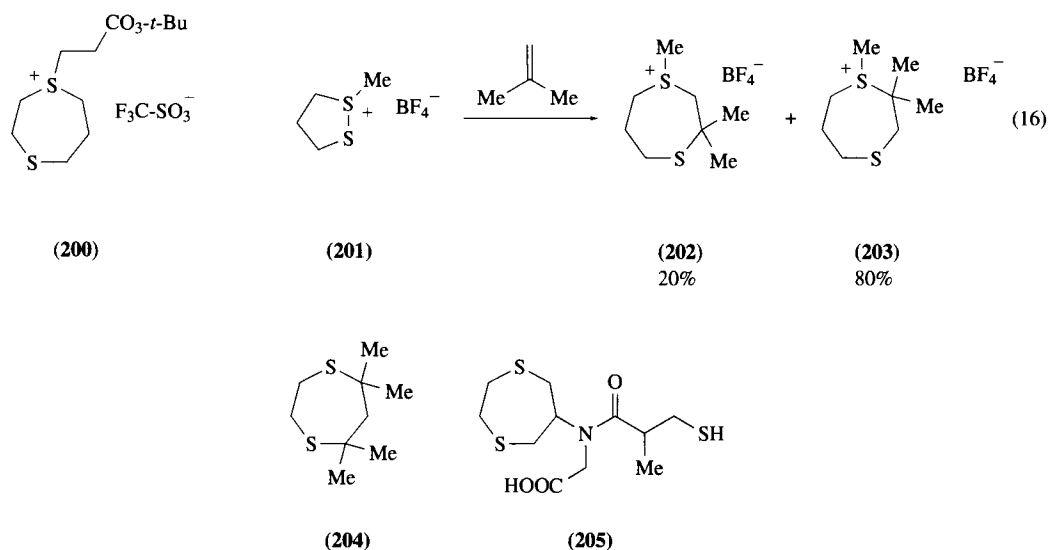
The synthesis of 2,2-dimethyl-3-methylene-1,4-dithiepane (**196**) was achieved either by treatment of α -hydroxy-1,3-dithiane (**195**; R = H) with POCl₃ in pyridine, or by thermolysis of the corresponding acetate (**195**; R = Ac) <85JOC4218>. 6-Methylene-1,4-dithiepane (**198**) could be obtained from 2-methylene-1,3-dithiol and dibromoethane <73GEP100001>, and the synthesis of derivative (**199**) has also been reported <71IJC904>.



Scheme 24

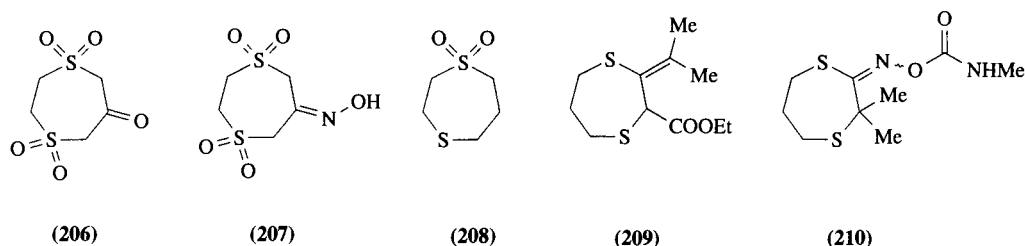
9.12.3.1.2 Reactivity and applications

The anodic oxidation of 1,4-dithiepane has been studied <79JA1040>, and laser flash photolysis of sulfonium salt perester (**200**) gave two-sulfur, three-electron stabilized radical cations <92TL1721>. 1,2,2- and 1,3,3-Trimethyl-1,4-dithiepanium tetrafluoroborates (**202**) and (**203**) have been prepared by the reaction of (**201**) with 2-methylpropene, and they have been reacted with tertiary amines to give thioammonium ions (Equation (16)) <82JA3231>. 1,4-Dithiepane (**204**) has found interest as potential complexing agent precursor for technetiated radiopharmaceuticals <91BSF286>. 1,4-Dithiepane (**205**) was prepared, and its angiotensin converting enzyme-inhibiting activity has been tested <83JMC1267>. The coordination chemistry of 1,4-dithiepanes as a bidentate ligand was reviewed <92CCR133>, and the conformations of 1,4-dithiepanes and 1,4-dithiepan-6-ones have been studied <81T2735, 83OMR(21)339>.



1,4-Dithiepan-6-one and its derivatives have been used for the synthesis of dithiaalkenylphosphates and phosphorothioates, which have been tested as pesticides <89USP4814325>, and it has been used for the preparation of (oximinoalkyl)spiropyranones and 3-amino-2-hydroxypropyloximino heterocycles, which have found interest as herbicides <88MIP8800945> and betablockers, respectively <89USP4803286>. Similarly, *O*-(alkyl- or aryl-carbamoyl)oximes of 1,4-dithiepan-6-ones have found interest as insecticides <69GEP(O)1812762>.

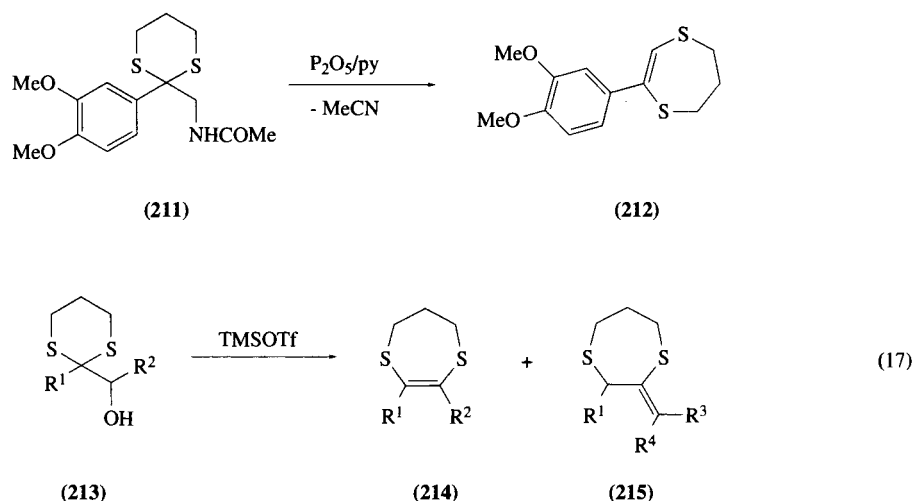
1,4-Dithiepanes can readily be oxidized to give the disulfones, and several functionalized disulfones (e.g., (206) and (207)), have been prepared <71IJC904>. The preparation of monosulfones (e.g., (208)) was achieved using *m*-chloroperbenzoic acid, DMSO, or sodium periodate, but the latter reagent has proved to be the reagent of choice for monooxidation <78JA6416, 78JOC4295, 87JOC4254>. 1,4-Dithiepane (209) was used as a precursor for the synthesis of antisecretory and antiulcer agents <78USP4109006>, and derivatives (210) have found interest as acaricidal, insecticidal, and nematocidal compounds <75JAP(K)50025733, 76BRP1422360>.



9.12.3.2 1,4-Dithiepins

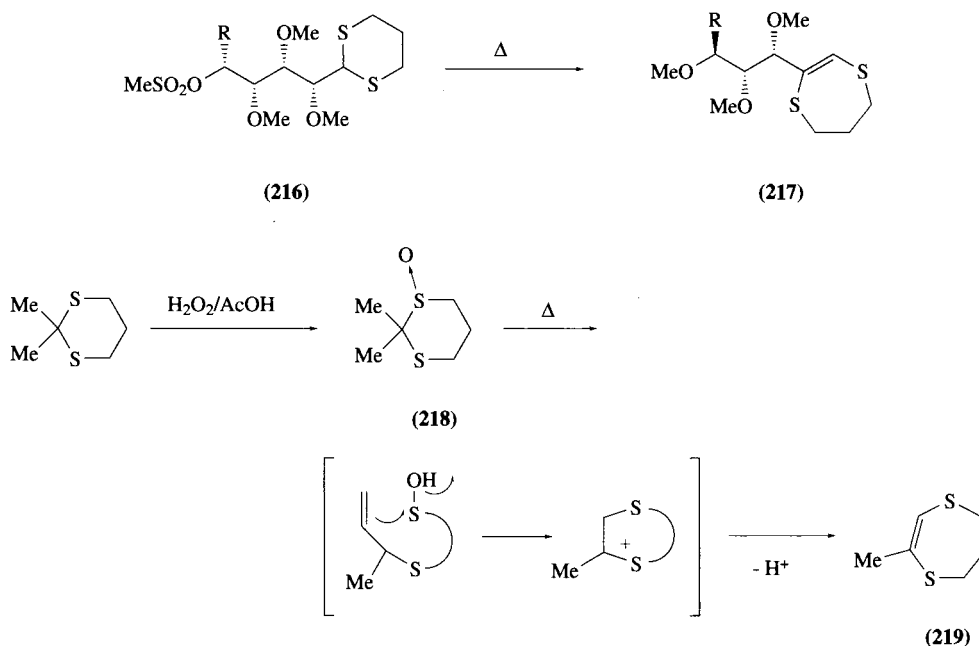
9.12.3.2.1 Synthesis

6,7-Dihydro-5*H*-1,4-dithiepins have mainly been prepared by ring-expansion reactions. Thus, 1,3-dithian derivative (211) upon treatment with P_2O_5 in pyridine gave dithiepin (212) by a one-carbon ring-expansion <70JOC823>. Similarly, trimethylsilyl triflate-catalyzed dehydration of 2-(hydroxymethyl)-1,3-dithiane derivatives (213) gave 1,4-dithiepins (214) as the major products, together with 2-alkylidene-1,4-dithiepanes (215) (Equation (17)) <79JHC1081, 89H(29)2079>.

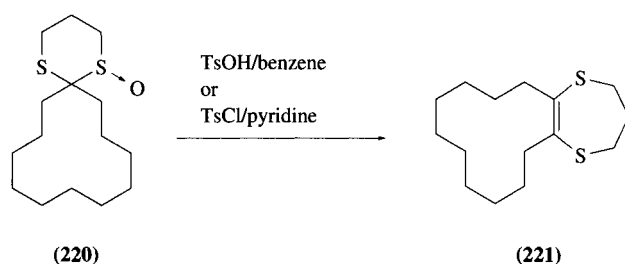


Reaction of 1,3-dithianes derived from alkylated or arylated ketones with tellurium tetrachloride also gave 6,7-dihydro-5*H*-1,4-dithiepins <92PS(67)261>. *O*-Methylated 1,3-dithiane derivatives of common sugars (216) bearing a mesylate at the five-position undergo ring expansion on heating with concomitant intramolecular relay of the 2-alkoxy group to the five-position to give dithiepins (217) <93H(36)1213>. Moreover, thermal β -*cis*-elimination of cyclic sulfone (218) and subsequent ring-expansion gave dithiepins (219), but in a poor yield (Scheme 25) <77JOC1530>. This process could be

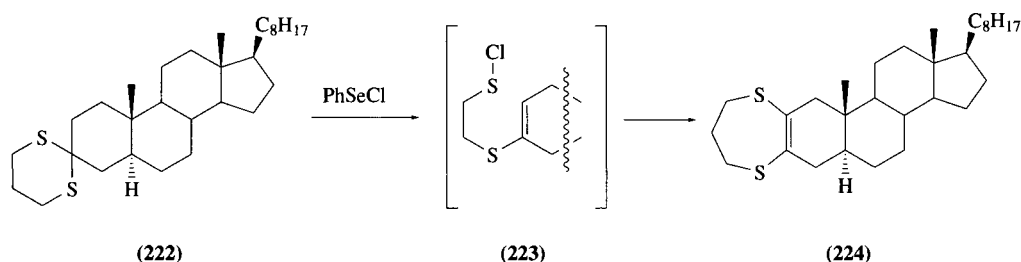
improved by use of TsOH in benzene or TsCl in pyridine, for example, the ring-expansion of cyclic sulfone (220) to (221) <85JOC4218>.



Scheme 25

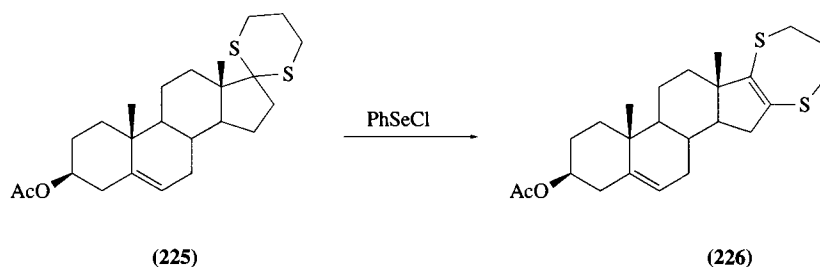


A closely related ring-expansion of the steroidal 1,3-dithianes (222) and (225) to dihydro-1,4-dithiepins (224) and (226) by use of phenylselenenyl chloride in methylene chloride has also been reported <84TL1621>.

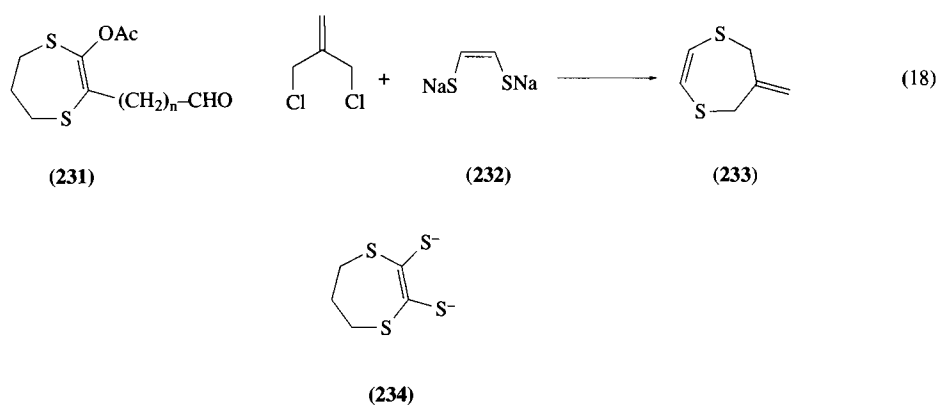
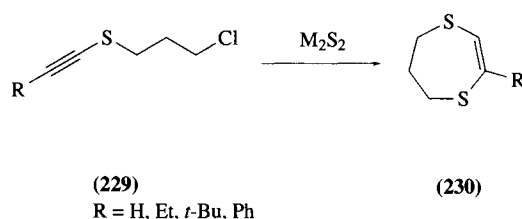
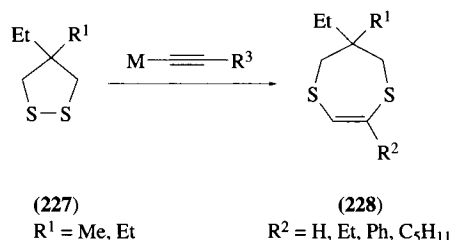


Scheme 26

Cleavage of the S—S bond of polymerization-resistant 1,2-dithiolanes (227) with acetylides gave dihydro-1,4-dithiepins (228) <95CC1763>. A number of two-substituted dihydro-1,4-dithiepins (230) have been synthesized by reaction of alkynes (229) with alkali metal sulfides <81MI912-01>. Dihydro-1,4-dithiepins (230) could also be obtained by the addition of Grignard reagents to halogen-substituted ketene dithioacetals <78TL4315>, and dihydro-1,4-dithiepins of type (231) with an unprotected aldehyde group in the side chain have been prepared by Pb(OAc)₄ oxidation of α-hydroxy

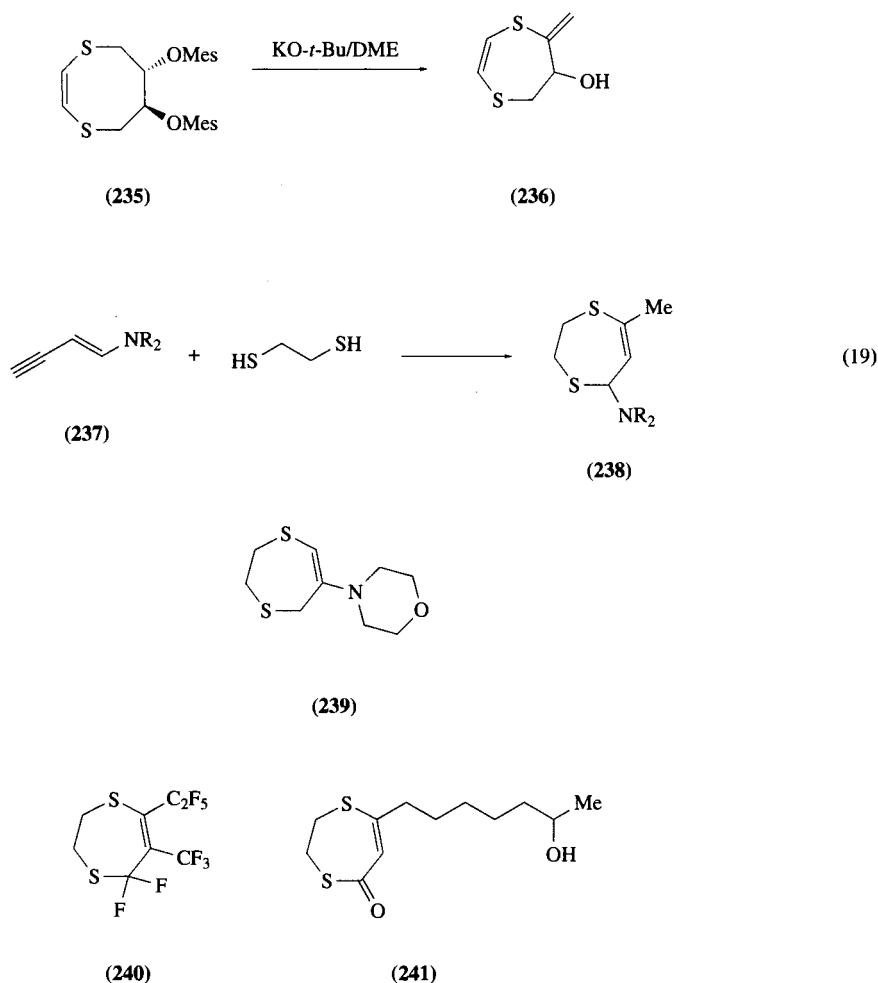


thioacetal precursors <78HCA3087>. Reaction of 1,3-dichloro-2-methylene-propane with *cis*-thioethene (**232**) afforded dihydro-1,4-dithiepin (**233**) <68ZC220>. The electrochemical synthesis of 6,7-dihydro-2,3-dithiol-5*H*-1,4-dithiepin (**234**) has been described <78MI 912-02>, and the disodium salt of (**234**) and its 6-methylene derivative or the dipotassium salt have often been used as a ligand in the synthesis of metal complexes <93ICA53, 94MI 912-03, 94MI 912-04, 95SM1101>.

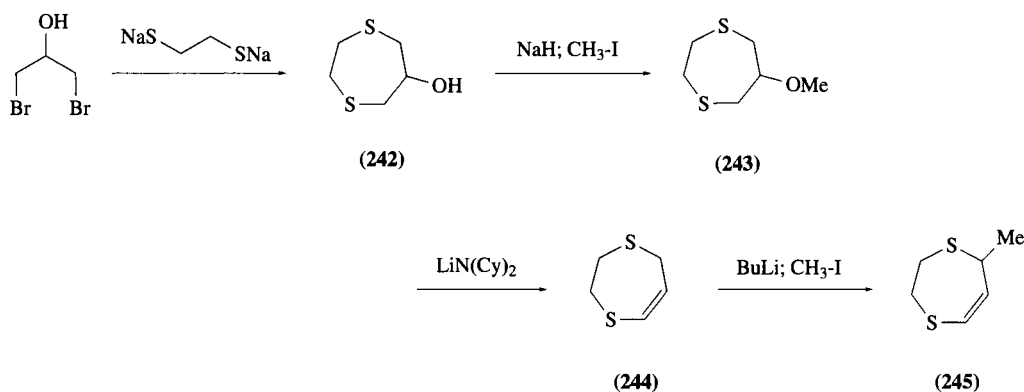


Alcohol (**236**) with an exocyclic double bond in the five-position of the dihydro-1,4-dithiepin ring was formed by ring-contraction of dithiocin (**235**) <77T2151>.

Only a few reports deal with the synthesis of 2,3-dihydro-5*H*-1,4-dithiepins. Thus, reaction of enynes (**237**) with ethanedithiol gave the amino-substituted derivatives (**238**) <84URP1109401, 88ZOR88>, and the syntheses of compounds (**239**) <71IJC904>, (**240**) <85IZV2066>, and (**241**) <79JCS(P1)323> have been reported.



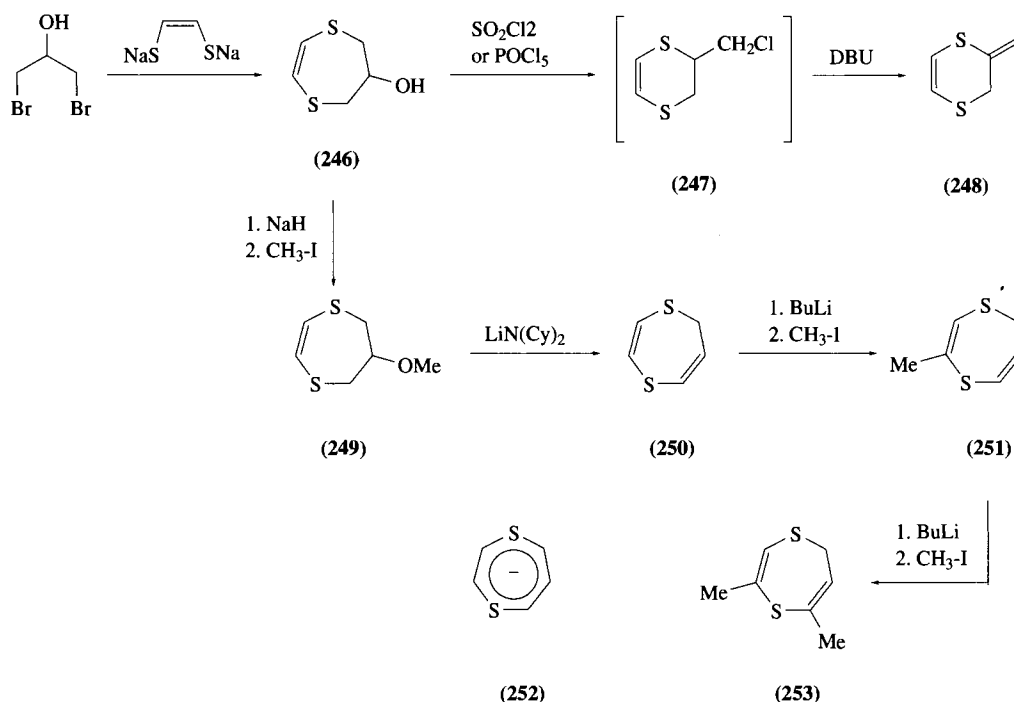
The parent member of this class of compounds, 2,3-dihydro-5*H*-1,4-dithiepin (**244**), was obtained from (**242**) by *O*-methylation and elimination with lithium dicyclohexylamide, and further lithiation and treatment with methyl iodide gave 5-methyl derivative (**245**) (Scheme 27) <75TL1895>.



Scheme 27

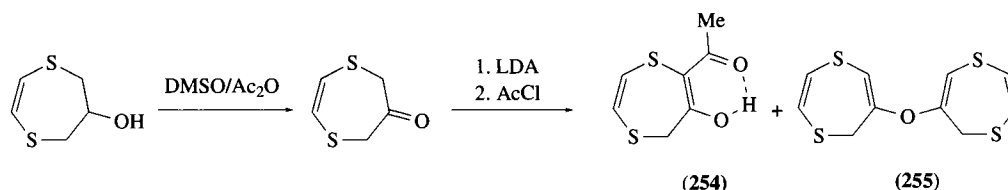
The synthesis of the fully unsaturated 5*H*-1,4-dithiepin (**250**) could be achieved by the same methodology starting with *cis*-dithioethene <75TL1895>. Earlier attempts to transform alcohol (**246**) into the chloride only gave ring-contraction product (**248**) via intermediate (**247**). The fully unsaturated 5*H*-1,4-dithiepin has been of interest because its anion (**252**) may be regarded as a potential

10 π -electron monocyclic aromatic system. However, treatment of (250) with BuLi and trapping with methyl iodide gave the methyl-substituted dithiepin (251), and repetition of this process led to dimethyl derivative (253). From these results, it was concluded that the anion (252) is lacking any aromatic stabilization by a 10 π -electron delocalization.



Scheme 28

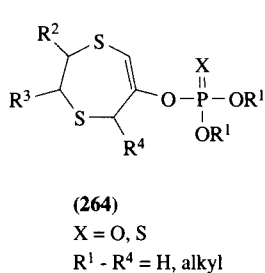
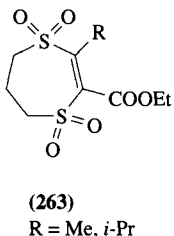
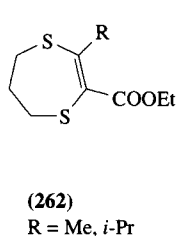
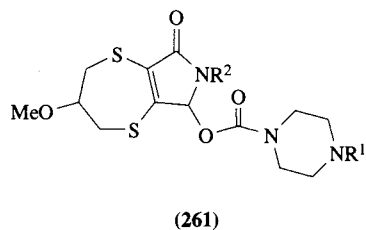
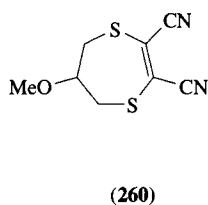
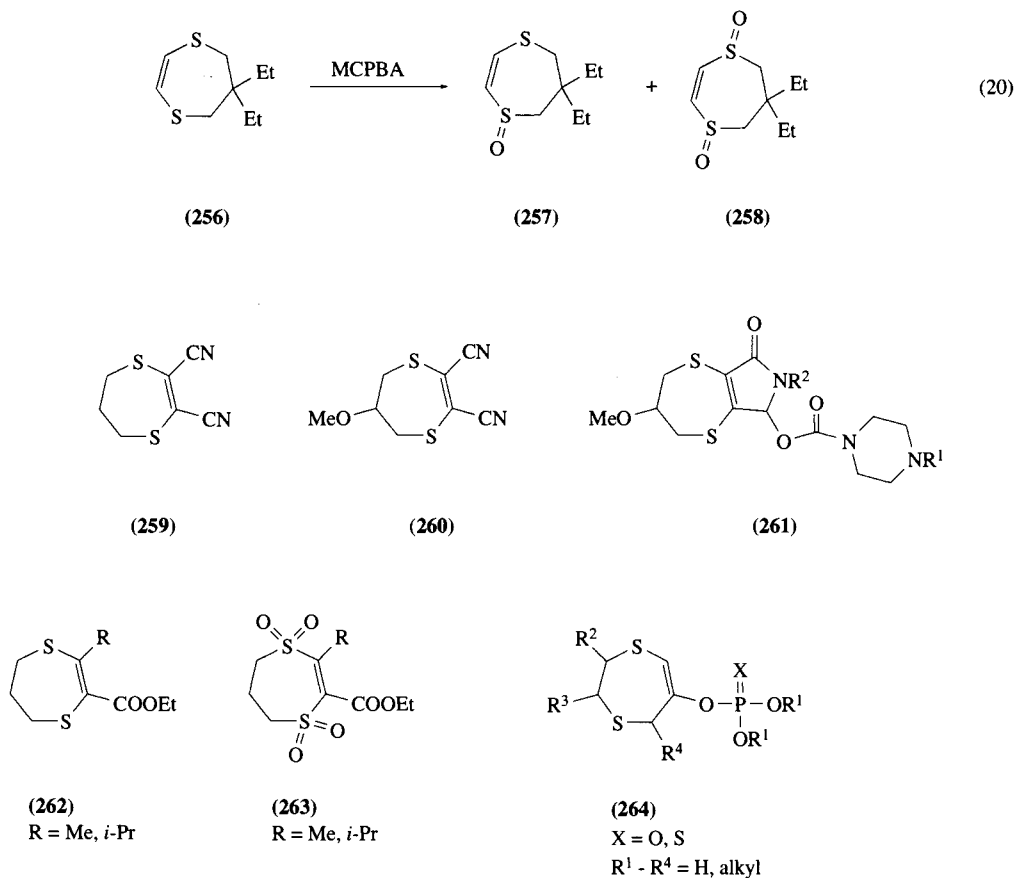
The substituted dithiepin derivatives (254) and (255) have been prepared from 6,7-dihydro-5*H*-1,4-dithiepin-6-one by formation of the anion and acylation <76CB2928>.



Scheme 29

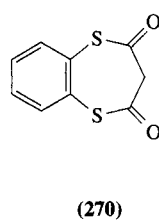
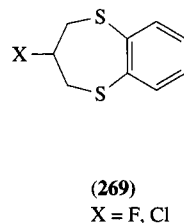
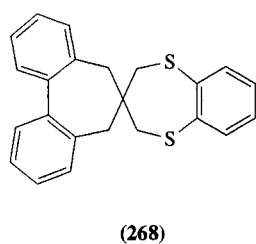
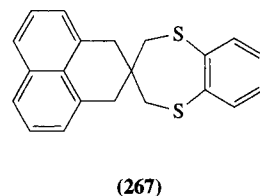
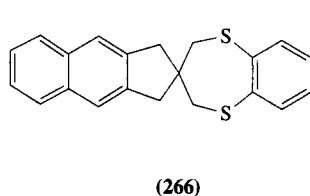
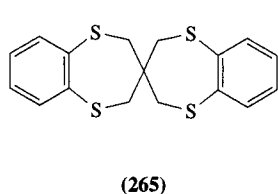
9.12.3.2.2 Reactivity and applications

Oxidation of dithiepin (256) with *m*-chloroperbenzoic acid afforded a nearly equal amount of monosulfoxide (257) and a diastereomeric mixture of bis-sulfoxides (258) <93SUL243>. Cleavage of 6,7-dihydro-2,3-diphenyl-5*H*-1,4-dithiepin with low-valent metallic reductants gave 1,2-diphenylethyne <89H(29)2079>. Dicyano derivative (259) was applied in the synthesis of dithiacrown ethers <96IC959>. The synthesis of esters (261), which have found interest as tranquilizers, muscle relaxants, and anticonvulsants, involves cyclization of dicyano derivative (260) <77GEP2707072, 80EUP17523>. Dihydrodithiepins (262) and the corresponding sulfoxes (263) were prepared for use as antisecretory and antiulcer agents <78USP4109006>, and a number of phosphates and phosphorothioates of type (264) and the corresponding sulfoxides and sulfones have been prepared and tested for use as pesticides <89USP4814325>.

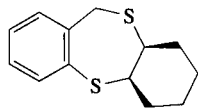


9.12.3.3 Benzoannelated Derivatives

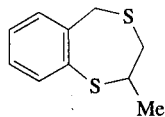
A number of spirobenzodithiepins (**265**)–(**268**) have been synthesized ^{<77M885, 94M1145>}, and a steroidal derivative has been prepared ^{<93LA11>}. The conformations of (**269**) have been studied ^{<90CJC513>}, and thiolactones (**270**) have been tested for antimicrobial activity against gram positive microorganisms and blastomycetes ^{<90MI 912-02>}.



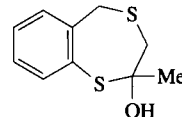
The syntheses of compounds (271), (272), and (273) have also been reported <71JOC3971, 92TL2517>.



(271)



(272)



(273)

9.13

Seven-membered Rings with Three Heteroatoms 1,2,3

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9.13.1 INTRODUCTION

Numerous isomeric ring systems are possible in the seven-membered rings with three heteroatoms (triheteroepines), depending upon the type and the relative positions of the three heteroatoms and the degrees of unsaturation. Based on the positions, there are four possible classes of triheteroepine ring systems, 1,2,3- **(1)** (this Chapter), 1,2,4- **(2)** (Chapter 9.14), 1,2,5- **(3)** (Chapter 9.15), and 1,3,5-triheteroepines **(4)** (Chapter 9.16); wherein, X, Y, and Z may be the same or different heteroatoms and represent N, O, and S. Within each of the above triheteroepines, there are ten further theoretically possible ring systems depending on the type of the heteroatoms. These are triazepine, oxadiazepine, thiadiazepine, dioxazepine, dithiazepine, oxathiazepine, trioxepine, dioxathiepine, oxadithiepine, and trithiepine rings.



(1)

1, 2, 3-



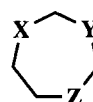
(2)

1, 2, 4-



(3)

1, 2, 5-



(4)

1, 3, 5-

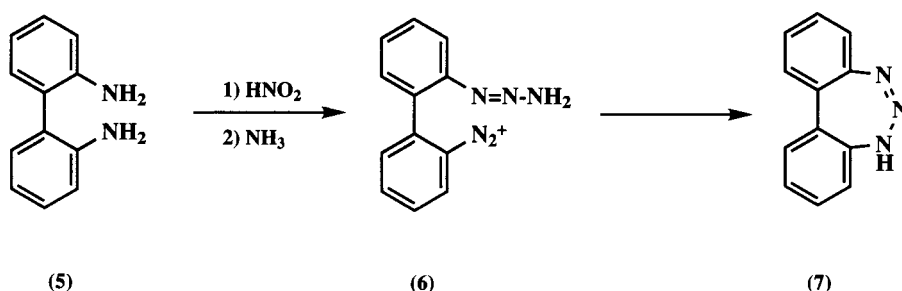
However, there has been less systematic study of these triheteroepines than those of monoheteroepines and diheteroepines. Some of them have received considerable attention and are well-known, but others receive considerably less and some are still unknown. Although a wide variety of triheteroepine systems has been reported in the literature, little is presently known about the reactivities of the majority of these systems, many of which have been prepared merely to explore their biological activities. Therefore, in the four related chapters (9.13–9.16), the preparative methods are mainly described and important aspects of the reactivity of the products are shown in the same section, because the organization of the chapters into separate sections on theoretical method, experimental and structural methods, reactivities, and syntheses is difficult. Some of the important literature, which was published before 1982 but had not appeared in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I), is also covered in the present chapters.

9.13.2 TRIAZEPINES

Of the four triazepine systems, the 1,2,3-diazepine system is by far the least studied class and only a few papers dealing with fused 1,2,3-triazepine systems have been published and the number of known compounds of this type is still low. Monocyclic 1,2,3-triazepines have not been prepared.

9.13.2.1 Fused 1,2,3-Triazepines

A series of 5*H*-dibenzo[*d,f*]-1,2,3-triazepines (**7**) has been prepared as the first reported 1,2,3-triazepine systems by the reaction of 2,2'-diaminobiphenyl (**5**) with nitrous acid followed by aqueous ammonia <72BCJ2507, 72CC982, 74JCS(P1)1248, 75JCS(P1)19>. Although various mechanisms are considered for the formation of (**7**) from (**5**) since complexities are revealed when ammonia is replaced by methylamine, the intermediacy of the triazenodiazonium species (**6**) has been suggested (Scheme 1).

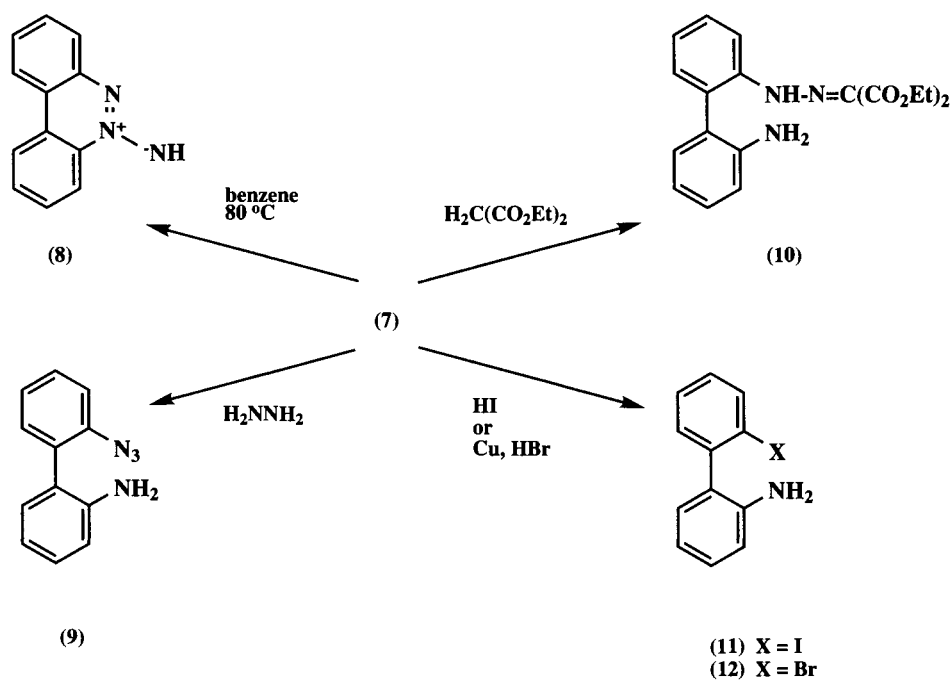


Scheme 1

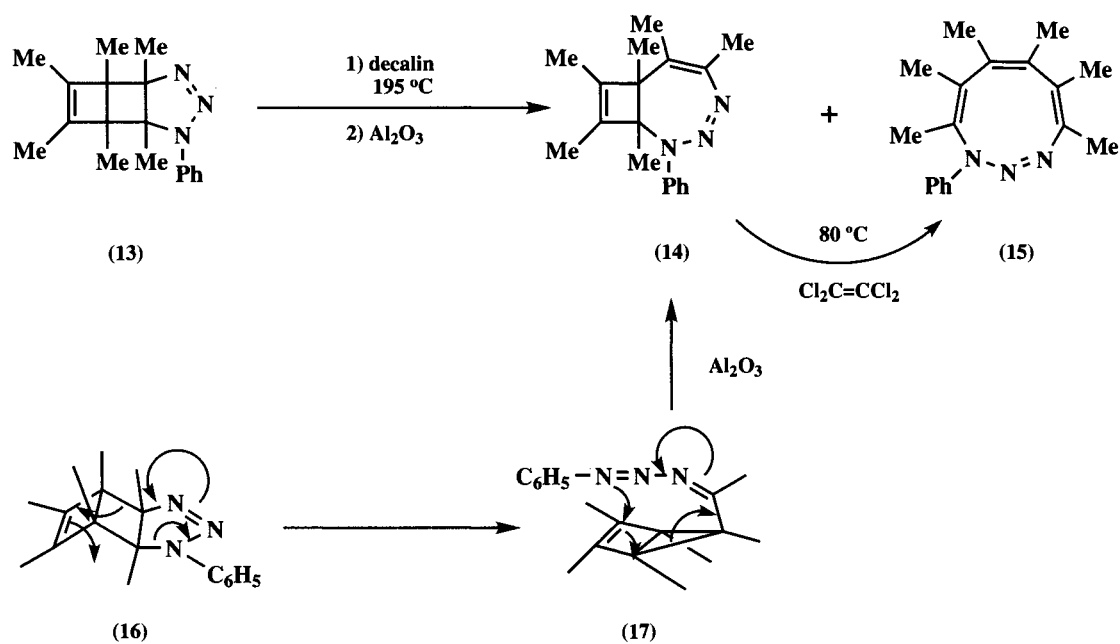
Several reactions of the triazepine (**7**) have been examined. Heating (**7**) at 80°C in benzene results in isomerization to form quantitatively benzo[*c*]cinnoline *N*-imide (**8**), which is also obtained directly from the diaminobiphenyl (**5**) by aprotic diazotization without isolation of the triazepine intermediate (**7**). The triazepine (**7**) reacts as a masked diazonium compound with hydrazine, hydriodic acid, hydrobromic acid and copper, or diethyl malonate to give the corresponding products (**9**)–(**12**), respectively (Scheme 2).

Thermolysis of the triazolo-hexamethyl (Dewar benzene) (**13**), prepared from hexamethyl (Dewar benzene) and phenyl azide <72JA529>, in refluxing decalin affords the cyclobuteno[*d*]-1,2,3-triazepine (**14**) (14% yield), together with the 10π electronic triazonine derivative (**15**) (42% yield) <72JA534>. A conceivable pathway could involve backside participation of the alkenic π system in (**16**) with simultaneous rupture of the triazoline ring to afford the bicyclopentene intermediate (**17**), which was converted into (**14**) on the alumina absorbent employed in the chromatographic separation. In addition, the triazepine (**14**) has been found to be smoothly transformed into the triazonine (**15**) at 80°C in tetrachloroethylene (Scheme 3).

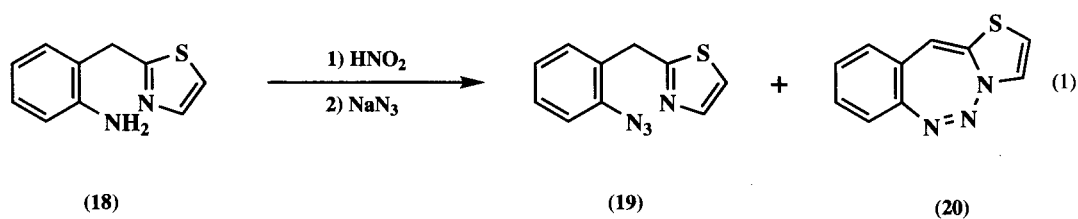
The third known example is thiazolo[3,2-*c*]-1,2,3-benzotriazepine (**20**) <81JCS(P1)1132>, which was obtained in 21% yield as a by-product in the diazotization of 2-(2-aminobenzyl)thiazole (**18**), followed by treatment with sodium azide, with the aim of obtaining the azide compound (**19**) (Equation (1)).



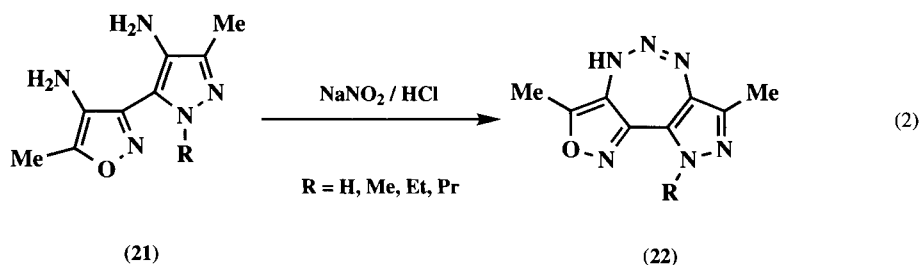
Scheme 2



Scheme 3



The diazotization in hydrochloric acid of the diaminopyrazolylisoxazoles (**21**) resulted in a subsequent intramolecular coupling reaction to lead to the isoxazolo[4,3-*d*]pyrazolo[3,4-*f*]-1,2,3-triazepines (**22**) in high yields (Equation (2)) <87JHC1309>. In the IR spectra of (**22**), very broad bands have been observed at 3200–2700 cm⁻¹ attributable to the imino group, but in the ¹H NMR spectra it was not possible to observe the NH signal of the triazepine ring, because of its high mobility.

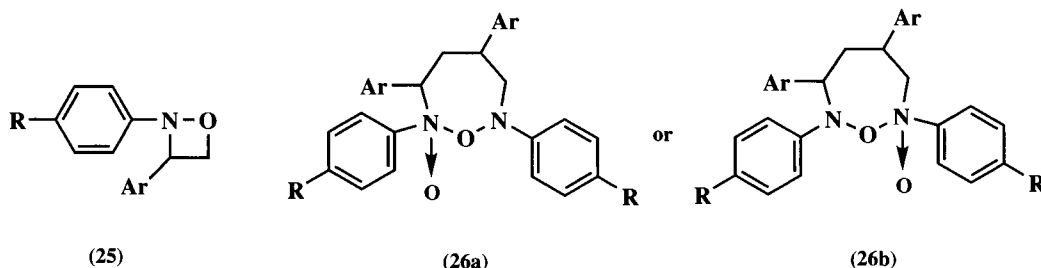
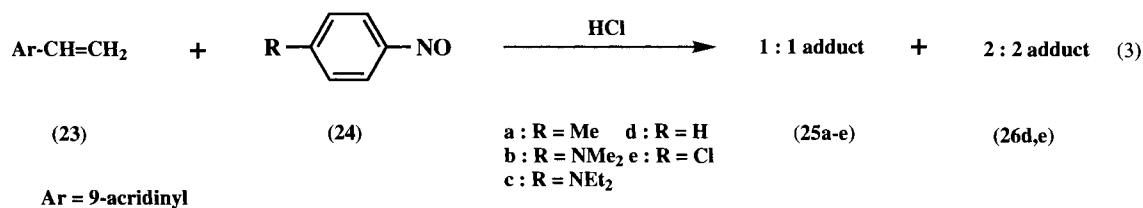


9.13.3 OXADIAZEPINES

Only one class of fully saturated 1,2,7-oxadiazepine ring system has been reported, although no examples of 1,2,3-oxadiazepine systems are yet known.

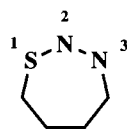
9.13.3.1 1,2,7-Oxadiazepines

In the presence of hydrochloric acid, 9-vinylacridine (**23**) reacts with nitrosobenzenes (**24**) possessing an electron-donating group (Me, NMe₂ or NEt₂) in the 4-position to yield only the 1:1 cycloadducts (**25**), four-membered oxazetidines; whereas, the reaction of (**23**) with nitroso- or *p*-chloronitrosobenzene gave the 2:2 cycloadducts (**26**), to which the perhydro-1,2,7-oxadiazepine structures (**26a**) or (**26b**) have been tentatively assigned, in about 20% yields, together with a large quantity of tarry material and traces of the oxazetidines (**25**) (Equation (3)) <72BCJ3187>.

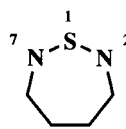


9.13.4 THIADIAZEPINES

Both of the two possible ring systems, 1,2,3- (**27**) and 1,2,7-thiadiazepines (**28**), have been reported.



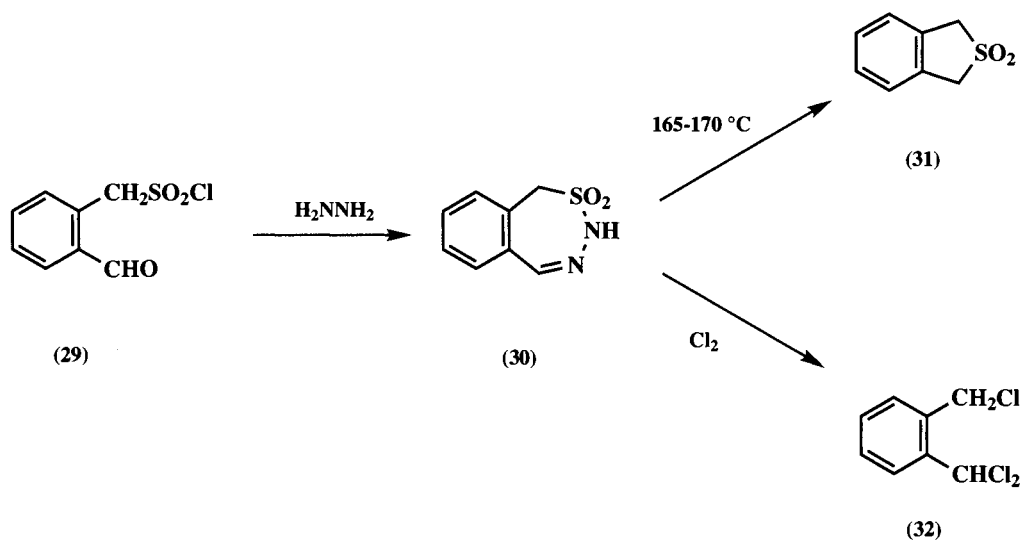
(27)



(28)

9.13.4.1 1,2,3-Thiadiazepines

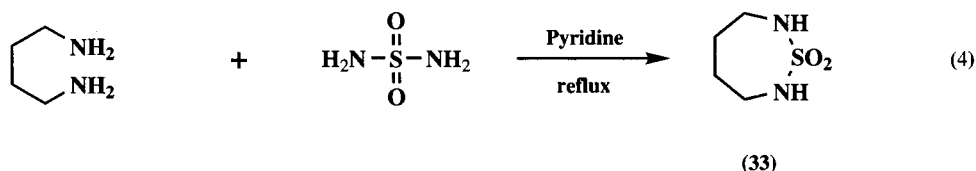
The only known example of this ring system is the 3*H*-2,3,4-benzothiazepine 2,2-dioxide (**30**), which can be prepared by the reaction of (*o*-formylphenyl)methanesulfonyl chloride (**29**) with hydrazine hydrate in 76% yield (Scheme 4) <71CJC943>. On heating (**30**) just above its melting point (163–167°C, dec.) for a few minutes, the evolution of gas ceases and the sulfone (**31**) is formed in good yield. The thiadiazepine (**30**) reacts readily with chlorine at 0°C with loss of both nitrogen and sulfur dioxide to give *o*-chloromethylbenzal chloride (**32**) (Scheme 4).



Scheme 4

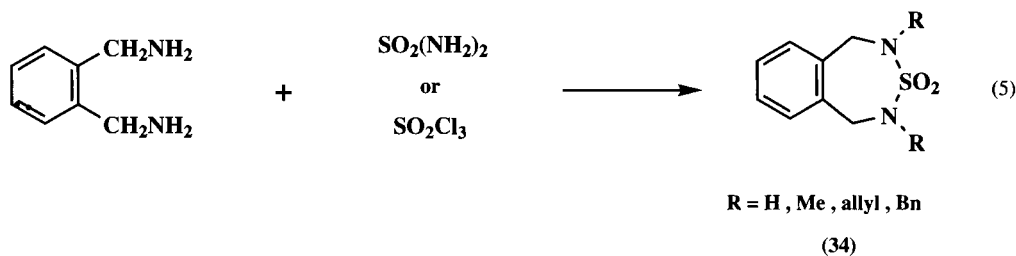
9.13.4.2 1,2,7-Thiadiazepines

Several 1,2,7-thiadiazepine derivatives have been prepared. Polyalkylenediamines react with sulfamide to afford cyclic sulfamides. Thus, 1,4-diaminobutane reacts with sulfamide in refluxing pyridine to give the hexahydro-1,2,7-thiadiazepine (**33**) in 93% yield (Equation (4)) <76IJC766, 78CB1915>.

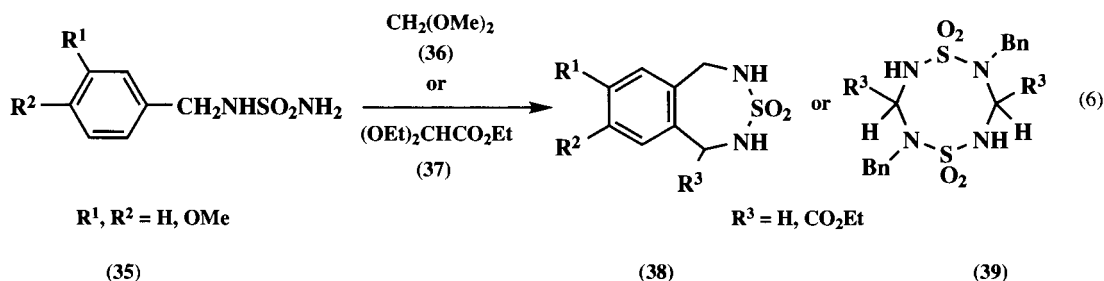


(33)

The synthesis of the benzo analogue (**34**; R = H), 3,2,4-benzothiadiazepine derivative, has also been achieved by the reaction of *o*-xylylenediamine with sulfamide or sulfonyl chloride <76IJC766, 74M114>. The dialkylation of the sodium salts of (**34**; R = H) with alkyl halides gives the corresponding dialkyl derivatives (**34**; R = Me, Bn or allyl), several of which can be prepared directly from *o*-xylylenediamine by treatment with *N,N'*-dialkylsulfamides (Equation (5)).

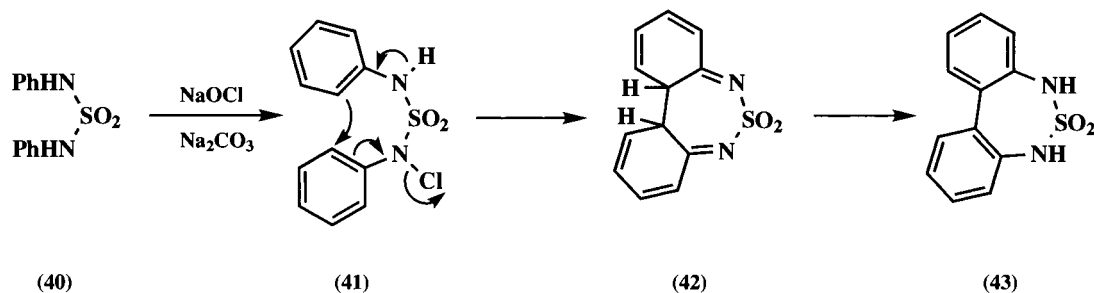


Treatment of the parent *N*-benzylsulfamide (35; $\text{R}^1 = \text{R}^2 = \text{H}$) with either dimethoxymethane (36) or ethyl diethoxyacetate (37) in trifluoroacetic acid (TFA) yielded only dimers (39), while the intramolecular α -sulfamide alkylation proceeded predominantly in the reaction of the electron-rich 3-methoxy-benzylsulfamides (35; $\text{R}^1 = \text{OMe}$, $\text{R}^2 = \text{H}$ or OMe) with (36) or (37) giving rise to the 1,2,4,5-tetrahydro-3,2,4-benzothiadiazepine 3,3-dioxides (38) in good yields (Equation (6)) <90JHC2107, 90JOC6098>.



The structural identity of (38; $\text{R}^1 = \text{OMe}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{CO}_2\text{Et}$) has been verified by conversion of this adduct to the *N,N'*-dimethyl derivative, of which x-ray crystallographical analysis confirmed the proposed benzo-annulated thiadiazepine structure. In the crystal structure, the ring adopts a seven-membered chair-like conformation, and significant delocalization of the electron pairs on both nitrogens is indicated by the sum of the torsion angles ($346\text{--}350^\circ$) around each of these atoms.

The dibenzo[*c,e*]-1,2,7-thiadiazepine (43) can be prepared by oxidation of *N,N'*-diphenylsulfamide (40) with sodium hypochlorite in the presence of a base, probably via a type of oxidative coupling mechanism involving the intermediates (41) and (42) (Scheme 5) <71JCS(C)993>.



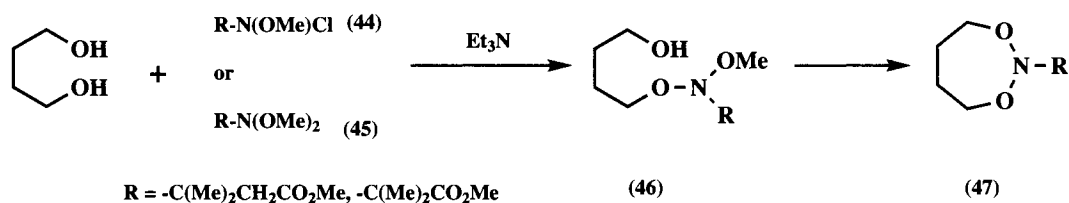
Scheme 5

9.13.5 DIOXAZEPINES

Only one class of fully saturated 1,3,2-dioxazepines is known.

9.13.5.1 1,3,2-Dioxazepines

The tetrahydro-1,3,2-dioxazepines (47) were obtained by the reaction of tetramethylene glycol with *N*-chloro-*N*-methoxyamines (44) or *N,N*-dimethoxyamines (45) in the presence of a base, such as triethylamine, via the intermediate (46) (Scheme 6) <89IZV2382>.



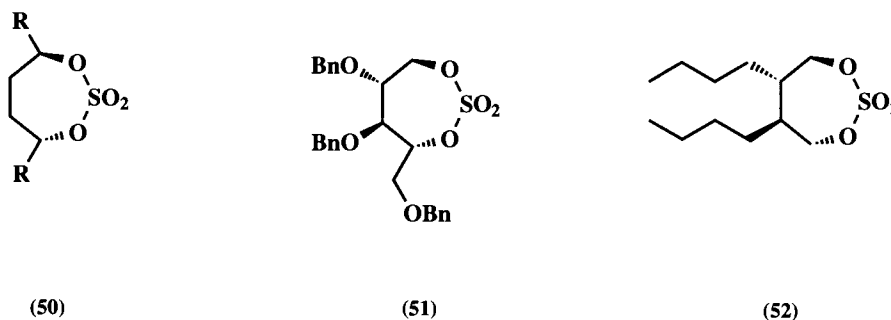
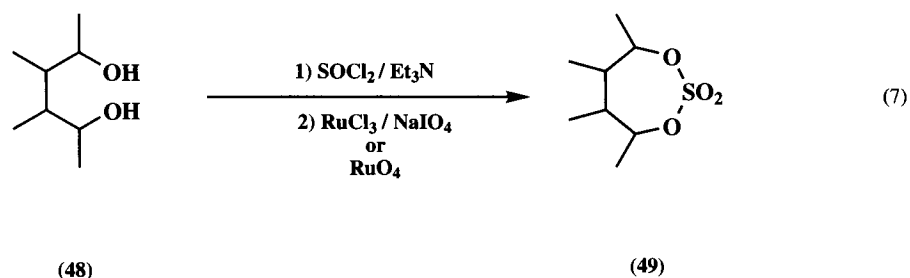
Scheme 6

9.13.6 DIOXATHIEPINES

Of the two theoretically possible 1,2,3- and 1,3,2-dioxathiepies, only the latter is known.

9.13.6.1 1,3,2-Dioxathiepies

Fully saturated monocyclic 1,3,2-dioxathiepies, of the type (49), can be prepared from a variety of 1,4-butanediol derivatives (48) upon treatment with thionyl chloride and triethylamine, followed by ruthenium tetroxide (Equation (7)) <88JA7538, 89TL655>. Thus, the 1,3,2-dioxathiepine 2,2-dioxides (50) <91JA8518>, (51) <91S347> and (52) <91JOC1386, 92JOC5178> have been synthesized from the corresponding 1,4-diols, respectively.



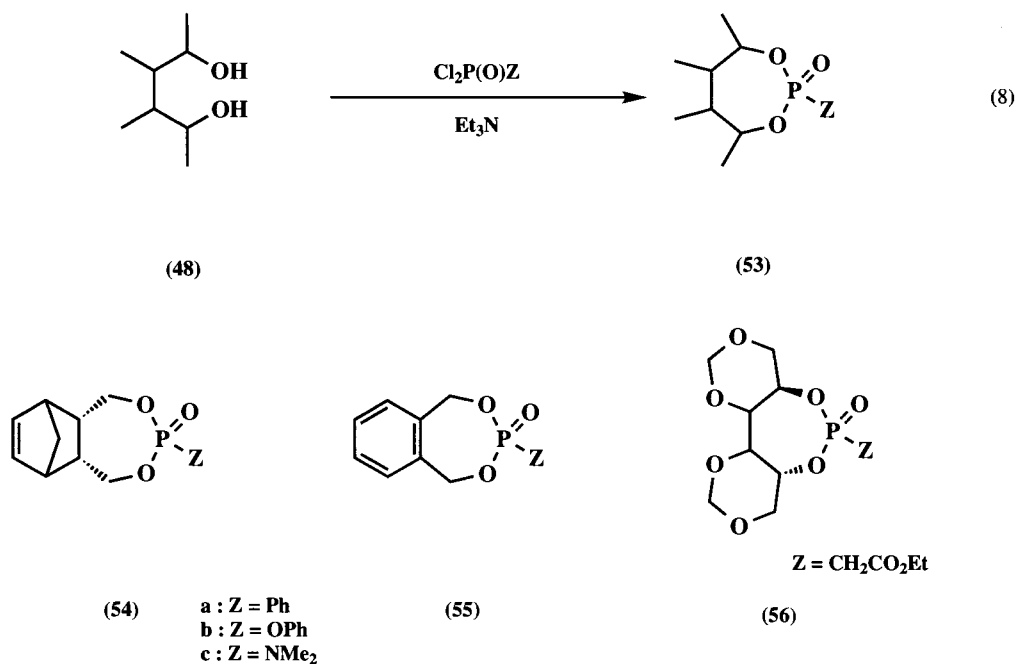
9.13.7 RINGS WITH PHOSPHORUS

Two classes, 1,3,2-dioxa (or diaza)phosphepines, of this system have been reported.

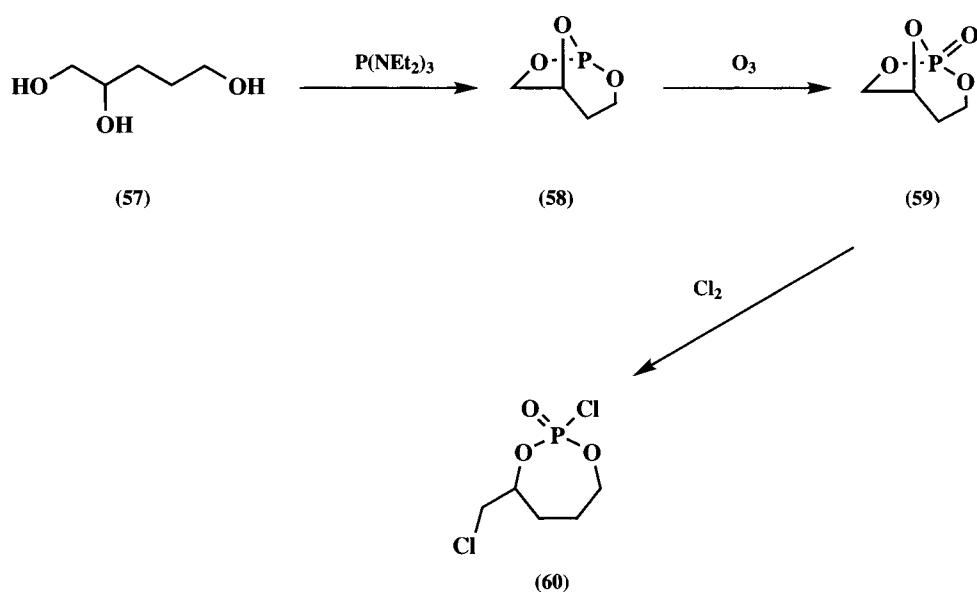
9.13.7.1 1,3,2-Dioxaphosphepines

Three types of the dioxaphosphepine ring system are known. 1,3,2-Dioxaphosphepines of type (53) are conveniently prepared by the reaction of 1,4-diols (48) with an appropriate ZP(O)Cl₂ reagent in good yields (Equation (8)). The dioxaphosphepines (54a,b) and (55a,b) (Z = Ph or OPh)

have been prepared from 5-norbornene-*endo*, *endo*-2,3-dimethanol and 1,2-benzenedimethanol, respectively <92JOC2812>, and conformationally studied by ^1H and ^{31}P NMR and IR spectroscopy, and x-ray crystallography. Preparation of the series with Z being NMe_2 was accomplished by heating the diols with hexamethylphosphorus triamide, followed by oxidation with *t*-butyl hydroperoxide. The tricyclic compound (**56**) was also obtained from the corresponding diol derived from mannitol <93CC102>.

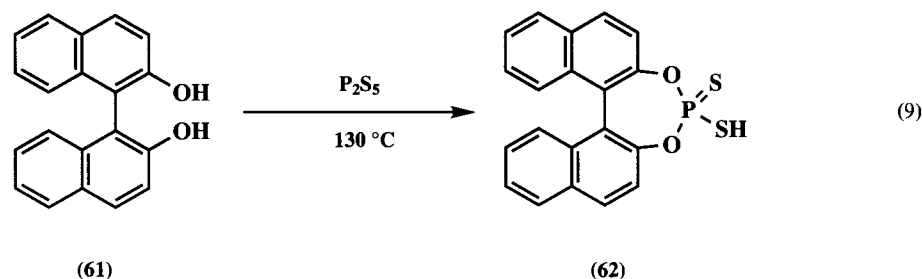


The monocyclic 1,3,2-dioxaphosphepine oxide (**60**) can also be synthesized starting from triol (**57**) by treating with hexaethylphosphorus triamide, followed by oxidation with ozone and chlorination of the resulting bicyclic compound (**59**) (Scheme 7) <93ZOB69>.



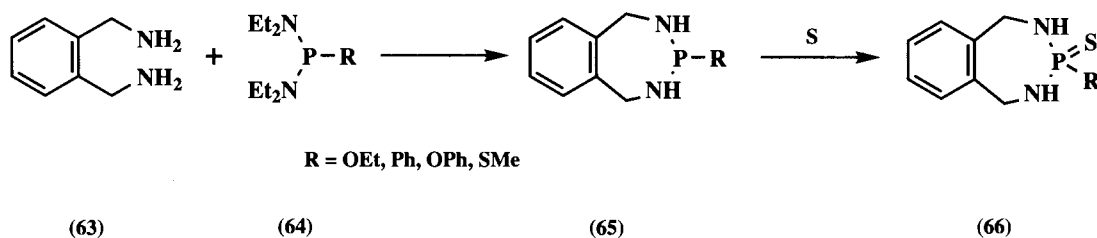
Scheme 7

Treatment of binaphthol (**61**) with phosphorus pentasulfide at 130°C afforded the dinaphtho-1,3,2-dioxaphosphepine (**62**) (Equation (9)) <91PS(57)87>.

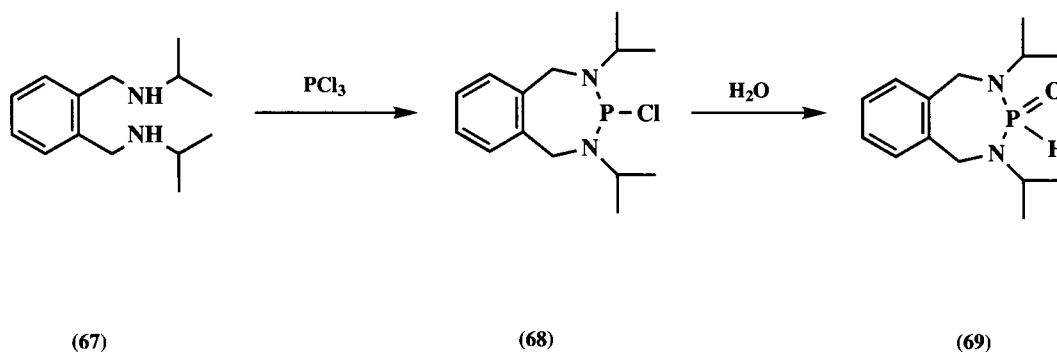


9.13.7.2 1,3,2-Diazaphosphepines

Two examples of the diazaphosphepine ring system are known. *o*-Xylylenediamine (**63**) reacts with the phosphorus reagents (**64**) to give the corresponding 2,4,3-benzodiazaphosphepines (**65**), which were converted into the sulfides (**66**) upon treatment with sulfur powder (Scheme 8) <93ZOB1739>. The 2,4-diisopropyl-2,4,3-benzodiazaphosphepine (**68**) can also be prepared from diamine (**67**) and was easily converted into the oxide (**69**) by treatment with water (Scheme 9) <93ZOB1726>.



Scheme 8



Scheme 9

9.14

Seven-membered Rings with Three Heteroatoms 1,2,4

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9.14.1 INTRODUCTION

This chapter is organized in a manner similar to Chapter 9.13. Of the ten possible 1,2,4-triheteroepine ring systems, the following five systems, triazepine, oxadiazepine, thiadiazepine, dioxazepine, and oxathiazepine ring systems, have been prepared and the other five systems are still unknown.

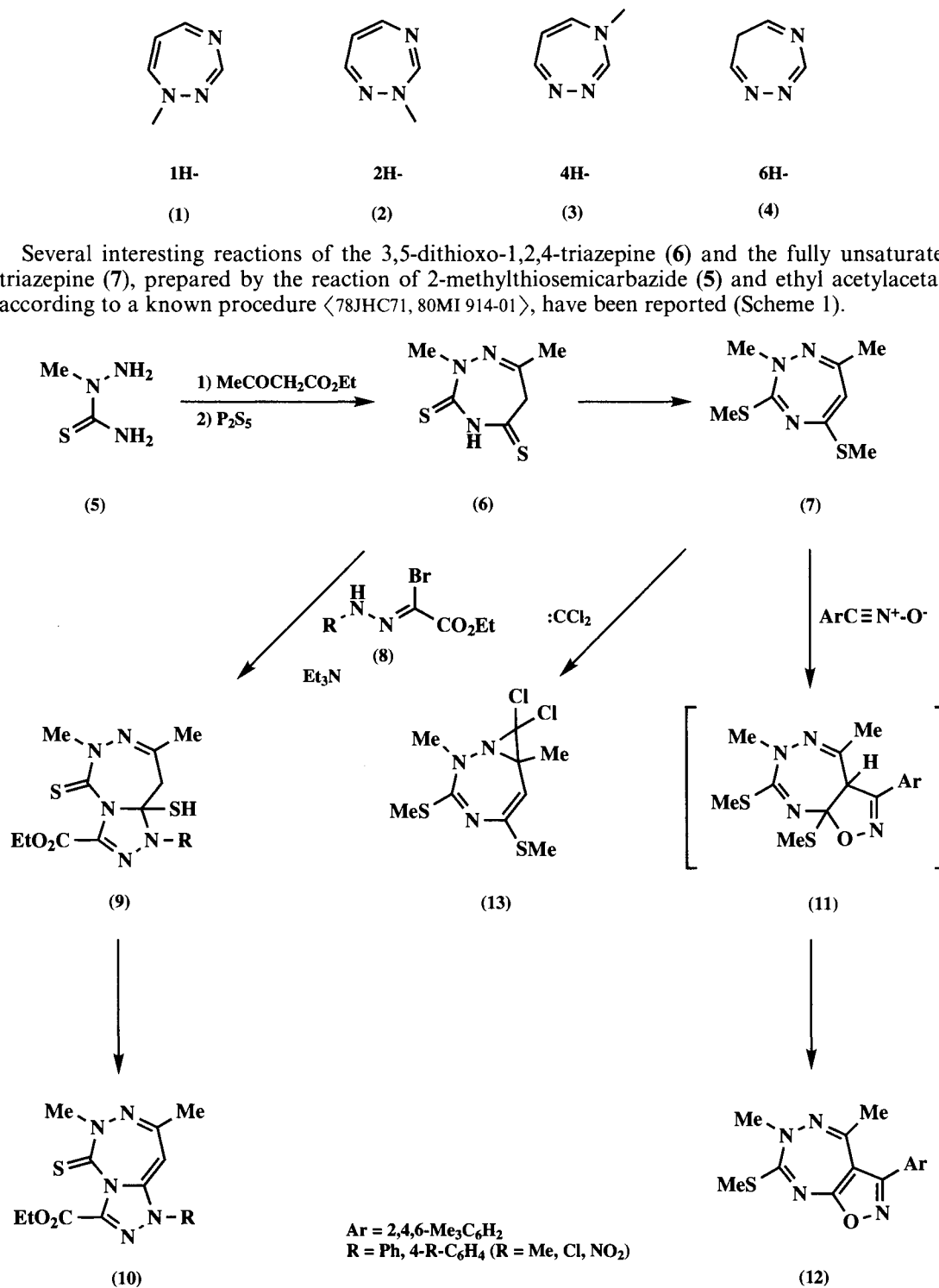
9.14.2 TRIAZEPINES

1,2,4-Triazepines have received considerable attention among the four triazepine ring systems, especially the fused 1,2,4-triazepines.

9.14.2.1 Monocyclic 1,2,4-Triazepines

Prior to 1981, there were many reports concerning the syntheses and reactions of the fully unsaturated monocyclic 1,2,4-triazepines, and all possible tautomers, 1*H*- (1), 2*H*- (2), 4*H*- (3), and 6*H*- (4) forms, have been prepared by the cycloaddition of 1-azirines to 1,2,4,5-tetrazines ^{74CC45}.

74TL2303, 75BCJ2605, 75JHC183) or by a photochemical walk-rearrangement of 3,4,7-triaza-2,4-norcaradienes (76TL2459, 76TL4753). 5,6,7-Trichloro-1,3-diphenyl-1*H*-1,2,4-triazepine has also been prepared by the reaction of tetrachlorocyclopropane with diphenylnitrilimine (81S322). However, few reports have appeared since.



Scheme 1

The reaction of the dithioxo compound (**6**) with *N*-aryl-*C*-ethoxycarbonylnitrilimines (**8**) led to the 1,2,4-triazino-[4,3-*d*]-1,2,4-triazepine (**10**) via the 1,3-dipolar cycloadduct (**9**) <92BSB977>. Treatment of 2,7-dimethyl-3,5-dimethylthio-1,2,4-triazepine (**7**) with mesitronitrile oxide in aqueous medium resulted in peri- and regioselective cycloaddition, giving rise to the isoxazolo[5,4-*e*]-1,2,4-triazepine (**12**) (80% yield) via the cycloadduct (**11**). The cycloaddition of dichlorocarbene to (**7**) also proceeded to form the azirino[2,1-*g*]-1,2,4-triazepine (**13**) <85RTC129>.

Cycloaddition reactions of (**7**) with various dienophiles have also been studied <85JHC25>. 4-Phenyl-1,2,4-triazolin-3,5-dione, diethyl acetylenedicarboxylate, and maleic anhydride react with (**7**) to form the corresponding [4 + 2] π -cycloadducts (**14**), (**17**), and (**20**), which then undergo elimination of methylthioisocyanate or 1,3-sigmatropic rearrangement, leading to the final products (**16**), (**19**), (**23**), and (**24**), via the intermediates (**15**), (**18**), (**21**), and (**22**), respectively, as shown in Scheme 2.

The β -isothiocyanatoketone (**25**) was reacted with hydrazine or methylhydrazine via an intramolecular cyclization affording the 3-thioxo-1,2,4-triazepines (**26**), which can be converted to the 2*H*-5,7-diphenyl-3-methylthio-5,6-dihydro-1,2,4-triazepines (**27**) upon treatment with methyl iodide (Scheme 3) <84MI 914-01>.

9.14.2.2 Benzotriazepines

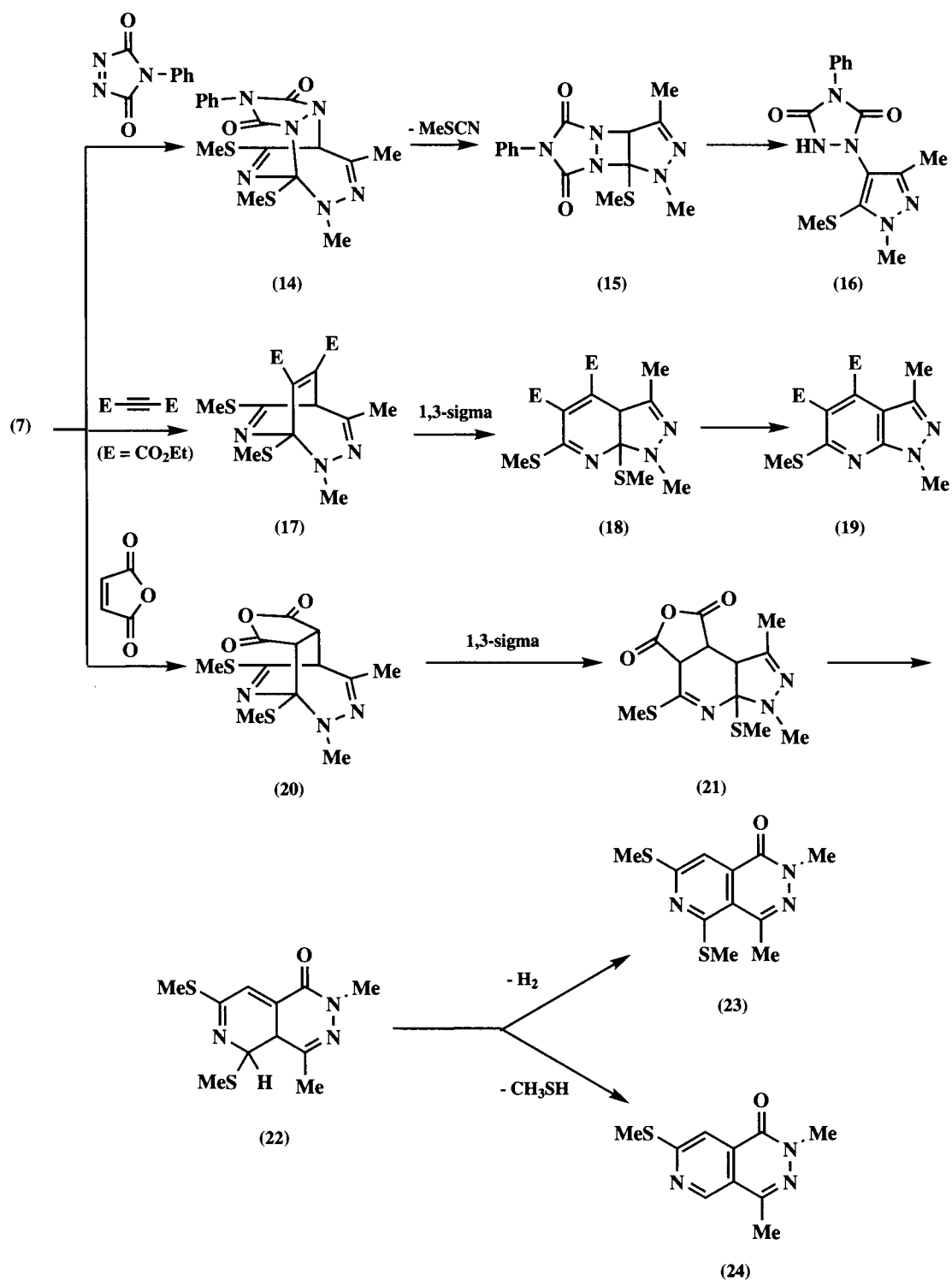
There are two classes of benzotriazepines: 1,2,4-(**28**) and 1,3,4-(**29**). The former is less well known.

9.14.2.2.1 1,2,4-Benzotriazepines

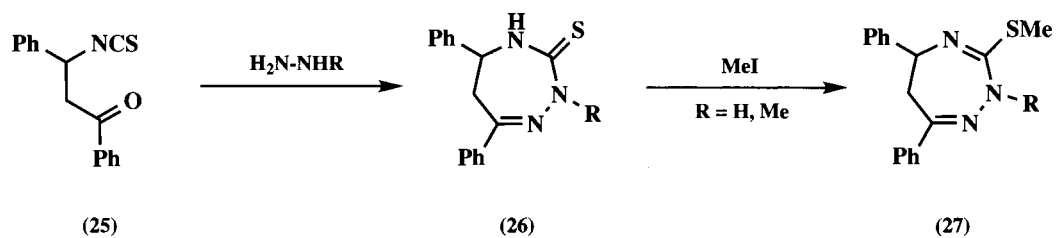
There has been relatively little research on this system and only two classes of synthetic routes to fully unsaturated 1,2,4-benzotriazepines have been reported. A series of 1*H*-1,2,4-benzotriazepines (**31**) can be prepared in good yields (50–85%) by the reaction of the benzhydrazidoyl chloride (**30**), obtained by the reaction of *N*-phenylbenzhydrazide with an equimolecular amount of phosphorus pentachloride, with nitriles in the presence of aluminum chloride, via the nitrilium ions shown in Scheme 4 <74T195>. The 1*H*-1,2,4-benzotriazepines (**33**) can be obtained in moderate yields (30–65%) by the thermal intramolecular aza-Wittig condensation of the *N*-(2-acylphenyl)-*C*-(triphenylphosphinimido)hydrazones (**32**) in refluxing acetonitrile or 2-methoxyethanol, together with trace amounts of several by-products <91JCR(S)2>. The starting hydrazones (**32**) are readily available by submitting the corresponding *C*-azidohydrazones to the Staudinger reaction.

9.14.2.2.2 1,3,4-Benzotriazepines

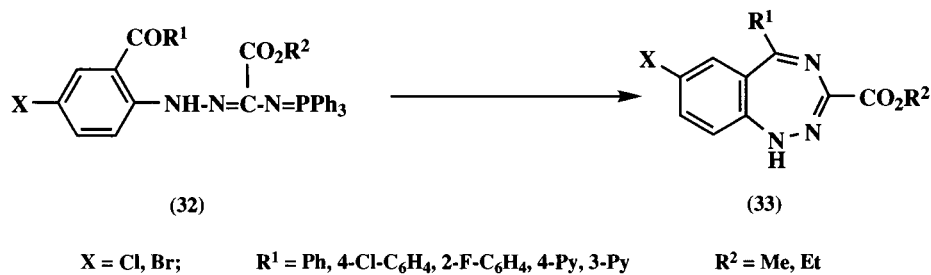
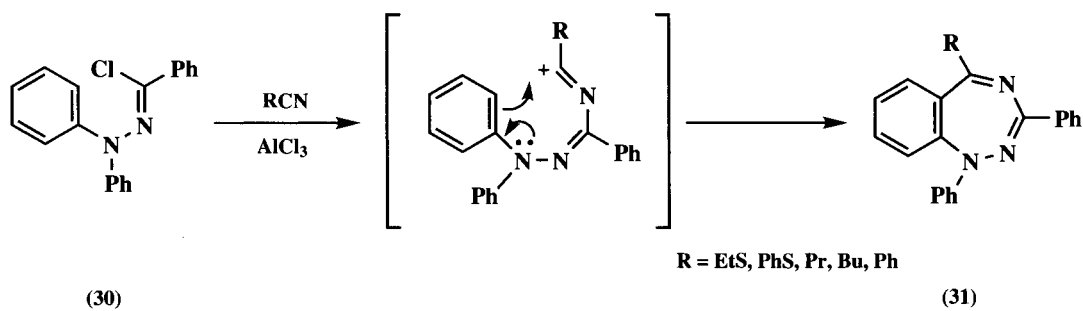
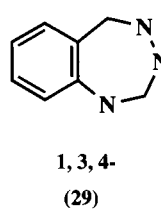
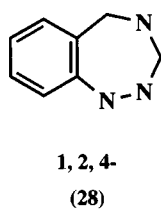
Synthesis of the 1,3,4-benzotriazepin-5-ones of the type (**35**) was simultaneously reported by three research groups <84JHC1807, 84JHC1817, 84JHC1825>. *o*-Aminobenzoylhydrazines (**34**) were reacted with triethyl orthoesters to produce the 3,4-dihydro-1,3,4-benzotriazepin-5-ones (**35**) (20–60% yield) as well as 2-(2-aminophenyl)-1,3,4-oxadiazoles (**36**) and 3-amino-3,4-dihydro-4-quinazolinones (**37**) (Equation (1)). Product distributions depend on the nature of the substituents R^1 and R^2 , solvent, and reaction time. Yields of the triazepines (**35**) have been found to be strikingly time dependent. For example, prolonged reaction times greatly diminished the triazepinone formation and afforded greater quantities of the oxadiazoles (**36**), and correspondingly less aminoquinazolinones (**37**), as the bulk of the R^2 substituent increased. Based on these results, a possible pathway was proposed for the reaction as illustrated in Scheme 5. This reaction provides an interesting example of competitive cyclization to five-, six-, and seven-membered ring products, respectively.



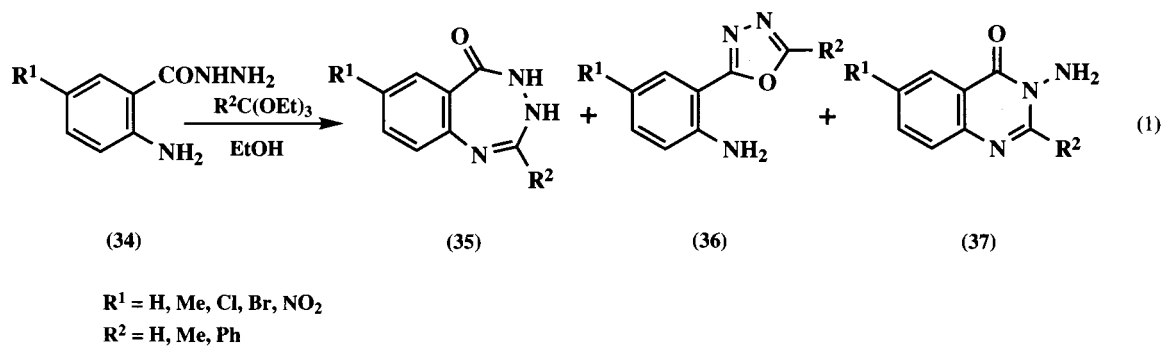
Scheme 2



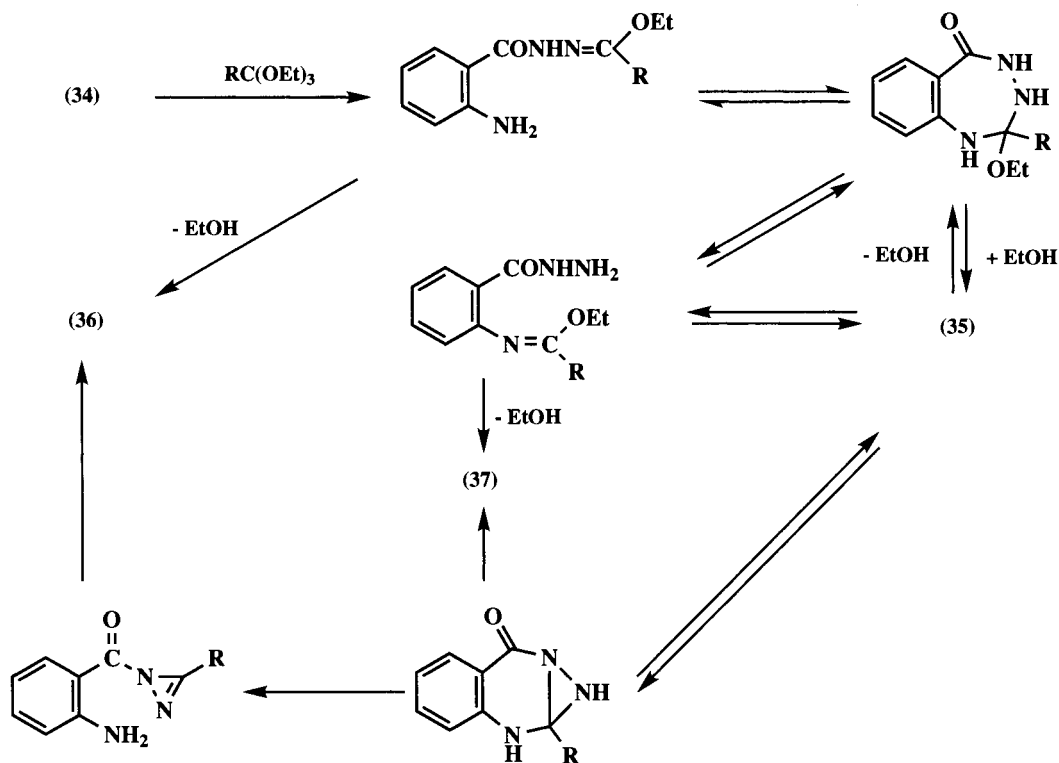
Scheme 3



Scheme 4

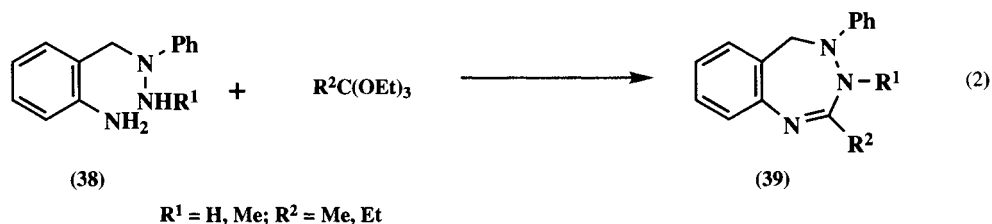


(1)



Scheme 5

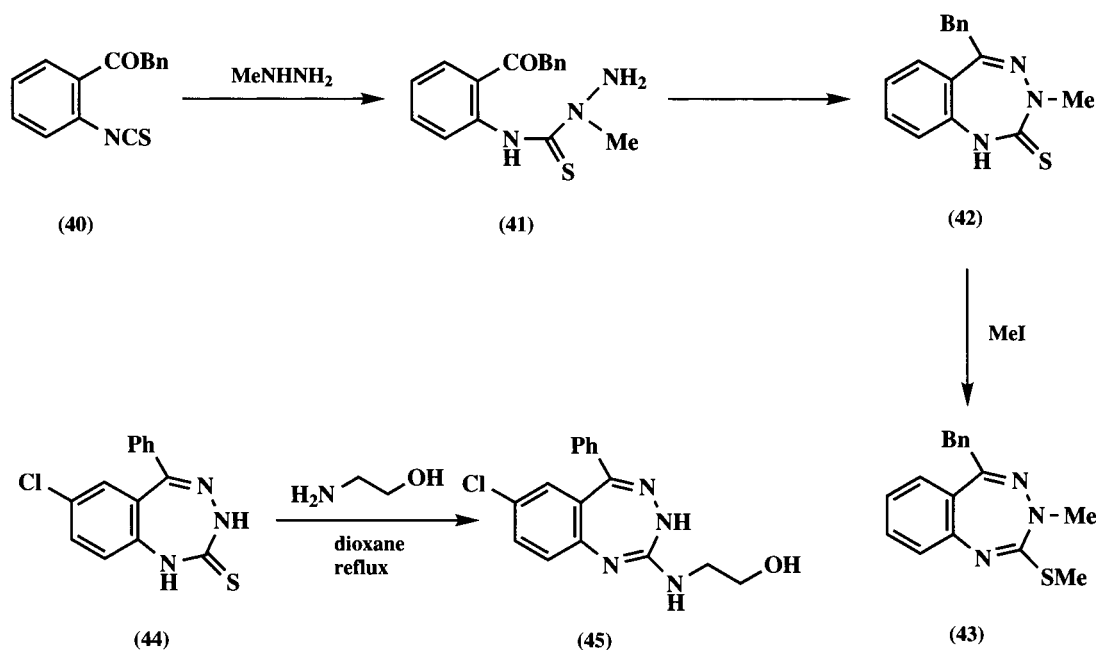
The 1-[(2-aminophenyl)methyl]-1-phenylhydrazines (38), prepared from phenylhydrazine and 2-nitrobenzyl chloride, readily cyclized with either triethyl orthoacetate or orthopropionate in refluxing glacial acetic acid to give the 4,5-dihydro-3*H*-1,3,4-benzotriazepines (39) (ca. 60% yield) (Equation (2)) <85JHC1105>.



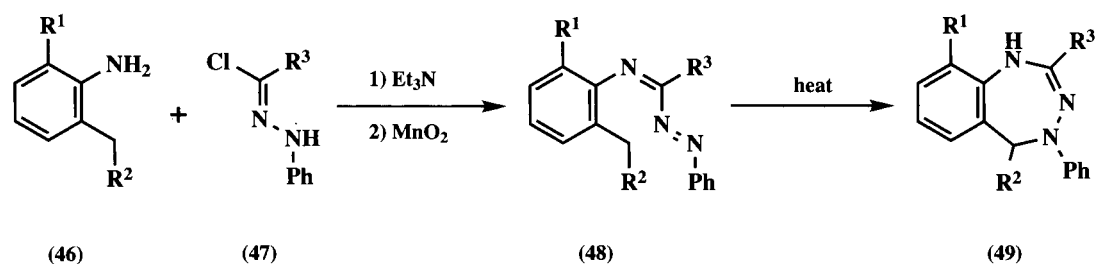
Treatment of 2-isothiocyanatodesoxybenzoin (40) with methylhydrazine supplied the thiosemicarbazide (41), which underwent intramolecular cyclization by heating under loss of water to give the 2-thioxo-1,3,4-benzotriazepine (42). Methylation of (42) with methyl iodide afforded the fully unsaturated 2-methylthio-3*H*-1,3,4-benzotriazepine (43) <92PHA25>. When a mixture of 2-aminoethanol and a 2-thioxotriazepine possessing no *N*-substituent, such as (44) <88PHA606>, was heated in refluxing dioxane, the S–N exchange takes place to give the 2-(2-hydroxyethyl)amino-3*H*-1,3,4-benzotriazepine (45) (Scheme 6) <88PHA760>.

The arylazoarylimines (48), carrying an aromatic methyl or ethyl group on the *ortho* position to the imine function and prepared by the reaction of anilines (46) with chlorohydrazone (47) in the presence of triethylamine followed by oxidation with manganese dioxide of the resulting arylaminohydrazones, underwent thermal intramolecular cyclization in refluxing xylene in the presence of a catalytic amount of dabco to give the 1*H*-4,5-dihydro-1,3,4-benzotriazepines (49) in 50–87% yields (Scheme 7) <86JHC1795>.

The mass spectra of eighteen 2-amino-1,3,4-benzotriazepines of types (50) and (51) have been recorded under electron ionization <88PHA606, 88PHA679, 88PHA760, 88PHA830, 89PHA18, 90PHA434>. Their fragmentation patterns were elucidated by metastable ion analysis and exact mass measure-

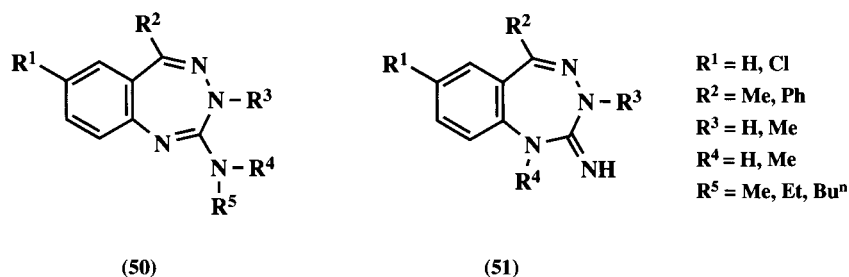


Scheme 6



Scheme 7

ments <91JHC1987>. The most typical fragmentations were ring contraction reactions with the loss of nitrogen atoms at positions 3 and 4. Extensive rearrangement takes place and in these cases the 2-amino group plays an important role.

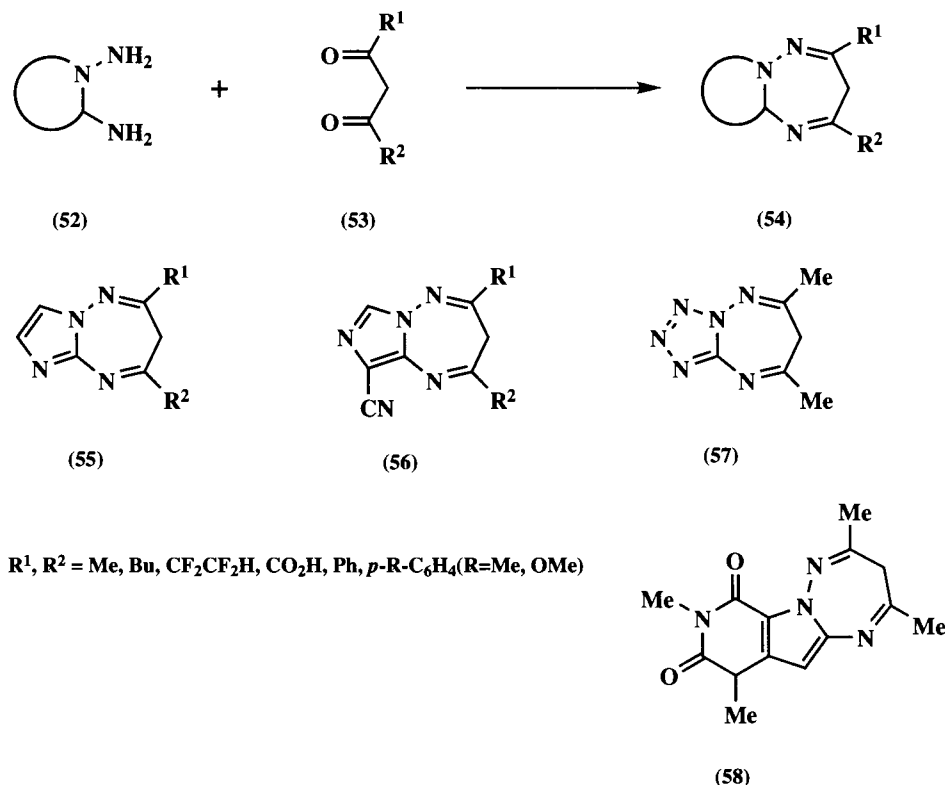


9.14.2.3 Fused 1,2,4-Triazepines

Various synthetic routes to diverse fused 1,2,4-triazepines condensed with rings other than benzene are available.

9.14.2.3.1 Syntheses from diamino compounds

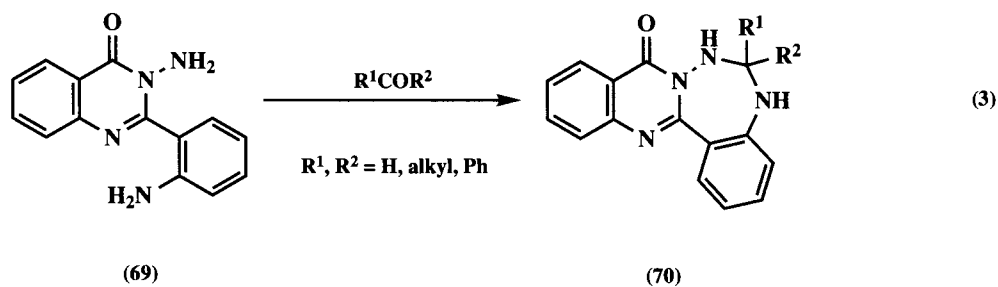
Cyclic diamino compounds, of the type (52), react with 1,3-diketones (53) in the presence of an acid catalyst, such as boric acid and ppa, leading to a variety of annulated fused 1,2,4-triazepines, for example (54) (Scheme 8). For example, imidazo[1,2-*b*]-1,2,4-triazepines (55) <83ZOR433, 88UKZ612>, imidazo[1,5-*b*]-1,2,4-triazepines (56) <93JCR(S)260>, and tetrazolo[1,5-*b*]-1,2,4-triazepine (57) <84KGS1683> have been synthesized from the corresponding diaminoimidazoles and diamino-tetrazoles. The (1,2,4-triazepino)[3,2-*f*]purine derivative (58) has also been prepared from 7,8-diamino-1,3-dimethylxanthine <88JHC791>.

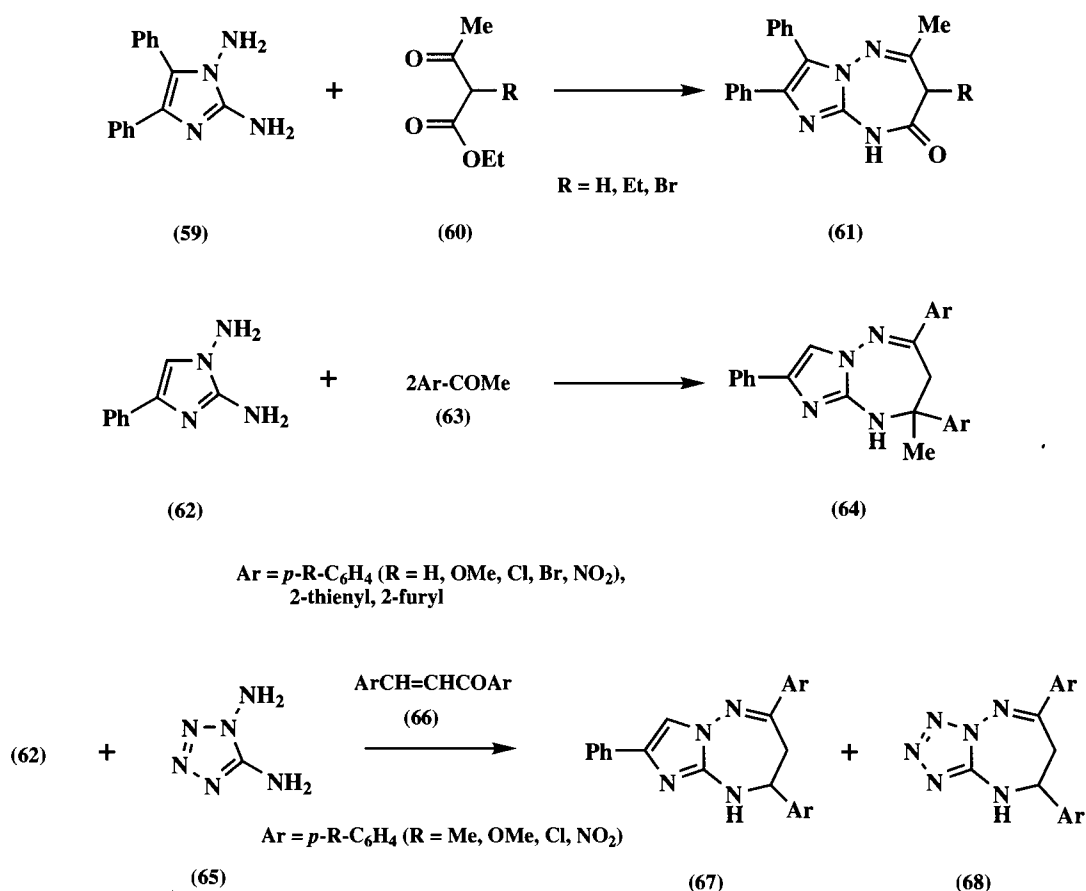


Scheme 8

When β -ketoesters (60) or aryl methyl ketones (63) were used instead of the 1,3-diketones (53), the 8-oxo-imidazo[1,2-*b*]-1,2,4-triazepines (61) <85KGS694> or the dihydro compounds (64) <84KGS1396> were produced from the corresponding diaminoimidazoles (59) and (62), respectively. The cyclocondensation of the diamino compounds (62) and (65) with vinyl ketones (66) also proceeded to yield the corresponding dihydroimidazo-1,2,4-triazepines (67) <83KGS93> and tetrazolo-1,2,4-triazepines (68) <90KGS1533> respectively, in moderate yields (Scheme 9).

The diaminoquinazolinone derivative (69) was also condensed with ketones to give quinazolino[3,2-*d*]-1,3,4-benzotriazepines (70) (Equation (3)) <92IJC(B)648>.





Scheme 9

9.14.2.3.2 Syntheses from hydrazino and related compounds

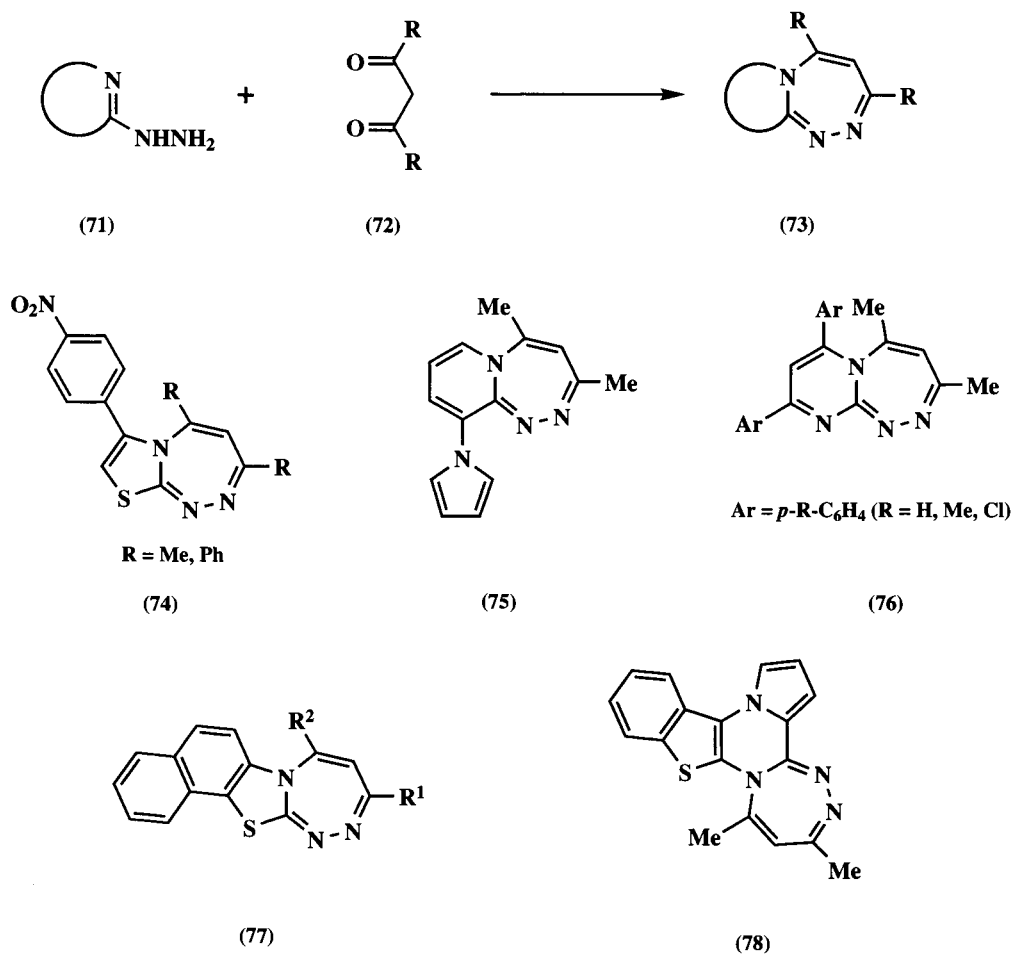
α -Hydrazino azacyclic compounds, for example (71), react with 1,3-diketones (72) to afford a variety of fused 1,2,4-triazepines, for example (73). Thus, the thiazolo[2,3-*c*]- (74) <82IJC1168>, pyrido[2,1-*c*]- (75) <85H(23)909>, pyrimido[2,1-*b*]- (76) <91MI 914-01, 93IJC(B)449>, naphtho[4,5-*b*]thiazolo[2,3-*c*]- (77) <81H(15)1077>, and 1-benzothieno[2',3':5,6]pyrrolo[1',2':1,2]pyrazino[3,4-*c*]-1,2,4-triazepine (78) <86JHC161> have been prepared from the corresponding α -hydrazinoazaheterocycles and 1,3-diketones (Scheme 10).

Treatment of the 6-cyano-9-ribofuranosylpurines (79) with hydrazine monohydrate in ethanol furnishes the 3*H*-pyrido[5,4-*e*]-1,3,4-triazepine (81) (62% yield) in one pot via a unique ring-opening and ring-closure procedure of the initially formed hydrazino derivative (80), as shown in Scheme 11 <91MI 914-02>. The 3*H*-tautomer (81) was stabilized by the *H*-bonding indicated in (81), while the 1*H*-isomer cannot form such *H*-bonding.

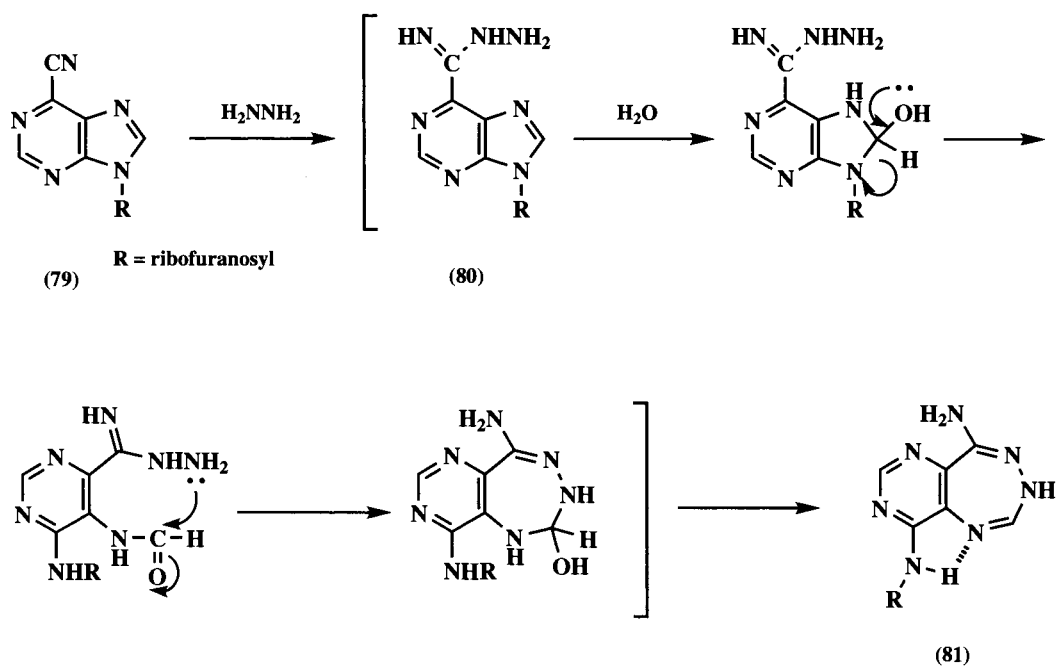
The 2-hydrazino-1-azaazulenes (82) reacted with diethyl ethoxymethylenemalonate (DEEM) in refluxing ethanol to give (83) (92–96% yield), which was then cyclized to the 1-azaazuleno[2,1-*c*]-1,2,4-triazepines (84) (75–92% yields) in refluxing *t*-butylbenzene (Scheme 12) <88BCJ1440>.

The reaction of the 1-acylamino-2-methylthio-1,4-dihydropyrimidines (85) with 80% hydrazine in acetic acid resulted in ring enlargement with loss of methanethiol to give the 1,2,4-triazolo[4,3-*b*]-1,2,4-triazepines (86) (30–85% yields), probably via the mechanism indicated in Scheme 13 <90ZC91>. The hydrazone derivative, derived from the 1,2,4-triazole (87), was also cyclized (70% yield) to the 1,2,4-triazolo[3,2-*c*]-1,2,4-triazepine (88) <82KGS1113>.

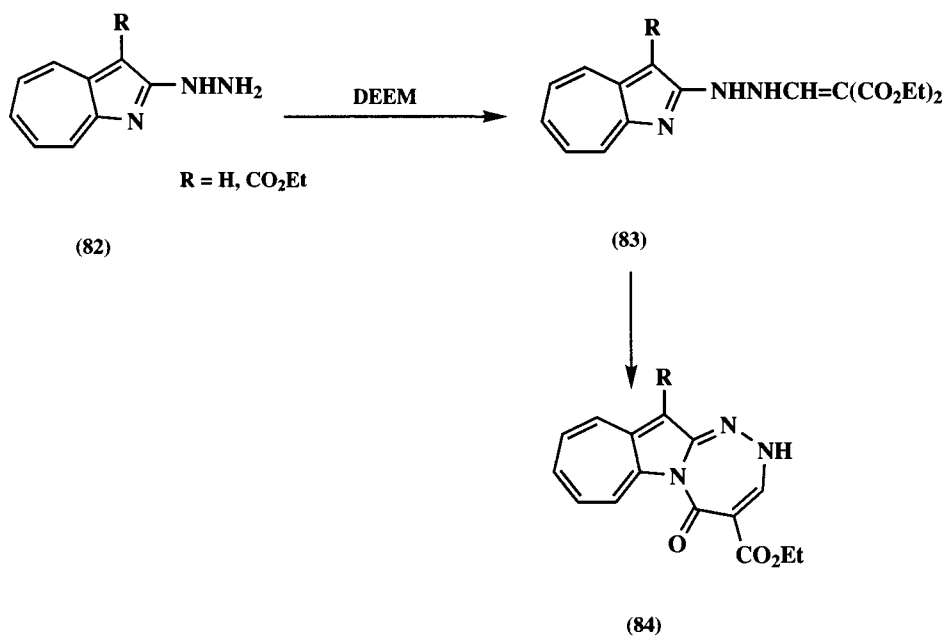
When the 1,3-indanedione 1-phenylhydrazine (89) was subjected to a double Mannich reaction using benzylamine or methylamine and formaldehyde in the presence of a small amount of acetic acid, it afforded (60–65% yield) the indano-1,2,4-triazepines (90) (Scheme 14) <90ZN(B)80>. The NMR spectra indicate that (90) existed in solution as mixtures of keto and enol tautomers. Similarly,



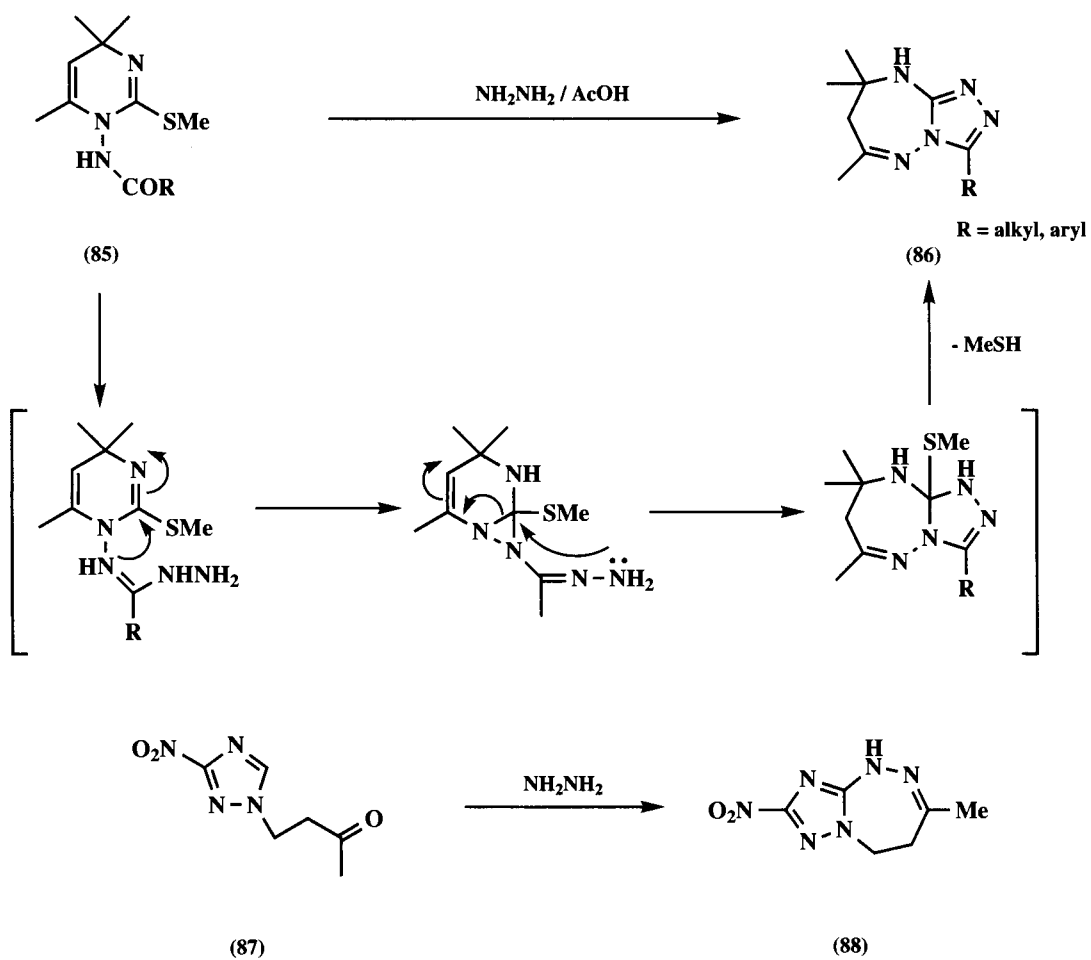
Scheme 10



Scheme 11

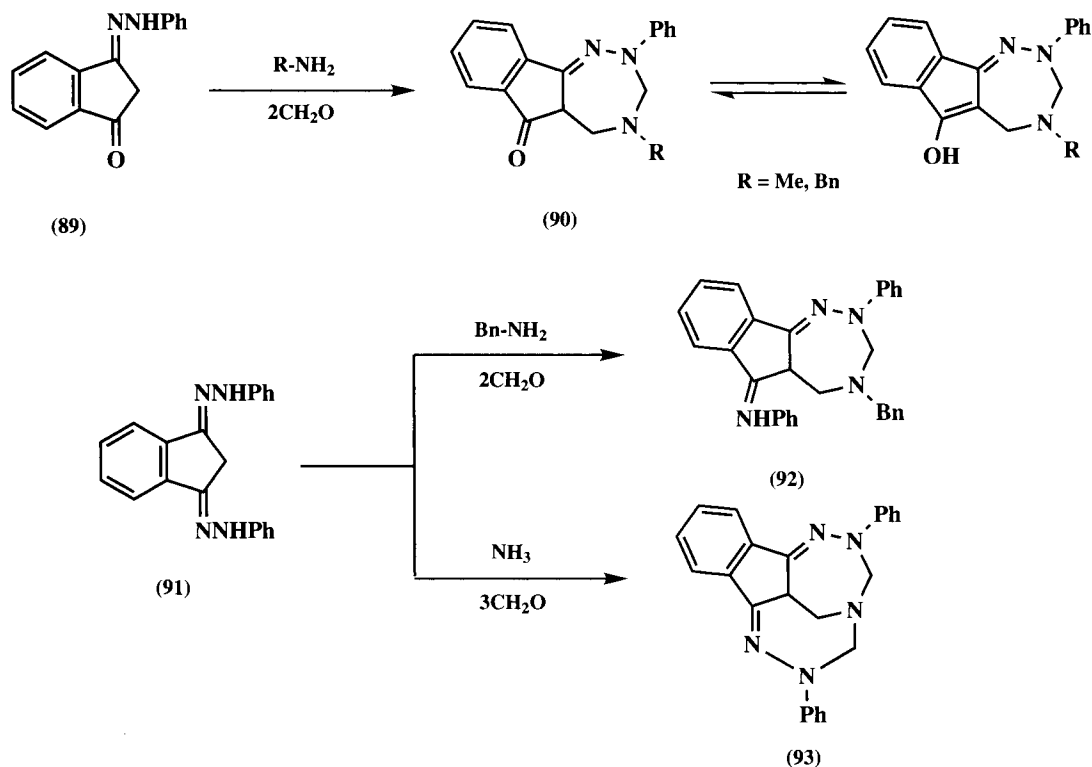


Scheme 12



Scheme 13

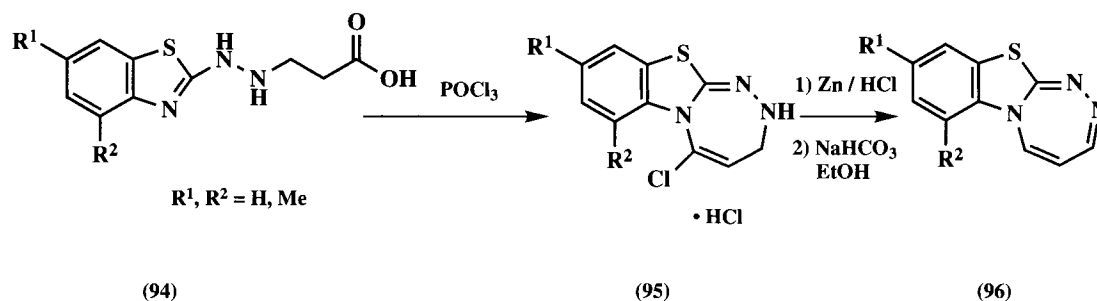
the 1,3-indanedione bisphenylhydrazone (**91**) underwent a Mannich reaction by treating with benzylamine and formaldehyde to give the indanotriazepine (**92**); whereas, interestingly, treatment of (**91**) with ammonium acetate instead of benzylamine afforded a tetracyclic compound (**93**) having two 1,2,4-triazepine rings in 85% yield.



Scheme 14

9.14.2.3.3 Syntheses from miscellaneous compounds

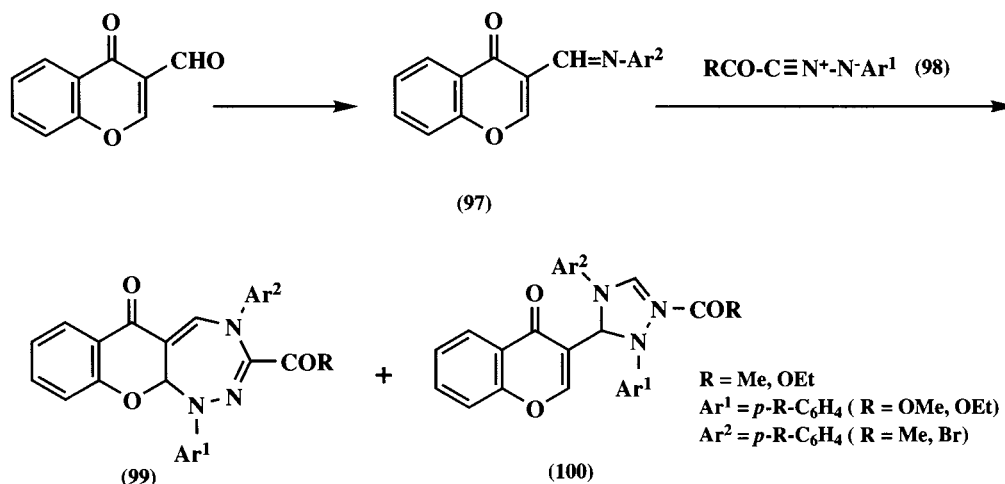
Synthesis of the benzothiazolo[2,3-*c*]-1,2,4-triazepines (**96**) from the corresponding benzothiazolylhydrazinopropionic acids (**94**) has been reported (Scheme 15) (93IJC(B)1168). It involves reduction of the initial cyclization products (**95**) to yield the dechlorination products, which on aerial oxidation in ethanol gave the fully unsaturated triazepines (**96**).



Scheme 15

The chromone imines (**97**), prepared from 3-formylchromone by treatment with *p*-anisidine or *p*-phenetidine, react smoothly with the nitrile imines (**98**), generated *in situ* from the corresponding hydrazoneyl halides in the presence of dry triethylamine in chloroform, to yield the 1,2,4-tri-

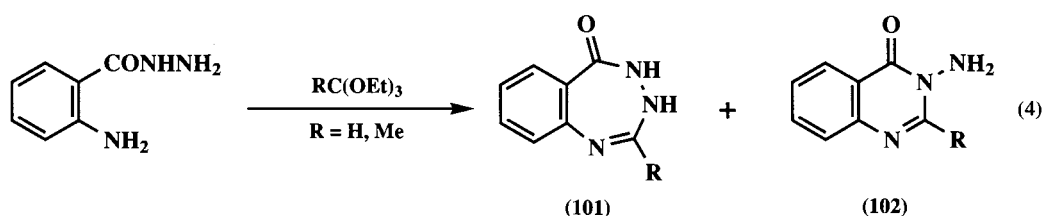
azepinochromones (**99**) (10–20% yields), together with the 1,2,4-triazolylchromones (**100**) (40–50% yields) (Scheme 16). The mechanistic pathway for the formation of both products (**99**) and (**100**) has been proposed <87JCS(P1)1995>.



Scheme 16

9.14.2.4 Fused 1,2,4-Triazepinones and 1,2,4-Triazepinethiones

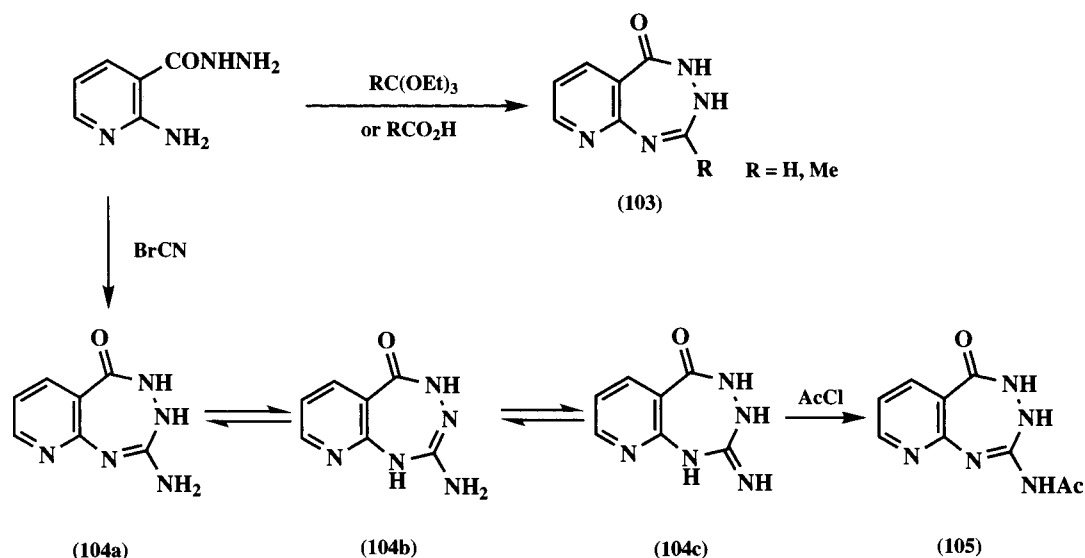
The reaction of 2-aminobenzoylhydrazine with triethyl orthoformate or orthoacetate resulted in two competing cyclocondensations to form the 1,3,4-benzotriazepin-5-ones (**101**) (20–40% yields) and the 3-aminoquinazolin-4-ones (**102**) (10–15% yields) (Equation (4)) <82JHC1425>.



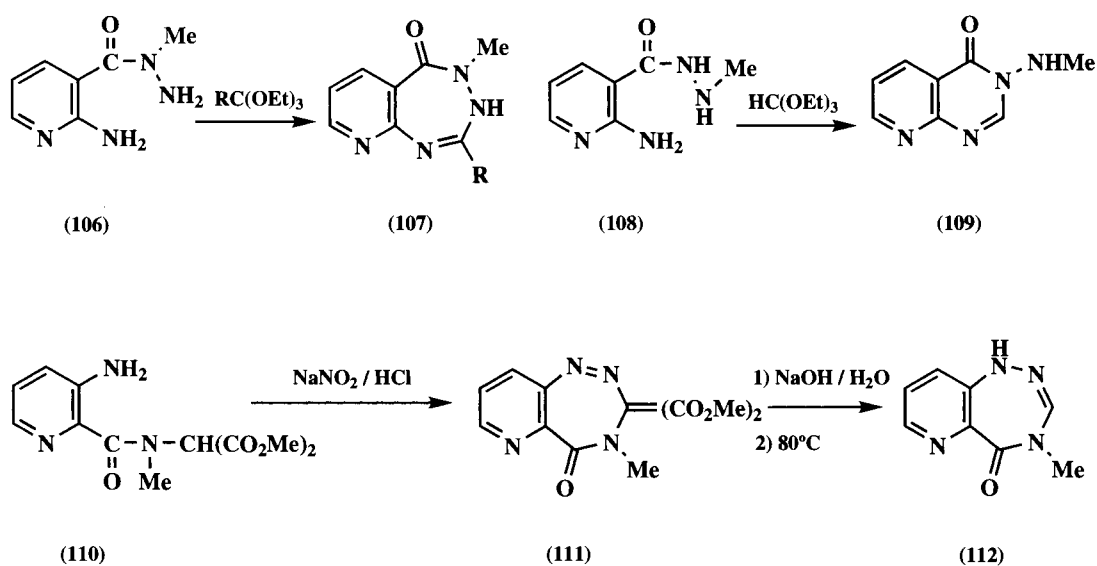
2-Aminonicotinic acid hydrazide also afforded the pyrido[2,3-*e*]-1,3,4-triazepin-5-ones (**103**) (ca. 60% yield) upon treatment with triethyl orthoesters or carboxylic acids, and gave the 2-amino derivative (**104**) (72% yield) in the reaction with bromocyan <88MI 914-01>. Its IR, ^1H NMR, and UV spectra have shown that (**104**) exists as a mixture of three tautomeric forms (**104a**), (**104b**), and (**104c**); however, the acetylation takes place predominantly at the primary 2-amino group to give only the 2-acetyl amino derivative (**105**) (Scheme 17).

Although 2-aminonicotino-*N*-methylhydrazide (**106**) also gave the seven-membered triazepinone derivative (**107**), its *N'*-methyl isomer (**108**) afforded only the six-membered pyrimidine derivative (**109**) (Scheme 18) <87CPB80>. Diazotization of the 3-aminopicolinamide (**110**), prepared from the *N*-carbobenzyloxy derivative of 3-aminopicolinic acid by treatment with dimethyl methylaminomalonate in the presence of hobt and dcc, followed by reductive removal of the carbobenzyloxy group, resulted in intramolecular cyclization of the initially formed diazonium ion to lead to the pyrido[2,3-*f*]-1,2,4-benzotriazepin-5-one derivative (**111**), which was readily decarboxylated upon treatment with two molar equivalents of aqueous sodium hydroxide in methanol, followed by heating at 80°C to give (**112**), an isomer of (**107**). The structure of (**112**) has been confirmed by x-ray crystallography <87CPB80>.

The alkoxycarbonylhydrazines (**114**), prepared by the reaction of the imidazolylcarbonylhydrazide (**113**) with chloroformates, readily underwent base (triethylamine, sodium methoxide, or



Scheme 17

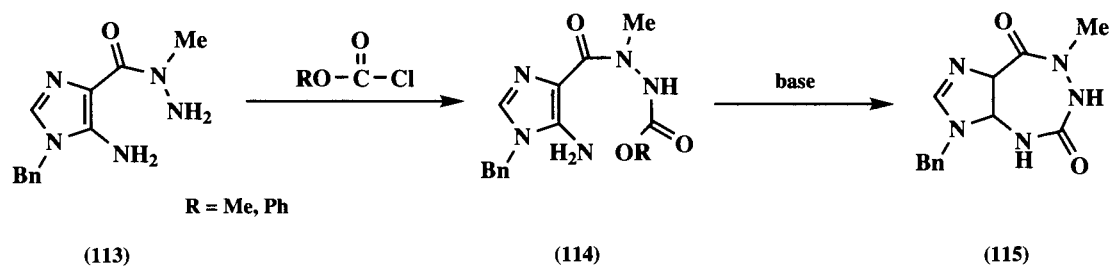


Scheme 18

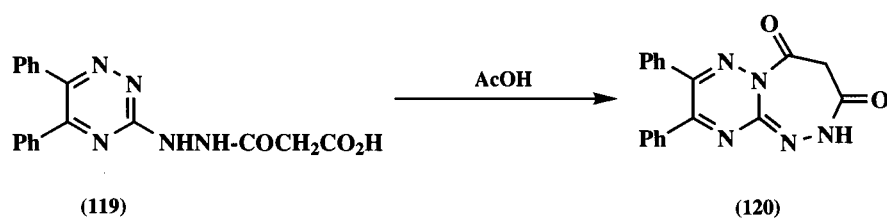
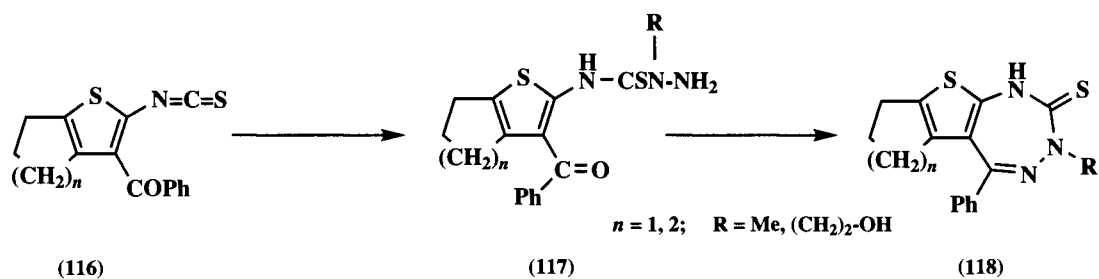
sodium hydroxide) catalyzed cyclization to give the imidazo[4,5-*e*]-1,2,4-triazepin-5,8-dione (**115**) (89% yield) (Scheme 19) <90S1095>.

The thieno-1,2,4-triazepin-5(1H)-ones (**118**) were synthesized in 50–70% yields by thermal cyclization of the hydrazinothiocarbonylamino compounds (**117**), obtained from the thiopheneisothiocyanates (**116**) and substituted hydrazines, in refluxing 1-butanol or 1-propanol in the presence of *p*-toluenesulfonic acid <88PHA753>. The 3-hydrazino-1,2,4-triazine derivative (**119**), on heating in glacial acetic acid, led to the 1,2,4-triazino[3,2-*c*]-1,2,4-triazepindione (**120**) (76% yield) (Scheme 20) <89PJS240>.

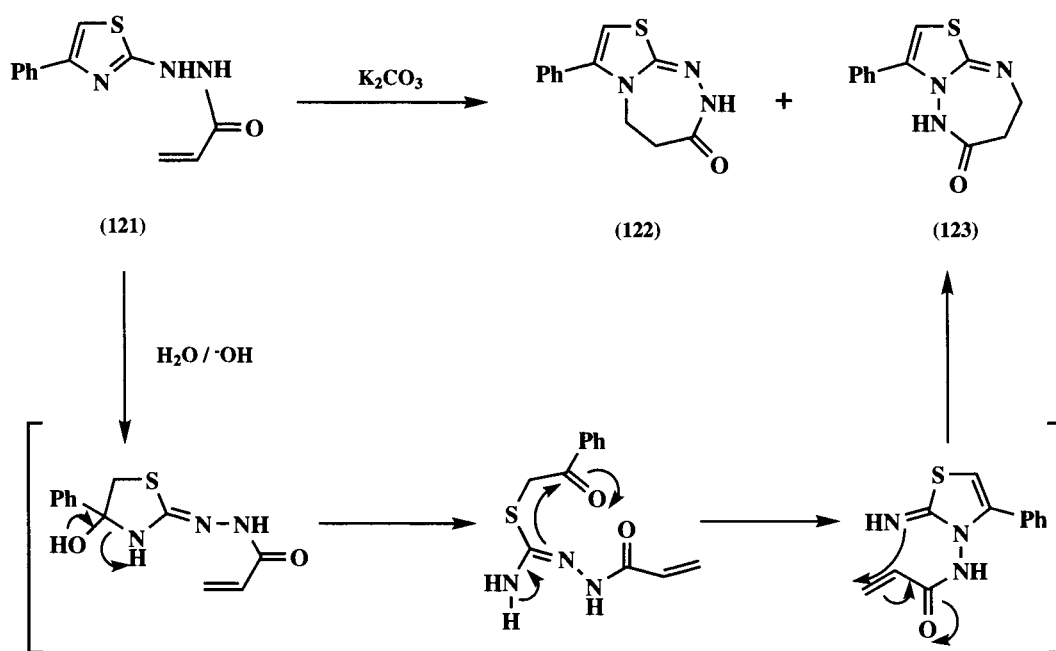
Cyclization of 2-propenoic acid 2-(4-phenyl-2-thiazolyl)hydrazide (**121**), prepared from 2-hydrazino-4-phenylthiazole and acryloyl chloride, with potassium carbonate yielded two kinds of thiazolo-1,2,4-triazepinones (**122**) (15% yield) and (**123**) (27% yield). The former, thiazolo[2,3-*c*]-1,2,4-triazepine (**122**), was the predicted product, but the production of the unexpected [3,2-*b*]-isomer (**123**) may have proceeded via the rearrangement pathway shown in Scheme 21 <82JHC747>.



Scheme 19

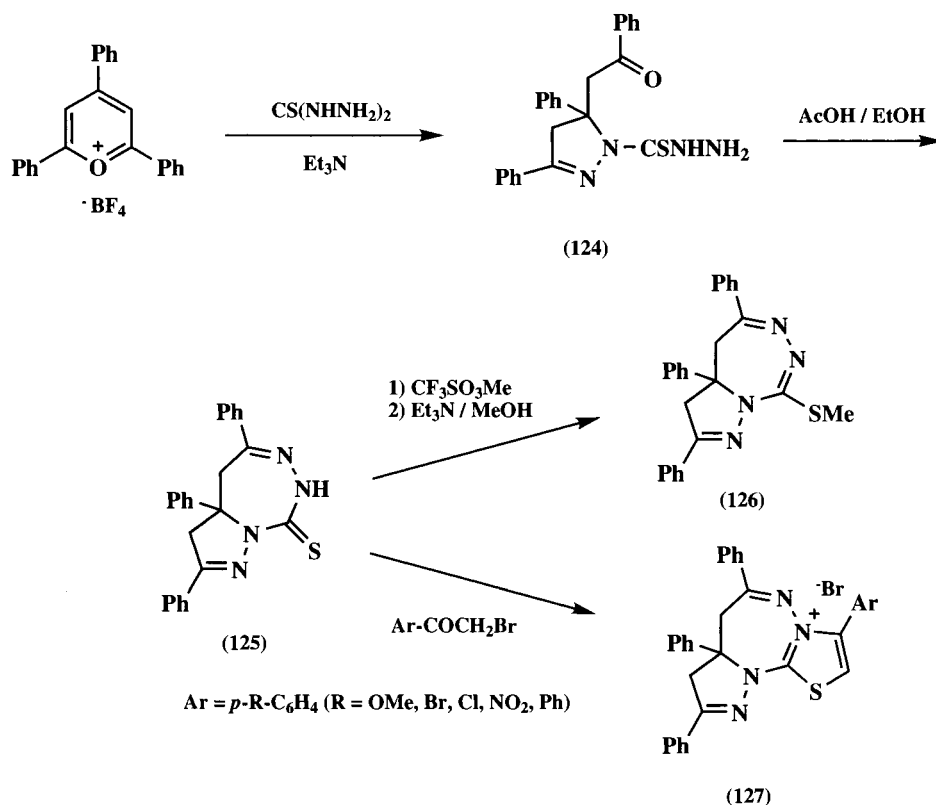


Scheme 20



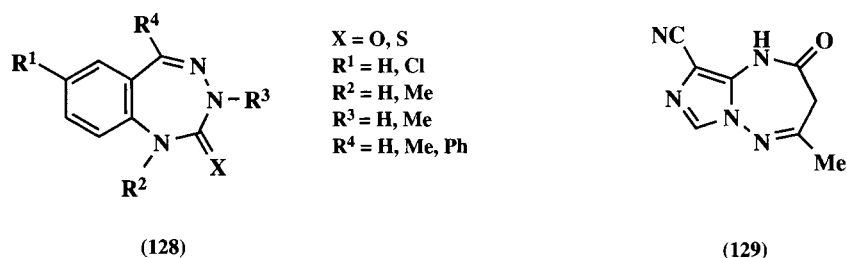
Scheme 21

2,4,6-Triphenylpyrylium tetrafluoroborate reacted with thiocarbohydrazide in the presence of triethylamine to give the pyrazoline derivative (124), which cyclized to the pyrazolo[1,5-*d*]-1,2,4-triazepinethione (125) (90% yield) in boiling ethanol containing acetic acid <84T4901>. *S*-Methylation of (125) with methyl trifluoromethanesulfonate followed by treatment with triethylamine produced (50% yield) the methylthio compound (126) and the reaction with phenacyl bromides resulted in cyclization to the thiazole ring affording the tricyclic triazepinium salts (127) in high yields (76–87%) (Scheme 22).



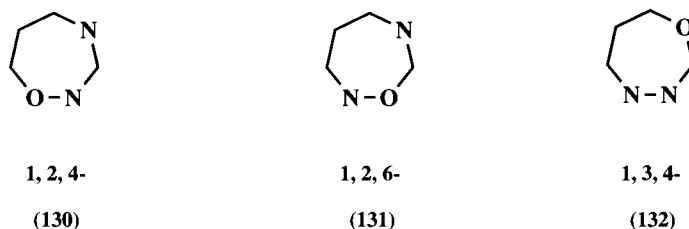
Scheme 22

The mass spectra of seven 2-thio- and four 2-oxo-1,3,4-benzotriazepines, for example (128), have been recorded and the fragmentation patterns elucidated by exact mass measurement and metastable ion analysis <90JHC259>. The x-ray crystallographic analysis of the imidazo[1,5-*b*]-1,2,4-triazepine (129) showed that a double bond possesses a 1 and 2 linkage (C=N; 1.276 Å) with no evidence of an alternative tautomer in which the double bond is between the 2 and 3 positions (C—C; 1.490 Å) <93AX(C)1693>.



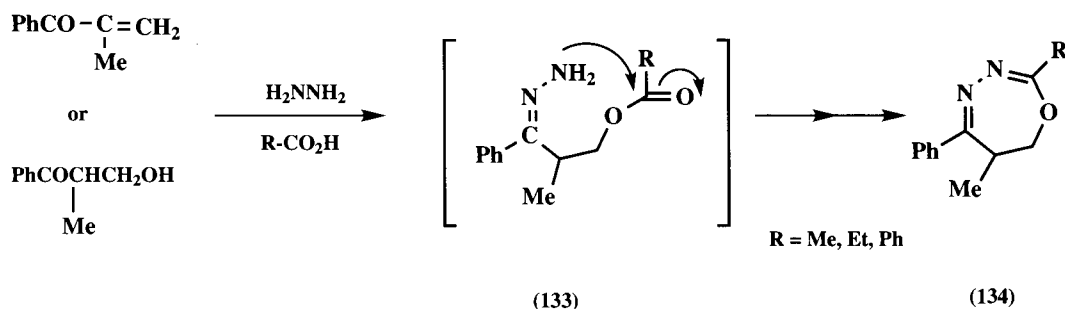
9.14.3 OXADIAZEPINES

There are three isomers in this system: 1,2,4-, 1,2,6-, and 1,3,4-oxadiazepines, (130), (131), and (132) respectively. Several examples of (131) and (132) <75CB3387, 77JOC1496, 77ZOR1563, 80CB3373> and only one example of (130) <75TL2979> had been reported up to 1980.



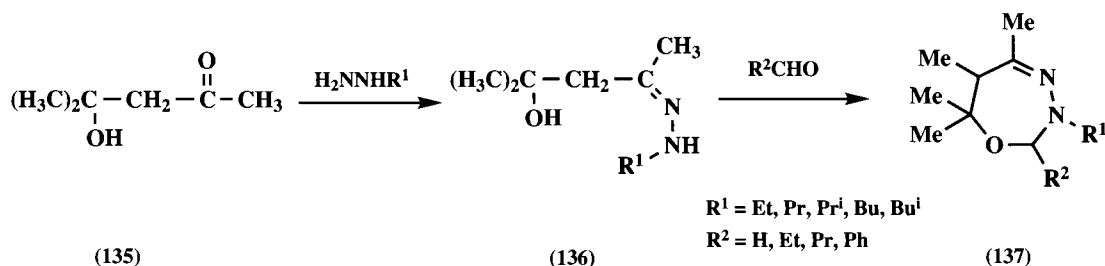
9.14.3.1 Monocyclic 1,3,4-Oxadiazepines

Two examples of monocyclic 1,3,4-oxadiazepines have been reported. The fully unsaturated compounds have, however, not been isolated, although the photolysis of pyrimidine *N*-oxides is known to involve such oxadiazepines as unisolable intermediates <69TL4899>. 2-Benzoylpropene or 2-benzoylpropanol condensed with hydrazine hydrate and an appropriate carboxylic acid to form the hydrazone esters (133), which were converted into the 6,7-dihydro-1,3,4-oxadiazepines (134) (30–72% yields) by intramolecular attack of the amino group to the ester carbonyl, followed by acid-catalyzed loss of water (Scheme 23) <84S342>.



Scheme 23

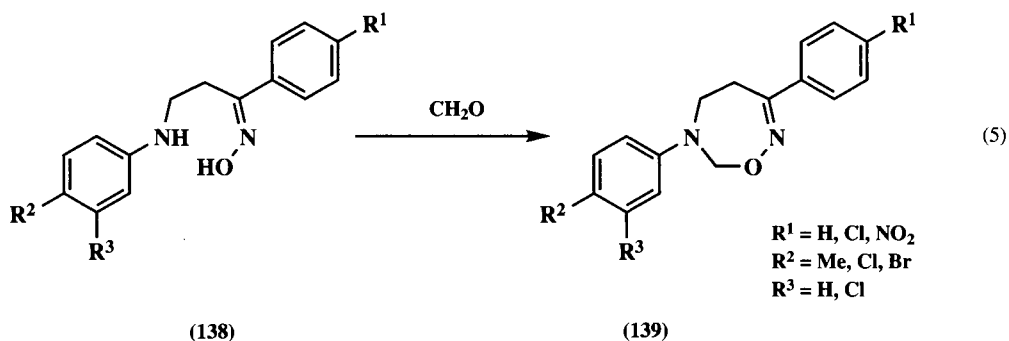
The hydrazones (136), prepared from 2-hydroxy-2-methyl-4-oxopentane (135) and substituted hydrazines, react with aldehydes to give the corresponding tetrahydro-1,3,4-oxadiazepines (137) in 60–70% yields (Scheme 24) <82KGS1319>.



Scheme 24

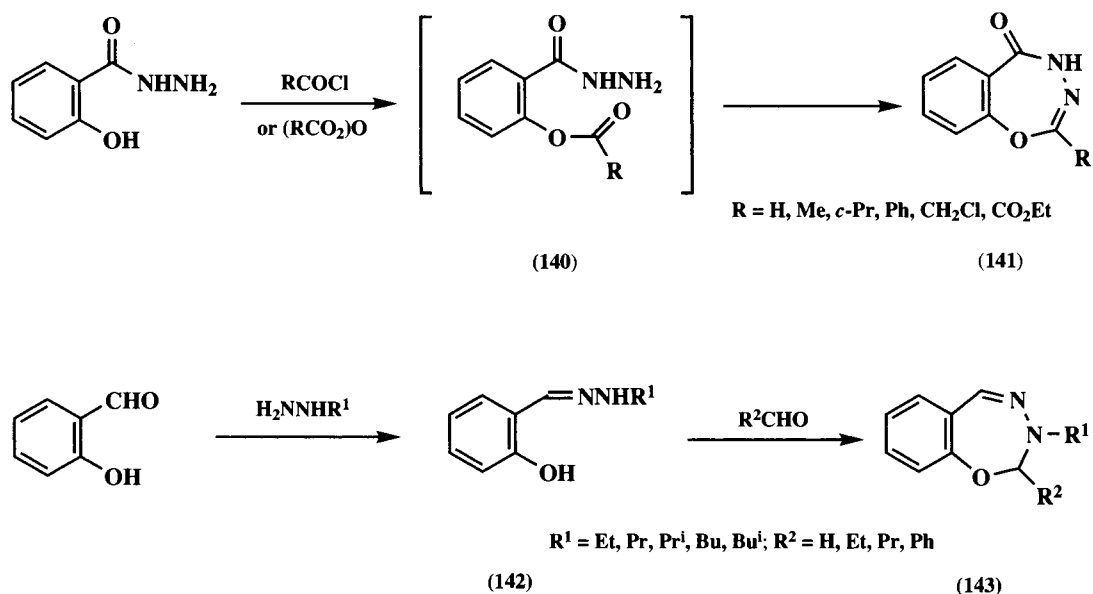
9.14.3.2 Monocyclic 1,2,6-Oxadiazepines

The only example of this system that has been prepared is (139). Refluxing β -arylamino-propionophenone oximes (138) with formaldehyde in ethanol resulted in the condensation with ring closure to give the tetrahydro-1,2,6-oxadiazepines (139) in good yields (Equation (5)) <91MI 914-03>.



9.14.3.3 1,3,4-Benzoxadiazepines

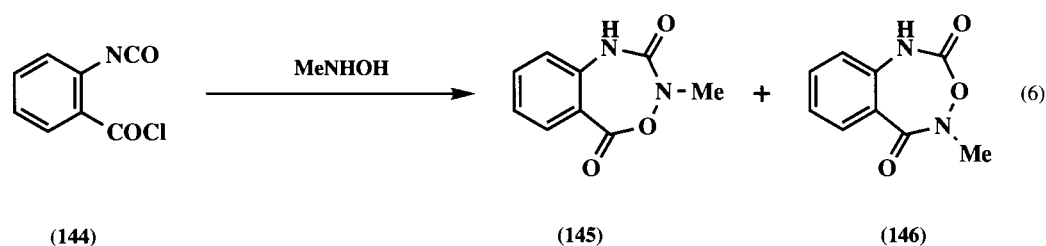
Treatment of salicylic hydrazide in toluene with a single carbon insertion unit, such as carboxylic acid anhydride, acid chlorides, and orthoesters in the presence of an equimolecular amount of methanesulfonic acid, gave the 1,3,4-benzoxadiazepin-5-ones (141) (43–68% yield), via the *O*-acylation intermediates (140) (Scheme 25) <92S929>. In the second example, 2,3-dihydro-1,3,4-benzoxadiazepines (143) were prepared by the condensation of salicylic aldehyde hydrazones (142) with an appropriate aldehyde in 50–60% yields <82KGS1319>.



Scheme 25

9.14.3.4 1,2,4- and 1,2,6-Benzoxadiazepines

2-Isocyanatobenzoyl chloride (144) reacts with *N*-methylhydroxylamine hydrochloride in pyridine, resulting in two competitive cyclization processes to yield two isomeric products, 1,2,4-(145) (73%) and 1,2,6-oxadiazepine (146) (9%) ring systems (Equation (6)) <88IJC(B)840>.



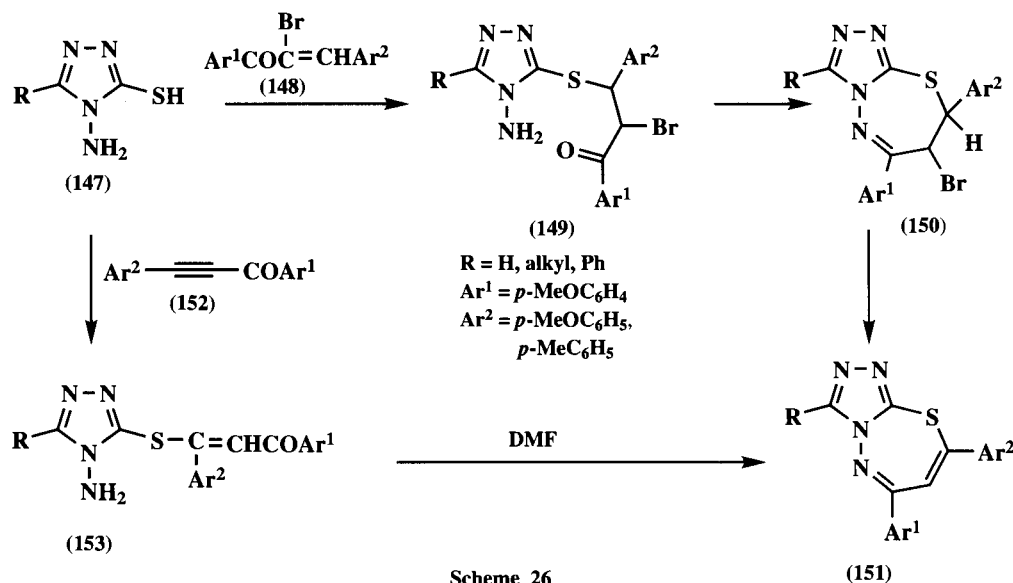
9.14.4 THIADIAZEPINES

A variety of 1,2,4- and 1,3,4-thiadiazepines has been prepared; however, the monocyclic rings are still unknown.

9.14.4.1 Fused 1,3,4-Thiadiazepines

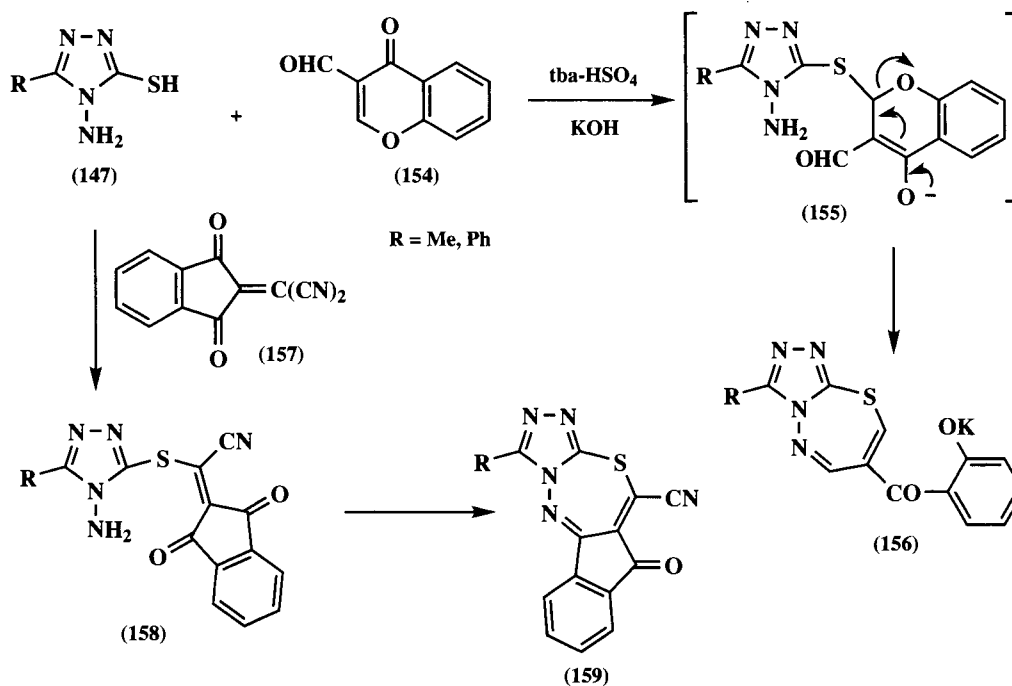
4-Amino-3-thiol-1,2,4-triazole derivatives have been extensively utilized for the synthesis of 1,3,4-thiadiazepines, condensed with a 1,2,4-triazine ring.

Condensation of the thioltriazoles (**147**) with α -bromochalcones (**148**) in the presence of ethanolic potassium hydroxide under reflux yielded (60–80%) the 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazepines (**151**) via intermediates (**149**) and (**150**) (Scheme 26) <91IJC(B)672>. The thiadiazepines (**151**) were also obtained via another route. Treatment of (**147**) with acylacetylenes (**152**) gave (**151**) via the addition intermediates (**153**) <91KGS990, 92KGS267>.

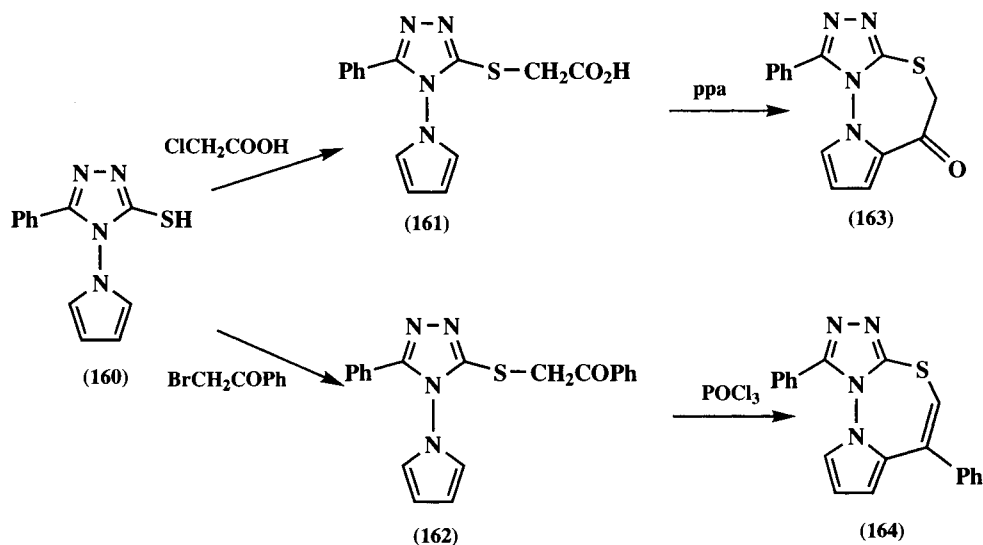


The reaction of aminothioltriazoles (**147**) with 3-formylchromone (**154**) under phase-transfer catalysis, consisting of aqueous potassium hydroxide as a base, methylene chloride or benzene, and *t*-butylammonium hydrogensulfate as a phase-transfer catalyst, furnished the triazolo[3,4-*b*]-1,3,4-thiadiazepines (**156**) (60–75% yield), via the condensation intermediates (**155**) (Scheme 27) <87SC1851>. 2-(Dicyanomethylene)-1,3-indanedione (**157**) also reacted with (**147**) to give the tetracyclic thiadiazepines (**159**) (ca. 20% yield) via the intermediates (**158**) <93BCJ2612>.

By reacting 3-thiol-5-phenyl-4-pyrrolyl-1,3,4-triazole (**160**) with chloroacetic acid or phenacyl bromide, the 3-carboxymethylthio- (**161**) and 3-phenacylthiotriazole (**162**) were obtained, and underwent intramolecular cyclization reactions via electrophilic substitutions. The cyclization of the former in boiling ppa produced thiadiazepinone (**163**) (38% yield), while the latter was cyclized to the phenyl derivative (**164**) (50% yield), 3,9-diphenyl-1,2,4-triazolo[3,4-*b*]pyrazolo[1,2-*d'*]-1,3,4-thiadiazepine, by heating with phosphorus oxychloride (Scheme 28) <82G345>.



Scheme 27

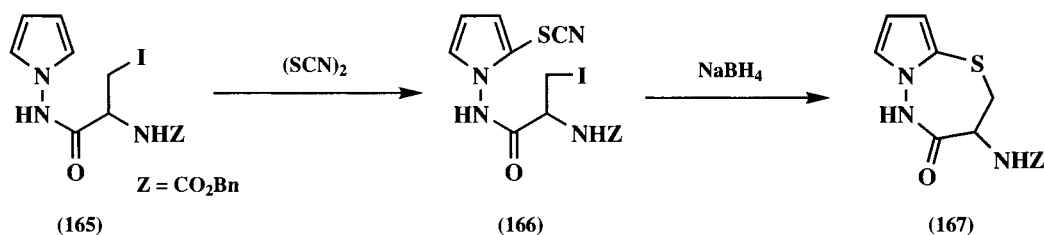


Scheme 28

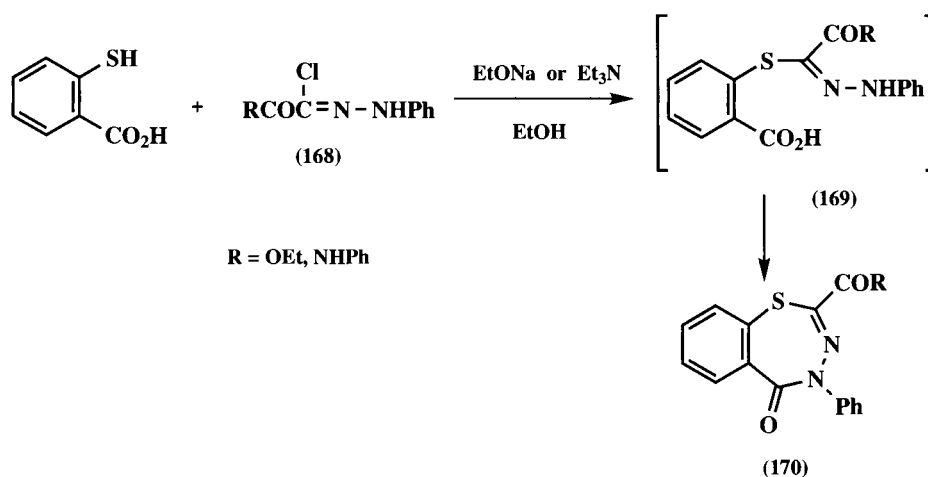
The pyrrolo[2,1-*b*]-1,3,4-thiadiazepine (167) has been prepared (68% yield) through a sequence involving thiocyanation of the acylaminopyrrole derivative (165), followed by reductive cleavage of the thiocyanate group in (166), and the cyclization of the resulting thiol intermediate in the key synthetic step (Scheme 29) <92TL9567>.

The reaction of the hydrazidoyl chloride (168) with thiosalicylic acid in basic medium gave the 1,3,4-benzothiadiazepin-5-ones (170). The initial alkylation occurred at the thiol group to give the intermediates (169), which immediately underwent cyclization to (170) (Scheme 30) <88IJC(B)836>.

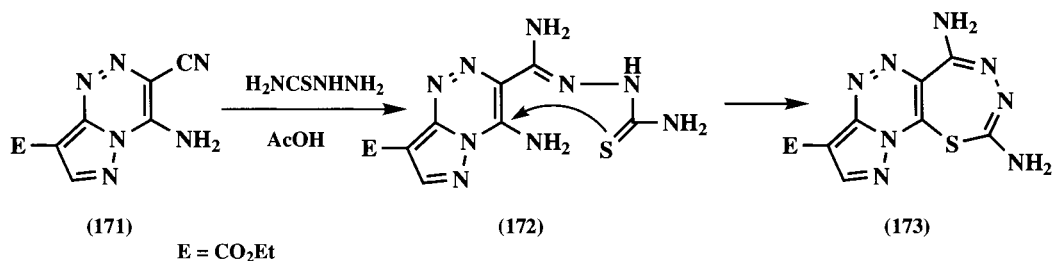
The reaction of the pyrazolo[5,1-*c*]-1,2,4-triazine derivative (171) with thiosemicarbazide hydrochloride in acetic acid provided the tricyclic pyrazolo[5',1': 3,4]-1,2,4-triazino[6,5-*f*]-1,3,4-thiadiazepine (173) (83% yield), via the intermediate (172) (Scheme 31) <89JHC861>.



Scheme 29



Scheme 30



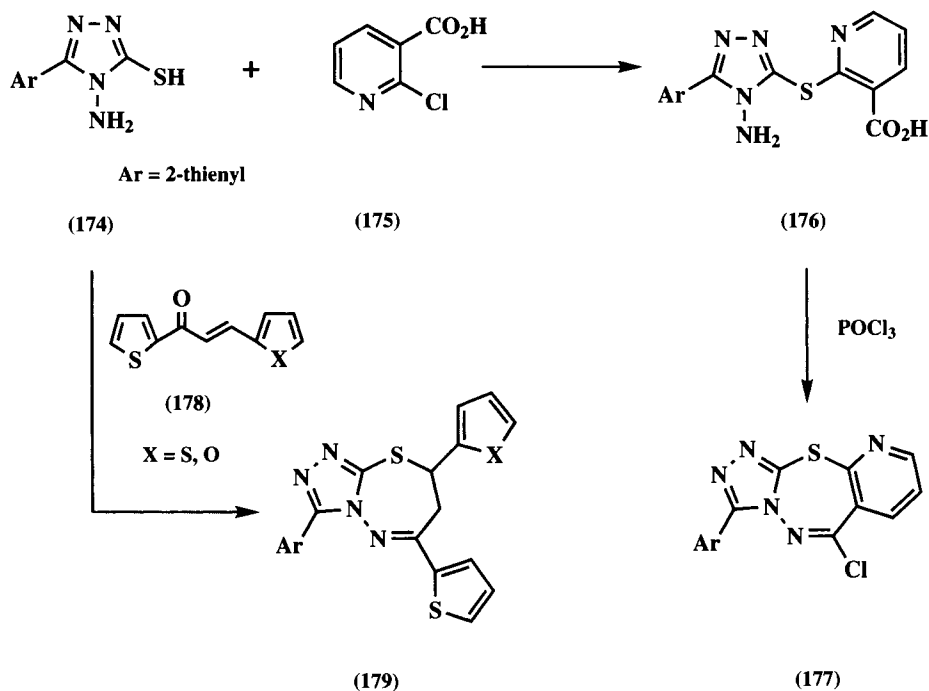
Scheme 31

Condensation of 3-(2-thienyl)-4-amino-5-thiol-1,2,4-triazole (174) with 2-chloronicotinic acid (175) in refluxing ethanol in the presence of sodium acetate produced the sulfide (176), which was treated with phosphorus oxychloride to result in cyclization giving rise to the triazolo[3,4-*b*]pyrido[3,2-*f*]-1,3,4-thiadiazepine (177) (45% yield). The triazole (174) also reacted with the α,β -unsaturated ketones (178) to give the triazolo-1,3,4-thiadiazepines (179) (75% yield) (Scheme 32) <91SUL201>.

9.14.4.2 Fused 1,2,4-Thiadiazepines

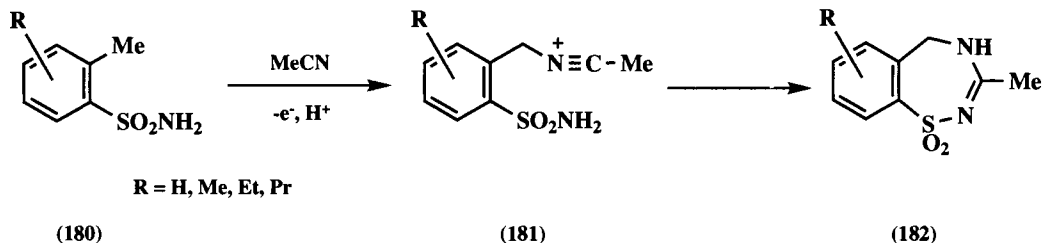
Although several examples of these ring systems had been reported prior to 1980 <60JA1594, 68JHC719, 72CB2575>, to date only one example, 1,2,4-benzothiadiazepines (182), has appeared since.

Controlled potential oxidation of *o*-toluenesulfonamides (180) at a platinum anode in acetonitrile using a divided cell provided 4,5-dihydro-1,2,4-benzothiadiazepine 1,1-dioxides (182) in generally good yields via (181) (Scheme 33). The scope and limitation of this one-step heterocyclization



Scheme 32

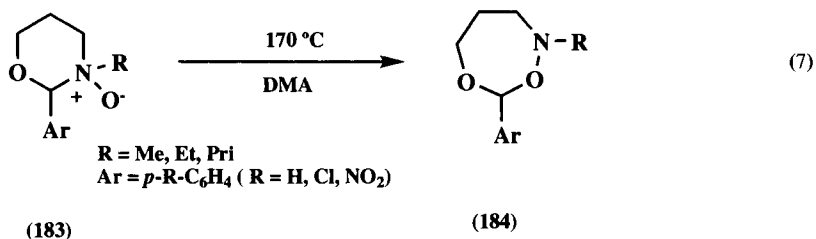
sequence are also discussed <88TL1545>. The fragmentation pathways of compounds (182) have been discussed on the basis of metastable transition data, exact mass measurements, and labeling experiments <84OMS(19)280>.



Scheme 33

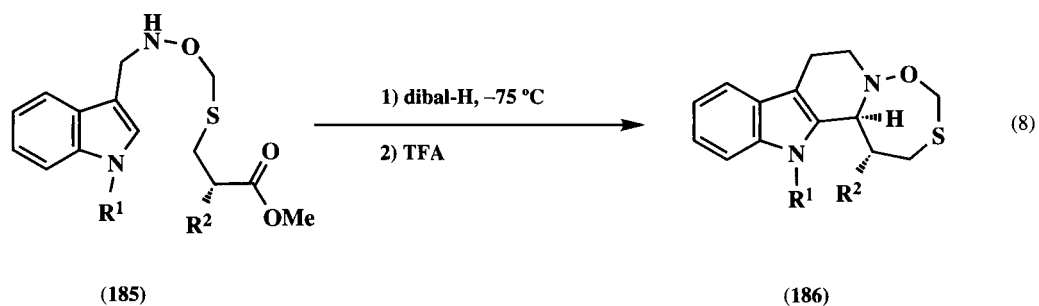
9.14.5 DIOXAZEPINES

Only one class of 1,6,2-dioxazepines is yet known. Several fully saturated 2-alkyl-7-aryl-1,6,2-dioxazepines (184) have been synthesized in moderate yields (45–75%) by a Meisenheimer-type rearrangement of the 3-alkyl-2-aryltetrahydro-1,3-oxazine *N*-oxides (183) (Equation (7)) <91JHC1789>. The structures of (184) have been confirmed by spectral and x-ray crystallographical analyses.



9.14.6 OXATHIAZEPINES

A series of the 1,6,2-oxathiazepines (**186**) has been prepared, as mixtures of two diastereomers, from the indole derivatives (**185**) via an intramolecular Pictet–Spengler condensation (Equation (8)) <92JMC3223>.



	<i>R</i> ¹	<i>R</i> ²	<i>cis:trans</i>
a :	Me	NHBoc	31:69
b :	H	OH	38:62
c :	H	Me	100:0

9.15

Seven-membered Rings with Three Heteroatoms 1,2,5

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9.15.1 INTRODUCTION

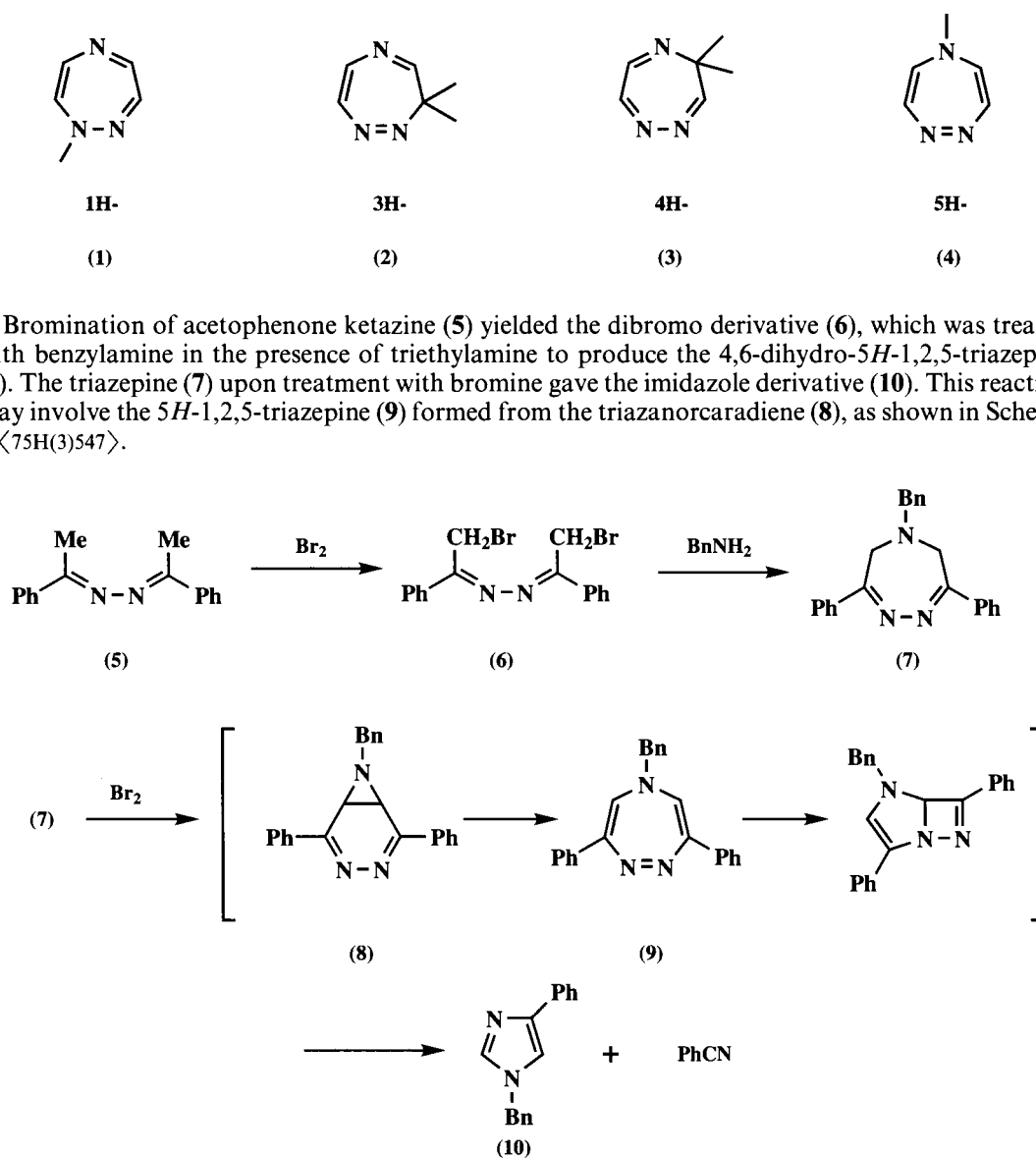
This chapter is organized in a manner similar to Chapters 9.13 and 9.14. Of the ten theoretically possible 1,2,5-triheteroepine ring systems, the following six have been prepared: triazepine, oxadiazepine, thiadiazepine, dithiazepine, oxathiazepine, and trithiepine.

9.15.2 TRIAZEPINES

9.15.2.1 Monocyclic 1,2,5-Triazepines

There are four possible tautomers, 1*H*- (1), 3*H*- (2), 4*H*- (3), and 5*H*-form (4), in the monocyclic 1,2,5-triazepine system; however, there has been relatively little research conducted with these systems and there are few synthetic routes to them. The fully unsaturated compounds had not been

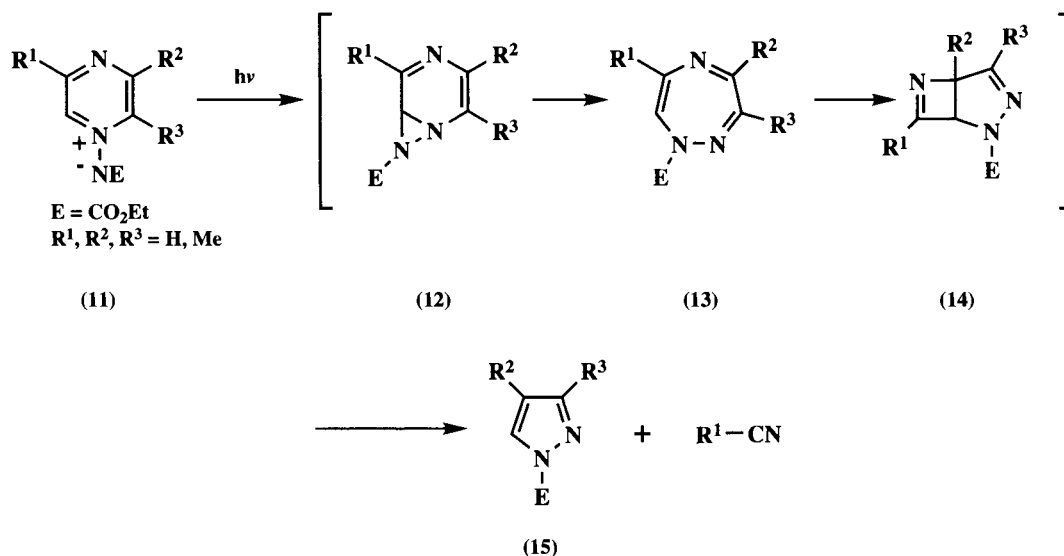
reported up to 1987, although some reactions involving such triazepines as unisolated intermediates and the syntheses of related di- and perhydo compounds were known.



Scheme 1

It is interesting to note that intermediates similar to those described in the transformation of (7) to the imidazole (10) have been proposed in the photolytic conversion of *N*-ethoxycarbonyliminopyrazinium ylides (11) to pyrazoles (15), although attempts to isolate the proposed intermediary triazanorcaradienes (12), 1*H*-1,2,5-triazepines (13), or azetidinopyrazoles (14) have not been successful (Scheme 2) <76CC250, 80CPB2676>.

In 1988, the first isolated examples of fully unsaturated monocyclic 1,2,5-triazepines were obtained by photochemical ring expansion of 4-azidopyridazines <88CPB4240, 90CPB2992>. Photolysis of the 3-methoxy-4-azidopyridazines (16; $\text{R}^1 = \text{OMe}$) in the presence of a base such as methoxide ion and diethylamine resulted in ring expansion to produce the 1*H*-1,2,5-triazepines (21) (Scheme 3). These 1*H*-triazepines (21) are too unstable to be isolated, but rather tautomerize to the stable 4*H*-isomers (22) on further treatment with sodium methoxide in 40–60% yields and can also be converted into the stable 1-acetyl-1*H*-1,2,5-triazepines (25) in 35–50% yields by treatment with acetyl chloride in pyridine. On the contrary, the 4-azidopyridazines (16; $\text{R}^1 = \text{H}$ or Me) having no methoxy group,



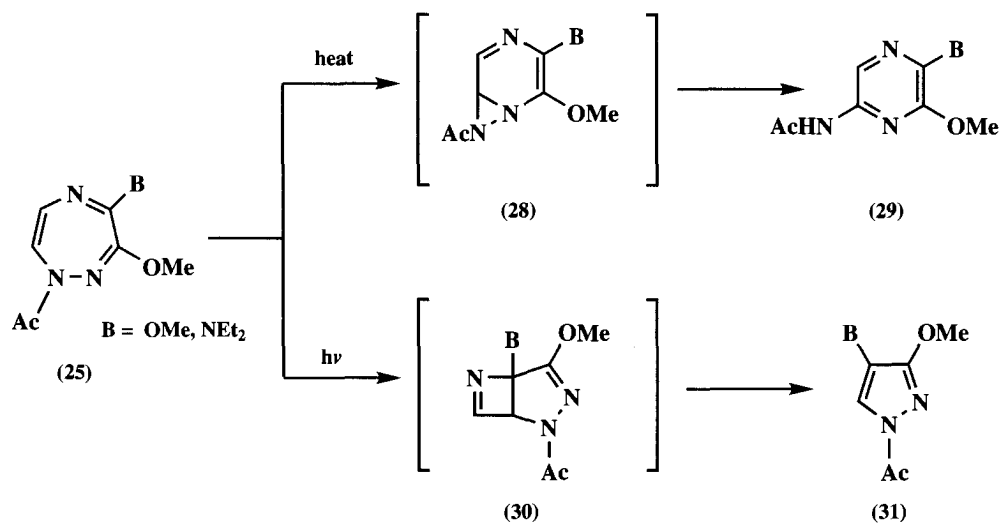
Scheme 2

upon irradiation under similar conditions, gave only the substitution products (17) in low yields and no ring-expansion products.

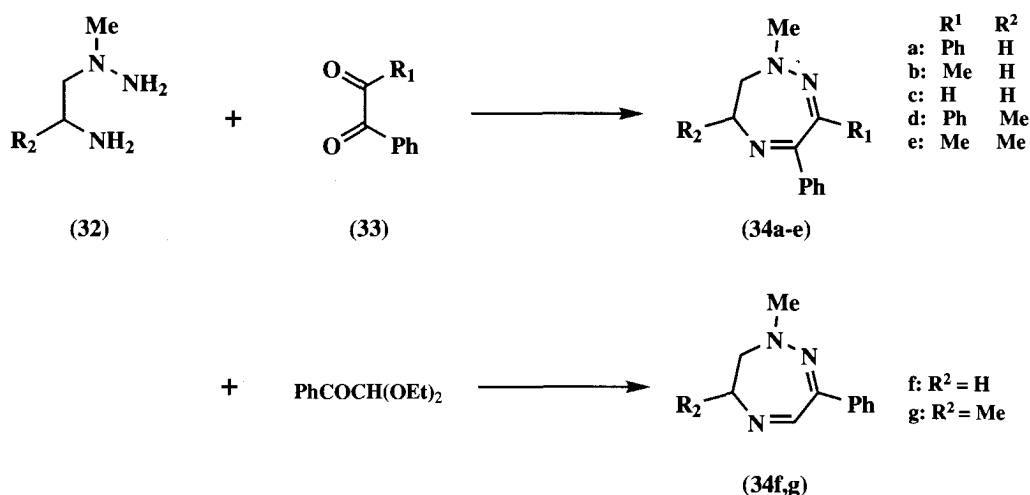
The formation of (21) from azides (16) may proceed via the azirine intermediates (19), derived from the initially formed singlet nitrenes (18), but 1,2,4-triazepines, such as (24), expected from the other possible azirine intermediates (23) have not been observed in the photolysis. This direction of the azirine formation is analogous to those of 2-substituted phenylnitrenes <75JCS(P2)554> and 3-pyridylnitrenes <85CPB5603, 87CPB1179>, which are known to cyclize preferentially at the vacant α -position. Although the effect of the methoxy group is, at present, not clear, it is assumed that the strong electron-donating methoxy group may provide assistance for the cyclization of the nitrenes (18) to the azirines (19), and for the stabilization of the triazepine ring formed. It is known that the CH-forms of diazepines undergo acetylation with tautomerization to give the corresponding *N*-acetyl derivatives <82CPB3764, 84CPB4694, 87CPB3175, 87CPB3182, 87CPB4110>; however, attempts to convert the 4*H*-isomers (22) into the 1-acetyl-1*H*-1,2,5-triazepines (25) have been unsuccessful, resulting only in decomposition. Lithium aluminum hydride reduction of (22) gave the related 3,4-dihydro compounds (26). Treatment of (26) with acetyl chloride afforded the dihydroacetyl derivatives (27), which were also obtained from (25) by hydrogenation over Pd-C.

Heating the 1-acetyl-1*H*-1,2,5-triazepines (25) in *o*-dichlorobenzene at 190–200°C resulted in isomerization to give the 6-acetylaminopyrazines (29), presumably via the diaziridine intermediates (28). Irradiation of (25) led to the 1-acetylpyrazoles (31) via the bicyclic intermediates (30) (Scheme 4). These thermal and photochemical reactions are similar to those observed for a variety of fully unsaturated diazepines <81H(15)1569, 81YGK99, 83YGK641, 83YZ373> and to the formations of (10) (Scheme 1) and (15) (Scheme 2) from (7) and (11), respectively.

The 6,7-dihydro-1*H*-1,2,5-triazepines (34a–f) can be easily prepared in moderate yields (30–80%) by the reaction of 1-(2-aminoethyl)-1-methylhydrazines (32) with diketones (33) or phenylglyoxal diethyl acetal (Scheme 5) <86MI 915-01, 92JCS(P1)3233>. They undergo a novel ring contraction which is thought to proceed via a covalently hydroxylated intermediate under base-catalyzed conditions. When the base-catalyzed reaction of (34) was conducted in refluxing 10% ethanolic sodium hydroxide, the 4-phenyltriazepines (34a–c; $\text{R}^2 = \text{Ph}$) were converted into the 1,2,3,6-tetrahydro-6-hydroxy- (35) and 1,2-dihydro-1,2,4-triazines (36); whereas the triazepines (34f; $\text{R}^1 = \text{H}$), having no phenyl group on the 4-position, gave only the 1,6-dihydrotriazine derivative (37f). The reaction may be initiated by attack of a hydroxy ion on the 3-position of (34) to form anion (38). Anion (38) with a 4-phenyl group was converted into the ion (39), where the negative charge was delocalized through conjugation with the phenyl group. The products (35) might be produced from (39) on exposure to the conditions used for the starting triazepines (34); however, when the 4-substituent is other than a phenyl group, the anion (39) cannot be formed. The triazine (37f) may be formed via the ring-opened anions (41) and (42) (Scheme 6).



Scheme 4



Scheme 5

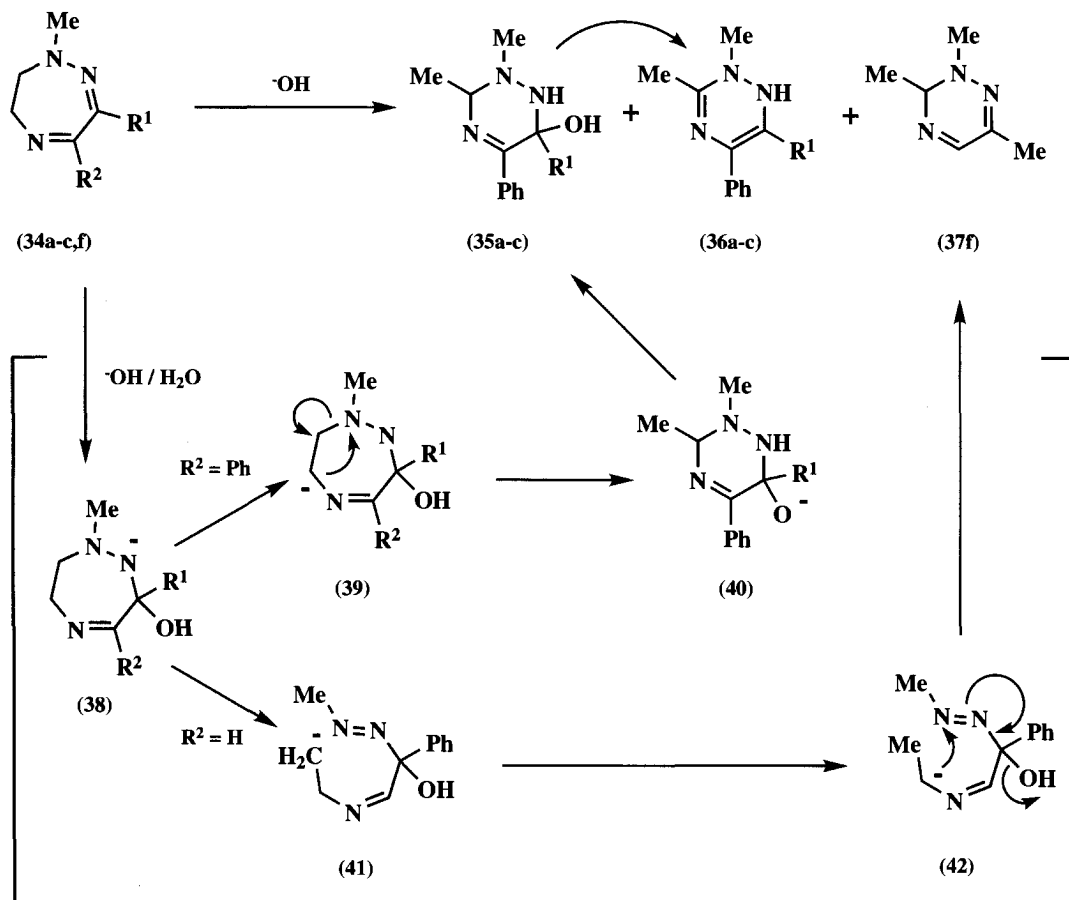
obtained, but rather three kinds of products, pyrrolidines (47) and (48) and the morpholine derivative (49), derived from the extrusion of nitrogen from (44), were isolated in low yields, accompanied with intractable tarry materials (Scheme 7) <85H(23)1675>.

9.15.2.2 Fused 1,2,5-Triazepines

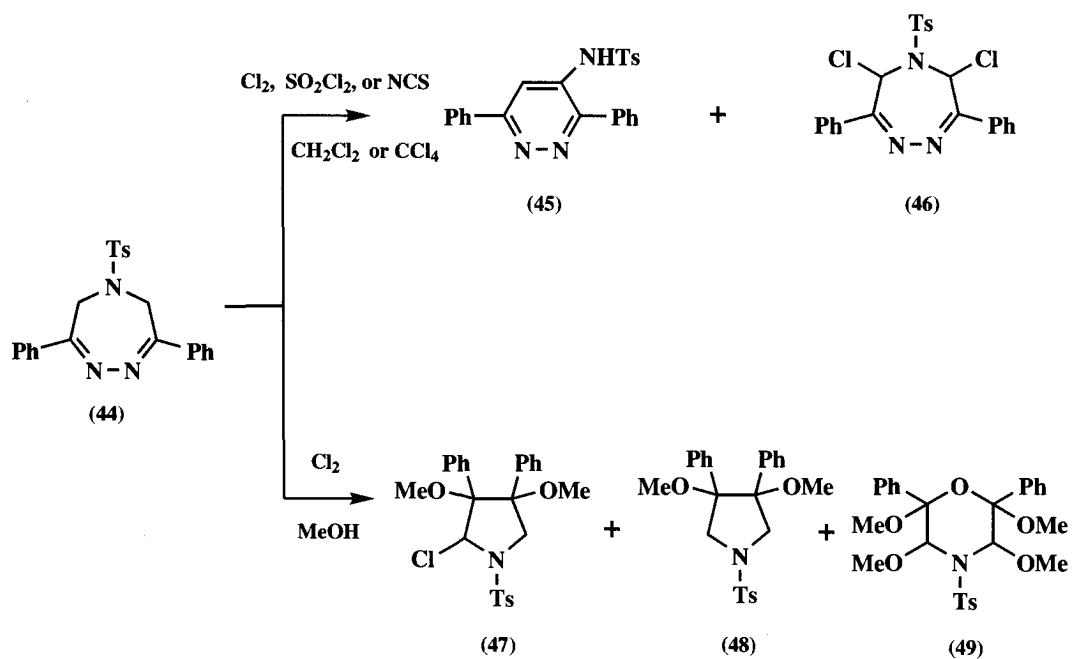
Although numerous dihydro-1,2,5-benzotriazepin-4-ones and fused 1,2,5-benzotriazepines condensed with one more heterocyclic ring, such as pyrrole and triazole rings, have been reported <84CHE719>, to date fully unsaturated simple 1,2,5-benzotriazepines are still unknown.

Treatment of *N*-(2-acetylamino-phenyl)-1*H*-pyrrole-1-amine (50; X = H) with phosphoryl chloride resulted in intramolecular cyclization to give the five-membered ring benzimidazole (51) (80% yield), while the *N*-methyl compound (50; X = Me) underwent cyclization to form a seven-membered ring such as the pyrrolo[1,2-*b*]-1,2,5-benzotriazepine (52) (95% yield) (Scheme 8) <83S757, 90FES1, 90FES817>.

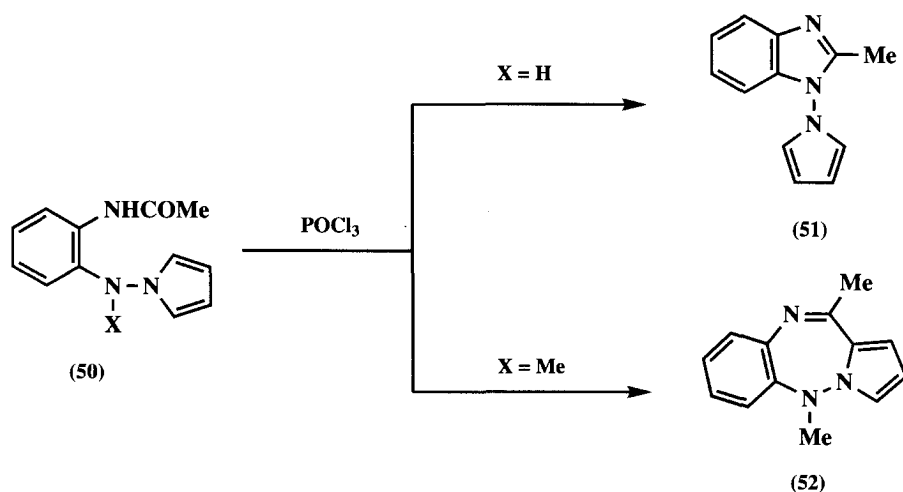
N-Methyl-*N*-(2-nitrophenyl)-2-formyl-1*H*-pyrrole-1-amine (53) also cyclized spontaneously upon



Scheme 6

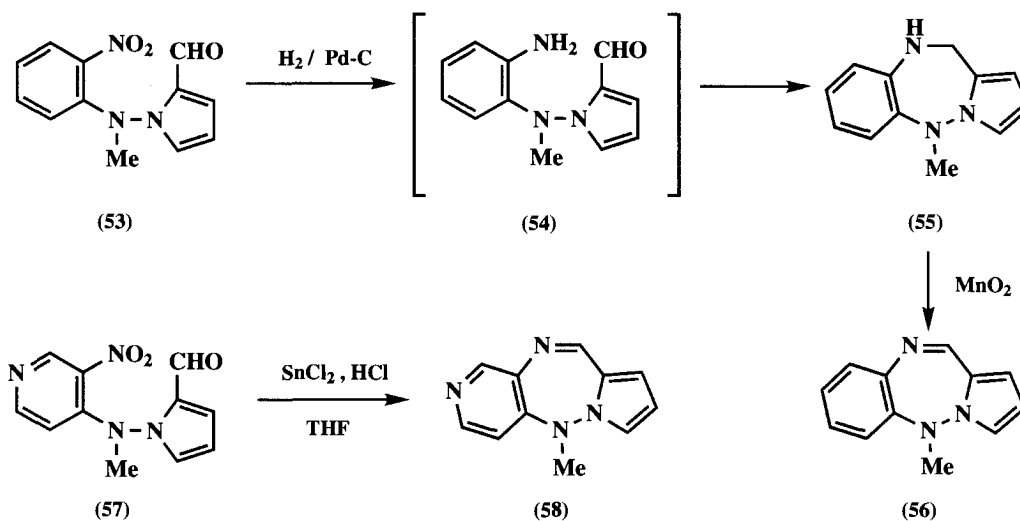


Scheme 7



Scheme 8

catalytic reduction of the nitro group to give the dihydrobenzotriazepine (55) (50% yield) via the amino intermediate (54). Oxidation of (55) with activated manganese dioxide leads to the pyrrolo[1,2-*b*]-1,2,5-benzotriazepine (56) (80% yield) <83S757>. Similarly, the pyrido[3,4-*f*]-pyrrolo[1,2-*b*]-1,2,5-triazepine (58) can be prepared from the nitropyridine derivative (57) by treatment with stannous chloride and hydrochloric acid in tetrahydrofuran (Scheme 9) <90JHC1015>.

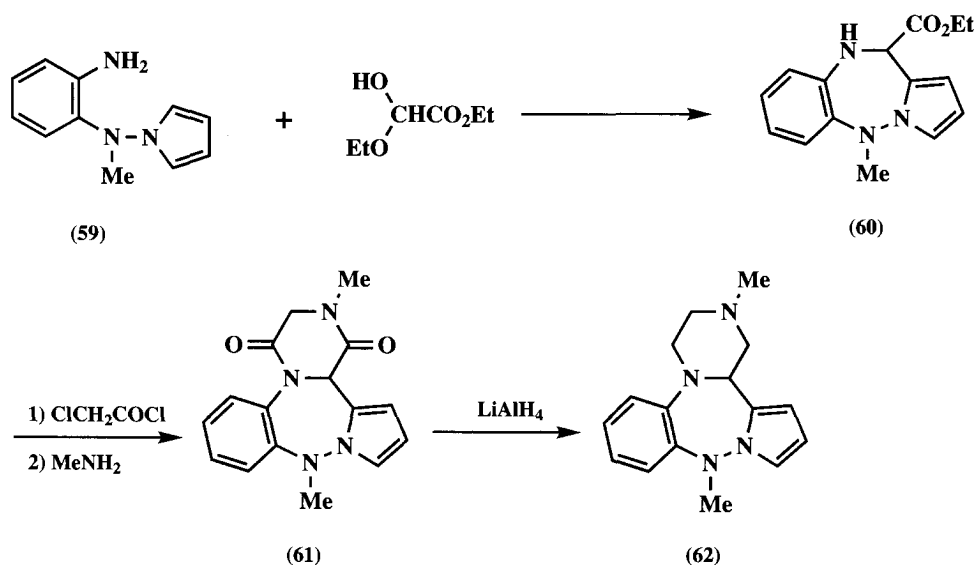


Scheme 9

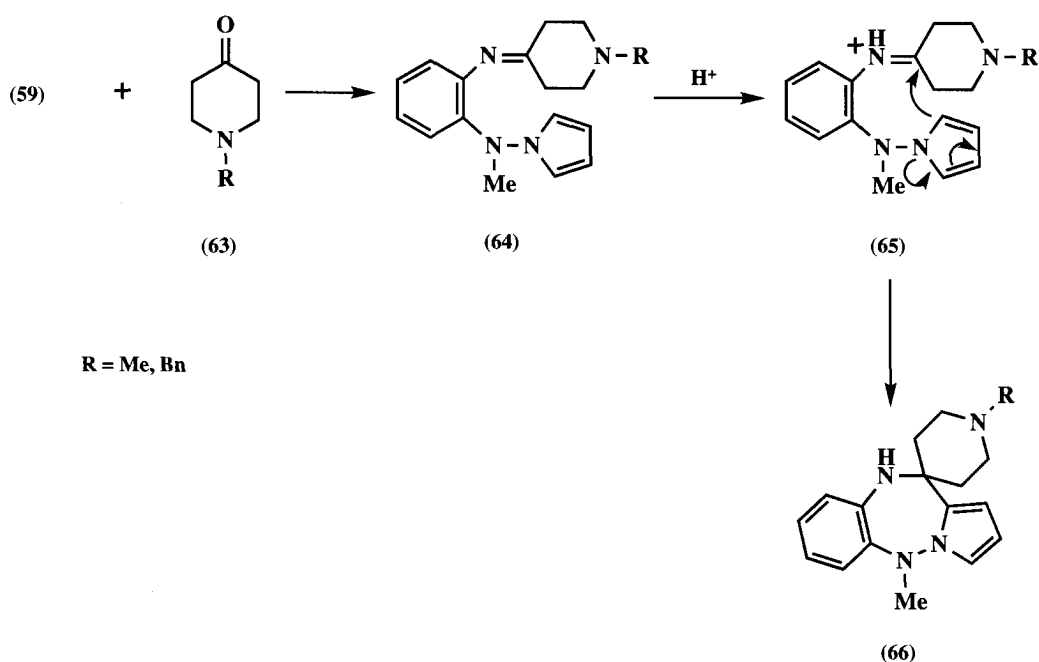
The reaction of the (aminophenyl)pyrrolylamine (59) with ethyl glyoxalate ethoxy hemiacetal in ethanol afforded the pyrrolo-1,2,5-benzotriazepine (60) (77% yield) via a Pictet-Spengler type condensation. Treatment of (60) with chloroacetyl chloride, followed by cyclization with methylamine, gave the diketopiperazine derivative (61), which was reduced with lithium aluminum hydride to yield the pyrazino[2,1-*d*]pyrrolo[1,2-*b*]-1,2,5-benzotriazepine (62) (80% yield) (Scheme 10) <89JHC745>.

The new tetracyclic ring system (66), containing a pyrrolo[1,2-*b*]-1,2,5-benzotriazepine ring bounded by a spiro linkage to the piperidine nucleus, has been synthesized in 40–60% yields by a simple reaction between the aromatic amine (59) and 4-oxopiperidines (63) in the presence of maleic acid, as a catalyst, via the intermediates (64) and (65) (Scheme 11) <92JHC241>.

The reaction of the pyrrolylchloropyridines (67a; $\text{R} = \text{CHO}$) and (67b; $\text{R} = \text{CO}_2\text{Me}$) with hydrazine hydrate resulted in cyclization to give the pyrido[2,3-*c*]pyrrolo[1,2-*e*]-1,2,5-triazepine (68) (11%

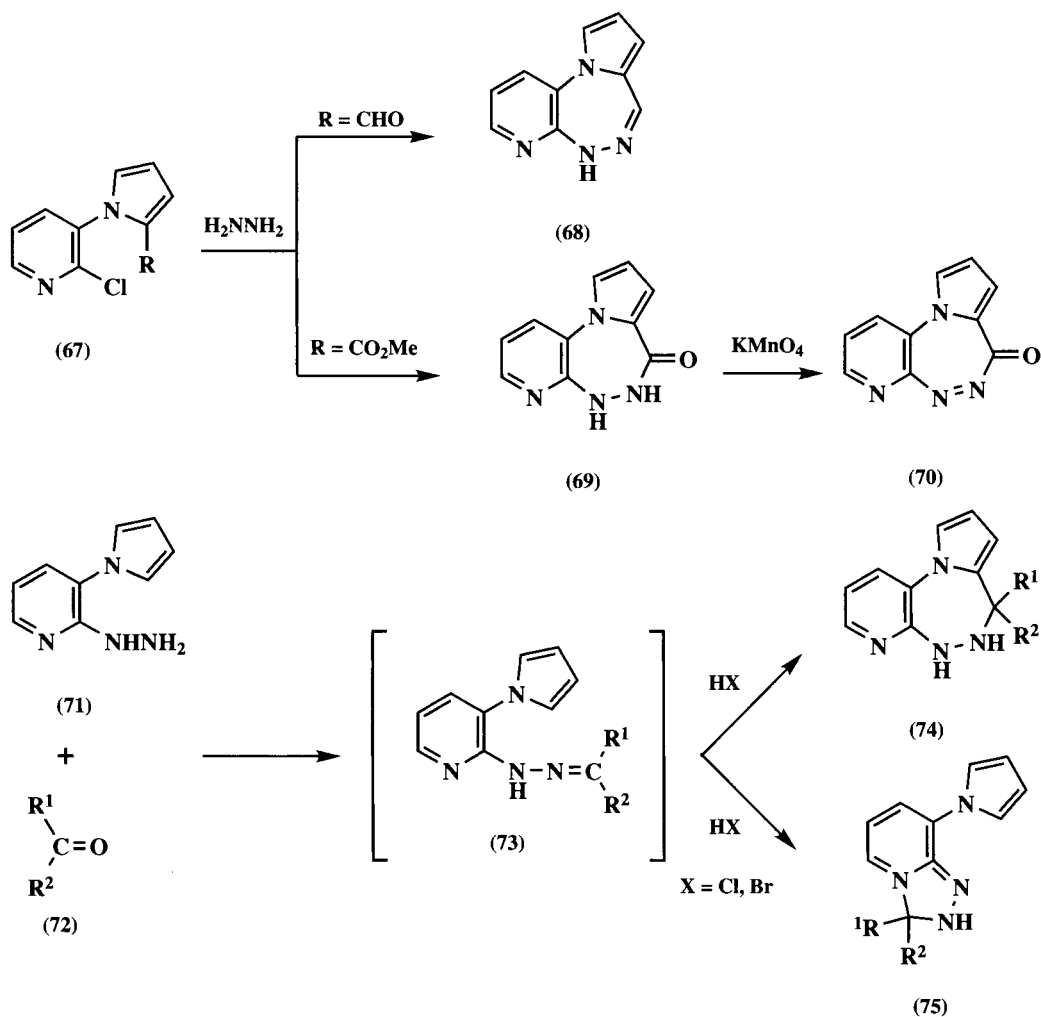


Scheme 10



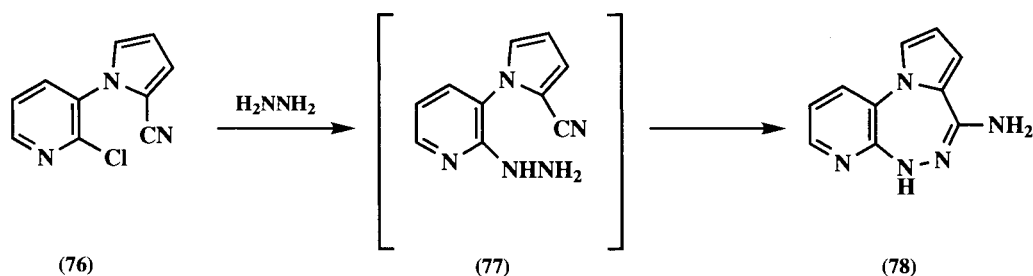
Scheme 11

yield) and triazepinone derivative (69) (75% yield), respectively. The latter was oxidized with potassium permanganate to produce (70) <88CPB2381>. Treatment of the 2-hydrazino-3-pyrrolylpyridine (71) with various alicyclic and aromatic carbonyl compounds (72) afforded the corresponding hydrazones (73), which, being very unstable, were immediately cyclized with hydrogen chloride or bromide. There are two possible sites for cyclization, either the α -pyrrolic carbon or the pyridine nitrogen, and the orientation appears to be dependent on the size of the hydrazone substituents. Hydrazones (73), which carry small aliphatic substituents, such as five- and six-membered alicyclic rings having no substituent at the α -position, led to the isolation of the triazepines (74); whereas those with bulky substituents, such as adamantane, cycloheptane, and 2-methoxycyclohexane, or with aromatic substituents afforded the triazolopyridines (75) (Scheme 12) <91CPB81>.



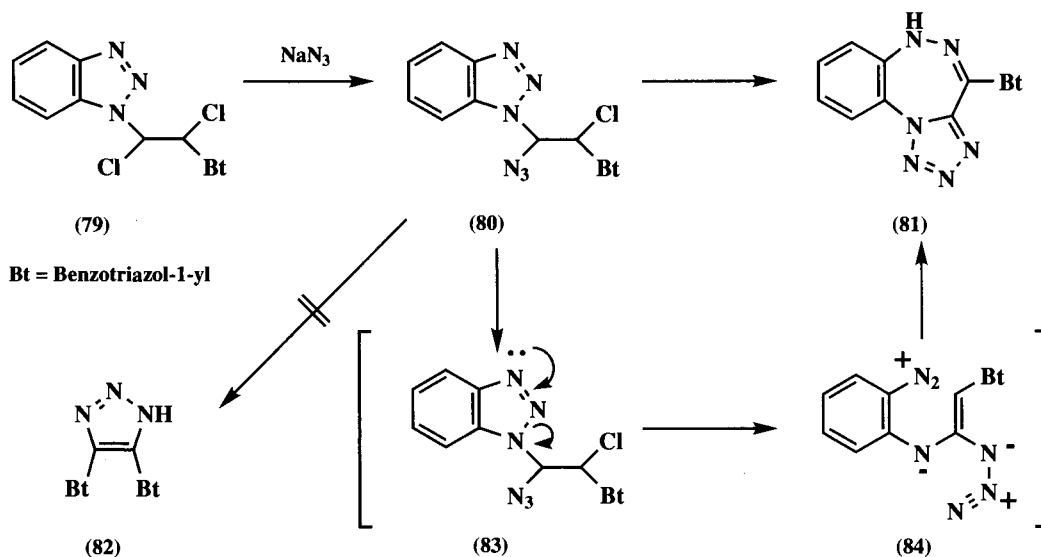
Scheme 12

The 2-cyanopyrrolyl derivative (76) reacted with hydrazine hydrate to give the amino-pyridotriazepine (78) via the intermediate (77), which was derived from initial interaction of hydrazine with the 2-position of pyridine rather than the cyano group (Scheme 13) <85H(23)909, 86H(24)3213>.



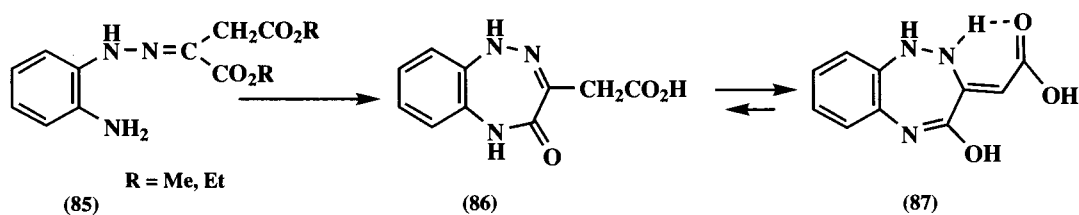
Scheme 13

The reaction of 1,2-bis(benzotriazol-1-yl)-1,2-dichloroethane, prepared from benzotriazole and glyoxal in two steps, with sodium azide produced the tetrazolo[5,1-*d*]-1,2,5-benzotriazepine (81), presumably via the mechanism involving the intermediates (83) and (84) shown in Scheme 14. In this reaction, the formation of the expected triazole product (82) has not been observed <91JOC1299>.



Scheme 14

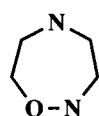
Thermal cyclization of the hydrazones (85) gave the 1,2,5-benzotriazepin-4-one (86), which exists predominantly as the tautomer (87) stabilized by hydrogen bonding, rather than (86) (Scheme 15) <92PHA60>.



Scheme 15

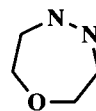
9.15.3 OXADIAZEPINES

There are two theoretically possible ring systems; several examples of the 1,4,5-oxadiazepine system (89) are known, while the 1,2,5-system (88) has not been prepared.



1, 2, 5 -

(88)

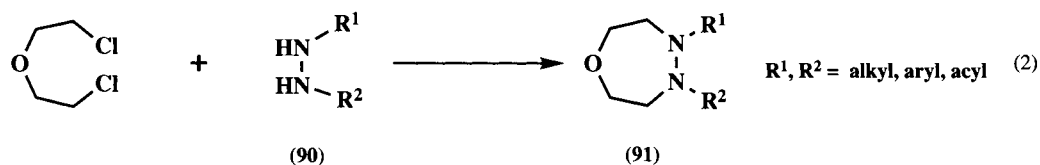


1, 4, 5 -

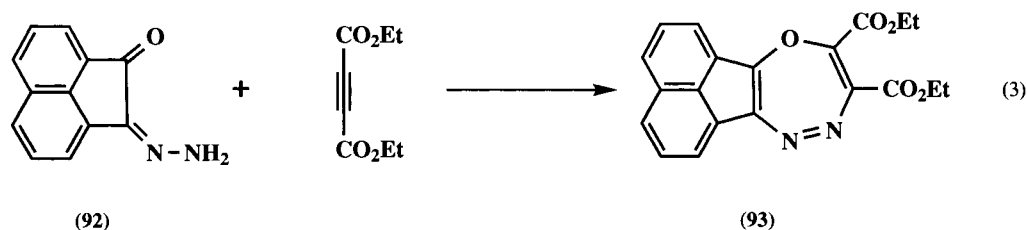
(89)

9.15.3.1 1,4,5-Oxadiazepines

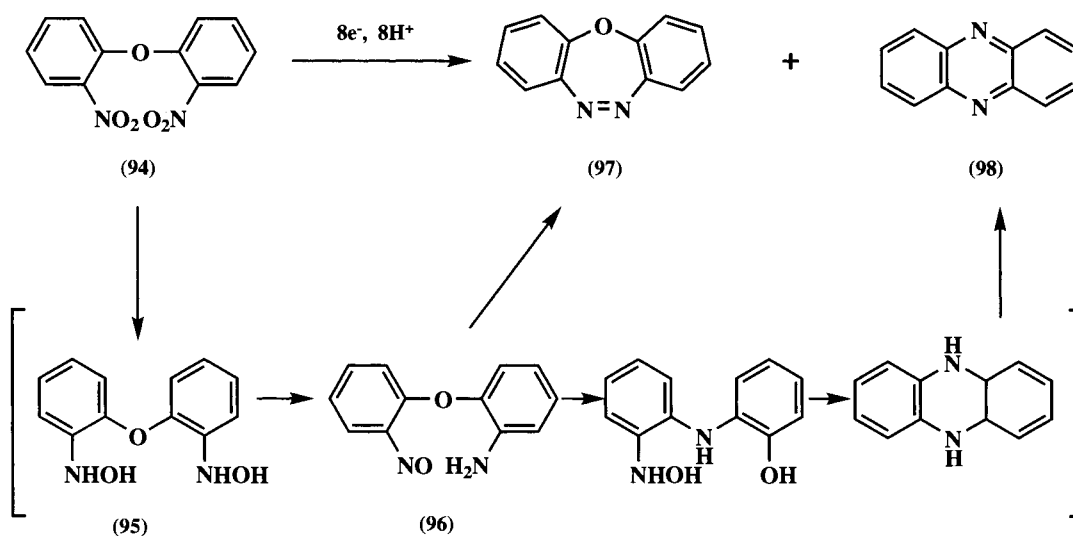
The fully saturated monocyclic 1,4,5-oxadiazepines of type (91) can be prepared by the reaction of 2,2'-dichlorodiethyl ether with various substituted hydrazines (90) (Equation (2)) <75MI 915-01, 79MI 915-01, 81MI 915-01>.



The reaction of acenaphthenequinone monohydrazone (92) with diethyl ethynedicarboxylate in boiling tetrahydrofuran gave the fully unsaturated fused 1,4,5-oxadiazepine derivative (93) (12% yield), together with two other products (Equation (3)) <72IJC875>.

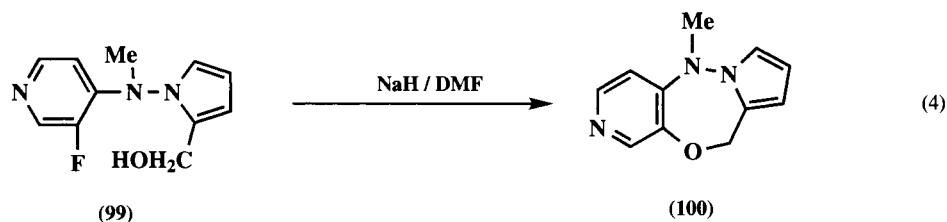


2,2'-Dinitrodiphenyl ether (94) was electrolytically reduced in a single wave with an uptake of eight electrons per molecule, giving rise to the bishydroxylamino intermediate (95), which underwent an intramolecular disproportionation. The resulting 2-nitroso-2'-aminodiphenyl ether (96) underwent a chemical follow-up reaction leading to dibenzo[*b,f*]-1,4,5-oxadiazepine (97) and phenazine (98) via two steps as shown in Scheme 16 <83CCC379>.

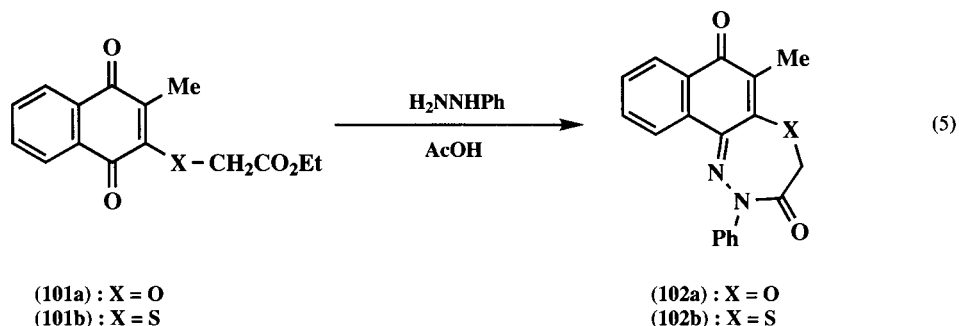


Scheme 16

The pyridylmethylaminopyrrole (99), prepared from 4-chloro-3-fluoropyridine and *N*-(methylamino)pyrrole via three steps, was heated with sodium hydride in DMF to give the pyrido[3,4-*b*]-pyrrolo[1,2-*e*]-1,4,5-oxadiazepine (100) (Equation (4)) <91UPS015637>.



The 1,4-naphthoquinones (**101a,b**) reacted with phenylhydrazine in glacial acetic acid to form the 1,4,5-oxadiazepine (**102a**) and the 1,4,5-thiadiazepine (**102b**), respectively (Equation (5)) <90AP(323)471>.



9.15.4 THIADIAZEPINES

Both the 1,2,5- and 1,4,5-thiadiazepine ring systems are known.

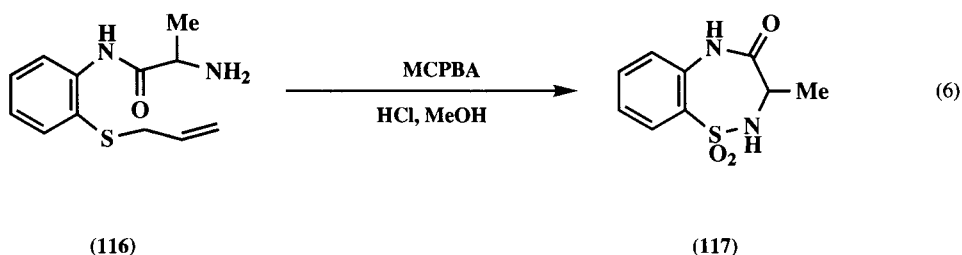
9.15.4.1 1,2,5-Thiadiazepines

Pyrrolo[1,2-*b*]-1,2,5-benzothiadiazepine 1,1-dioxide (**105**) has been obtained by cyclization of the *N*-formamide derivative (**104**), derived from 1-(2-aminobenzenesulfonyl)pyrrole (**103**) and acetic formic anhydride, with phosphorus oxychloride via a Bischler–Napieralski reaction in 47% yield, or by iron powder–acetic acid reduction of the nitro-aldehyde derivative (**106**) and subsequent ring closure of the resulting aminoaldehyde intermediate in 92% yield <94JHC1033>. The reaction of (**103**) with ethyl glyoxylate hemiacetal via a Pictet–Spengler type condensation afforded the benzo-thiadiazepine (**107**) in a high yield (94%) <94JHC867> (Scheme 17).

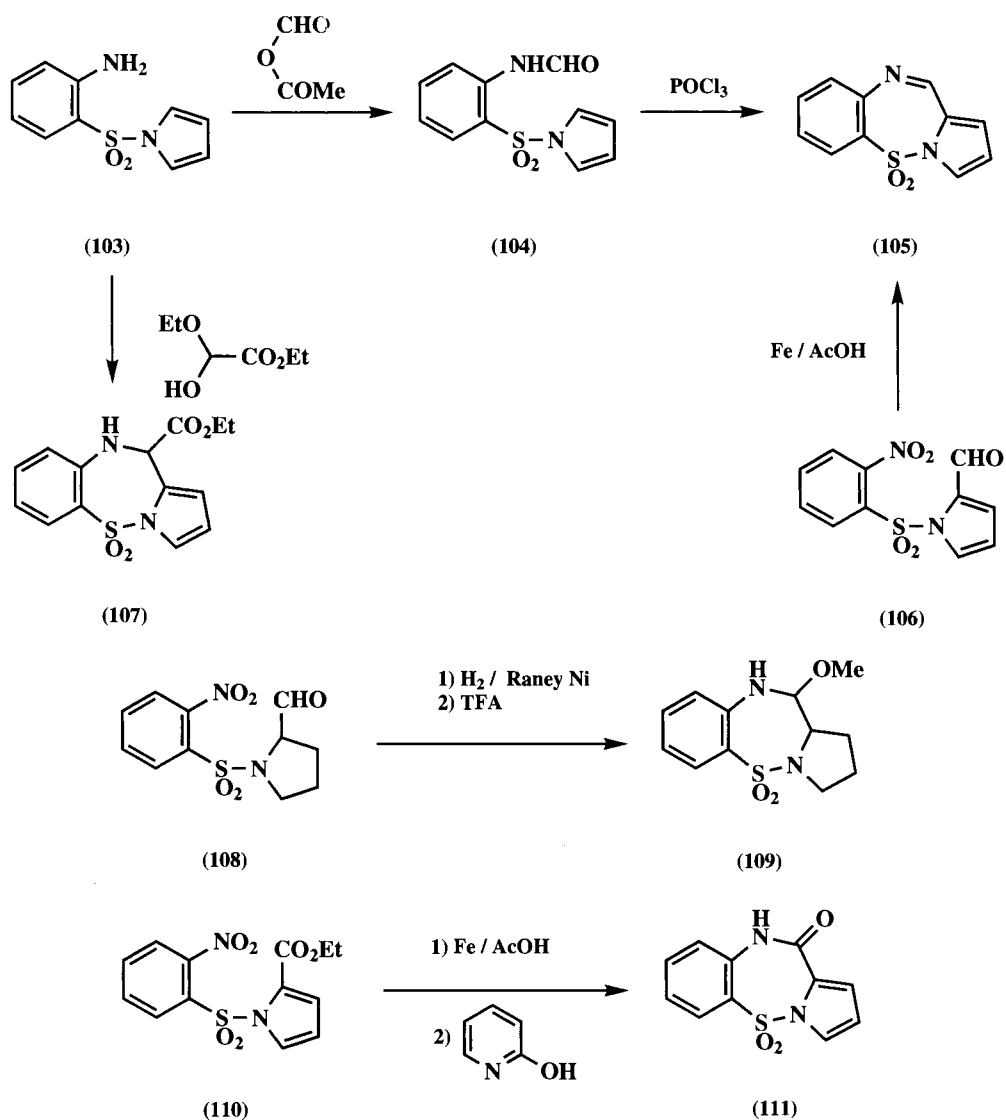
Similarly, the formylpyrrolidine compound (**108**) was reduced with an excess of Raney nickel to afford the amino intermediate, which was then treated with trifluoroacetic acid in dichloromethane–methanol to result in cyclization, thus giving rise to the pyrrolidinobenzothiadiazepine (**109**) (75% yield) <89H(29)1529>. The ethoxycarbonyl derivative (**110**) was also reduced with iron powder in glacial acetic acid to form the corresponding amino derivative, which was then cyclized to the 1,2,5-benzothiadiazepin-4-one (**111**) (60% yield) by heating at 170 °C in the presence of 2-hydroxypyridine as a bifunctional catalyst <92SC1433>.

The condensation of 2-nitrobenzenesulfonyl chloride with glycine gave the acid (**112**), which was converted (43% yield) into 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-dioxide (**113**) by reductive cyclization with zinc powder in acetic acid <92CPB2442>. Selective alkylation on the 2-position of (**113**) was accomplished using an appropriate alkyl halide in the presence of potassium carbonate in DMF to give the corresponding *N*-alkyl derivatives (**114**) in good yields. The second alkylation on the 5-position of (**114**) using alkyl halides in the presence of sodium hydroxide proceeded smoothly to afford the di-*N*-alkyl compounds (**115**) (Scheme 18).

The 1,2,5-benzothiadiazepin-4-one (**117**) was also prepared from the allyl phenyl sulfide (**116**) upon treatment with *m*-chloroperbenzoic acid in concentrated hydrochloric acid and methanol (Equation (6)) <90JAP(K)2138272>.

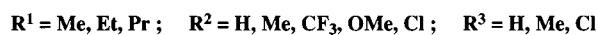
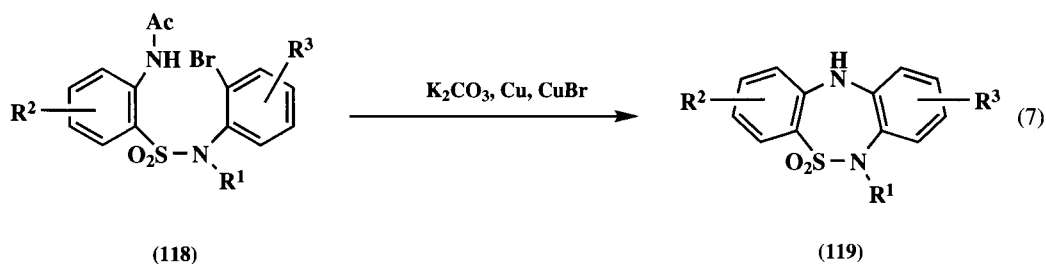


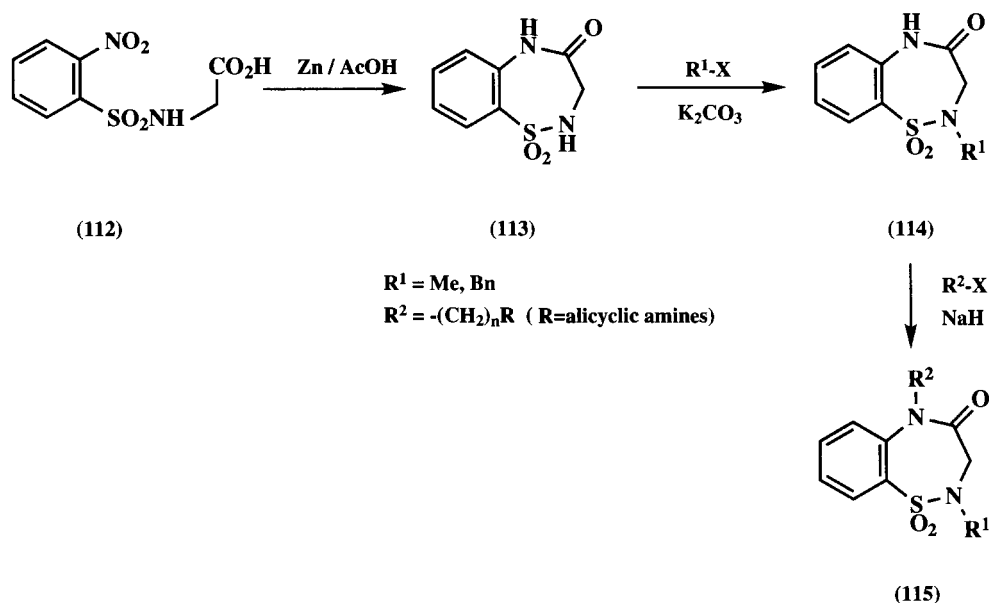
N-(2'-bromophenyl)-*N*-alkyl-2-(acetylamino)benzenesulfonamides (**118**), when treated with potassium carbonate, copper powder, and cuprous bromide, resulted in a cyclization giving the



Scheme 17

dibenzo[*c,f*]-1,2,5-thiadiazepines (**119**) (55–91% yield) (Equation (7)) <91JMC1356>. The starting sulfonamides (**118**) can be prepared by the reaction of the corresponding *o*-aminobenzenesulfonyl chloride with *o*-bromoanilines, followed by subsequent reduction with boiling iron powder–acetic acid, acetylation *in situ* with acetic anhydride, and *N*-alkylation with alkyl halides.



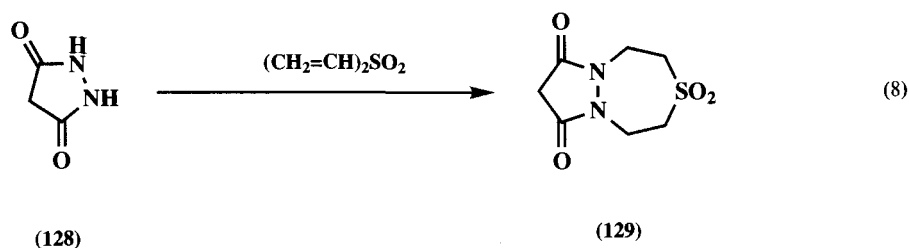


Scheme 18

9.15.4.2 1,4,5-Thiadiazepines

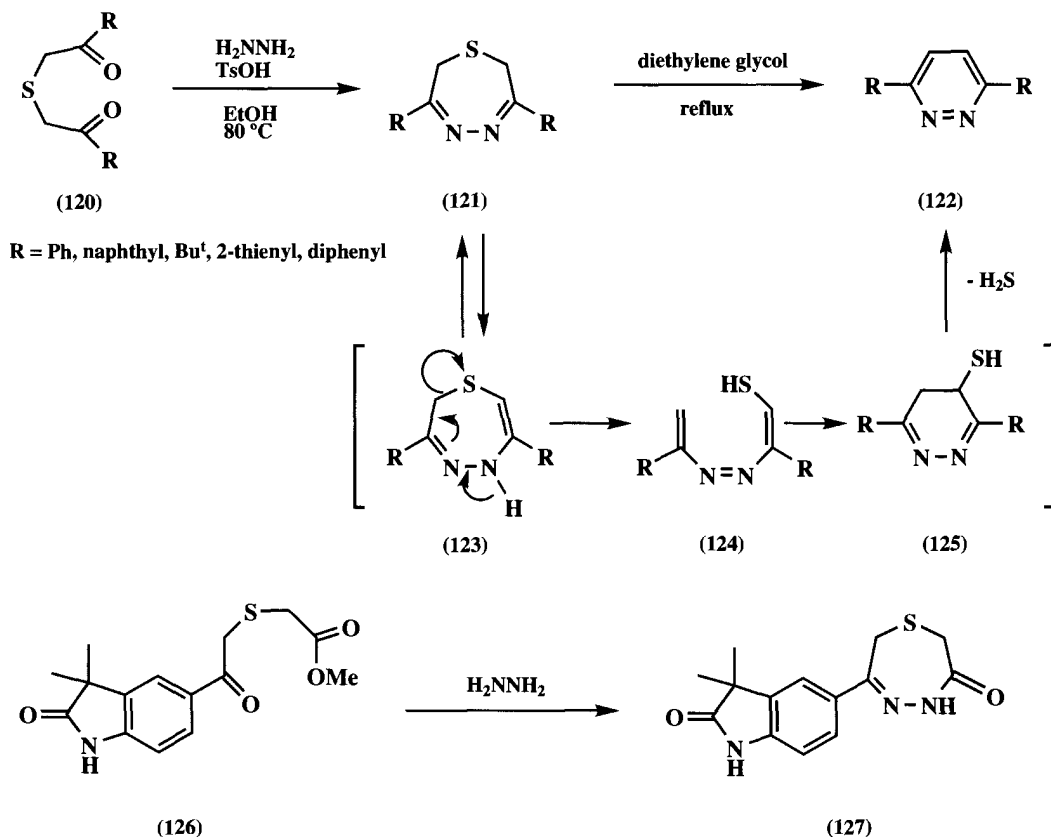
A series of 3-thiapentane-1,5-diones, for example (120), was condensed with hydrazine in the presence of a catalytic amount of *p*-toluenesulfonic acid in refluxing ethanol to give the 2,7-dihydro-1,4,5-thiadiazepines (121) in excellent yields. Thermal decomposition of (121) in refluxing diethylene glycol afforded the corresponding pyridazines (122) in high yields with evolution of hydrogen sulfide, probably via the intermediates (123) to (125) as illustrated in Scheme 19 <89BCJ2608>. The above procedure is generally applicable to the preparation of a wide variety of 3,6-disubstituted pyridazines, which are otherwise difficult to prepare. The starting 1,5-diketones (120) can be prepared easily by the reaction of α -haloketones with sodium sulfide. Similarly, the indolone derivative (126) gave the thiadiazepinyllindolone (127) upon treatment with hydrazine <92JMC163>.

Treatment of 3,5-pyrazolidinedione (128) with divinylsulfone resulted in a Michael-type addition to give the 1,4,5-thiadiazepine dioxide (129) in about a 50% yield (Equation (8)) <86AP(319)70>.

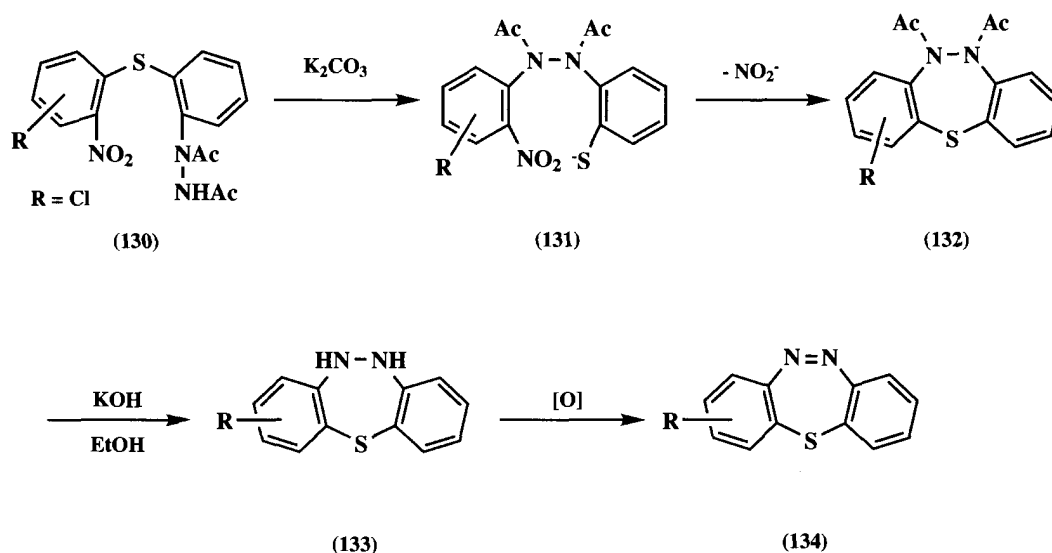


Several routes to dibenzo[*b,f*]-1,4,5-thiadiazepines are available. The 2-nitrophenyl 2-hydrazinophenyl sulfides (130) underwent a base-catalyzed Smiles rearrangement to the hydrazobenzene intermediates (131), which then cyclized to produce the 4,5-dihydrodibenzo[*b,f*]-1,4,5-thiadiazepines (132) (60–80% yields) (Scheme 20) <82JOC2214>. It should be noted that R must be an electronegative substituent for the reaction to occur. The reaction did not occur for (130; R = H), although no starting material was recovered; however, compounds in which R is 4-, 5- or 6-Cl do react to give (132) in high yields. These findings are consistent with the inductive as well as the mesomeric effects of the chloro group. The first should reinforce the action of the nitro group in (130), making the charge on C-1 more positive, thus facilitating attack. The diacetates (132) were easily hydrolyzed to (133) by refluxing in aqueous alcoholic potassium hydroxide. The hydrazino compounds (133) underwent aerial oxidation to the corresponding fully unsaturated dibenzo[*b,f*]-1,4,5-thiadiazepines (134).

Di(2-nitro-4-carboxyphenyl)sulfone (135), prepared from 3-nitro-4-chlorobenzoic acid in four

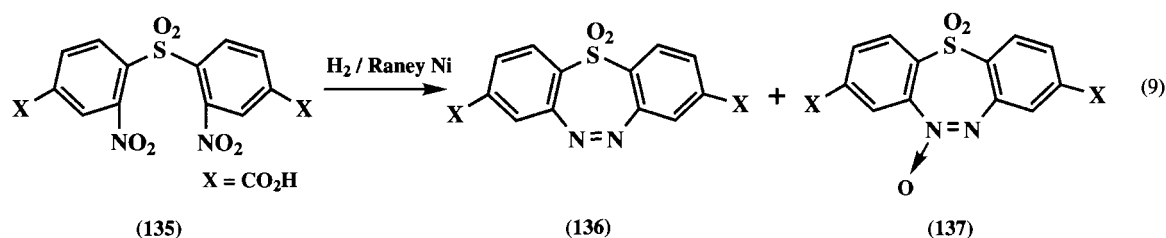


Scheme 19



Scheme 20

steps, was hydrogenated over Raney nickel to give a cyclic hydrazo compound, which, on subsequent aerial oxidation in an alkaline medium, formed a mixture of azo (136) and azoxy (137) compounds (Equation (9)). The mixture was heated under reflux with magnesium turnings in dry methanol to yield the dibenzo[*b,f*]-1,4,5-thiadiazepine 1,1-dioxides (136) (60% yield) <89CI(L)228>.

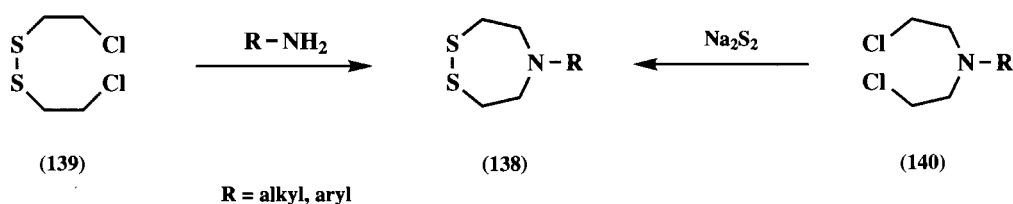


9.15.5 DITHIAZEPINES

Few examples of fully saturated monocyclic 1,2,5-dithiazepine systems are known.

9.15.5.1 1,2,5-Dithiazepines

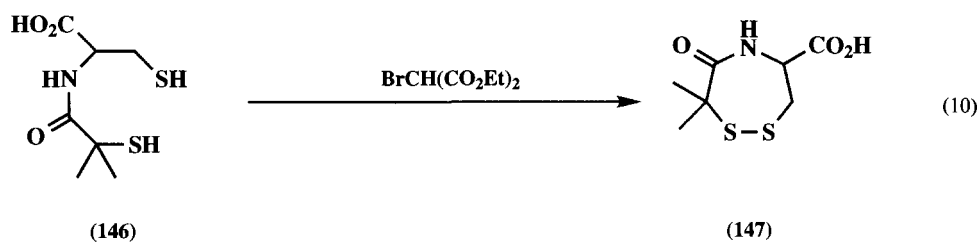
A number of *N*-alkyl or *N*-aryl derivatives of fully saturated 1,2,5-dithiazepines, for example (138), were prepared by condensation of bis(2-chloroethyl) disulfide (139) with primary amines in 20–60% yields (Scheme 21). The starting disulfide (139) can be obtained from 2-chloroethanol by treatment with sodium disulfide, followed by chlorination with thionyl chloride. The dithiazepines (138) were also prepared by treating bis(2-chloroethyl)amines (140) with sodium disulfide (84MI 915-01, 85MI 915-01).



Scheme 21

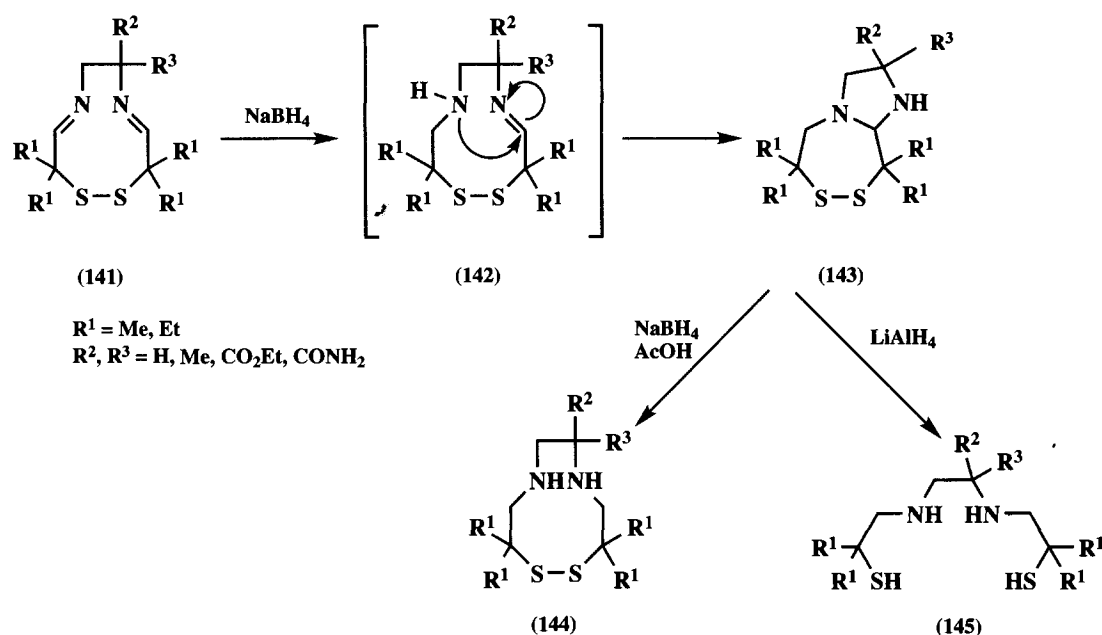
The 1,2-dithia-5,8-diazacyclodeca-4,8-dienes (141), prepared by condensation of 2,2'-dithiobis(2-methylpropanal) with an appropriate substituted ethylenediamine, underwent a reductive cyclization upon treatment with sodium borohydride in ethanol to give the imidazolidino[2,1-*d*]-1,2,5-dithiazepines (143), as the major products (60–80% yields) via the intermediates (142), in addition to smaller amounts of the ten-membered compounds (144) (87JOC2447, 88JOC4310). The bicyclic dithiazepines (143) were converted to (144) (30–50% yields) by further treatment with sodium borohydride in acidic media, such as glacial acetic acid (92T4767); whereas reduction of (143) with lithium aluminum hydride cleaved not only the disulfide bond, but also the transannular C—N bond, affording the open-chained dithiols (145) (74% yield) (88TL3219) (Scheme 22).

N-(2-Thiol-2-methylpropionyl)cysteine (146) was converted into the 1,2,5-dithiazepin-4-one (147) (40–50% yield) upon treatment with diethyl bromomalonate (Equation (10)) (86CPB486).



9.15.6 OXATHIAZEPINES

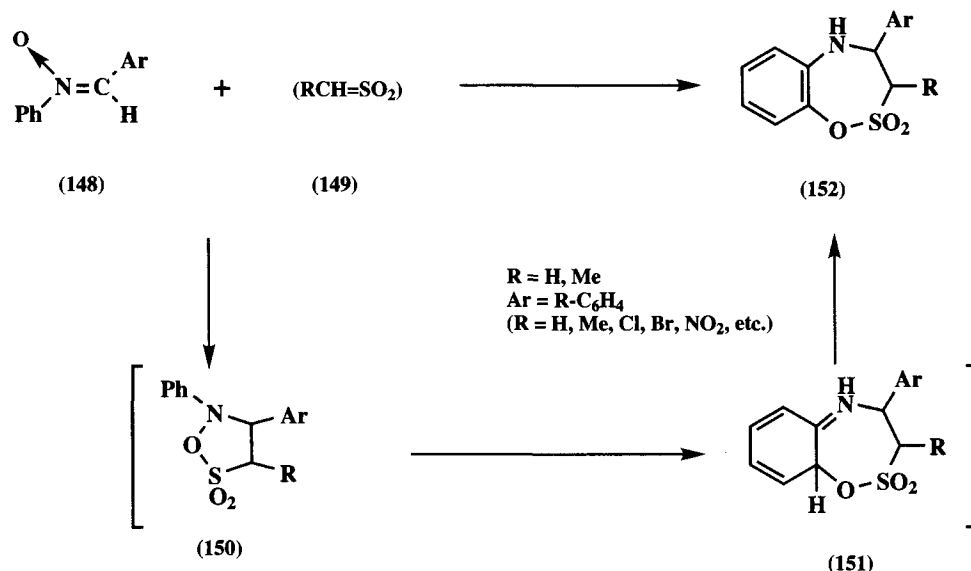
Several examples of 1,2,5-benzoxathiazepines and only one example of 1,4,5-benzoxathiazepines have been prepared.



Scheme 22

9.15.6.1 1,2,5-Oxathiazepines

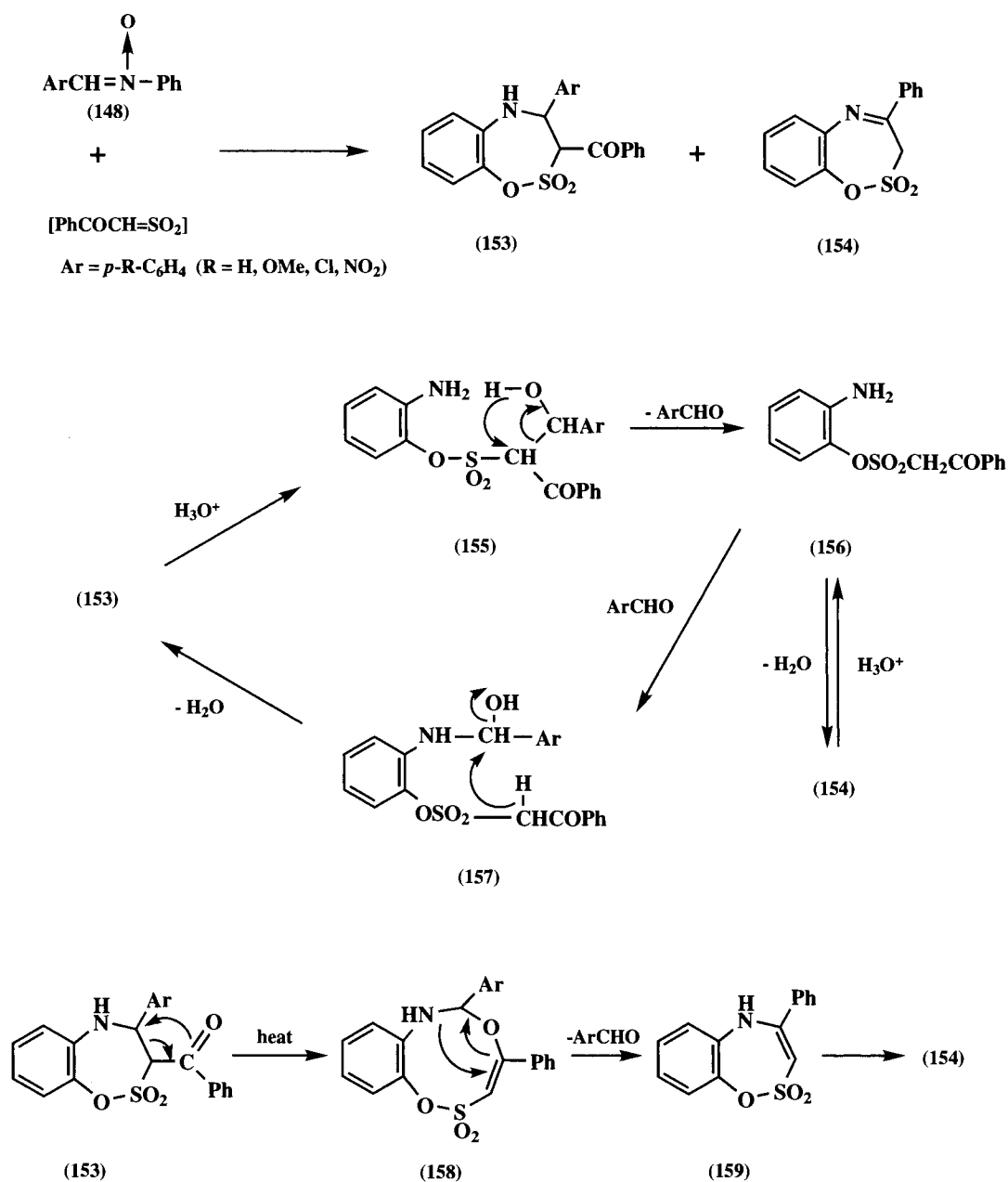
The sulfenes (149), generated *in situ* from the corresponding alkanesulfonyl chloride and triethylamine, add to the nitrones (148) to yield the 1,3-cycloadducts (150), which then rearrange to the final products (152), 1,2,5-benzoxathiazepines, via the intermediates (151) as shown in Scheme 23 <69JOC3097>. A mechanism has been proposed on the basis of ^{18}O -labeling studies.



Scheme 23

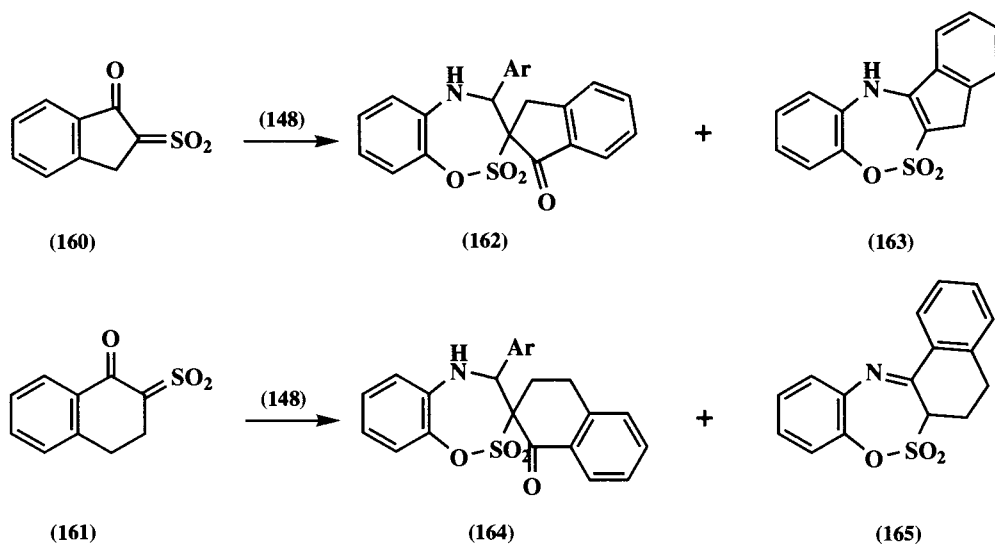
Benzoylsulfene reacted with the nitrones (148) to produce the 3-benzoyl-1,2,5-benzoxathiazepines (153) (10–36% yields), as well as a by-product (154) (5–8% yield), 4-phenyl-1,2,5-benzoxathiazepine derivative, which arose from (153) with the elimination of benzaldehyde (ArCHO). When (153) was treated with hydrochloric acid in methanol, it was converted into (154) along with benzaldehydes,

indicating that the formation of (154) in the reaction of (148) with benzoylsulfene was derived from the initially formed dihydrobenzoxathiazepines (153) and, on conversion of (153) into (154), the benzoyl group in (153) is not involved in the elimination of the benzaldehydes. The conversion might be interpreted as an initial formation of (156) via the ring-opened intermediates (155), followed by dehydration of (156) into (154), as illustrated in Scheme 24 <76JOC2438>. In addition, compound (156) reacted with benzaldehydes to revert back to the corresponding (153), probably via (157) and thermolysis (170–180 °C) of (153) under reduced pressure (2 mm Hg) afforded (154) (50–90% yield) and benzaldehydes; suggesting that water is not essential for the conversion. Therefore, another pathway has been proposed as depicted in Scheme 24. Ring-expansion of the oxathiazepine ring of (153) to the nine-membered dioxathiazonine ring (158), followed by elimination of the benzaldehydes gives (154) via the 5*H*-tautomer (159).



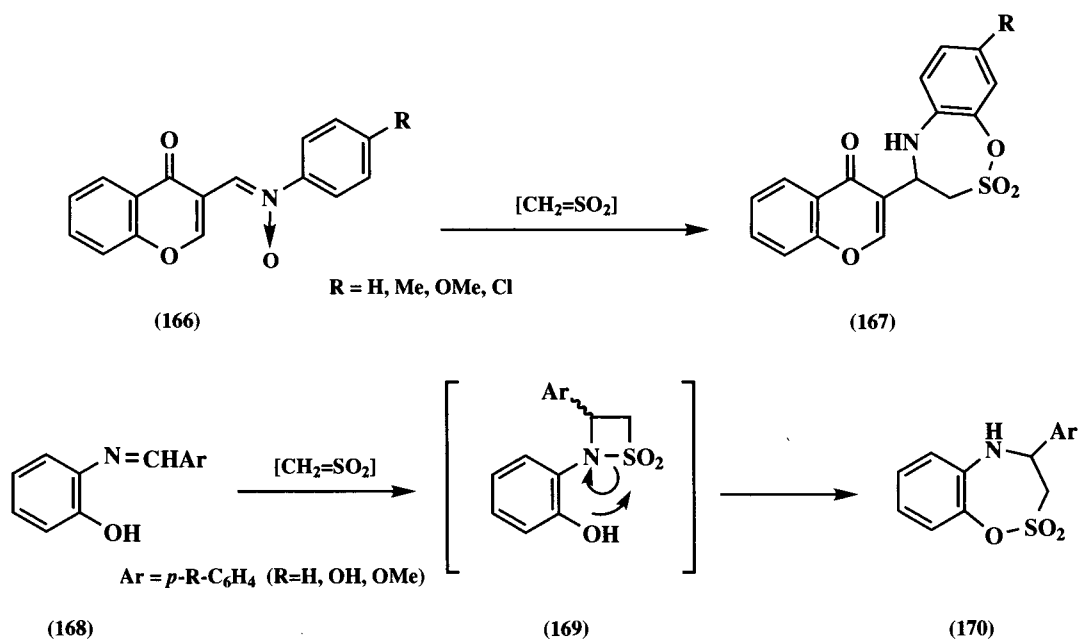
Scheme 24

Similarly, the nitrones (148) have been reacted with both cyclic α -ketosulfenes (160) and (161), generated *in situ* from 2-chlorosulfonylindanone and 2-chlorosulfonyl-1-tetralone by treatment with triethylamine, to give the rearranged spiro compounds (162) and (164), 1,2,5-benzoxathiazepine-3-spiro-2'-indanones and -2'-(1'-tetralones), together with small amounts of the tetracyclic 1,2,5-benzoxathiazepines (163) and (165), respectively (Scheme 25) <76JOC2438>.



Scheme 25

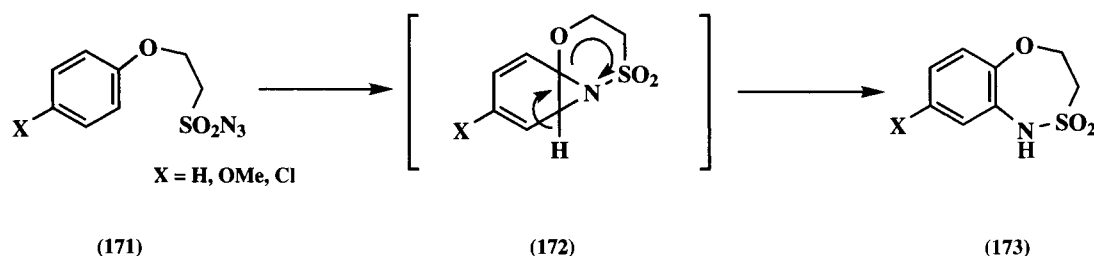
The reaction of the benzopyranylnitrones (166) with sulfene also gave the benzopyranyl-1,2,5-benzoxathiazepines (167) in high yields (Scheme 26) <93S468>. The dihydro-1,2,5-benzoxathiazepines (170) can also be prepared in about 50% yields through a novel rearrangement reaction of the unstable cycloadducts (169), formed initially by treatment of sulfene with *N*-benzylidene-2-hydroxyanilines (168) <81CC971>.



Scheme 26

9.15.6.2 1,4,5-Oxathiazepines

The only example of the 1,4,5-benzoxathiazepine system (**173**) has been obtained from 2-(aryloxy) ethanesulfonyl azides (**171**) either by thermal decomposition in oxygen-free Freon 113 or by flash vacuum pyrolysis via the adducts (**172**) derived from the initially formed ethanesulfonylnitrenes (Scheme 27) <84JOC3114>.

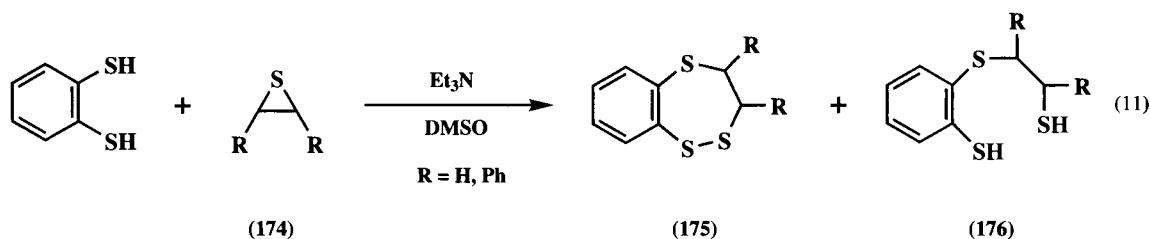


Scheme 27

9.15.7 TRITHIEPINES

9.15.7.1 1,2,5-Benzotrithiepies

1,2-Benzenedithiol readily reacted with various thiiranes (**174**) in the presence of triethylamine as a base, in a polar solvent such as DMSO and DMF, under air to give the 1,2,5-benzotrithiepies (**175**) in good yields (Equation (11)). Interestingly, when the reaction was conducted under argon instead of air, 2-thioethyl 2-thiolphenyl sulfides (**176**) were obtained as major products in about 50% yields, together with the trithiepies (**175**) (about 20% yields); suggesting apparently that the reaction proceeded via oxidation of the dithiol-sulfide (**176**), which is formed intermediately, with oxygen in air <94TL891>.



9.16

Seven-membered Rings with Three Heteroatoms 1,3,5

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9.16.1 INTRODUCTION

This chapter is organized in a manner similar to Chapters 9.13, 9.14, and 9.15. Among the ten possible 1,3,5-triheteroepine ring systems, the following six, triazepine, oxadiazepine, thiadiazepine, dioxazepine, dithiazepine and oxathiazepine are known.

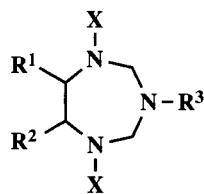
9.16.2 TRIAZEPINES

A number of monocyclic and fused 1,3,5-triazepines have been prepared.

9.16.2.1 Monocyclic 1,3,5-Triazepines

Until 1980, numerous fully saturated 1,3,5-triazepines (**1**) were prepared as biologically active compounds by condensation of *N,N'*-dinitroethylenediamines with primary amines and formal-

dehyde. In addition, various 1,3,5-triazepinones (**2**) and their thione derivatives were also synthesized by various routes $\langle 84\text{CHE}719 \rangle$; however, unsaturated monocyclic 1,3,5-triazepines had not yet been prepared.

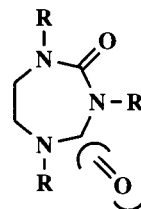


(1)

$X = \text{NO}_2, \text{SO}_2\text{Me}, \text{SO}_2\text{Ph}$

$R^1, R^2 = \text{H}, \text{alkoxy}$

$R^3 = \text{alkyl}, \text{aryl}$



(2)

$R = \text{H}, \text{alkyl}, \text{aryl}, \text{acyl}$

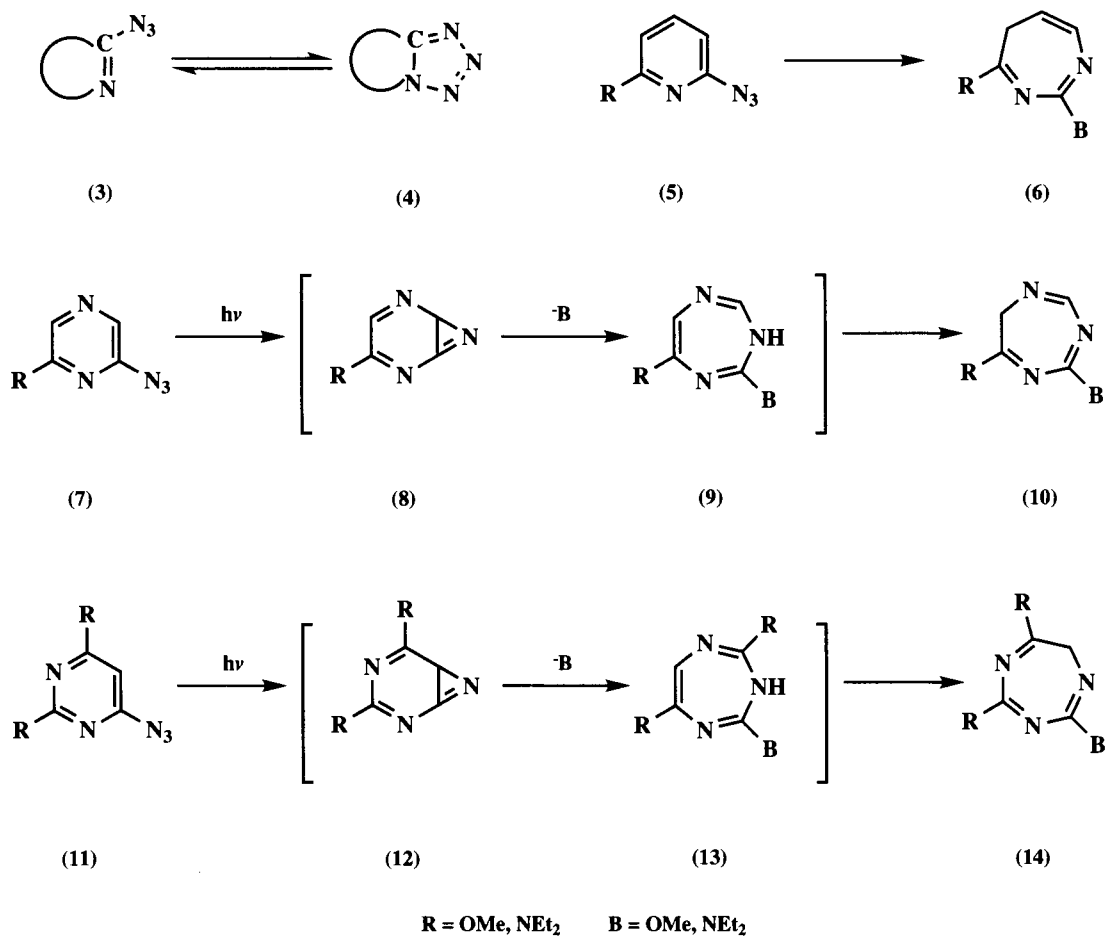
In 1990, the first examples of fully unsaturated monocyclic 1,3,5-triazepines were reported. Thermal and photochemical ring contractions of α -azidopyridines and α -azidoazines have been widely investigated, as well as their azido (**3**)–tetrazole (**4**) isomerism (Scheme 1) $\langle 77\text{AHC}(21)323 \rangle$. Although 3- and 4-azidopyridines are known to undergo ring expansion via the singlet nitrenes either by thermolysis or by photolysis in the presence of bases, giving rise to the corresponding 1,3-diazepines and/or 1,4-diazepines $\langle 84\text{CPB}4694, 85\text{CPB}5603, 87\text{CPB}3175, 87\text{CPB}1179 \rangle$, 2-azidopyridine and its methyl derivatives had not appeared to undergo such ring expansion because they exist predominantly as the tetrazole form (**4**). However, the 2-azidopyridines (**5**) with a strong electron-donating group, such as methoxy and diethylamino groups, are known to exist predominantly as the azide form and, on irradiation in the presence of methoxide ion or triethylamine, afforded the 1,3-diazepines (**6**) $\langle 90\text{CC}723 \rangle$. With regard to diazines, both the 2-azidopyrazines (**7**) and 4-azidopyrimidines (**11**), having a methoxy group or diethylamino group, upon irradiation in the presence of sodium methoxide or diethylamine for 20–30 min, also underwent ring expansion to afford the fully unsaturated 1,3,5-triazepines (**10**) and (**14**), respectively, in 50–70% yields, presumably via the azirine intermediates (**8**) and (**12**) derived from the corresponding nitrenes initially generated from the azides (**7**) and (**11**), and via the unstable NH tautomers (**9**) and (**13**) $\langle 90\text{CC}723 \rangle$. In addition, the photolysis of 2-azidopyrazines and 4-azidopyrimidines with no strong electron-donating substituent resulted only in decomposition or recovery of the starting compounds, and no ring expansion products were obtained, because their azido–tetrazole equilibria lie on the side of the tetrazole form.

Photolysis of 5-alkyl-6-azidouracil derivatives (**15**) in the presence of primary or secondary amines also caused ring expansion to give the 1,3,5-triazepinediones (**16**) (25–82% yields); whereas when the photolysis was conducted in the presence of alcohols instead of amines, the 6,6-dialkoxy-5-amino-5,6-dihydrouracils (**17**) were formed and no ring expansion products were obtained $\langle 78\text{TL}1531, 84\text{JCS}(\text{P}1)1719 \rangle$. Plausible mechanisms to explain the above results may be formulated as shown in Scheme 2. Photochemically initiated loss of nitrogen from azides (**15**) gave rise to singlet nitrenes which cyclize to the azirine intermediates (**18**). The formation of the triazepines (**16**) involves nucleophilic addition of amines to the azirines (**18**) and subsequent fission of the C(5)–C(6) bond of the resulting aziridines (**20**). When alcohols are used as nucleophiles, the addition of another molecule of alcohol to the aziridines (**22**) gives the dihydrouracils (**17**). The photolysis of the 5-cyanouracil (**23**), possessing an electron-withdrawing group as the 5-substituent, with diethylamine does not give the triazepine derivative but rather affords the 6-aminouracil (**24**), which is also formed by treatment of (**23**) with the amine without irradiation. However, the photolysis of (**23**) in alcohols leads to the 1,3,5-triazepinediones (**25**) (53–75% yields).

Pentacarbonyl(trichloromethylisocyanide)chrome (**26**) reacted with *N,N'*-dimethylethylenediamine to give the 1,3,5-triazepine derivative (**28**) via adduct (**27**) (Scheme 3) $\langle 88\text{AG}1391, 89\text{JOM}(369)105 \rangle$.

9.16.2.2 Fused 1,3,5-Triazepines

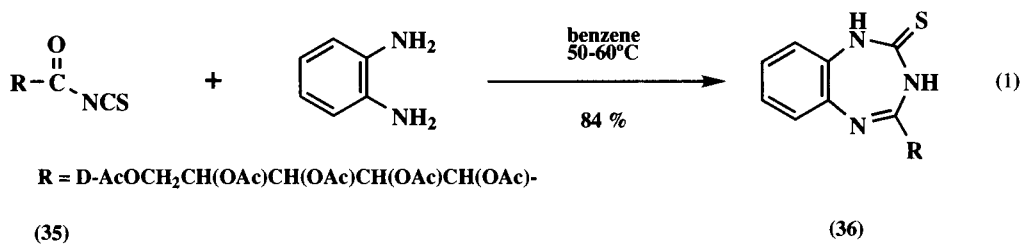
The fully unsaturated 2-phenyl-1*H*-1,3,5-benzotriazepine (**31**) has been prepared $\langle 91\text{MI} 916-01 \rangle$. 2-Aza-1-dimethylamino-3-methylthio-3-phenylpropeneiminium iodide (**29**), obtained from



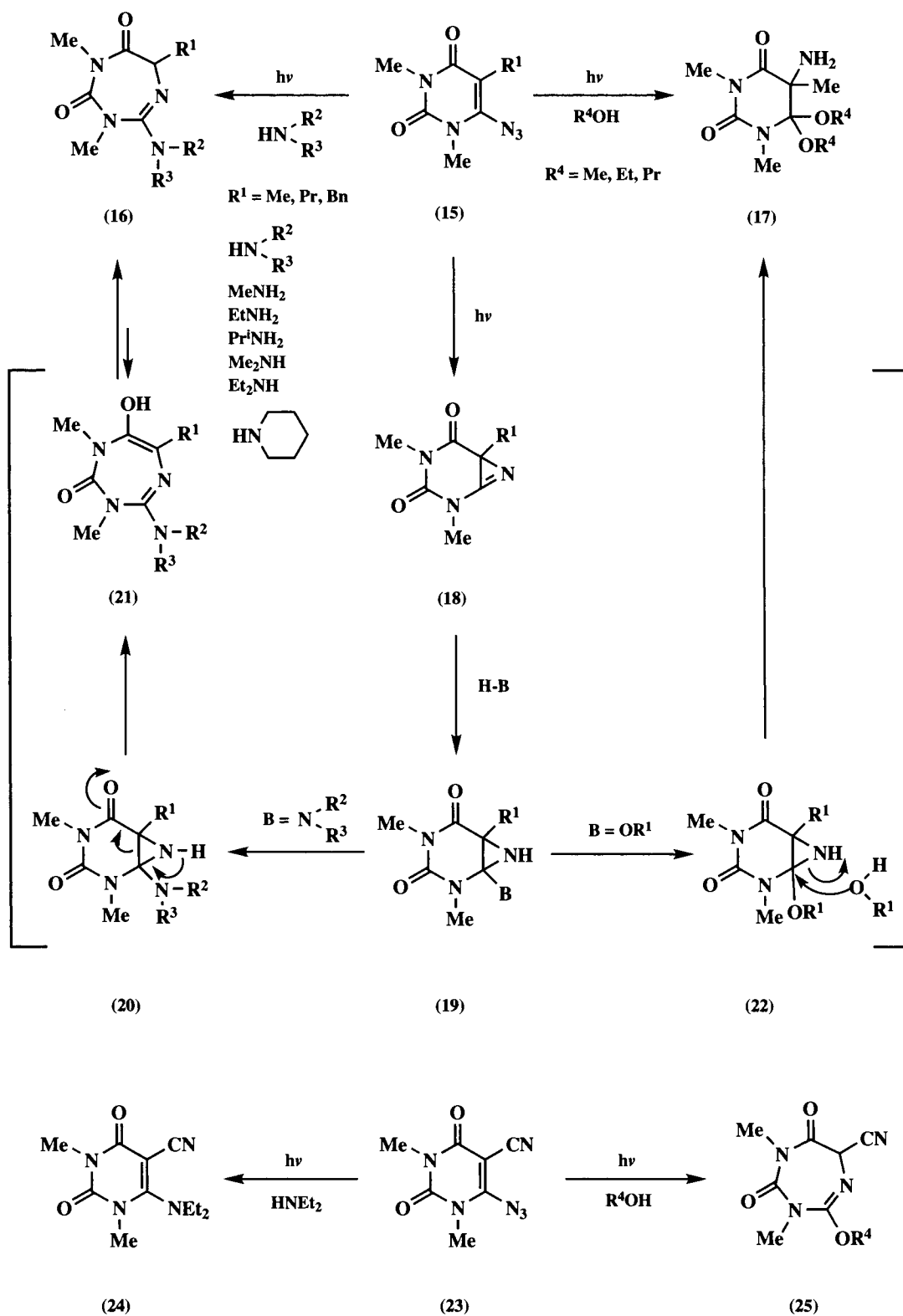
Scheme 1

N-thiobenzoylformamide and methyl iodide, can be considered as an ambident electrophile and used as a $[\text{C}=\text{C}-\text{C}]$ synthon. Thus, the formation of the 1,3,5-benzotriazepine (**31**) takes place by the reaction of (**29**) with *o*-phenylenediamine via the intermediate (**30**) (Scheme 4). The condensation of 3-acyl-1,3,4-oxadiazole-2-ones (**32**) with ethylenediamine and *o*-phenylenediamine in dry benzene afforded the 1,3,4-oxadiazolo[2,3-*b*]-1,3,5-triazepines (**33**) and 1,3,4-oxadiazolo[2,3-*b*]-1,3,5-benzotriazepines (**34**), respectively, in 65–70% yields (Scheme 5) <91H(32)237>.

The 1,3,5-benzotriazepine-2-thione (**36**) can be prepared by the reaction of the thioisocyanate (**35**) with *o*-phenylenediamine (Equation (1)) <84JAP(K)59216880>.



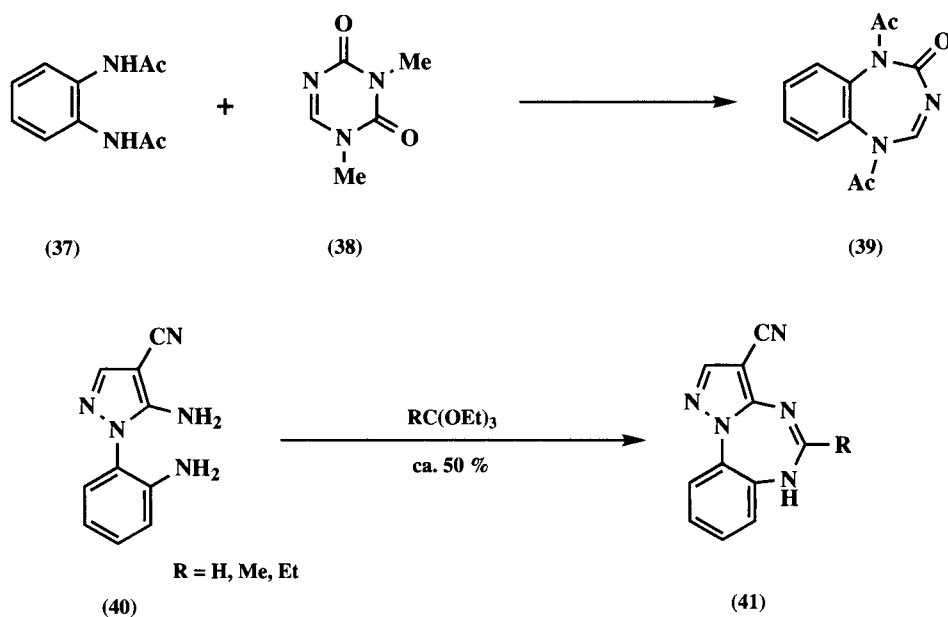
Treatment of *N,N'*-diacetyl-*o*-phenylenediamine (**37**) with the 5-azuracil (**38**) in the presence of potassium *t*-butoxide resulted in the formation of 1,3,5-benzotriazepin-2-one (**39**) via the fission of both $\text{N}(3)-\text{C}(4)$ and $\text{N}(1)-\text{C}(6)$ bonds <85MI 916-01>. The reaction of 5-amino-1-(2-aminophenyl)-1*H*-pyrazole-4-carbonitrile (**40**) with triethyl orthoesters formed the corresponding pyrazolo[1,5-*a*]-



Scheme 2



The two amino groups of the 1-(2-aminophenyl)-5-amino-1,2,4-triazole derivative (**42**) cyclized with a variety of C₁ components to give various tri- and tetracyclic fused 1,3,5-triazepines. Thus, the reaction of (**42**) with ethyl orthoformate led to the formation of the triazolo[2,3-*a*]-1,3,5-benzotriazepines (**43**) (ca. 60% yield), whose UV and NMR spectral data indicate that the 6*H*-tautomeric form (**43a**) is more predominant than the 4*H*-form (**43b**) in ethanolic solution. The reaction of (**42**) with carbon disulfide gave triazepinethiones (**44**) (60% yield), and with various alicyclic (C₄–C₁₁) and heterocyclic ketones (such as thiacyclohexan-3-one and 1-benzylpiperidin-4-one) afforded the corresponding spiro compounds (**45**) (50–80% yields) (<87JHC927>. Compound (**42**; R = CF₃) with refluxing excess methyl or ethyl acetoacetate yielded the unexpected triazepinones (**47**) (ca. 10% yield), besides the expected triazepines (**46**) (ca. 20% yield). The formation of the by-products (**47**) involved intermediates (**48**) formed by the reaction of the phenylamino group with



Scheme 6

the ester group of the β -ketoesters, and the intermediates (48) underwent intramolecular nucleophilic attack of the triazole amino group to the amide carbonyl to yield (49), which was accompanied by elimination of acetone to give (47). The diamino compounds (42) also reacted with a γ -oxo-ester, methyl or ethyl levulinate, leading to the regioisomeric mixtures of the tetracyclic compounds (51) (16% yield) and (52) (28% yield) via the initially formed triazepines (50) (Scheme 7) <88JHC1751>.

The dihydroimidazo[1,5-*a*]-1,3,5-triazepines (54) can also be prepared in good yields by the treatment of 5-amino-1-[2-(ethylamino)ethyl]imidazoles (53) with triethyl orthoformate. It should be noted that the reaction of triazepines (54) with ammonia resulted in ring opening to exocyclic amidines, which would subsequently undergo alternative cyclization to give purines (55) and (56), respectively (Scheme 8) <91S822>.

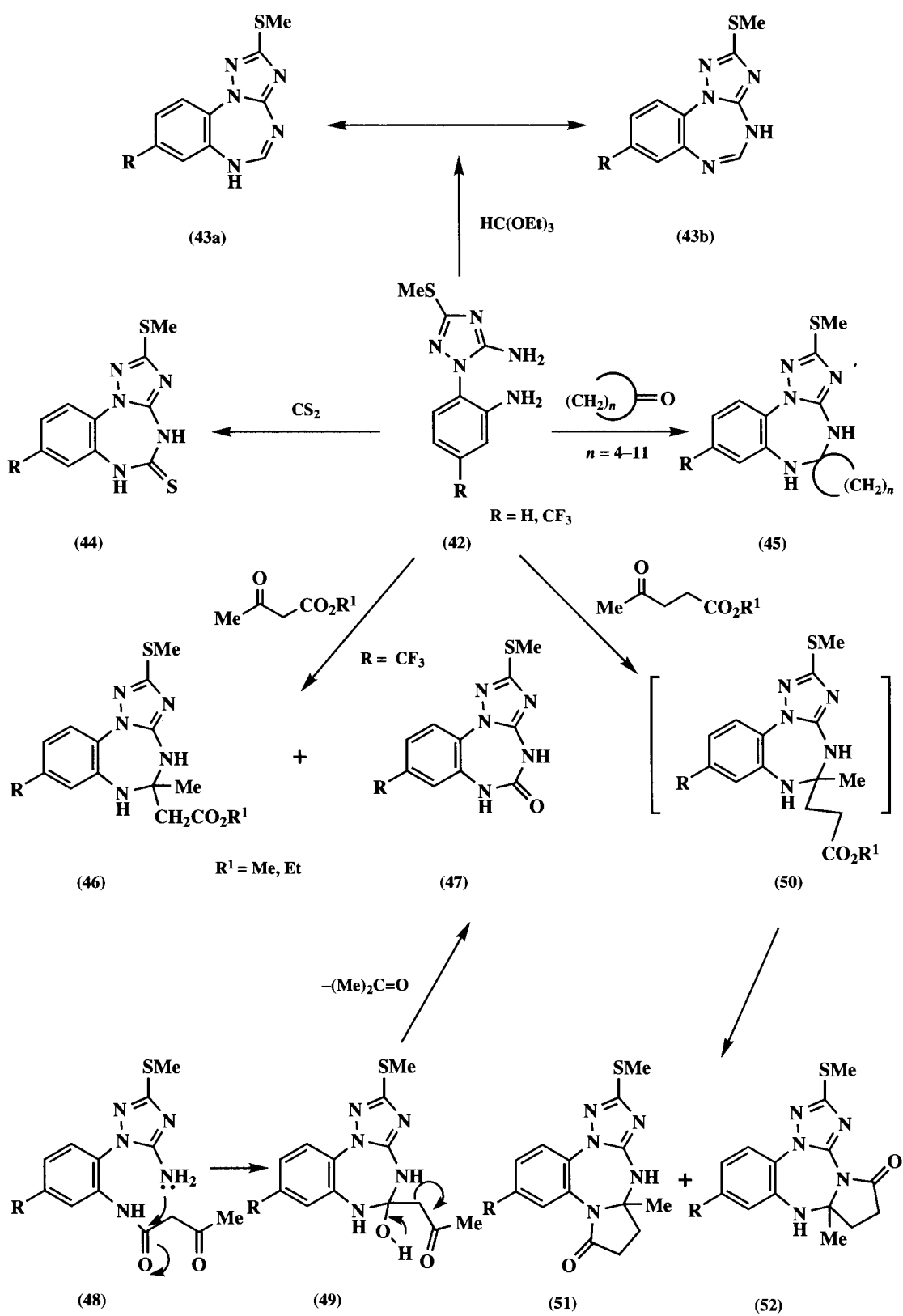
When treated with a C_1 component, such as benzaldehyde and triethyl orthoformate, the 3-(2-aminophenyl)-2-iminothiazolidine derivative (57) gave the thiazolidino[3,2-*a*]-1,3,5-benzotriazepines (58) and (59), respectively, in moderate yields (45–60%) (Scheme 9) <90T2009>.

Formamidine (60) reacted with benzaldehydes (61) or acetone in the presence of a base, such as dbu, to give the pyrrolo[3,4-*f*]-1,3,5-triazepines (63) in high yields (Scheme 10). The oxygen atom in (63) can only arise from the aldehyde, therefore the initial reaction is believed to occur by a base-catalyzed addition of the 2-amino group of (60) to the aldehyde to form an aminomethanol, followed by intramolecular hydrolysis of the 2-cyano group giving intermediates (62), which cyclize by attack of the 5-amino group at the carbon atom of the imine group <93CC834>.

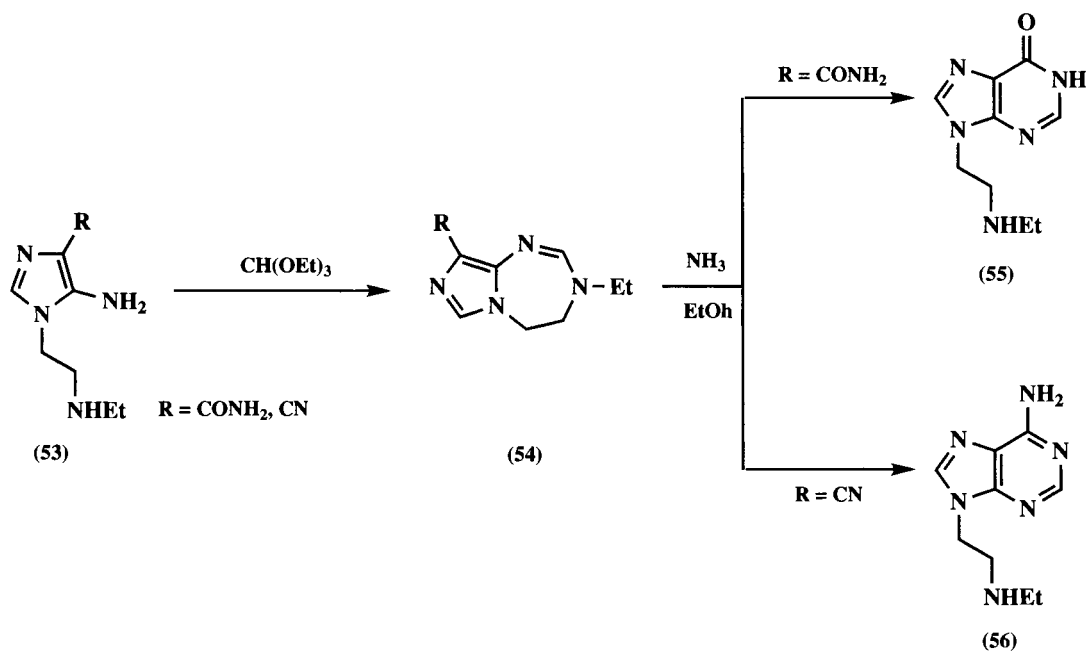
The ring closure of 1,2,4-triazolylthioamides (64) led to different products depending on the reaction conditions. The reaction in cold sulfuric acid led only to the triazolylthiazoles (65) (25% yield), while the ring closure in boiling acetic acid provided mixtures (ca. 1 : 1) of (65) and the isomeric triazolo-1,3,5-triazepines (66) in ca. 50% total yields <91JHC1597>. The tetracyclic benzo-thiazolo[2,3-*b*]-1,3,5-benzotriazepines (68) have been obtained from (67), prepared from 2-amino-benzothiazoles by Ullmann coupling with *o*-chloroaniline followed by acetylation, by intramolecular cyclization in the presence of phosphorus oxychloride (Scheme 11) <93OPP105>.

The reaction of 2-amino-1-pyrazolylbenzimidazole (69) with 1,2-dibromoethane in the presence of potassium carbonate yielded the substitution product (70), which then immediately cyclized to afford the benzimidazo[1,2-*c*]pyrazolo[2,3-*a*]-1,3,5-triazepine derivative (71) (Scheme 12) <94BSB57>.

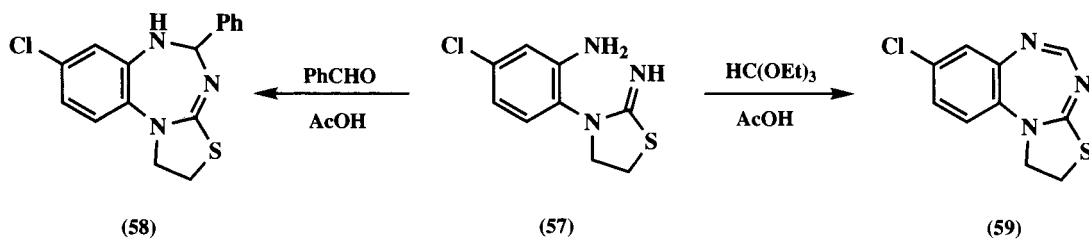
The reaction of 3-*N*-(6-amino-2-pyridyl)amino-2-cyano-2-butenitrile (72) with phenylacetic anhydride led to the unexpected tricyclic triazepine (73) (12% yield), in addition to the expected tetraazaphenalene derivative (74) (56% yield) (Equation (2)) <88JHC1837>.



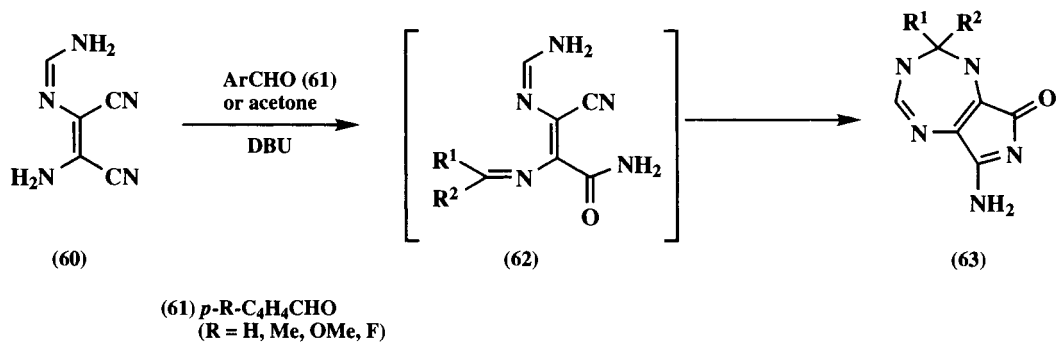
Scheme 7



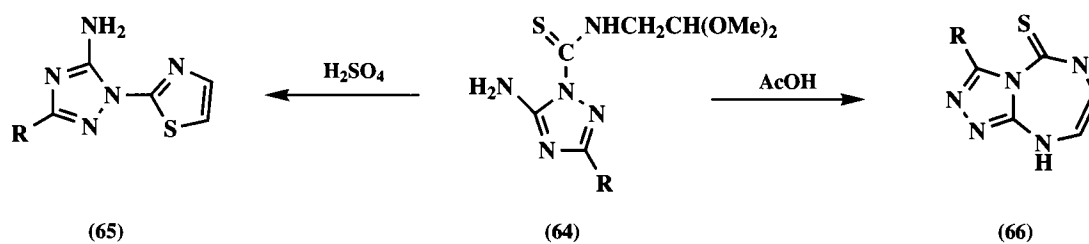
Scheme 8



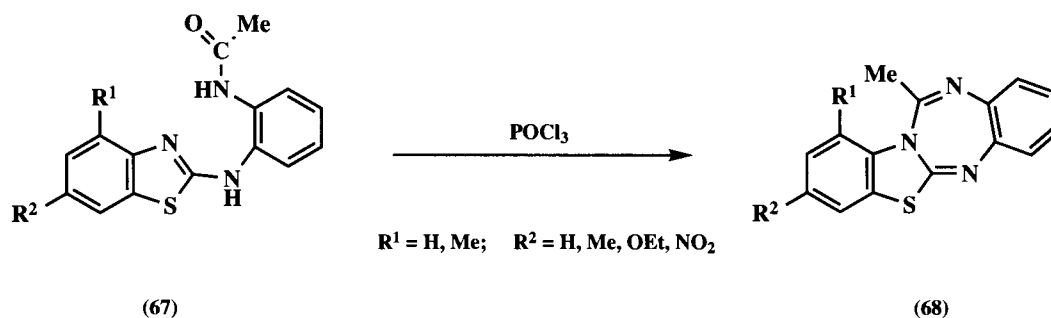
Scheme 9



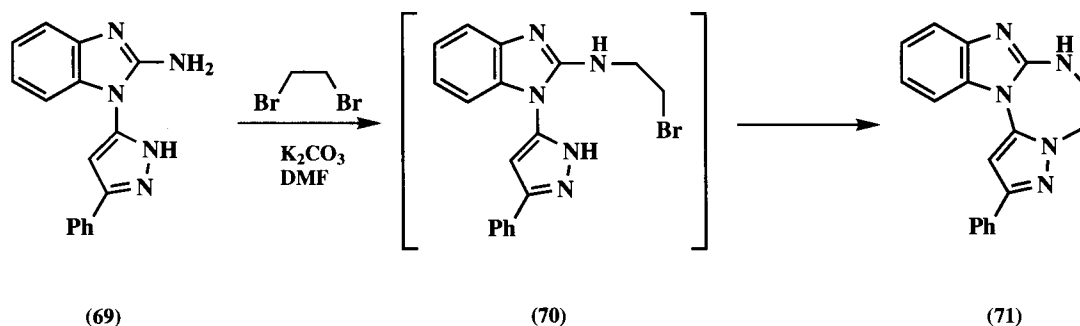
Scheme 10



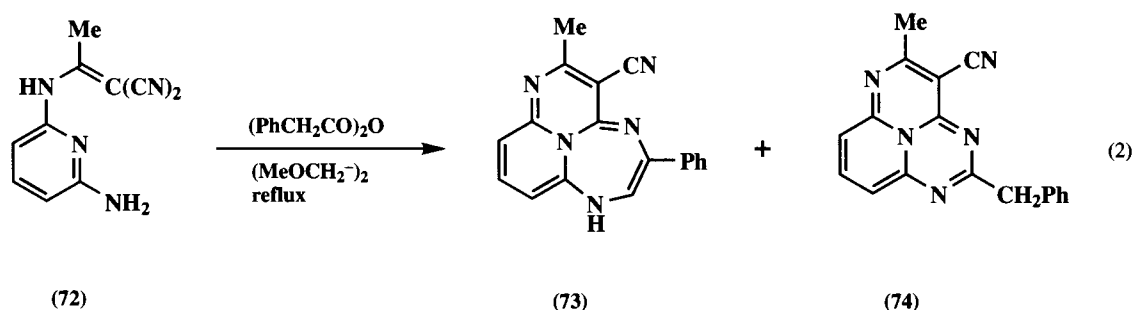
$\text{R} = \text{morpholino, piperidino, dimethylamino, methylthio}$



Scheme 11

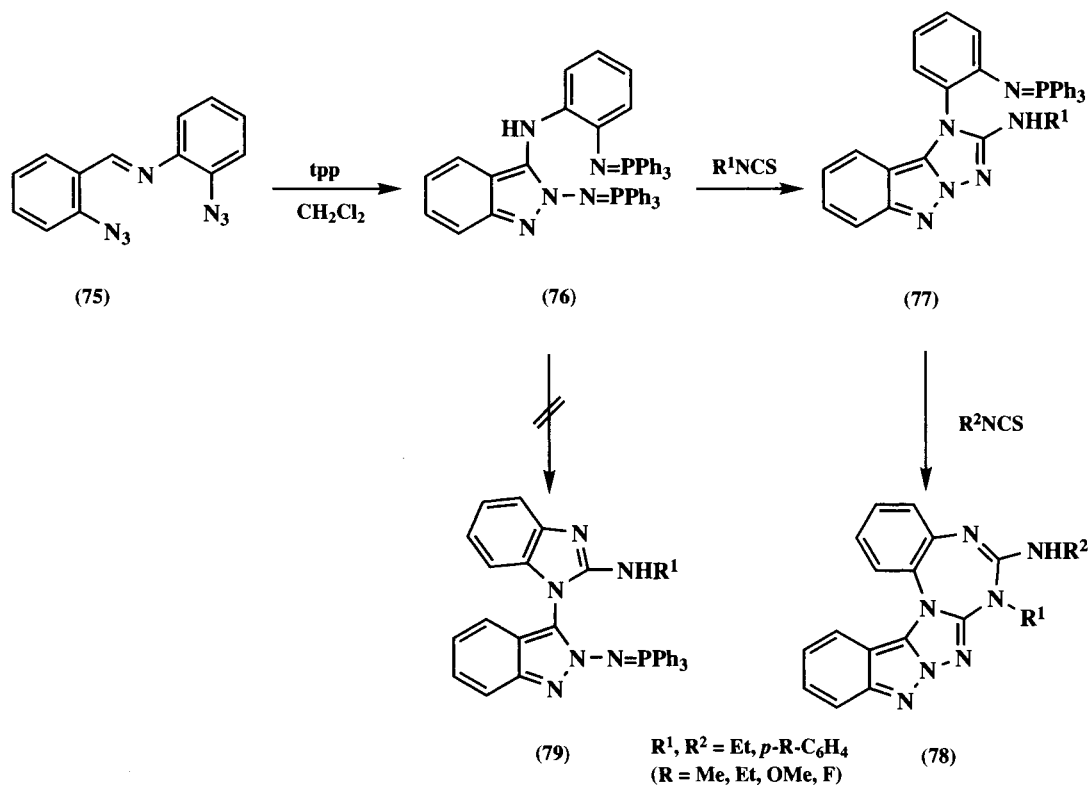


Scheme 12



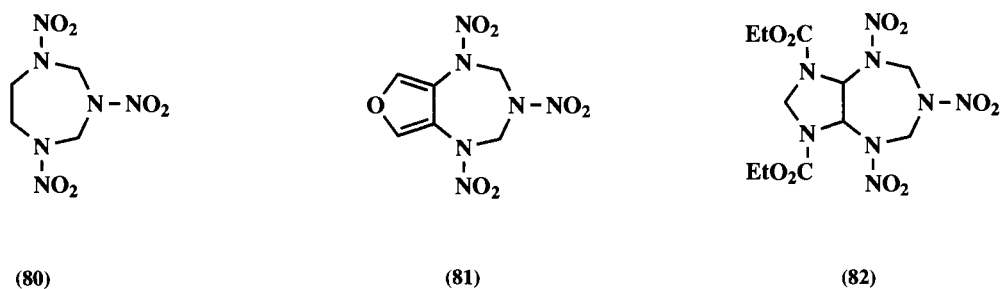
An aza-Wittig type reaction of the bis(iminophosphorane) derivative (76), available from the diazide (75) and triphenylphosphine (tpp), with one mole of alkyl or aryl isothiocyanates gave the monoiminophosphoranes (77), which reacted with a second mole of isothiocyanates to afford the pentacyclic indazolo[2',3':1,5]-1,2,4-triazolo[4,3-*a*]-1,3,5-benzotriazepines (78) (50–60% yields) (Scheme 13) <91TL2979, 92T3091>. Direct conversion of (76) into (78) was also achieved using two

moles of isocyanates. Although compound (76) bears two chemically different iminophosphorane groups in aza-Wittig type reactions, the formation of the alternative monoiminophosphorane (79) has not been observed.



Scheme 13

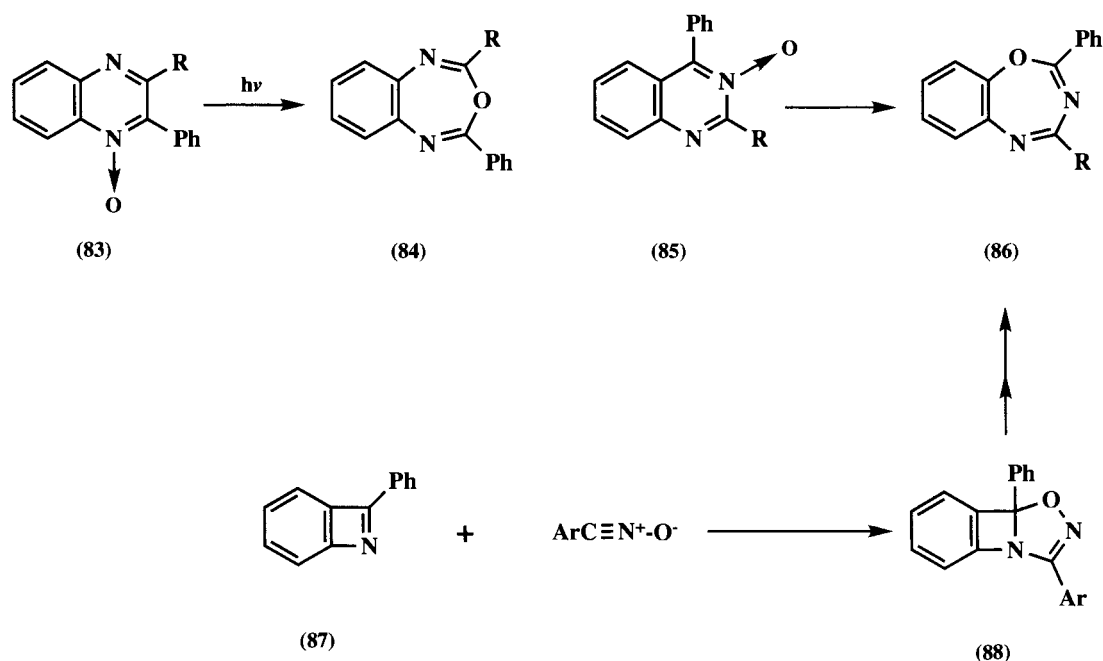
Mass spectral fragmentation pathways $\langle 90\text{OMS}(25)14 \rangle$ and x-ray crystal structures $\langle 91\text{AX}(B)782 \rangle$ of trinitro-1,3,5-triazepine (80) have been studied. The thermal stability of furotriazepine (81) in static air has been studied by means of differential scanning calorimetry $\langle 90\text{MI}916-01 \rangle$. The x-ray structural analysis of bicyclic trinitrotriazepine (82) indicates that the five-membered ring is essentially planar, while the seven-membered ring has adopted a chair conformation, and all three nitro groups are pyramidal with $\text{N}-\text{N}$ to $\text{C}-\text{N}-\text{C}$ angles of 19.8° , 28.6° , and 29.5° $\langle 92\text{AX}(C)1530, 92\text{AX}(C)1872 \rangle$.



9.16.3 OXADIAZEPINES

Up to the end of the 1970s, the fully unsaturated 3,1,5-benzoxadiazepines (84) $\langle 67\text{ACS}1399, 67\text{TL}1873, 78\text{JCS}(P1)924, 78\text{JHC}177 \rangle$ and 1,3,5-benzoxadiazepines (86) $\langle 67\text{TL}5233, 70\text{ZC}144 \rangle$ had been prepared by the photoisomerization of the quinoxaline 1-oxides (83) and quinazoline 3-oxides (85), respectively. The oxadiazepines (86) were also obtained by the reaction of 2-phenylbenzazete (87) with nitrile

oxides, followed by rearrangement of the resulting tricyclic labile intermediates (88) (Scheme 14) <75CC740, 78CC396>.



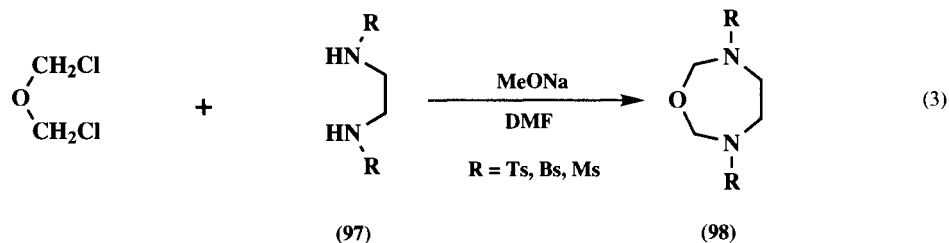
Scheme 14

However, the preparation of fully unsaturated monocyclic 1,3,5-oxadiazepine systems had not been reported. Also, since then, several more examples of this oxadiazepine ring system have been reported.

9.16.3.1 Monocyclic 1,3,6-Oxadiazepines

Treatment of the pyrazine endoperoxides (90), prepared by oxygenation of the corresponding 2,5-dimethoxypyrazines (89) with singlet oxygen, with triphenylphosphine resulted in a deoxygenation–rearrangement process to yield the 1,3,6-oxadiazepines (93) via the intermediates (91) and the oxiranes (92); however, they are unstable and readily converted to the imidazoles (96). Although oxirane intermediates (92) have not been detected even spectroscopically, these, once formed, rapidly rearrange via (94) to the 2-substituted imidazoles (95), which undergo a 1,5-acetyl shift to one of the adjacent nitrogen atoms to form the isolated products (96) (Scheme 15) <83CC399>.

Fully saturated 1,3,6-oxadiazepines, for example (98), can be prepared (35–55% yields) by condensation of bis(chloromethyl)ether with the ethylenediamines (97) in the presence of sodium methoxide (Equation (3)) <84PJC251>.



9.16.3.2 3,1,5-Benzoxadiazepines

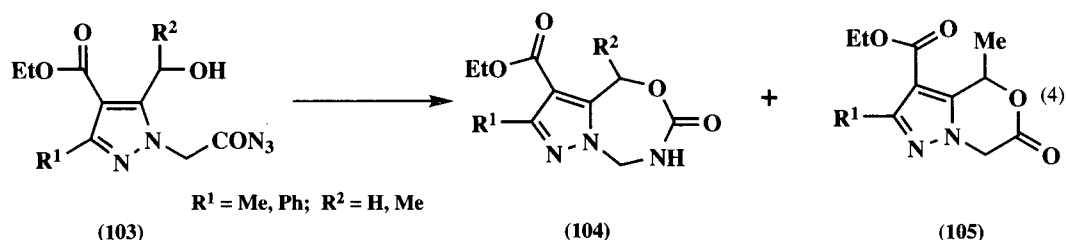
The *N,N'*-diacyl-*o*-phenylenediamines (99) reacted with dibromotriphenylphosphorane in the presence of triethylamine as a hydrogen bromide absorber to give the fully unsaturated 3,1,5-



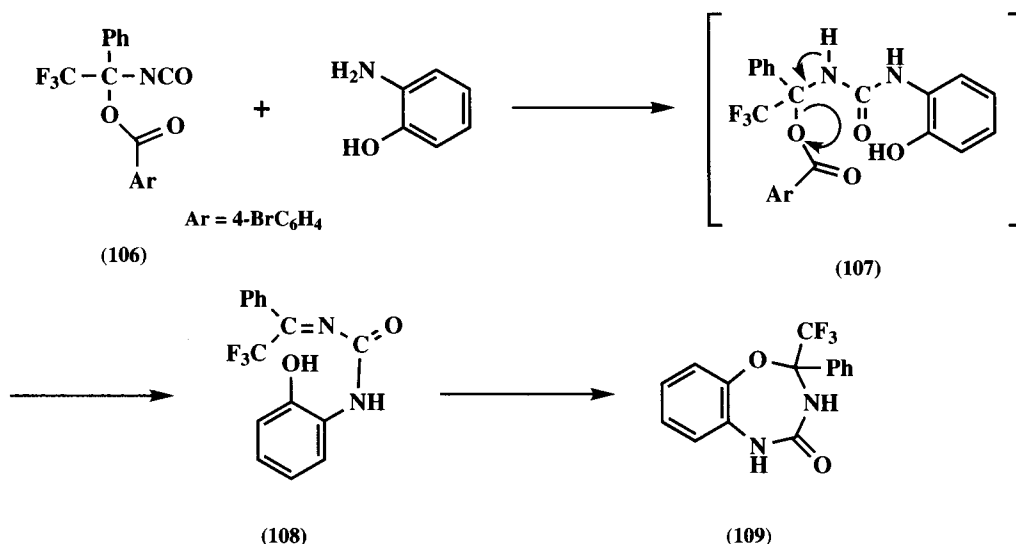
Scheme 16

9.16.3.3 Fused 1,3,5-Oxadiazepines

Curtius rearrangement of the azidocarbonylpyrazoles (**103**) afforded the pyrazolo[1,5-*e*]-1,3,5-oxadiazepines (**104**) (55–77% yields) by an intramolecular cyclization of the intermediate isocyanates with the hydroxy group of the pyrazole side chain. In the case of a secondary alcohol ($R^2 = \text{Me}$), the six-membered pyrazolo-oxazine derivatives (**105**) are also formed (Equation (4)) <82JCR(S)20>.



The isocyanate (**106**) reacted with *o*-aminophenol to afford the 1,3,5-benzoxadiazepin-4-one (**109**) (60–80% yield) via adduct (**107**) and imine intermediate (**108**) (Scheme 17) <89ZOR2394>.



Scheme 17

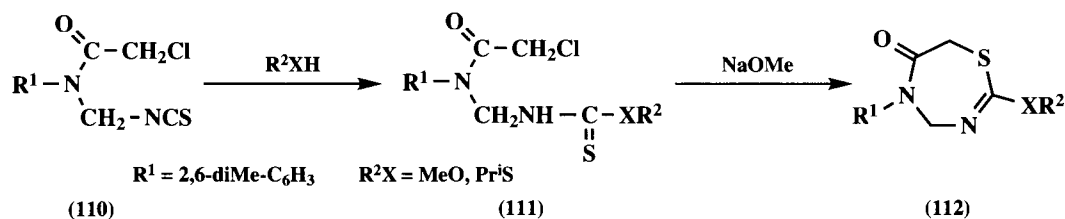
9.16.4 THIADIAZEPINES

9.16.4.1 Monocyclic 1,3,5-Thiadiazepines

2,6,7-Triphenyl-4,7-dihydro-1,3,5-thiadiazepin-4-one was prepared in 1974 by the reaction of thiobenzoyl isocyanate with 2,3-diphenyl-1-azirine <74JOC3763>. The second examples of this ring system, 1,3,5-thiadiazepin-6-ones (**112**), were prepared by the reaction of the isothiocyanate derivatives (**110**) with methanol or isopropylthiol. The initially formed adducts (**111**) were readily converted into the final products (**112**) upon treatment with a base, such as sodium methoxide (Scheme 18) <86S817>.

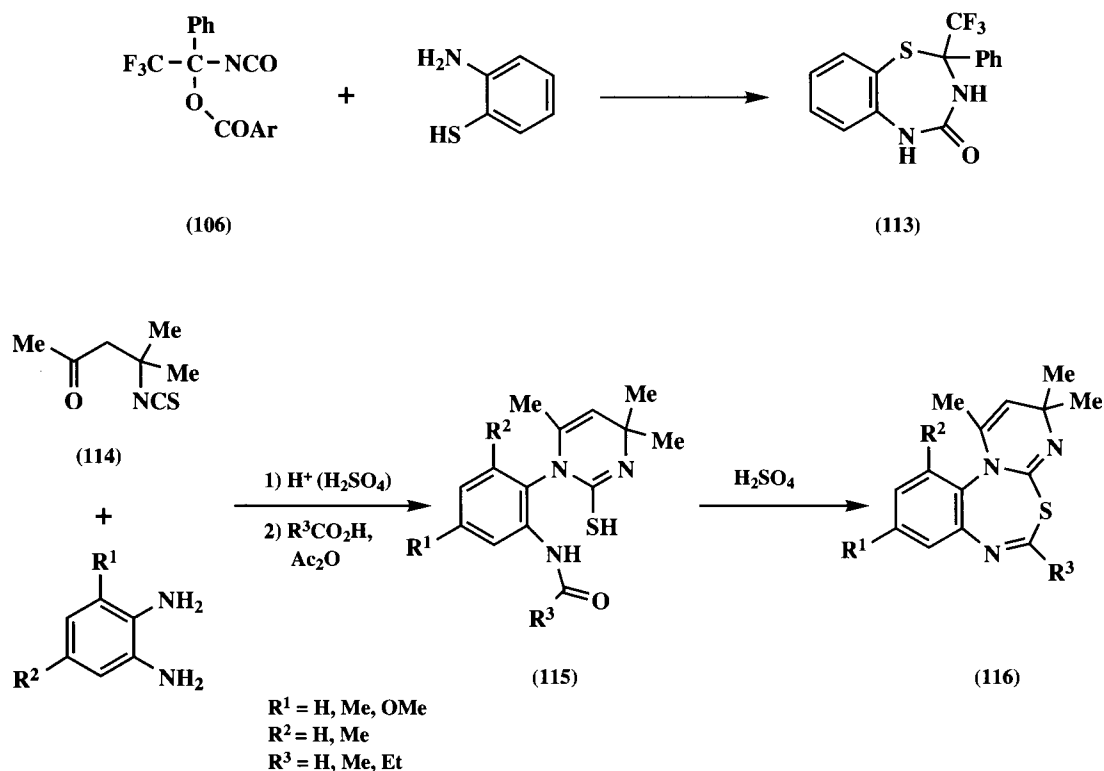
9.16.4.2 Fused 1,3,5- and 3,1,5-Thiadiazepines

1,3,5-Benzothiadiazepine (**113**) can be prepared by the reaction of the isocyanate (**106**) with *o*-aminothiophenol <89ZOR2394>. The acid-catalyzed cyclization of the thiolamides (**115**), prepared starting from *o*-phenylenediamine and 1,1-dimethyl-3-oxobutyl isocyanate (**114**) via two steps, has



Scheme 18

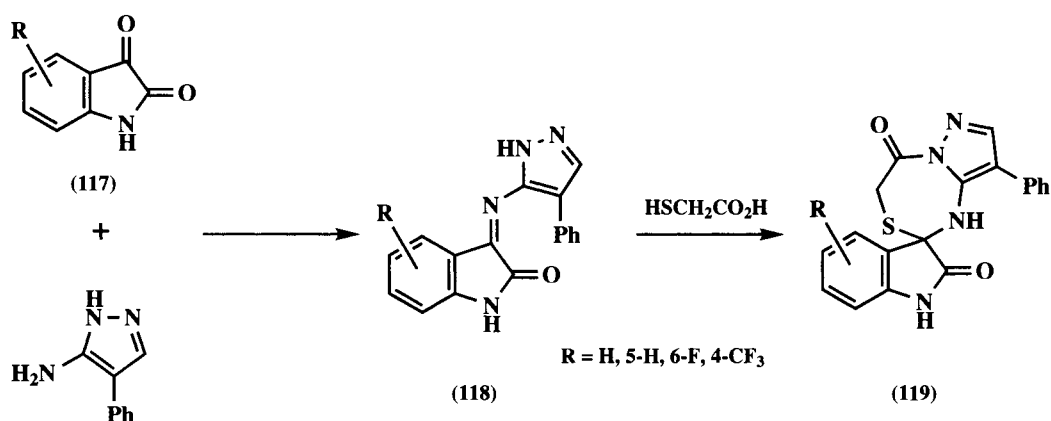
been achieved by the use of 80% sulfuric acid to give the pyrimido[1,2-*a*]-3,1,5-benzothiadiazepines (**116**) (50–60% yields) (Scheme 19) <77AJC2057>.



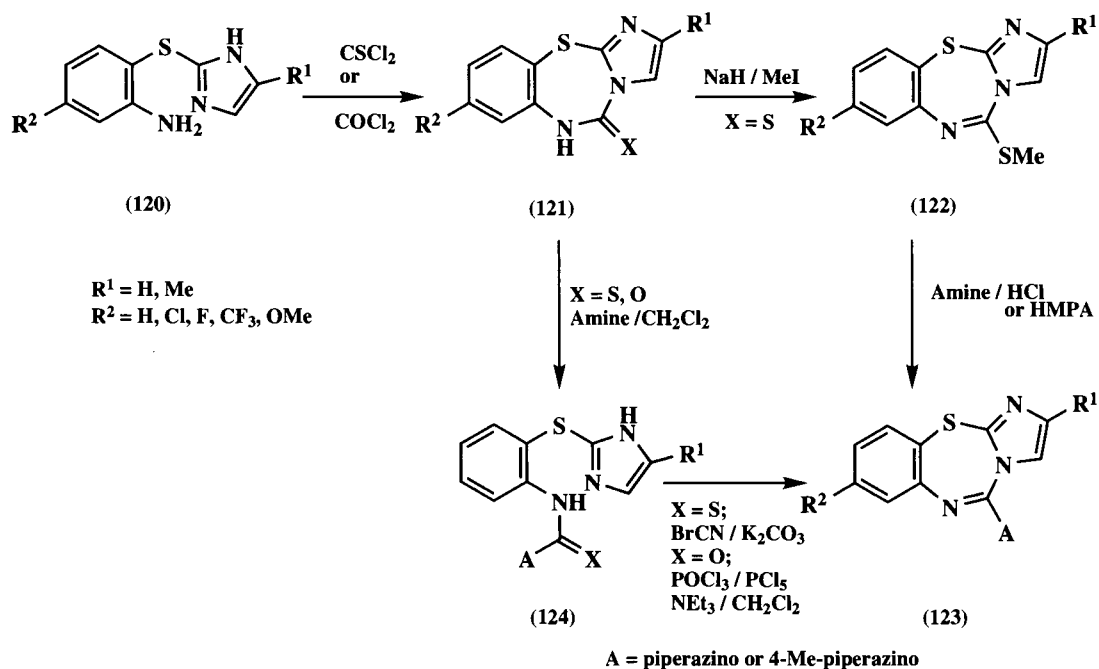
Scheme 19

Similarly, the thiol group of thiolacetic acid reacted intermolecularly with the imino carbon of the 3-(4-phenylpyrazolylimino)indole-2-ones (**118**), prepared by condensation of isatins (**117**) with 5-amino-3-phenylpyrazole, to form the spiro-1,3,5-thiadiazepines (**119**) (70–85% yields) (Scheme 20) <89IJC(B)639>.

The reaction of the 2-(2-aminophenylthio)imidazoles (**120**) with phosgene or thiophosgene resulted in ring closure to give the imidazo[2,3-*b*]-1,3,5-benzothiadiazepines (**121**) (40–85% yields). The thiones (**121**; X = S) were methylated with methyl iodide in the presence of sodium hydride to afford the methylthio compounds (**122**) in high yields, of which the methylthio group is readily replaced by an amino group to afford (**123**). The compounds (**121**) were reacted with piperazines to give the ring-opened ureas (**124**), which cyclized to the aminothiadiazepines (**123**) on treatment with cyanogen bromide and potassium carbonate or with a mixture of phosphorus oxychloride and phosphorus pentachloride in the presence of triethylamine (Scheme 21) <83JHC1287>.



Scheme 20



Scheme 21

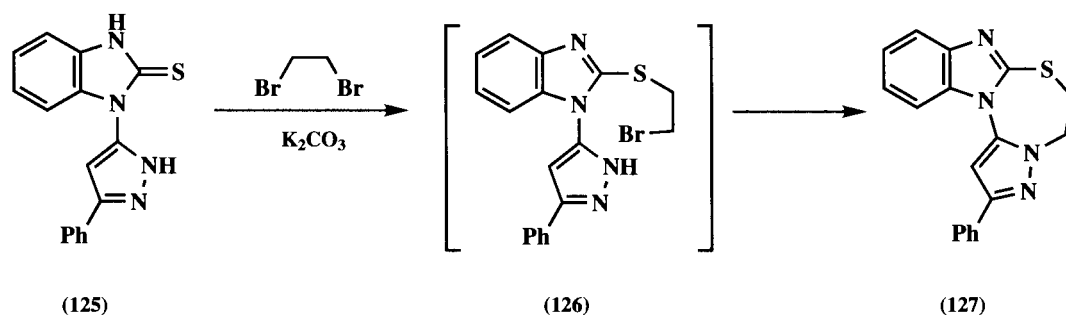
The reaction of pyrazolylbenzimidazole (125) with 1,2-dibromoethane in the presence of potassium carbonate afforded tetracyclic benzimidazo[2,1-*b*]pyrazolo[5,1-*d*]-1,3,5-thiadiazepine (127) via the substitution intermediate (126) (Scheme 22) $\langle 94\text{BSB}57 \rangle$, by analogy with the formation of the 1,3,5-triazepine (71) from (69).

9.16.5 DIOXAZEPINES

Only two classes of this system are known.

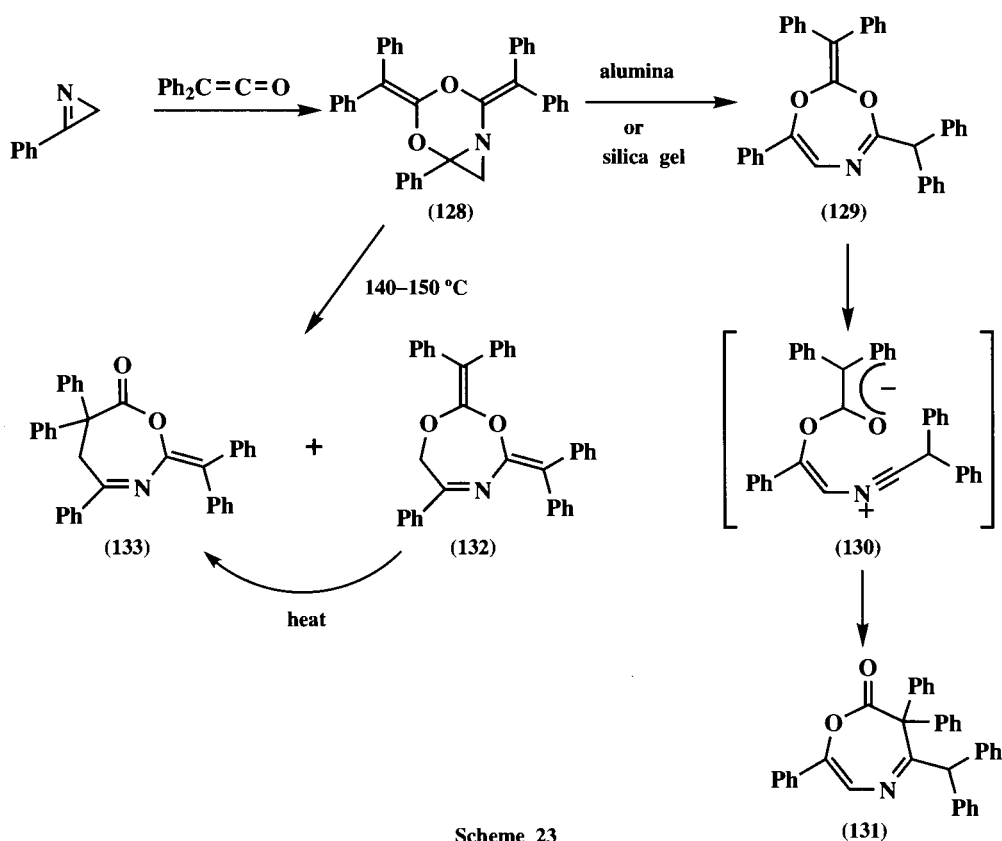
9.16.5.1 1,3,5-Dioxazepines

The 1:2 cycloadduct (128), obtained by the reaction of 2-phenyl-1-azirine with diphenylketene, rearranged on treatment with alumina or silica gel to give 1,3,5-dioxazepine (129) (33% yield),



Scheme 22

which underwent further transformation to yield 1,4-oxazepinone (131) (27% yield) via the ring-opened intermediate (130). On the other hand, thermolysis of adduct (128) at 140–150°C afforded the isomeric dioxazepine (132), an isomer of (129), and oxazepinone (133), an isomer of (131). Furthermore, it has been found that dioxazepine (132) rearranged into (133) when heated above its melting point (128°C) (Scheme 23) <73JOC3466>.



Scheme 23

9.16.5.2 1,5,3-Dioxazepines

A variety of fully saturated 1,5,3-dioxazepines (134) have been prepared by the reaction of ethylene glycol with primary amines and formaldehyde in moderate yields (Equation (5)) <70CC1123, 71KGS25, 80TL2949, 82USP4342687>.



9.16.6.1 1,3,5-Dithiazepines

reaction to give the 1,3,5-dithiazepines (**136**) in high yields (Equation (6)) <88MI 916-01>.



(136)

Ar = *p*-Me-C₆H₄

X = CH₂, NH, O

9.16.6.2 1,5,3-Dithiazepines

24) $\langle 72AG(E)511 \rangle$.



(138)

(139)

(140)

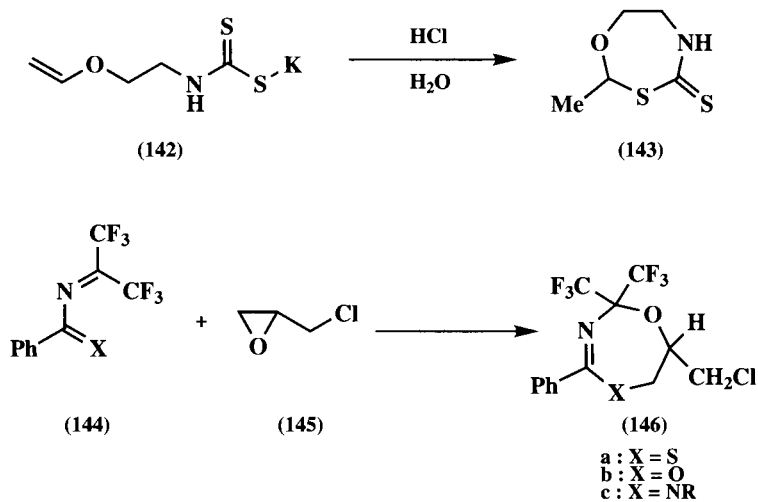
(141)

Ar = Ph, *o*-Tolyl

Scheme 24

9.16.7 OXATHIAZEPINES

Dithiocarbamic acid (**142**) underwent an acid-catalyzed intramolecular cyclization to give 1,3,5-oxathiazepine-4-thione (**143**) <92ZOR2201>. 4,4-Bis(trifluoromethyl) substituted hetero-1,3-dienes (**144**; X = S, O or NR) reacted with (chloromethyl)oxirane to give 1,5,3-oxathiazepine (**146a**), 1,5,3-dioxazepine (**146b**), and 1,3,5-oxadiazepine (**146c**), respectively, in 40–70% yields (Scheme 25) <88CZ111>.



Scheme 25

9.17

Seven-membered Rings with Four or More Heteroatoms

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Russian Academy of Sciences, Kazan, Russia

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9.17.1 INTRODUCTION

There has been little systematic study of seven-membered heterocycles with a high proportion of heteroatoms <84CHEC-I(7)647>. But since 1984, Rees *et al.* have developed the chemistry of some novel ring systems, consisting mostly of sulfur and nitrogen but with at least one ring carbon. The sulfur and nitrogen are mostly two-coordinate and alternate around the ring, which are consequently electron-rich (π -excessive). Such novel aromatic heterocycles, namely 1,3,5,2,4-trithiadiazepines and 1,3,5,2,4,6-trithiatriazepines <88RHA204, 89PS(43)261, 92JHC639>, and tetra- and pentathiepins, which have been widely studied by Chenard and Sato with their co-workers <90YGK797>, are now better known.

There are several reviews, which are devoted to the synthesis of seven-membered heterocycles, but rings with four or more heteroatoms are not typically described in these reviews <88S569, 91S181>. Only a few of the possible heterocyclic structures are actually known; most contain nitrogen and

sulfur atoms. In this chapter, tetrazepines, thiatriazepines, dithiadiazepanes, tetrathiazepines with the different disposition of heteroatoms, hexathiepanes, and 1,3,5,7-tetrathia-2,4,6,8-tetraaza-azulenes are considered; in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(7)647> oxatriazepines, oxathiadiazepines, dioxathiazepines, and dioxadithiepanes are also described. The standard nomenclature of heterocycles is used.

9.17.2 THEORETICAL METHODS

9.17.2.1 1,2,3,4,5-Pentathiepanes

Conformations of 1,2,3,4,5-pentathiepine (**62**), benzopentathiepine (**35**), and thieno[3,4-*f*]-1,2,3,4,5-pentathiepin (**37**) were studied by means of the semiempirical AM1 method <88JST(167)245>. According to experimental findings, the chair form of (**35**), (**37**), and (**62**) was found to be the most stable (see Section 9.17.4.3). To rationalize the observed UV absorption spectrum, CNDO calculations were carried out in which the main absorption band is well accounted for by theory, whilst the shoulders are less well understood (see Section 9.17.3.4) <88JST(167)245>.

The *ab initio* molecular orbital calculations (SCF and MP-2 level) were conducted for the investigation of the structure and conformational behavior of pentathiepin (**62**) and 3*H*-1,2,4,5-tetrathiepine <87JOC2411>. An excellent agreement is found between the calculated and real molecular structures. Theoretical data are also consistent with the real conformational behavior of pyrazolo-3*H*-1,2,4,5-tetrathiepins (**46**), but the ring inversion barrier of pentathiepins is overestimated (see Section 9.17.4.3).

9.17.2.2 1,3,5,2,4-Trithiadiazepines and 1,3,5,2,4,6-Trithiatriazepines

Molecular orbital calculations have been widely used both for the investigation of the structure and the aromaticity of these seven-membered heterocycles as well as for the determination of the reaction pathways. A qualitative analysis based on MNDO and *ab initio* molecular orbital calculations has been reported <87JCS(P1)1579, 87JCS(P2)1669> for the cycloaddition of several alkynes to tetrasulfur tetranitrile with the formation of trithiadiazepines and 1,2,5-thiadiazoles (see Scheme 28).

The calculations show that the highest occupied molecular orbitals ($3a_2$, $4b_1$ and $8b_2$) of S_4N_4 are almost degenerate, and group theory suggests that only two of these ($4b_1$ and $3a_2$) have the correct symmetry for overlap with the alkyne LUMO. Overlap with orbital $4b_1$ leads to 1,5-addition to sulfur; whereas, overlap with $3a_2$ leads to 1,3-addition to nitrogen. Hence both modes are possible, and almost equally favored. The high reactivity of butynedinitrile towards S_4N_4 is explained by its LUMO being polarized away from the central triple bond towards the nitrogen atoms such that it overlaps very effectively with the $4b_1$ orbital of S_4N_4 leading to initial C—S bond formation <87JCS(P1)1579>. These conclusions are consistent with experimental observations and with the calculations on tetrasulfur tetranitrile <87JCS(P2)1669>.

The two seven-membered ring compounds (**21**) and (**26**) (see Section 9.17.3.1) are new stable planar delocalized 10π electron aromatic systems <85CC398, 87JCS(P1)203>.

The delocalized 10π aromatic nature of the trithiadi- and trithiatriazepine rings was supported by MNDO and *ab initio* MO calculations on the parent trithiadiazepine (**21**) and trithiatriazepine (**26**). All procedures gave the same relative ordering of the π orbital energies for the trithiadiazepine. From the calculations, HOMO consists predominantly of an out-of-phase π overlap of the sulfur and nitrogen lone pair orbitals. The results of the calculations are consistent with the photoelectron spectrum of (**21**) (see Section 9.17.3.6) and confirm the fundamental aromatic nature of the trithiadiazepine ring, in accord with its stability, chemical reactivity, and other spectroscopic properties, notwithstanding its high proportion of heteroatoms <85CC398, 87JCS(P1)203>.

The molecular and electron structures of 1,3,5,2,4-benzotrithiadiazepine (**18**) have been investigated by means of semiempirical MNDO calculations, which showed relatively weak interactions between benzo and SNSNS fragments of the molecule <86IC1137, 91MI 917-01>. The HOMO and LUMO are localized mainly on the heterofragment (see Figure 1), although for other occupied π -orbitals considerable mixing is evident. In spite of relatively high energy of HOMO (−8.15 eV vs.

–8.91 for trithiadiazepin <85CC398>) the high energy of LUMO (–1.33 eV) and a large (π , π^*) splitting is consistent with the aromatic nature of 14 π -electron benzotrithiadiazepine, although the attachment of the benzo moiety destabilizes the trithiadiazepine. The data of photoelectron and inner-shell electron energy loss spectroscopy are followed reasonably closely by the semiempirical calculation <91MI 917-01>.

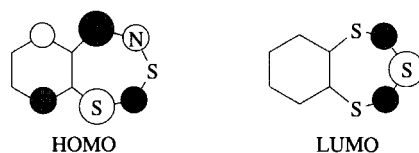


Figure 1 Schematic diagrams of the ground state HOMO and LUMO of 1,3,5,2,4-benzotrithiadiazepine.

9.17.3 EXPERIMENTAL STRUCTURAL METHODS

9.17.3.1 X-ray Diffraction

9.17.3.1.1 Tetrathiepinines

The molecular structure of 1,2,3,4-tetrathiepane-6,6-dicarboxylate (**8**) was shown from the low-temperature (110 K) x-ray diffraction data. Two intramolecular contacts (3.124 and 3.188 Å) between the two carbonyl atoms and the two terminal sulfur atoms are somewhat shorter than the sum of their van der Waals radii. These interactions appear to be important for its stabilization <94ACS652>.

The x-ray study of tetrathiepins (**45**; R = Me, Ph) was carried out <87JOC2411>. Both compounds have chair conformations.

9.17.3.1.2 Tetrazepines

In order to further ascertain the structure and geometry of the 1,2,3,5-tetrazepinone ring, the x-ray structure of (**11**) was determined. Atoms N-3, N-5, and O-4 are co-planar as expected for an ureido moiety; however, nitrogen N-2 of the N(1)=N(2) bond deviated from the plane of the aromatic ring by 0.5384 Å. This deviation makes the 1,2,3,5-tetrazepinone an essentially nonplanar seven-membered ring. The geometry of the tetrazepinone ring is similar to that of the diazepinone ring system in the diazepam-related drugs, the x-ray structures have been described <91JCS(P1)2525>.

9.17.3.1.3 Pentathiepanes

The x-ray investigation of (**27**) demonstrated that the conformation of heterocycle may be described as a plane of C₂, S₂, S₅ (with 0.05–0.7 Å atomic deviations) with S₃, S₄, S₅ inclined at 79°. This seven-membered heterocycle is highly distorted <83JOU133>.

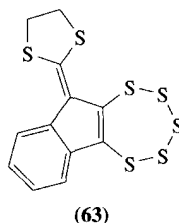
9.17.3.1.4 Pentathiepinines

The molecular structures of the pentathiepinines (**36**), (**37**), and (**38**) have been determined by x-ray analysis <80JOC5122, 85JA3871>. All pentathiepinines have chair conformations. The S—S bond length for these pentathiepinines is between the average S₆ and S₈ values (2.052–2.051 Å). The S—S—S bond angles and S—S—S—S torsional angles of the pentathiepinines are between the average S₆ and S₈ values: 102.48–105.53 and 72.9–79.6° for C₂S₅, 102.2 and 74.5° for S₆, 108.1 and 98° for S₈.

For 6,10-disubstituted 1,2,3-trithiolo[5,4-*H*]benzopentathiepinines (**34**) and (**55**), a butterfly-like conformation was observed by x-ray investigations <88TL6291, 89TL2453>.

The indene and dithiolane rings of 10-(1,3-dithiolan-2-ylidene)-10*H*-indeno[1,2-*f*]-1,2,3,4,5-pentathiepin (**63**) are, as expected, nearly co-planar as a consequence of maximizing π orbital overlap in the C(9)—C(10) double bond. The S₅C₂ ring is in the chair configuration, which minimizes

electronic repulsion, with an average S—S distance of 2.052 Å. The indenone ring shows no evidence of any delocalization, while the dithiolane ring is disordered at the two methylene positions <82JHC459>.



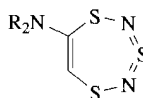
The bond lengths of C(6)—C(7), C(6)—S(1), and C(7)—S(5) of 6,7-bis(diphenyldimethylene)-1,2,3,4,5-pentathiepine (**28**) were 1.476, 1.790, and 1.792 Å, respectively, which were longer than that of the aromatic and heteroaromatic fused pentathiepins. The bond angles of S(1)—C(1)—C(2) (115.4°) and S(2)—C(2)—C(1) (119.9°) were narrower about 10° than that of fused pentathiepins <88TL1935>.

9.17.3.1.5 Trithiadiazepines and related compounds

The ring in the trithiadiazepine (**16**) is planar with maximum deviations from the least squares planes of 0.019 Å (C-6) <84CC55>. The S—N bond lengths in (**16**) (1.54–1.60 Å) are all similar and close to those of Woodward's dithiatetrazocine, and are nearer to double (1.55 Å) than to single (1.67 Å) bonds. The ring C—C and C—S bonds in (**16**) are very similar in length to the corresponding bonds in thiophene. The angles are 140° and 138° at N-2 and N-4.

1,3,4,5,2,4-Trithiadiazepine (**21**) and its benzo derivative (**18**) have planar delocalized 10 π and 14 π aromatic structures, respectively; in the dihydro compound (**20**), the five heteroatoms are coplanar, with the approximately *cis*- and *trans*-periplanar methylene protons rapidly interconverting <85CC398>. Surprisingly, despite their planar geometry, compound (**21**) does not adopt a parallel staking arrangement in the crystal; whereas (**18**) does pack with parallel overlap, the seven-membered ring of one directly overlying six-membered ring of another and vice versa. The interplanar separation is small at 3.54 Å.

The minimal interaction between the amine lone pair of electrons and the delocalized π system of the ring is confirmed by x-ray crystal structures for 6-amino- (**64**), 6-dimethylamino- (**65**), and 6-morpholino-1,3,5,2,4-trithiadiazepine (**66**) <90CC1315>. As in the parent compound <85CC398>, the trithiadiazepine ring in all aminotrithiadiazepines is planar. In each case, the amino group is tetrahedral and rotated out-of-the-plane of the ring such that the nitrogen lone pair is approximately orthogonal to the π -system. For dimethylamino- (**65**) and morpholinotrithiadiazepine (**66**), the amine nitrogen lone pair is antiperiplanar to the less polarizable carbon–carbon bond. The lone pair on the primary amino group in (**64**) is antiperiplanar to the more polarisable carbon–sulfur bond, and overlap between the nitrogen lone pair and the σ^* antibonding orbital of the carbon–sulfur bond should elongate the carbon–sulfur bond slightly. A possible explanation for the difference in orientation of the amino group in (**64**) compared to (**65**) and (**66**) may be found from a study of the packing of the molecules of (**64**) in the crystal. In the crystal face both crystallographically independent molecules, A and B, form infinite $p\pi$ – π overlapping stacks, the “A” stacks being approximately orthogonal to the “B” stacks. One of the amine hydrogen atoms of each molecule in the “B” stack is directed towards the lone pair of the nitrogen of an adjacent molecule in the “A” stack forming a series of weak interstack N—H $\cdots$ N hydrogen bonds.



(64) R = H; (65) R = Me; (66) R₂ = -(CH₂)₂-O-(CH₂)₂-

X-ray crystallographic analysis of the 6-nitro- (**67**) and 6,7-dinitro-1,3,5,2,4-trithiadiazepines (**68**) showed that in the crystalline state a single nitro group is almost co-planar with the ring, forming an angle of 5.9° with the ring plane, indicative of some charge delocalization, but in the dinitro

compound the two groups are in parallel planes inclined to the ring plane by 45° . In the mononitro compound (**67**), the C(7)—S(1) bond (1.67 Å) is slightly shorter than the C(6)—S(5) bond (1.72 Å), $\langle 87\text{JCS(P1)217} \rangle$.

The molecular structure of trithiatriazepine (**17**) is similar to (**16**) $\langle 84\text{CC55} \rangle$. The ring is planar with maximum deviations from the least squares planes 0.009 Å. The S—N bond lengths (1.57–1.60 Å) are similar to those of Woodward's dithiatetrazocine and are nearer to double than to single bonds. The angles are 141° , 135° , and 140° at N-2, N-4, and N-6, respectively.

The single crystal x-ray analysis of $1\lambda^4\delta^2,3,5,7\lambda^4\delta^2$ -tetrathia-2,4,6,8-tetraazaazulene (**61**) showed that (**61**) contains two crystallographically independent molecules with a completely delocalized 14π -structure. Both molecules have approximate C_{2v} symmetry and have equivalent bond lengths. An interesting and novel feature of the structure is the molecular packing. They form continuous parallel overlapping stacks. The minimum interplanar atomic separations in the both molecules are 3.26–3.48 and 3.46–3.50 Å $\langle 85\text{CC1654} \rangle$.

9.17.3.2 NMR Spectroscopy

9.17.3.2.1 Proton NMR spectroscopy

The ^1H NMR spectra of 1,3,5,2,4-trithiadiazepines and 1,3,5,2,4,6-trithiatriazepin are indicative of their aromaticity. The ring protons of unsubstituted $1,3\lambda^4\delta^2,5,2,4$ -trithiadiazepine (**21**) resonate in the aromatic region at δ 7.76 $\langle 87\text{JCS(P1)211} \rangle$. The electron withdrawing groups, except the nitro group and halogen atoms, deshield the ring proton (δ 8.10–9.48) $\langle 87\text{JCS(P1)217}$, 91JCS(P1)301 , $91\text{JCS(P1)2945} \rangle$. In contrast to the shielding effect of electron-releasing groups on *ortho*-protons in benzenoid systems, the trithiadiazepine ring protons of the amino derivatives have almost identical chemical shifts (δ 7.50–7.90) to that of the unsubstituted compound due to the limited interaction between the amino lone pair and ring π -system $\langle 91\text{JCS(P1)301} \rangle$.

The ring proton of the 1,3,5,2,4,6-trithiatriazepine (**26**) resonates at δ 9.0, supporting a diamagnetic ring current and heteroaromatic ring character $\langle 88\text{JCS(P1)1745} \rangle$.

The ring protons of 1,2,3,4,5-pentathiepin (**62**) appear at δ 7.42 $\langle 71\text{TL2125} \rangle$. The methylene and methyne ring protons of substituted 1,2,3,4,5-pentathiepins resonate near δ 2.9 and 3.7–4.0, respectively $\langle 83\text{JOU133}$, $87\text{JOC4937} \rangle$; whereas the methylene bridge protons of 1,2,3,5,6-pentathiepan (**48**) and different tetrathiepanes are at δ 4.30–5.26 $\langle 81\text{TL1939}$, 76JOC2465 , $88\text{BCJ1647} \rangle$.

9.17.3.2.2 Carbon-13 NMR spectroscopy

The ring carbon atoms of the aromatic 1,3,5,2,4,6-trithiatriazepines and $1,3\lambda^4\delta^2,5,2,4$ -trithiadiazepines resonate at low field (δ 145–160 and 115–157, respectively), indicative of a diamagnetic ring current. The former resonate at slightly lower field than the latter, presumably because of the deshielding effect of the additional imine type nitrogen atom $\langle 87\text{JCS(P1)203}$, 87JCS(P1)211 , 87JCS(P1)217 , 87JCS(P1)1579 , 87JCS(P1)1585 , 88JCS(P1)1745 , $91\text{JCS(P1)2945} \rangle$. The ^{13}C NMR spectrum of relative compound $1\lambda^4\delta^2,3,5,7\lambda^4\delta^2$ -tetrathia-2,4,6,8-tetraaza-2-azulene (**61**) shows a singlet at δ 161.8, suggesting a highly symmetrical and delocalized structure $\langle 85\text{CC1654} \rangle$.

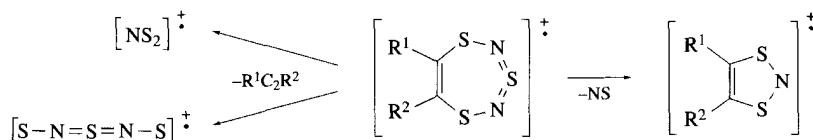
Ring carbon atoms of 1,2,3,4,5-pentathiepins also appeared at low field (δ 137–155) $\langle 87\text{TL4833}$, 88TL1935 , $88\text{CL657} \rangle$; whereas, the carbon atoms of saturated seven-membered polysulfides resonate at δ 44–76 $\langle 76\text{JOC2465}$, 87JOC4937 , $88\text{ACS(B)620} \rangle$.

9.17.3.2.3 Nitrogen-15 NMR spectroscopy

In the ^{15}N NMR spectra of the compounds (**10**)–(**12**) $\langle 91\text{JCS(P1)2525} \rangle$, the central nitrogen of the triazene function showed up as a quartet ($^3J_{\text{NH}} = 2.70$ Hz) at $\delta +72 \div 68.5$, as confirmed by diazotization reactions with $\text{Na}^{15}\text{NO}_2$. The fact that the peak showed up as a quartet ($^3J_{\text{NH}}$) confirmed the presence of the N(2)—N(3)—Me moiety. The chemical shift of N-2 is similar to those previously reported for the central nitrogen in 1-aryl-3,3-dialkyltriazenes $\langle 91\text{JCS(P1)2525} \rangle$.

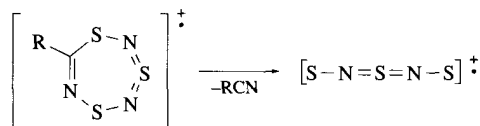
9.17.3.3 Mass Spectrometry

In mass spectra of 1,3,5,2,4-trithiadiazepines, intense peaks for the molecular ions are observed. Major fragmentation is attributed to the loss of NS unit; NS, NS₂, and N₂S₃ fragments are usually present (Scheme 1) <87JCS(P1)211, 87JCS(P1)217, 91JCS(P1)301, 91JCS(P1)311, 91JCS(P1)317>.



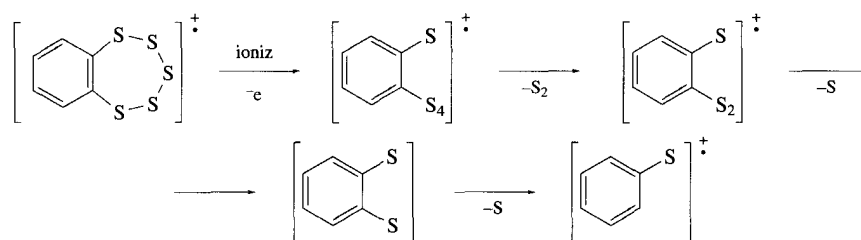
Scheme 1

The mass spectra of 1,3,5,2,4,6-trithiatriazepines almost always show a strong molecular ion and the N₂S₃ ion (Scheme 2); they do not readily lose an NS fragment. The compounds with lone pair substituents (NR₂) show weak peaks of (M⁺—NS) fragment, but those with the electron-withdrawing substituents show no trace of it <87JCS(P1)1579, 89JCS(P1)1405>.



Scheme 2

The mass spectra of 1,2,3,4-tetrathiepanes <87JOC2411>, 1,2,3,4,5-pentathiepins <87JCS(P1)211, 88CL657>, 1,2,3,4,5-pentathiepanes <83JOU133>, and 1,2,3,4,5,6-hexathiepanes <81BCJ3541> show the molecular ions with the loss of 1, 2, 3, 4 or 5 sulfur atoms (Scheme 3).



Scheme 3

The fragmentation of 1,2,4,5-tetrathiepanes <87JOC2411>, 1,2,4,6-tetrathiepanes <76JOC2465>, and 1,2,3,5,6-pentathiepan (48) <66TL573> is more individual and complex and consists of the loss of both S_n (n = 1,2) and CH₂, CH₂S (or CR₂S), CHS fragments.

9.17.3.4 UV Spectroscopy

The UV spectra of 1,3,5,2,4-trithiadiazepines show a characteristic long wavelength π - π^* absorption at 306–360 nm (log ϵ 3.6–3.9), that indicates highly delocalized structures <87JCS(P1)203, 87JCS(P1)211, 87JCS(P1)217, 87JCS(P1)1579, 87JCS(P1)1585, 91JCS(P1)301, 91JCS(P1)311, 91JCS(P1)317, 91JCS(P1)2945>. A long wavelength UV absorption of 6,7-benzo compounds (18), (19) and 6,7-dihydro-1,3,5,2,4-trithiadiazepine (20) has its maxima at around around ~380 and 408 nm, respectively <87JCS(P1)211, 87JCS(P1)217>. The theoretical study of UV spectrum of 1,3,5,2,4-benzotrithiadiazepine (18) by MNDO calculations has showed that its lowest energy absorption band at 384 nm is caused by HOMO–LUMO excitation, these MO are localized at S–N=S=N–S fragment <86IC1137>. The spectra of trithiadiazepines also have 1–3 bands at 218–300 nm range. Magnetic circular dichroism spectrum of 1,3,5,2,4-benzotrithiadiazepine (18) is consistent with somewhat restricted electron delocalization around the 11-atom perimeter <86IC3194>.

1,3,5,2,4,6-Trithiatriazepines fall into two broad classes: those bearing an electron-withdrawing substituent and those bearing a substituent having a lone pair of electrons. The first exhibits a simple two peak spectra with maxima near 276 nm (log ϵ ca. 4) and 330 nm (log ϵ 3.1–3.6), typical of an

aromatic π - π^* transition. The second group shows a more complex four band spectra with $\lambda_{\max}$ around 220 nm ($\log \epsilon$ 4), 250 nm ($\log \epsilon$ 4), 290 nm ($\log \epsilon$ 3.5) often as a shoulder and the longest wavelength absorption of very variable $\lambda_{\max}$ 330–410 nm <87JCS(P1)203, 87JCS(P1)1585, 88JCS(P1)1745, 89JCS(P1)1405>.

The character of the most intensive bands in the UV spectra of 1,2,3,4,5-pentathiepins is determined by the nature of the carbon fragment of the molecule. For the benzopentathiepins, there is only one $\lambda_{\max}$ at 208 ± 5 nm (ϵ ca. 30000), whereas for the pyrazolopentathiepins, it is shifted to 225 nm <85JA3871, 71TL2125>, for thienopentathiepin (**37**) two maxima at 235 and 270 nm are reported <88JST(167)245>, and for unsubstituted pentathiepin (**62**) there are weak shoulders at 315 nm, 253 nm, and 206 nm <71TL2125>. Similar shoulders at 228–370 nm are also observed for other pentathiepins <71TL2125, 85JA3871, 87JCS(P1)211, 88TL1935, 88CL657>. The CNDO calculations have shown that the main bands involve MOs mainly localized on carbon fragments of the molecules and the less predictable shoulders at higher wavelengths could originate from n - π^* transitions <88JST(167)245>. The spectra of 1,2,3,4,5-pentathiepins show two bands near 235 and 280 nm <71TL2125, 86ZOB1540>.

9.17.3.5 IR Spectroscopy

Some data for the ring vibrations are presented mainly for the most studied classes of heterocycles: 1,3,5,2,4-trithiadiazepines, 1,3,5,2,4,6-trithiatriazepines, and cyclic polysulfides. The spectra for these trithiadiazepines and trithiatriazepines exhibit the principal absorption at 1122–1180 and 1133–1157 cm^{-1} , respectively <87JCS(P1)203, 87JCS(P1)211, 87JCS(P1)1579, 88JCS(P1)1745, 89JCS(P1)1405>, which is characteristic of an asymmetric sulfur diimide stretching vibration; in some cases, there are absorptions near 635 cm^{-1} ($\text{N}=\text{S}=\text{N}$ bending vibrations) in the spectra of trithiadiazepines <87JCS(P1)211> and at 1745–1725 cm^{-1} ($\text{C}=\text{N}$ stretching vibrations) in the spectra of trithiatriazepines. The position of the $\text{N}=\text{S}=\text{N}$ stretching band of trithiadiazepines depends on the nature of substituent; as a rule, strong electron withdrawing groups (except the nitro group) heighten the NSN stretching frequency.

The mono- and dihydro-1,3,5,2,4-trithiadiazepines exhibit a lower energy $\text{N}=\text{S}=\text{N}$ stretching frequency at 1137–1140 cm^{-1} <87JCS(P1)211, 91JCS(P1)311>.

The ring vibrations of cyclic polysulfides fall into a range well below that commonly used. However, a detailed investigation of vibrational (IR and Raman) spectra of 1,2,3,5,6-pentathiepan (lenthionine) (**48**) has been carried out <88MI 917-01>. It showed, that the $\text{C}-\text{S}$ stretching bands of the $\text{S}-\text{CH}_2-\text{S}$ functionality appear in the 600–700 cm^{-1} region, ring bends at sulfur appear at 350–400 cm^{-1} , the methylene rocking motions and SSC bending vibrations are found at 800–850 and near 250 cm^{-1} , respectively, and the trisulfide functionality in cyclic compounds appears as a doublet centered at 485 cm^{-1} .

There are also strong $\text{S}-\text{S}$ absorptions in the 470–502 cm^{-1} region in the spectra for 1,2,3,4,5-pentathiepins and pentathiepins <71TL2125, 83JOU133, 85JA3871>; the benzopentathiepins and trimethylsilylpentathiepan (**27**) have additional characteristic absorptions at 425 ± 5 cm^{-1} .

The IR spectra of other classes of heterocycles are often presented along with the data on their synthesis, but as a rule the structural assignments are absent.

9.17.3.6 Photoelectron Spectroscopy

The vertical ionization potentials of 1,3,5,2,4-trithiadiazepine (**21**) <85CC398> and 1,3,5,2,4-benzotrithiadiazepine (**18**) <91MI 917-01> have been determined; the first ionization potentials are low (8.58 and 7.88 eV, respectively). These ionizations were assigned on the basis of MNDO calculations. From the calculations, the HOMOs consist predominantly of out-of-phase π overlap of sulfur and nitrogen lone pair orbitals <85CC398, 91MI 917-01>. As a whole, the photoelectron spectra and the inner-shell electron energy loss spectra (ISEELS) of 1,3,5,2,4-benzotrithiadiazepine, which provide probes for the unoccupied levels <91MI 917-01>, confirm the fundamental aromatic nature of the trithiadiazepine ring; the trithiadiazepine itself is more aromatic than benzo derivative <85CC398>.

The only example of photoelectron spectra of cyclic polysulfides is the spectrum of 1,2,3,4-tetrathiepane-6,6-dicarboxylate (**8**), which contains three separate signals in the low energy area at 8.7 eV (3π lone pairs on the sulfur atoms), 10.2 eV (lone pairs on the carbonyl oxygen), 11.4 eV (σ lone pairs on sulfur) <88ACS(B)620>. Photoelectron spectroscopy indicates that the dihedral angles around the $\text{S}-\text{S}$ bonds of (**8**) are comparable to the normal value exhibited by straight-chain disulfides <88ACS(B)620>.

9.17.4 THERMODYNAMIC ASPECTS

9.17.4.1 Physical Constants, Solubility, and Chromatographic Behavior

1,3,5,2,4-Trithiadiazepines and 1,3,5,2,4,6-trithiatriazepines are as a rule relatively low-melting solids. For example, unsubstituted compounds (**21**) and (**26**) melt at 58 and 43°C, respectively, and are very volatile, indicating the absence of significant intermolecular interactions. However, such heterocycles bearing polyaromatic substituents or groups capable of H-bonding are high melting <87JCS(P1)211, 87JCS(P1)217, 87JCS(P1)1579, 88JCS(P1)1745, 89JCS(P1)1405, 91JCS(P1)301, 91JCS(P1)311, 91JCS(P1)317, 91JCS(P1)2945>. Their di- (**20**) and tetrahydro- derivatives (**14**) and (**15**) also are low-melting solids or oils <87JCS(P1)211, 85CB2811>.

Annelated 1,3,4,6-thiatriazepines (**2**)–(**6**) and 2,4,6-triaza-7-thiacyclohepta-1,3-dieno-5-thiono-1-thioles are high-melting solids (m.p. 177–236°C) <80CC156, 83ZAAC(502)11>; whereas annelated 1,2,3,5-tetrazezin-4-ones (**10**)–(**12**) have the melting points near 100°C <91JCS(P1)2525>.

Most of seven-membered cyclic polysulfides are solids with variable melting points, which are strongly dependent on the nature of substituents <71TL2125, 81TL1939, 86CL349, 87JOC4937, 88TL6291>.

In spite of the large number of ring heteroatoms, the 1,3,5,2,4-trithiadiazepines and 1,3,5,2,4,6-trithiatriazepines are readily soluble in organic solvents and relatively nonpolar. 1,3,5,2,4-Trithiadiazepine (**21**), 1,3,5,2,4-benzotrithiadiazepine (**18**), and 1,3,5,2,4,6-trithiatriazepine (**26**) have the R_f values 0.30, 0.31, and 0.37, respectively. 6,7-Dihydro-1,3,5,2,4-trithiadiazepine (**20**) is more polar with an R_f of 0.07 (light petroleum-silica) <87JCS(P1)211, 88JCS(P1)1745>.

The seven-membered cyclic polysulfides are also soluble in both nonpolar and polar organic solvents. Most of them are purified by LC on silica with relatively nonpolar eluents (CCl₄, hydrocarbons) <85JA3871, 86CL349, 87JOC4937, 88TL6291>.

9.17.4.2 Thermal Stability and Aromaticity

1,3,5,2,4-Trithiadiazepine (**21**) and 1,3,5,2,4,6-trithiatriazepine (**26**) have remarkable thermal stability for molecules with such a high proportion of heteroatoms; they do not decompose even on the prolonged heating at 180°C; most of their substituted derivatives are also thermally stable. Such unusual stability indicates that these heterocycles are delocalized 10 π aromatic systems, and their chemical reactivity, spectroscopic properties, and x-ray analysis (see corresponding sections) all confirm the fundamental aromatic nature of trithiadi- and trithiatriazepine rings. The 14 π -electron 1,3,5,2,4-benzotrithiadiazepine is less stable and less aromatic than the 10 π -electron trithiadiazepine <86IC1137, 87JCS(P1)217, 88RHA204, 87JCS(P1)1745>. 1,3,5,7-Tetrathia-2,4,6,8-tetraazaazulene (**61**) is also a thermally stable 14 π -electron aromatic compound, its x-ray analysis supports its aromaticity <85CC1654>. The thermal stability of di- and tetrahydro-1,3,5,2,4-trithiadiazepine is variable and substituent dependent <85CB2811, 87JCS(P1)211>.

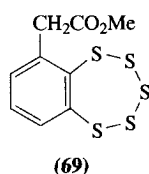
Nonplanar nonaromatic 1,2,3,4,5-pentathiepins and 1,2,3,4,5-pentathiepanes have relatively low thermal stability and readily release sulfur on heating or even at room temperature especially in polar solvents <83JOU133, 87JOC4937, 88CL657>.

9.17.4.3 Conformations

1,3,5,2,4-Trithiadiazepines and 1,3,5,2,4,6-trithiatriazepines are planar <88RHA204>. 6,7-Dihydro-1,3,5,2,4-trithiadiazepine (**20**) has a planar SNSNS fragment, and the two carbon atoms lie symmetrically above and below this plane. Their ¹H NMR spectra indicate rapid axial-equatorial hydrogen interconversion with a relatively low (≤ 9.6 kcal mol⁻¹) energy barrier <87JCS(P1)211>. 6,6,7,7-Tetrafluoro-2,4-bis(trimethylsilyl)-1,3,5,2,4-trithiadiazepan-3,3-dioxide (**15**) is in the chair conformation. Its ring inversion barrier is 16.1 kcal mol⁻¹ according to its ¹⁹F NMR spectra <85CB2811>.

Seven-membered cyclic polysulfides are as a rule in chair conformation both in crystal (see Section 9.17.3.1) and in solution, because these conformers have the lowest torsion strain. Experimental ring inversion energy barriers for 6-carbomethoxymethyl-1,2,3,4,5-benzopentathiepin (**69**) and unsymmetric pyrazolo-2*H*-1,3,4,5- or pyrazolo-4*H*-1,2,3,5-tetrathiepins (**45**) and (**47**) are 19.3 and 18.5 kcal mol⁻¹, respectively <87JOC2411>. Molecular orbital calculations, which have been carried out for 1,2,3,4,5-pentathiepin (**62**), 1,2,3,4,5-benzopentathiepin (**35**), and thieno[3,4-*f*]-1,2,3,4,5-pentathiepin (**37**) by means of the semiempirical AM1 method <88JST(167)245> and for the pen-

tathiepin by means of *ab initio* method <87JOC2411> show the same order of the stability for the different conformers. The chair conformer is most stable, the twist-boat and boat conformers are $\cong 2$ –6 and $\cong 8$ –15 kcal mol⁻¹ less stable, respectively. The calculated ring inversion barriers are 12.5–15 kcal mol⁻¹ (AM1 method). According to the ¹H NMR spectra in solutions of symmetric pyrazolo-3,3-dimethyl-3*H*-1,2,4,5-tetrathiepins (**46**), the unusual equilibrium between the dominant chair and the minor twist-boat conformer occurs. The twist-boat conformer is only 1.16 kcal mol⁻¹ less stable, but the chair–twist-boat interconversion barrier is relatively high (21.2 kcal mol⁻¹), so the twist-boat form is seen by NMR <87JOC2411>.



9.17.5 REACTIVITY OF FULLY CONJUGATED RINGS

The reactivity of 1,3,5,2,4-trithiadiazepines is indicative of their aromaticity. Unsubstituted trithiadiazepine (**21**) is stable towards a variety of mineral and Lewis acids, however, it is decomposed by strong bases. It does not react with a variety of electron-rich and electron-poor 2 π and 4 π cycloaddition reagents. Trithiadiazepines readily undergo the electrophilic substitution on carbon, which is characteristic for aromatic heterocycles. A special feature of their reactivity is the easy generation of trithiadiazepyne from 6-halo-1,3,5,2,4-trithiadiazepines with bases. The hetaryne is intercepted by nucleophiles, dienes, and 1,3-dipoles to give products of the nucleophilic replacement or cycloaddition, respectively. The properties of trithiadiazepines are broadly similar to those of the 10 π aromatic dithiatetrazocine <88RHA204, 89PS(43)261, 92JHC639>. The aromatic electrophilic substitution is also characteristic for 1,3,5,2,4,6-trithiatriazepines.

In contrast with these aromatic compounds, nonaromatic 1,2,3,4,5-pentathiepins are unstable and readily lose sulfur under the action of heating, electrophilic and nucleophilic reagents. The reactivity of pentathiepins is similar with that of other cyclic polysulfides with long polysulfide fragments <90CL139, 93PS(74)389>.

9.17.5.1 Thermal and Photochemical Unimolecular Reactions

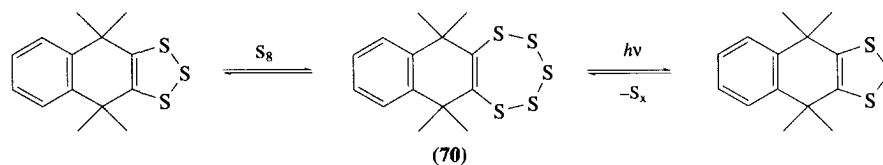
9.17.5.1.1 Reactions of 1,3,5,2,4-trithiadi- and 1,3,5,2,4,6-trithiatriazepines

These compounds are thermally very stable (see Section 9.17.4.2), but photochemically labile. Irradiation at 300–350 nm led to their rapid and extensive degradation <87JCS(P1)217>.

9.17.5.1.2 Reactions of 1,2,3,4,5-pentathiepins

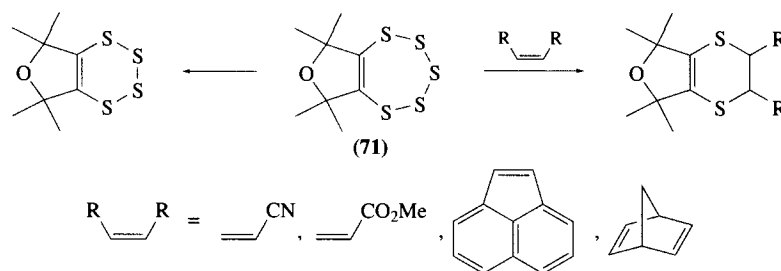
The thermolysis of pentathiepin (**70**) at 140°C in *o*-dichlorobenzene readily reached an equilibrated mixture of parent pentathiepin (**70**), corresponding trithiole and sulfur (trithiole–pentathiepin ratio was 3 : 1), which was alternatively generated by heating of *o*-dichlorobenzene solution of trithiole mixed with sulfur at the same temperature (Scheme 4) <88CL657>. With the light of $\lambda = 365$ nm, (**70**) smoothly desulfurized into trithiole quantitatively <88CL657>.

Photolysis of (**71**) in the presence of various alkenes gave the corresponding adducts, presumably



Scheme 4

via the formation of the 1,2-dithione. 1,2,3,4-Tetrathiin was formed in the absence of alkenes (Scheme 5) <87TL4833, 89NKK1447>.

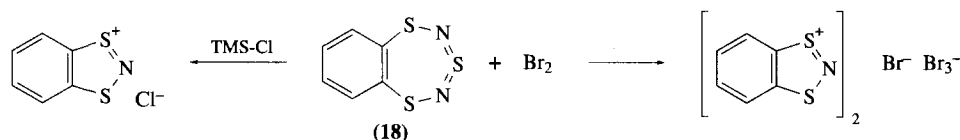


Scheme 5

9.17.5.2 Electrophilic Attack on Nitrogen Atom of 1,3,5,2,4-Trithiadiazepins

This mode of electrophilic attack is rare; however, an interesting product was obtained by treatment of trithiadiazepine (**18**) with bromine in dichloromethane. The structure of this compound was solved by x-ray crystallography which showed it to be bis(1,3,2-benzodithiazolium)bromide tribromide; the reaction is probably initiated by prior rapid and reversible attack by bromine on a ring nitrogen atom (Scheme 6) <87JCS(P1)217>.

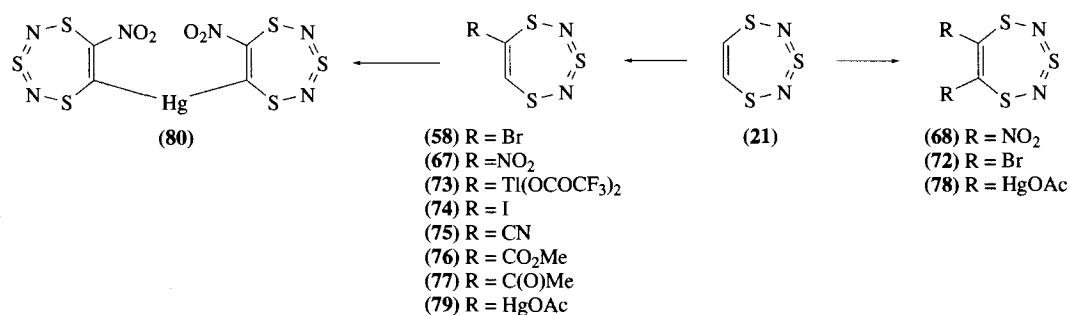
Benzotrithiadiazepine (**18**) interacts with trimethylchlorosilane and gives the salt 1,3,2-benzodithiazolium chloride <91ZOB441>.



Scheme 6

9.17.5.3 Electrophilic Attack on Carbon Atom of 1,3,5,2,4-Trithiadiazepins and 1,3,5,2,4,6-Trithiatriazepins

The electrophilic substitution is the most characteristic reaction for these classes of compounds. Compound (**21**) undergoes standard electrophilic aromatic substitution reactions. Thus it forms the 6-bromo compound (**58**) with *N*-bromosuccinimide and 6,7-dibromo compound (**72**) with the excess of the same reagent. It also forms the 6-nitro compound (**67**) with copper(II) nitrate trihydrate and 6,7-dinitro compound (**68**) with excess of nitronium tetrafluoroborate. The bis(trifluoroacetoxy)thallium derivative (**73**) was formed from trithiadiazepine (**21**) and thallium(III) trifluoroacetate in refluxing acetonitrile. Without isolation, (**73**) was directly converted into the pale yellow 6-iodo compound (**74**) with aqueous potassium iodide, into the 6-cyano compound (**75**) with copper(I) cyanide, and into methyl trithiadiazepine-6-carboxylate (**76**) with carbon monoxide and methanol in the presence of palladium chloride, lithium chloride, and magnesium oxide. Compound (**21**) is acetylated in the presence of trifluoromethanesulfonic acid (Scheme 7) <85CC396, 87JCS(P1)217, 91JCS(P1)2945>.



Scheme 7

Monosubstituted trithiadiazepines (**77**) and (**76**) also underwent bromination and nitration with the formation of corresponding derivatives (**81**), (**82**), and (**83**) (Scheme 8) (91JCS(P1)2945).



(26) $\xrightarrow{i}$ (84) R = NO₂
 (85) R = Br

i = NO₂BF₄, BrN

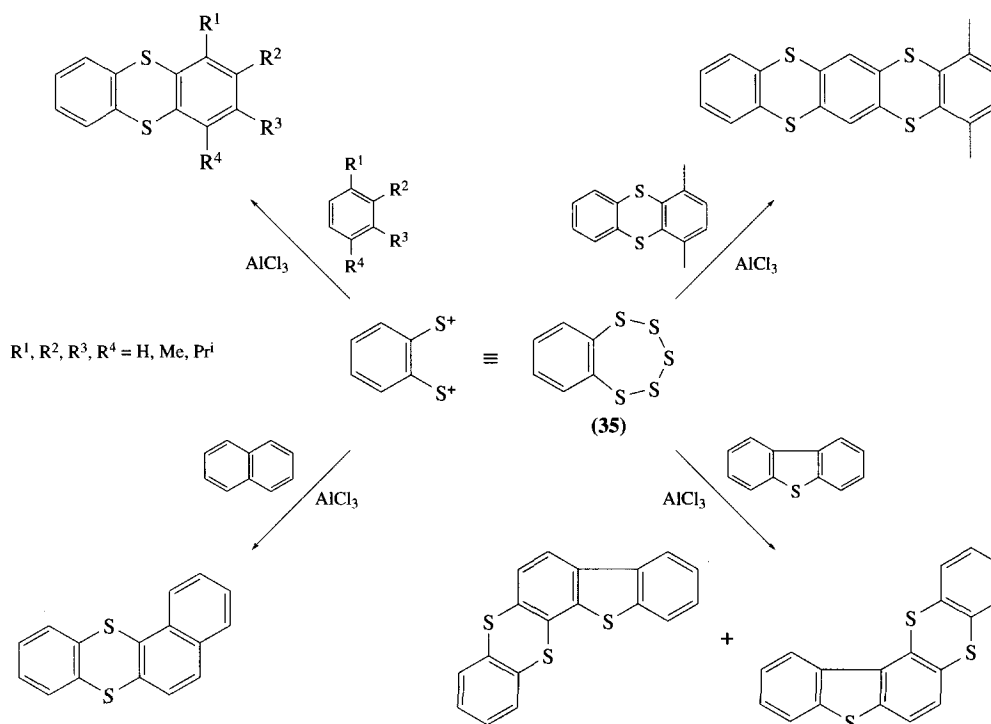
9.17.5.4 Electrophilic Attack at Sulfur of 1,2,3,4,5-Pentathiepins

Benzopentathiepin (**35**) reacts with many aromatic compounds, such as benzene, 1,4-dimethylbenzene, and naphthalene in the presence of Lewis acid to give various thianthrenes in moderate yields. This benzopentathiepin was found to serve as a 1,4-dication synthon (Scheme 9) [⟨88H\(27\)2563⟩](#).

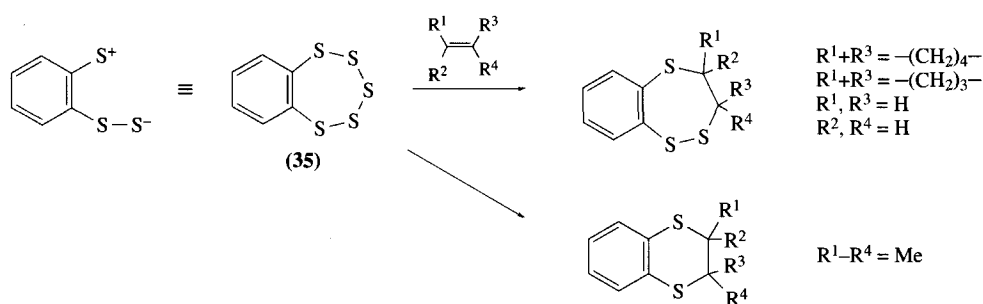
9.17.5.5 Nucleophilic Attack at Hydrogen Attached at Carbon

9.17.5.5.1 Nucleophilic substitution in 1,3,5,2,4-trithiadiazepines

Nucleophilic substitution on 6-halo-1,3,5,2,4-trithiadiazepines proceeds via the elimination–addition mechanism (89PS(43)261, 91JCS(P)1301, 92JHC639). The nucleophilic attack at proton at the C-



Scheme 9



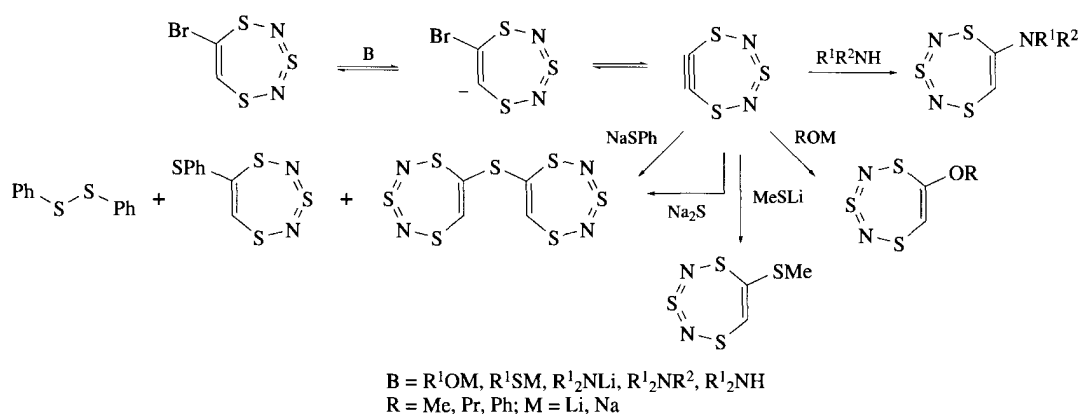
Scheme 10

7-atom results in reversible formation of trithiadiazepyne via a carbanion. The hetaryne reacts irreversibly with amines, amide ions (91JCS(P11)301), alkoxides, and phenoxides or their sulfur analogues (89PS(43)261) in mild conditions to give nominally the products of the displacement of the halogen (Scheme 11).

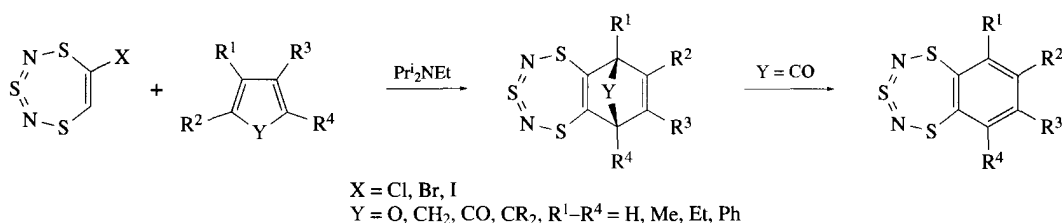
9.17.5.5.2 Reactions of 1,3,5,2,4-trithiadiazepines with dienes and 1,3-dipoles

The trithiadiazepyne formed by treatment of halotrithiadiazepines with the base could also be intercepted by active dienes, namely furans, cyclopentadienes, and cyclopentadienones to give the cycloadducts (Scheme 12) (91JCS(P1)301, 91JCS(P1)317).

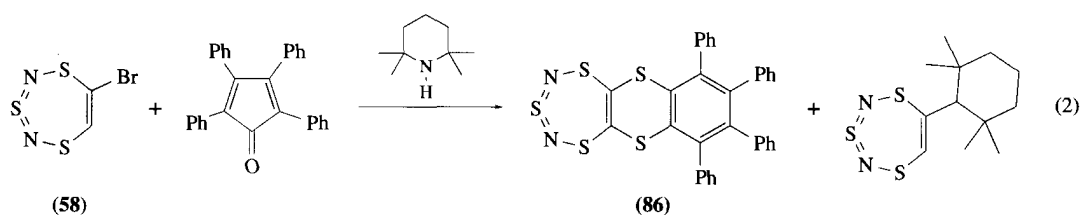
In THF, (53) with tetraphenylcyclopentadienone and with tetramethylpiperidine, as base, gave the unexpected dithiin (86) in low yield (Equation (2)) together with the product of reaction of the aryne with the very hindered amine used. The dithiin structure (86) is interesting since the aryne appears to have been incorporated twice. A possible pathway for its formation is proposed in (89PS(43)261, 91JCS(P1)317).



Scheme 11

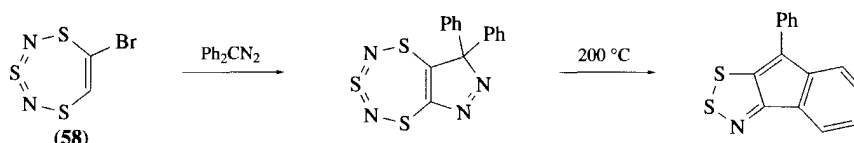


Scheme 12



Dienes with low Diels–Alder reactivity do not intercept the aryne; the same applies to 1,3-dipoles. Thus the aryne did not react with azides and nitrones, though it formed high yields of the expected cycloadducts with diaryl diazomethanes (Scheme 13) (89PS(43)261, 90CC1319, 91JCS(P1)311).

The mechanism of this unexpected conversion of pyrazolotrithiadiazepines to 1,2,3-dithiazoles has been proposed (90CC1319).



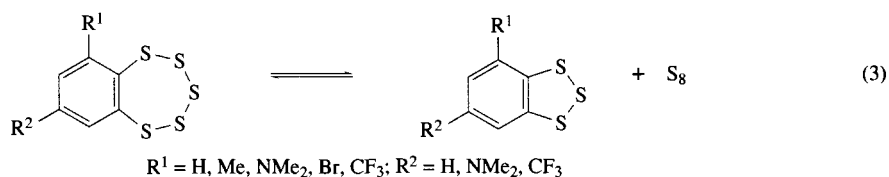
Scheme 13

9.17.5.6 Nucleophilic Attack at Sulfur Atom

9.17.5.6.1 Nucleophilic attack at sulfur atom of 1,2,3,4,5-pentathiepins

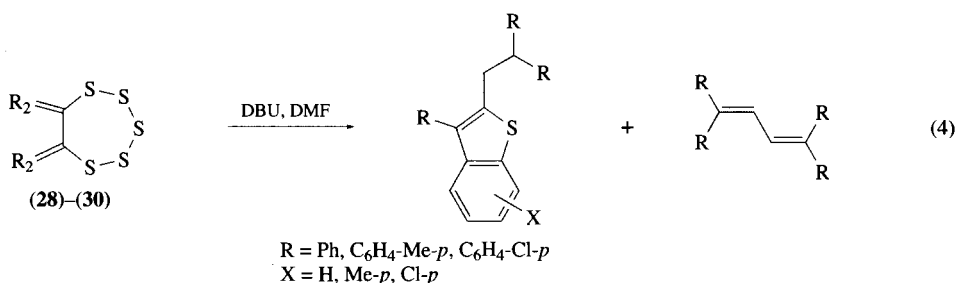
The nucleophilic attack at the sulfur atom of cyclic polysulfides results in heterolytic cleavage of the S—S (as a rule S(1)—S(2)) bond. The active intermediate can lose several sulfur atoms or can be intercepted by unsaturated or active methylene compounds. Thus some benzopentathiepins readily equilibrate to a mixture of pentathiepin, trithiol, and S₈ in methanol or in hexane in the

presence of diethylamine; no reaction takes place in the absence of the amine (85JA3871). The reverse equilibrium also occurred (Equation (3)).

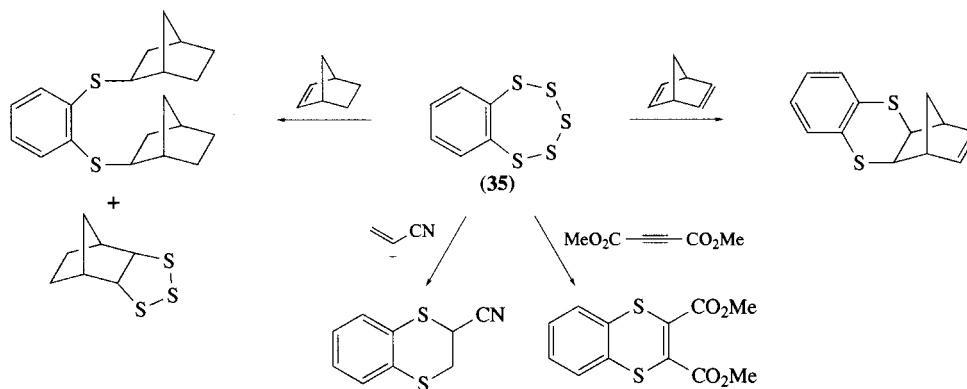


An *ortho* electron-withdrawing substituent may be more important than more steric bulk when stabilizing benzotrithioles. The stability of benzopentathiepin and benzotrithioles is based on the combination of both steric and electronic effects. Benzotrithioles will only be prepared when there is an electron-withdrawing group *ortho* to the polysulfide ring or when a very bulky *ortho* electron-donating group is present. In all other cases, the benzopentathiepin will be the preferred polysulfides.

The pentathiepanes (28)–(30) were desulfurized to the corresponding benzothiophenes and 1,3-butadienes (88TL1935) (Equation (4)).



Formation of 1,4-benzodithianes and 1,4-benzodithiins by reaction of benzopentathiepin (35) with unsaturated compounds under basic conditions has been described (Scheme 14) (90SUL233).

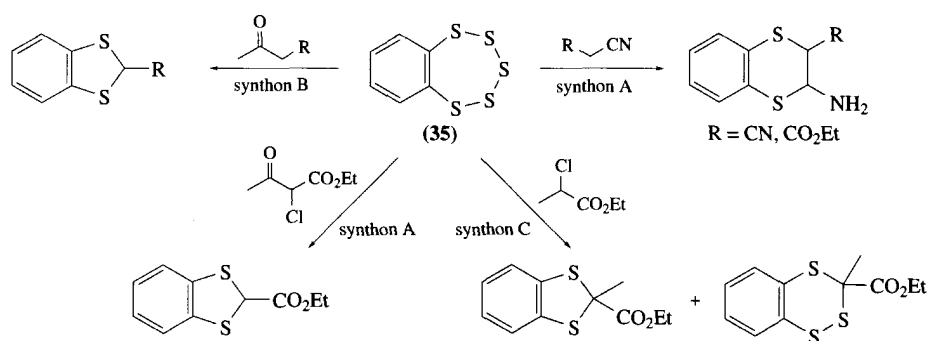


Scheme 14

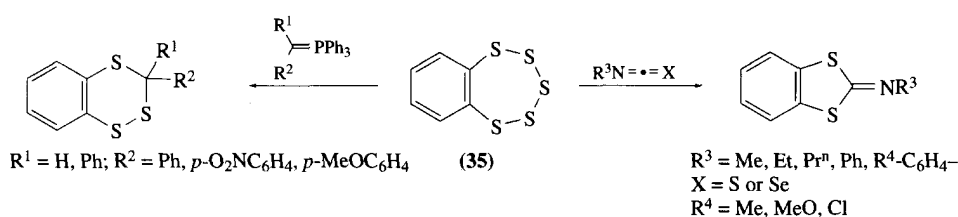
Benzopentathiepin (35) reacts with various active methylene compounds such as malononitrile, ethyl cyanoacetate, ethyl acetoacetate, and ethyl α -chloropropionate in the presence of base such as triethylamine or sodium ethoxide to give dithiins, dithioles, or 1,2,4-trithiin in satisfactory yields. In the present reaction benzopentathiepin (35) was found to act as a 1,4-dipole, 1,4-dication, or 1,5-dipole synthons A, B, or C (89H(29)2087), respectively (Scheme 15).

The reactions of alkyl or aryl isochalcogenocyanates with benzopentathiepin (35) in the presence of Et_3N , as base, gave the corresponding 2-imino-1,3-benzodithioles in good yields (Scheme 16) (91CL355). A novel synthesis of 1,2,4-benzotrithiins from benzopentathiepin (35) with alkylidene-phosphoranes was described (Scheme 16) (91TL6345).

Benzopentathiepin (35) was used as a sulfurization reagent in usual organic solvents at room

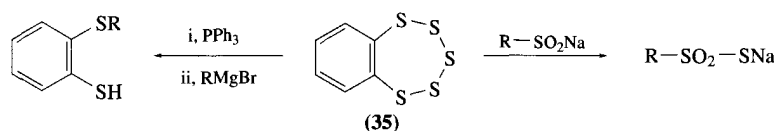


Scheme 15



Scheme 16

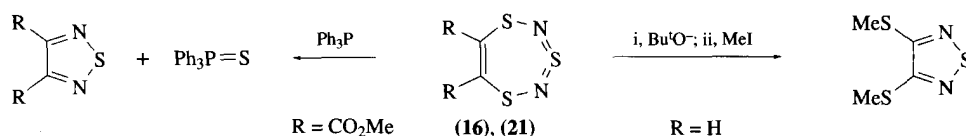
temperature affording the corresponding thiosulfonates in good yields (Scheme 17) (87CL2161). Treatment of (35) with Grignard reagents in the presence of triphenylphosphine gives alkyl and arylthiobenzenethiols (90SUL61).



Scheme 17

9.17.5.6.2 Nucleophilic attack at sulfur atom of 1,3,5,2,4-trithiadiazepines

Nucleophiles attack the imide sulfur atom of trithiadiazepines. Thus, unsubstituted (21), which is resistant to amines and triphenylphosphine, is rapidly decomposed by sodium hydroxide (87JCS(P1)217). On addition of potassium *t*-butoxide to a solution of trithiadiazepine (21) in dry THF, the trithiadiazepine was rapidly consumed and after addition of iodomethane to the orange precipitate 1,2,5-thiadiazole was obtained. This unexpected product results from a rearrangement in which two of the ring sulfur atoms have become exocyclic. This reaction takes place only with the strong bases. More active trithiadiazepine (16) and benzotrithiadiazepine (18) are decomposed by triphenylphosphine in toluene; whereas (21) gives dimethyl 1,2,5-thiadiazole-3,4-dicarboxylate under these conditions (Scheme 18) (87JCS(P1)217).



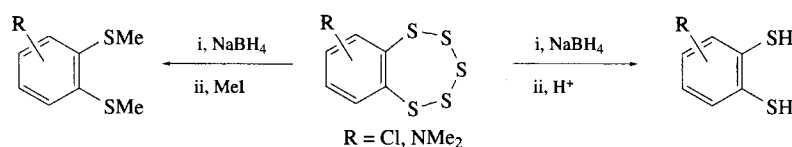
Scheme 18

9.17.5.7 Reduction

9.17.5.7.1 Reduction of 1,2,3,4,5-pentathiepins

Sodium borohydride cleanly reduces benzopentathiepins to dithiols (Scheme 19) <85JA3871>.

The trithiol ring of 1,2,3-trithiolo[5,4*H*]benzopentathiepins (**33**) and (**45**) is reduced more easily than the pentathiepine ring, which is reduced only with an excess of sodium borohydride <88TL6291, 89TL2453>.

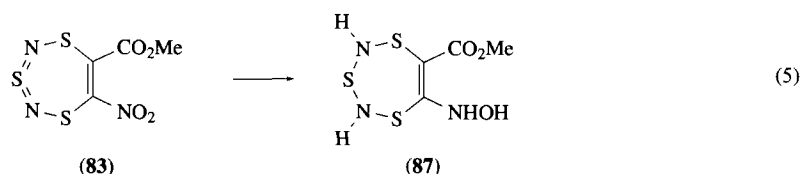


Scheme 19

9.17.5.7.2 Reduction of 1,3,5,2,4-trithiadiazepines

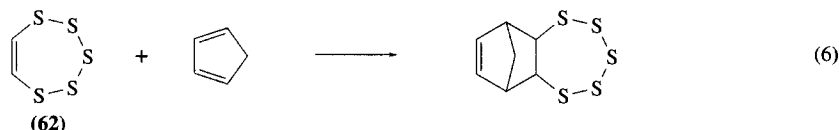
1,3,5,2,4-Trithiadiazepines (**21**) and (**18**) are resistant toward catalytic hydrogenation <87JCS(P1)217> but reduction of methyl 7-nitro-1,3,5,2,4-trithiadiazepine-6-carboxylate (**83**) gives methyl 2,4-dihydro-7-hydroxylaminotrithiadiazepine-6-carboxylate (**87**) (Equation (5)) <91JCS(P1)2945>.

1,3,5,2,4-Benzotrithiadiazepine (**18**) is easily reduced electrochemically ($E_{1/2} = \sim 0.83$ V) <86IC1137>.



9.17.5.8 Cyclic Transition State Reactions with the Second Molecule

Only a few such reactions of seven-membered heterocycles with a high proportion of heteroatoms are known. The 1,2,3,4,5-pentathiepin (**62**) gives the Diels–Alder adduct with cyclopentadiene (Equation (6)) <71TL2125>.



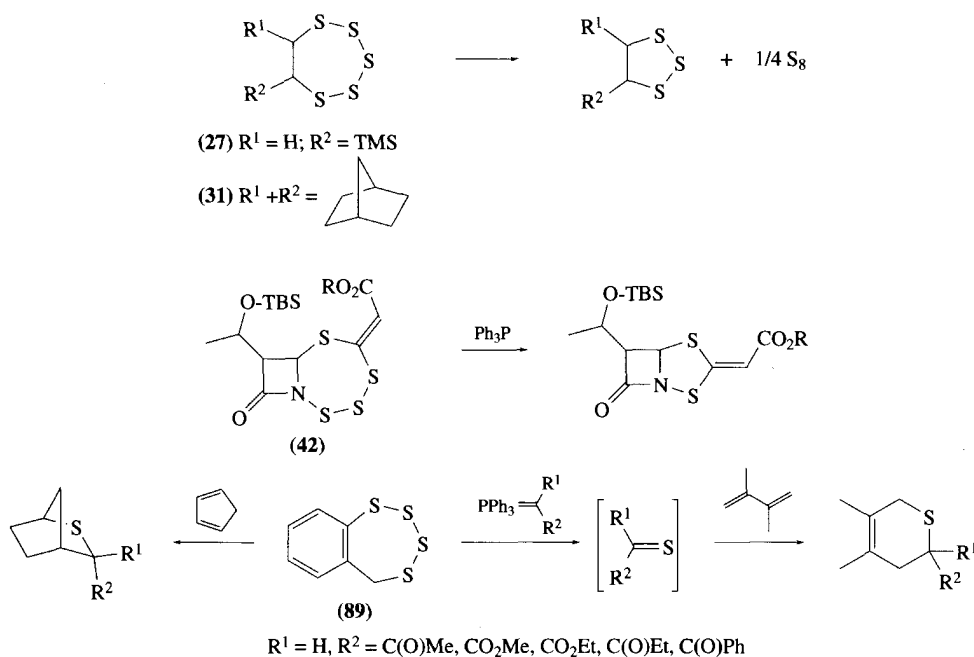
1,3,5,2,4-Benzotrithiadiazepine gives a 1,3-cycloadduct with norbornadiene, which readily dissociates in solution (Equation (7)) <86IC1137>.



The more aromatic parent trithiadiazepine (**21**) does not participate in cycloaddition reactions <86IC1137, 87JCS(P1)217>. The cycloaddition reactions of 1,3,5,2,4-trithiadiazepyne, which is generated only *in situ*, are considered in Section 9.17.5.5.

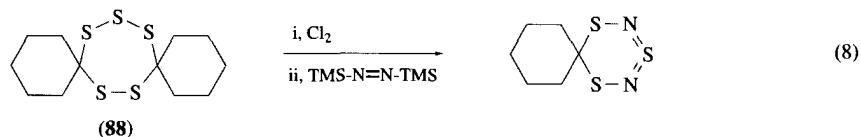
9.17.6 REACTIVITY OF NONCONJUGATED RING

The reactivity issues have been investigated mainly for hydro derivatives of polythiepins and relative compounds. The reactivity of 1,2,3,4,5-pentathiepins, 5*H*-1,2,3,4-tetrathiepins (**89**), and 6,7*H*-1,3,4,5,6-tetrathiazepins is similar with that of 1,2,3,4,5-pentathiepins. They also reversibly release sulfur with the formation of trithiolanes <83JOU133, 87JOC4937> and undergo the extrusion of sulfur by base reagents and alkenes (Scheme 20) <90CL139, 91S785, 91TL3771>.

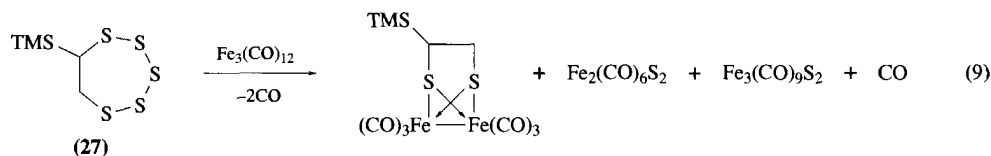


Scheme 20

Chlorinolysis of the pentathiepane (**88**), prepared from cyclohexanone and ammonium disulfide <59ACS1031, 90JCS(P1)509>, and treatment with bis(trimethylsilyl)sulfuriimide gave the spiro compound in 22% yield (Equation (8)) <90JCS(P1)509>.

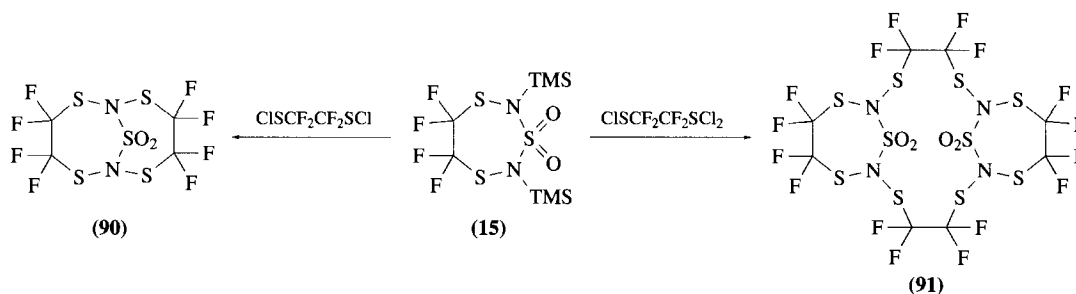


1,2-Ethylenepolysulfide (**27**) containing trimethylsilyl group reacts with iron carbonyl and formed the carbonyl complexes of thioles (Equation (9)) <86ZOB1540>.



6,7-Dihydro-1,3,5,2,4-trithiadiazepine (**20**) is readily dehydrogenated by 2,3-dichloro-5,6-cyano-benzoquinone with the formation of aromatic 1,3,5,2,4-trithiadiazepine <87JCS(P1)211>.

Addition of one or two equivalents of tetrafluoro-1,2-ethanedithiendichloride to trithiadiazepane (**15**) leads to the formation of the bicyclic product (**90**) or the tricyclic product (**91**), respectively (Scheme 21) <85CB2811>.

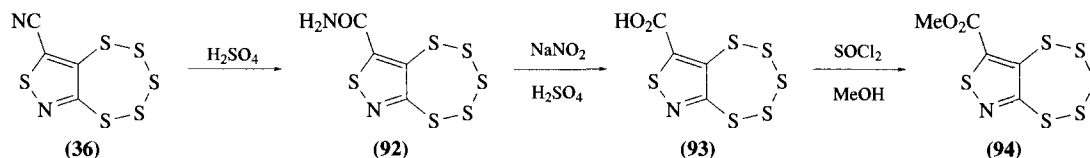


Scheme 21

9.17.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

9.17.7.1 Reactivity of Substituents in Pentathiepins

The pentathiepin ring has considerable stability toward acidic reagents which allows substituent manipulation. The cyano group of (36) can be readily hydrolyzed to the corresponding amide (92) in cold sulfuric acid; the amide (92) can be further hydrolyzed to the acid (93) on treatment with NaNO_2 in H_2SO_4 . When standard conditions were used, (93) was converted to its chloride, which was reacted with alcohols or amines to give esters (94) or amides (Scheme 22) <85JA3871>.

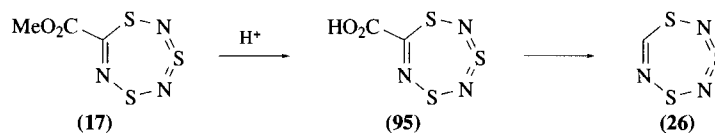


Scheme 22

9.17.7.2 Reactivity of Substituents in 1,3,5,2,4-Trithiadiazepines and 1,3,5,2,4,6-Trithiatrizepines

As a rule functional groups as substituents on the carbon atoms of trithiadi- and trithiatrizepines exhibit their typical reactivity, but it should be noted that these rings are unstable towards strong bases. Thus, demethylation of methyl 1,3,5,2,4,6-trithiatrizepine (17) was carried out by treatment with boron tribromide in dichloromethane or hydrochloric acid and gave the desired acid (95).

Decarboxylation of trithiatrizepine-7-carboxylic acid (95) was best achieved by heating; then evaporation gave trithiatrizepine (26) (Scheme 23) <88JCS(P1)1745>.



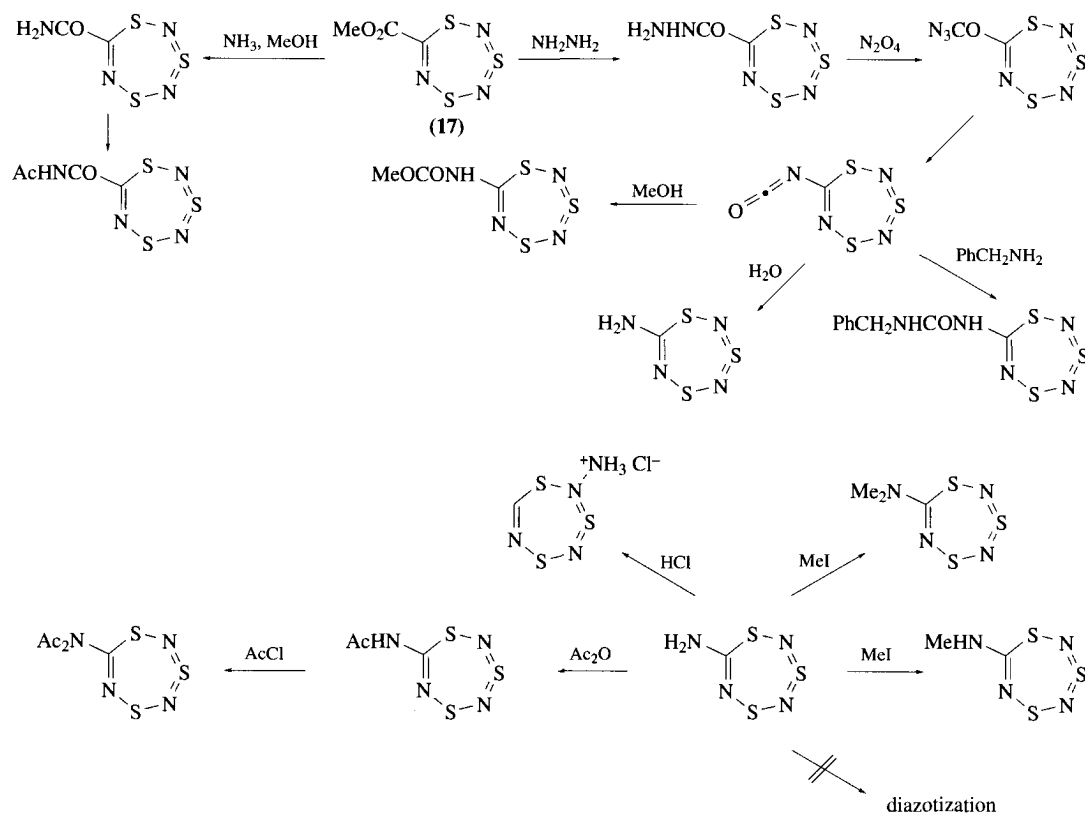
Scheme 23

The treatment of carboxylic acid with 1 : 1 mixture of trifluoroacetic anhydride and benzene gave its anhydride <89JCS(P1)1405>.

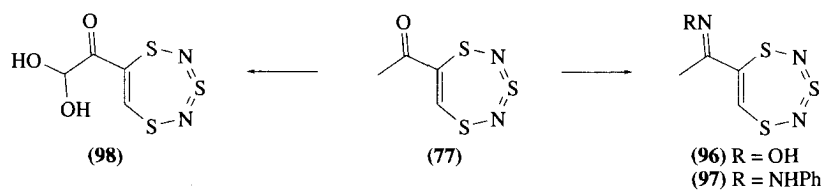
Some reactions of 7-substituted trithiatrizepines are presented in Scheme 24 <88RHA204, 89JCS(P1)1405>.

Oxime (96) and phenylhydrazone (97) are also formed from 6-acetyltrithiadiazepine (77). The methyl group of (77) was oxidized to give trithiadiazepinyl glyoxal monohydrate (98) (Scheme 25) <91JCS(P1)2945>.

6-Nitrotrithiadiazepine (67) is resistant to reduction to the amine. It does not undergo catalytic



Scheme 24

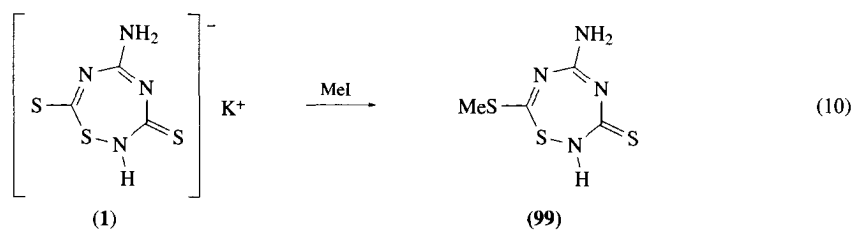


Scheme 25

hydrogenation and chemical reduction. The benzotrithiadiazepine (18) gives the 7-nitro derivative with low yield <87JCS(P1)217>.

9.17.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

Compound (1) reacts with methyl iodide to give $\text{Me}-\text{S}-\text{C}=\text{N}-\text{C}(\text{NH})=\text{N}-\text{CS}-\text{NH}-\text{S}$ (99) (Equation (10)) <83ZAAC(502)11>.

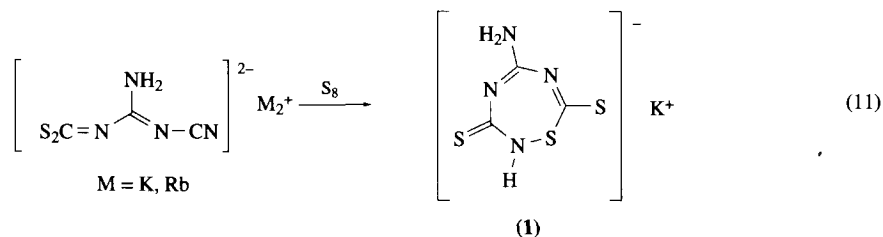


9.17.9 RING SYNTHESIS CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

9.17.9.1 1,2,4,6-Thiatriazepines

9.17.9.1.1 Type (S—C—N—C—N—C—N)

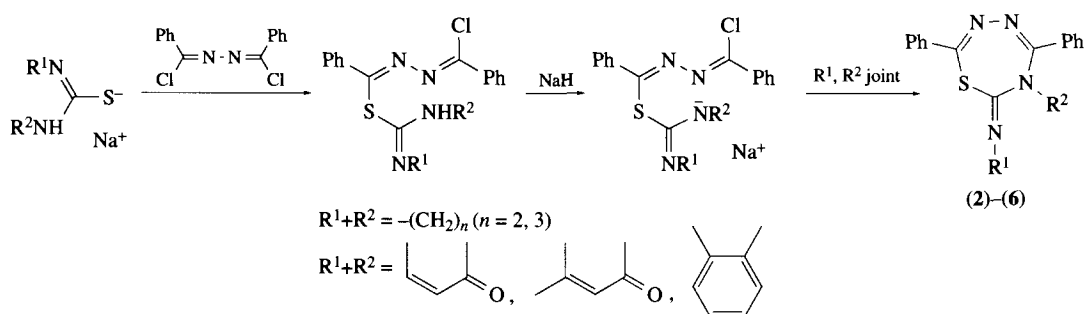
N-Cyanoforamidino dithiocarbamates react with elemental sulfur to yield 1,2,4,6-thiatriazepines (1) (Equation (11)) <83ZAAC(502)11>.



9.17.9.2 1,3,4,6-Thiatriazepines

9.17.9.2.1 Type (N—C—S + C—N—N—C)

The treatment of 1,4-diphenyl-1,4-dichloro-2,3-diazabutadiene with the sodium salts of cyclic thioureas in the presence of one-molar excess of sodium hydride has yielded the first examples (2)–(6) of seven-membered, annelated 1,3,4,6-thiatriazepines (Scheme 26) <80CC156>.

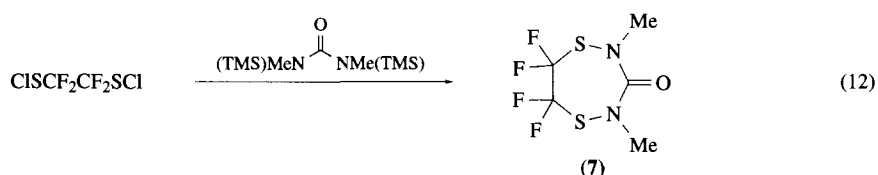


Scheme 26

9.17.9.3 1,5,2,4-Dithiadiazepanes

9.17.9.3.1 Type (S—C—C—S + N—C—N)

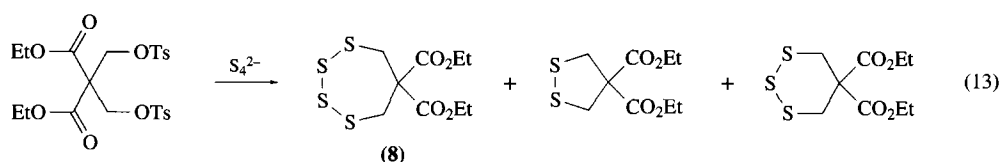
Treatment of tetrafluoro-1,2-ethanodisulfonyldichloride with a functionalized urea afforded dithiadiazepane (7) (Equation (12)) <85CB2811>.



9.17.9.4 1,2,3,4-Tetrathiepins

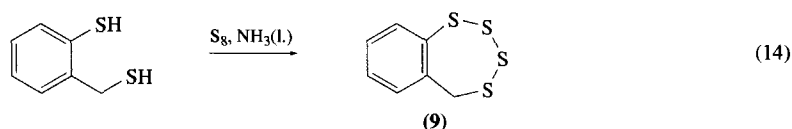
9.17.9.4.1 Type (C—C—C + S—S—S—S)

The diethyl 1,2,3,4-tetrathiepane-6,6-dicarboxylate (**8**) has been identified from the reaction mixture of diethyl bis(*p*-tolylsulfonyloxymethyl)malonate and tetrasulfide ion, along with 1,2-dithiolane and 1,2,3-trithiane. Reaction of 1,2-dithiolane with elemental sulfur in DMF at elevated temperatures is a useful route to (**8**) (Equation (13)) <88ACS(B)620>.



9.17.9.4.2 Type (S—C—C—C—S + S—S)

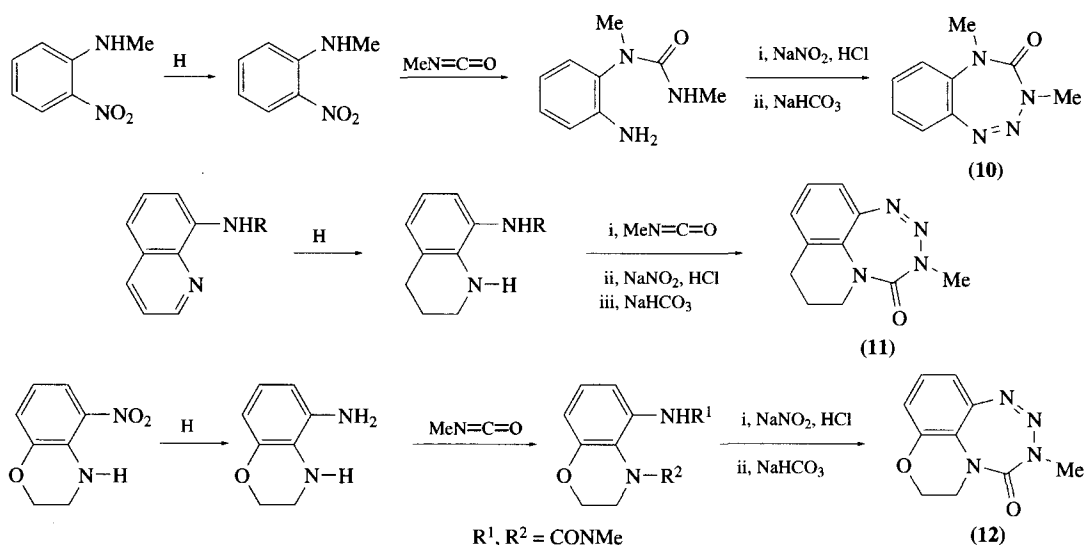
5*H*-Tetrathiepin (**9**) was obtained by the interaction of dithiole with elemental sulfur in liquid ammonia (Equation (14)) <88BCJ1647>.



9.17.9.5 1,2,3,5-Tetrazepines

9.17.9.5.1 Type (N—N—C—C—N—C—N)

The synthesis of bi- and tricyclic tetrazepinone derivatives was based on the strategy developed for the synthesis of imidazotetrazinone <87JMC357, 90MRC729>. Diazotization of *N,N'*-dialkyl-*N*-(*o*-aminophenyl)ureas gave 3,5-dimethyl-3*H*-1,2,3,5-benzotetrazepin-4(5*H*)-one (**10**), 3-methyl-6,7-dihydro-1,2,3,5-tetrazepino[7,6,5-*ij*]quinolin-4(3*H*)-one (**11**), and 3-methyl-6,7-dihydro[1,4]oxazino-[4,3,2,5-*ef*]-1,2,3,5-benzotetrazepin-4-one (**12**) (Scheme 27) <91JCS(P1)2525>.

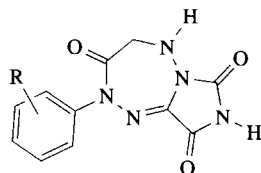


Scheme 27

9.17.9.6 1,2,4,5-Tetrazepines

9.17.9.6.1 Type ($N-N-C-N-N+C-C$)

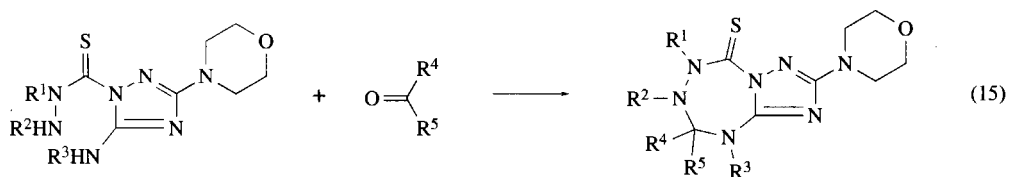
Reactions of 1-aminohydantoin with aryldiazonium salts followed by the cyclization with ethyl chloroacetate lead to novel imidazolotetrazepinones (13) <89JPS145>.

(13) R = F, Cl, CF₃, MeCO, SMe, NO₂

9.17.9.7 1,2,4,6-Tetrazepins

9.17.9.7.1 Type ($N-N-C-N-C-N+C$)

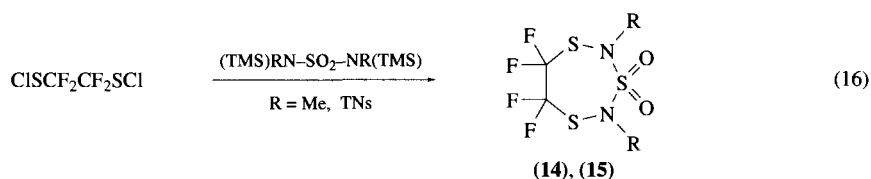
Different 2-morpholino-6,7,8,9-(bi-, tri- or tetra-)substituted 1,2,4-triazolo[1,5-*d*]-1,2,4,6-tetrazepine-5-thio-derivatives were synthesized (Equation (15)) <93JHC1009>.



9.17.9.8 1,3,5,2,4-Trithiadiazepanes

9.17.9.8.1 Type ($S-C-C-S+N-S-N$)

The tetrafluoro trithiadiazepanes (14) and (15) have been described (Equation (16)) <85CB2811>.



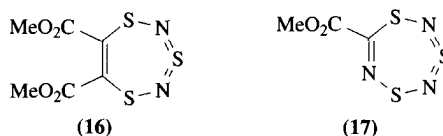
9.17.9.9 1,3,5,2,4-Trithiadiazepines

9.17.9.9.1 Type ($S-N-S-N-S+C-C$)

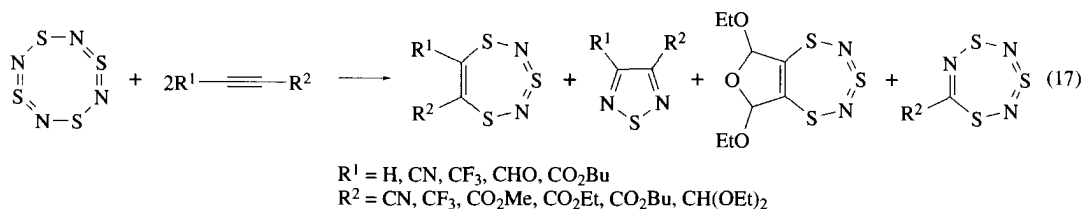
The first reported synthesis of the new class of 10 π heteroaromatic systems was made by Daley, Rees, and Williams <84CC55>. The method of obtaining these compounds was the reaction of tetrasulfur tetranitride, S₄N₄, with dimethyl ethynedicarboxylate in boiling toluene, which was reported <79JHC1009>; however, the incorrect structures of products were proposed.

Later, the structures of these compounds were solved by x-ray diffraction and found to be dimethyl

1,3 $\lambda^4\delta^2$ 5,2,4-trithiadiazepine-6,7-dicarboxylate (**16**) and methyl 1,3 $\lambda^4\delta^2$ 5,2,4,6-trithiatiazepine-7-carboxylate (**17**), respectively.



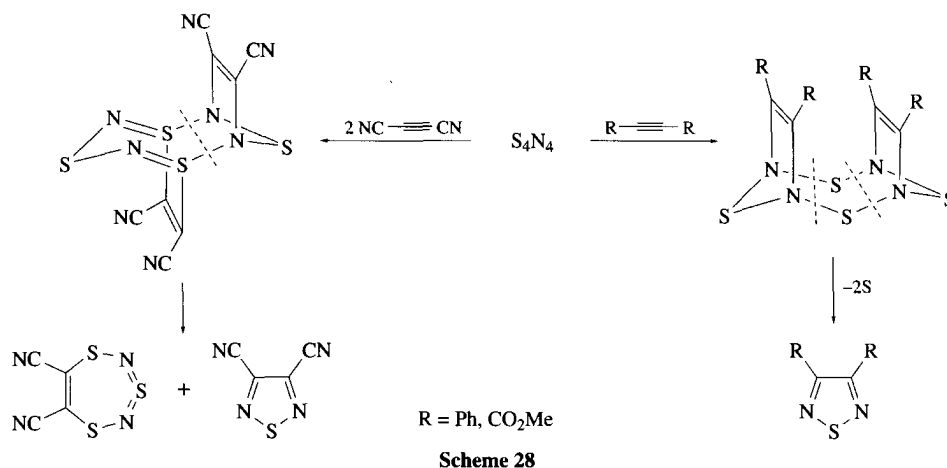
It was showed that tetrasulfur tetranitride, S_4N_4 , and alkynes $NC-C\equiv C-CN$, $NC-C\equiv C-CF_3$, and $CF_3-C\equiv C-CF_3$, which are highly reactive in cycloadditions, gave the corresponding trithiadiazepines in much higher yield, and that with other alkynes the trithiadiazepine yield is improved either at elevated temperatures (150–160°C) or by the addition of titanium(IV) chloride $\langle 87CC59, 87JCS(P1)203, 87JCS(P1)211, 87JCS(P1)1579, 87JCS(P1)1585 \rangle$. This method permits the formation of trithiadiazepines with two strongly electron-withdrawing groups, including the asymmetrical substituted heterocycles $\langle 87JCS(P1)1579 \rangle$. This reaction also produces 1,2,5-thiadiazoles and in some cases ($R^1 = CHO$, $R^2 = CH(OEt)_2$) 1,3,5,2,4,6-trithiatiazepines along with trithiadiazepines (Equation (17)).



The stoichiometry of this reaction suggests a simple cycloaddition–cycloreversion mechanism via a 2 : 1 adduct; this could be formed by 1,3-cycloaddition of the alkyne across the nitrogen and 1,5-cycloaddition across sulfur, and could dissociate directly into the observed aromatic products $\langle 87CC59 \rangle$. In $\langle 87JCS(P1)203, 87JCS(P1)1579 \rangle$ the reaction mechanisms involving cycloaddition, rearrangement, and ring cleavage for the formation of the products were proposed. The combination proceeds according to the scheme $8 + 2 + 2 - 5 \langle 88S569 \rangle$.

In $\langle 88RHA204 \rangle$, authors described and rationalized the reactions of S_4N_4 with a range of alkynes, bearing substitutions with widely differing electronic properties. Focusing attention on the yield of the trithiadiazepine, they found that this increased dramatically with the electron-withdrawing power of the alkyne substituents (Scheme 28).

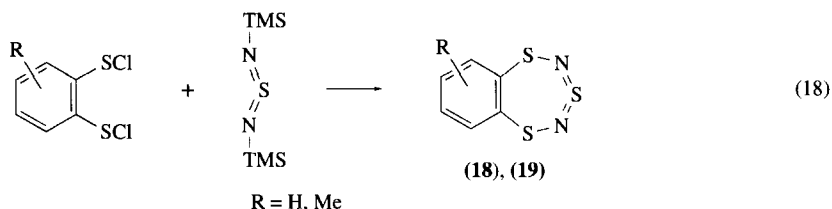
The results can be rationalized by FMO theory $\langle 88RHA204 \rangle$.



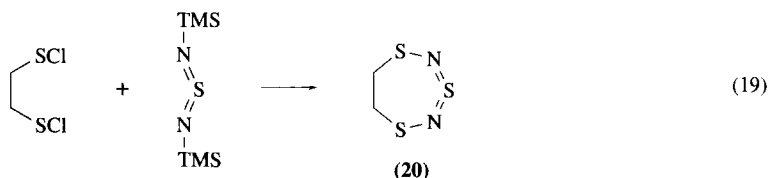
9.17.9.9.2 Type ($S-C-C-S + N-S-N$)

Another synthesis of 1,3,5,2,4-trithiadiazepines, based upon the reaction of benzo-1,2-bis(sulfonyl) chloride with bis(trimethylsilyl)sulfur diimide was initially devised for benzo-1,3 $\lambda^4\delta^2$ 5,2,4-

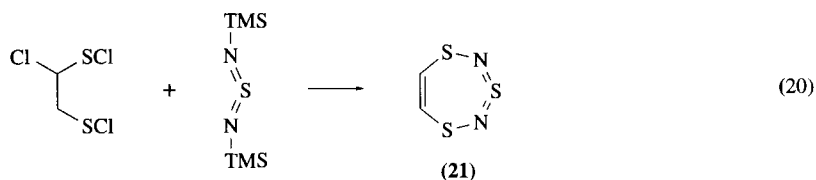
trithiadiazepine (**18**) <85CC396, 87JCS(P1)211>, which take the form of stable, bright yellow crystals (50%). The aromatic nature of (**18**) was supported by its spectral properties and was confirmed by x-ray. Its 7-methyl derivative (**19**) was prepared analogously in good yield. Analogous path of obtaining (**18**) was independently used in (Equation (18)) <86IC1137>.



This synthesis could not be extended directly to the monocyclic compound because of the instability of *Z*-ethene-1,2-dithiol and the associated difficulties of its chlorination to the bis(sulfonyl chloride). However, ethane-1,2-dithiol was readily and quantitatively converted into ethane-1,2-bis(sulfonyl chloride). Reaction of this compound with sulfur diimide in dichloromethane, as above, gave the orange dihydro derivative (**20**) (20%) (Equation (19)) <85CC396, 87JCS(P1)211>.



Trithiadiazepine (**21**) was obtained with spontaneous loss of hydrogen chloride, in 30% overall yield, from 1-chloroethane-1,2-bis(sulfonyl chloride) and sulfur diimide as before (Equation (20)) <85CC396, 87JCS(P1)211>. The spectral properties and x-ray diffraction of (**21**) support a fully delocalized structure.



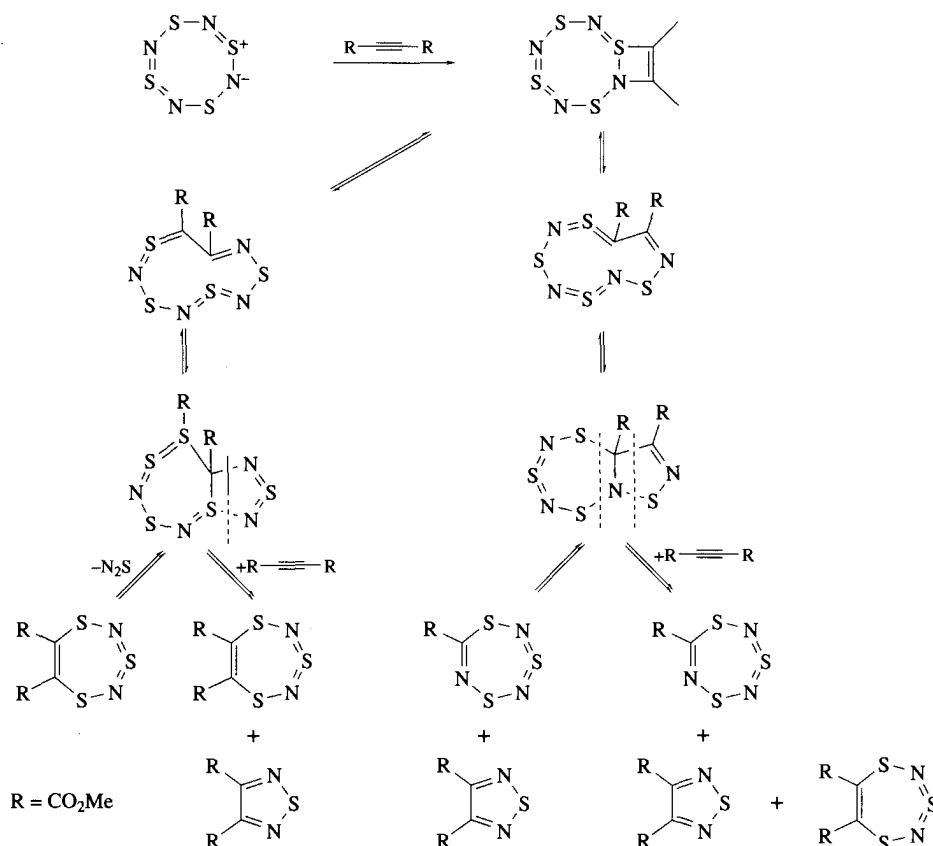
9.17.9.10 1,3,4,5,2,4,6-Trithiatriazepines

9.17.9.10.1 Type (N—S—N—S—N—S + C)

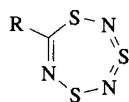
The first 1,3,4,5,2,4,6-trithiatriazepine (**17**) was described in <84CC55> and after that in following papers by Rees and co-workers. Schemes of the syntheses and some properties of this class of compounds are given in a series of reviews. Formation of the trithiatriazepine upon the interaction of tetrasulfur tetranitride with alkynes requires a more complex pathway for the reaction mechanisms. A concise route is shown in Scheme 29; with slight modification this route also leads to the trithiadiazepine <87JCS(P1)203>.

Trithiatriazepines with electron-withdrawing groups (**17**) and (**22**)–(**25**) were formed in very minor amounts in the reactions of substituted alkynes with tetrasulfur tetranitride <87JCS(P1)211, 87JCS(P1)1579, 87JCS(P1)1585, 89JCS(P1)1405>.

Numerous derivatives of trithiatriazepines and the parent 1,3,5,2,4,6-trithiatriazepine (**26**) were obtained by the conversion of the substituents at carbon ring atom (see Section 9.17.7.2).



Scheme 29

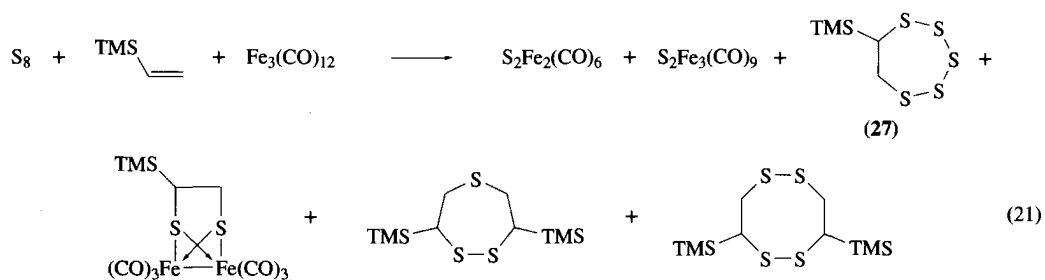


(17) R = CO₂Me; (22) R = CHO; (23) R = CO₂Et; (24) R = CO₂Bu; (25) R = MeCO

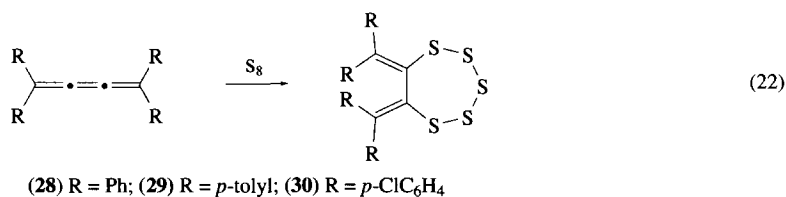
9.17.9.11 1,2,3,4,5-Pentathiepins

9.17.9.11.1 Type (S—S—S—S—S + C—C)

An unusual example of electrophilic addition to trimethylvinylsilane involved the iron carbonyl-catalyzed addition of elemental sulfur. The elemental sulfur reacts with excess trimethylvinylsilane under mild conditions (benzene, 55°C) in presence of Fe₃(CO)₁₂ giving 1-trimethylsilyl-2,3,4,5,6-pentathiepane (27), among the other products. These products were isolated chromatographically. The elemental sulfur in the absence of Fe₃(CO)₁₂ does not react with the alkene under conditions described (Equation (21)) <83JOU133, 83JOU143, 88T281>.

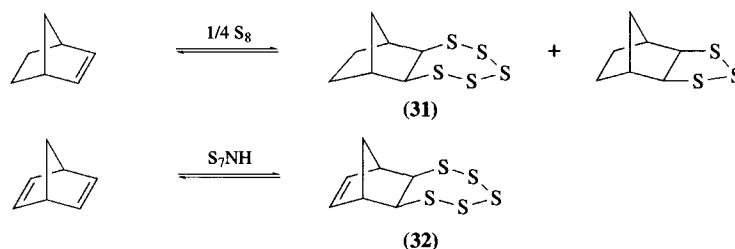


Sulfurization reactions of 1,1,4,4-tetraaryl-1,2,3-butatrienes with excess of elemental sulfur gave the 1,2,3,4,5-pentathiepine ring systems (28)–(30) (Equation (22)) <88TL1935, 91PS(58/59)179>.

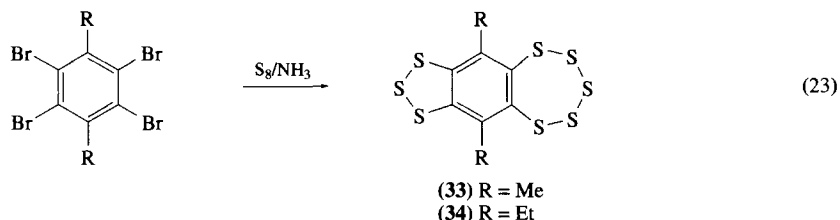


Norbornene reacts with elemental sulfur in DMF (100°C) to give the trithiolane and pentathiepan (31). Similar sulfuration has been observed for benzonorbornadiene and dicyclopentadiene. Under the relatively vigorous conditions of reaction between sulfur and norbornadiene, the pentathiepane (32) was not found among the products <87JOC4937>; however, the cyclic S₇NH is a more active sulfurating agent, and its reaction with norbornadiene yielded pentathiepane (32) (Scheme 30).

Trithiolobenzopentathiepins (33) and (34) were obtained by treatment of 1,4-dialkyl-2,3,5,6-tetrabromobenzenes with elemental sulfur in liquid ammonia (Equation (23)), under these conditions *o*-diiodobenzene gave (35) with low yield <89TL2453>.



Scheme 30



Unexpectedly, when 3,3-dimethyl-1-(2-carboxyphenyl)triazene was used, as benzyne precursor, in refluxing xylene, the S₄N₄ was consumed in three hours and benzopentathiepine (35) was isolated <87JCS(P1)211>. The S₄N₄ has clearly been extensively degraded in this unexpected reaction (Equation (24)).

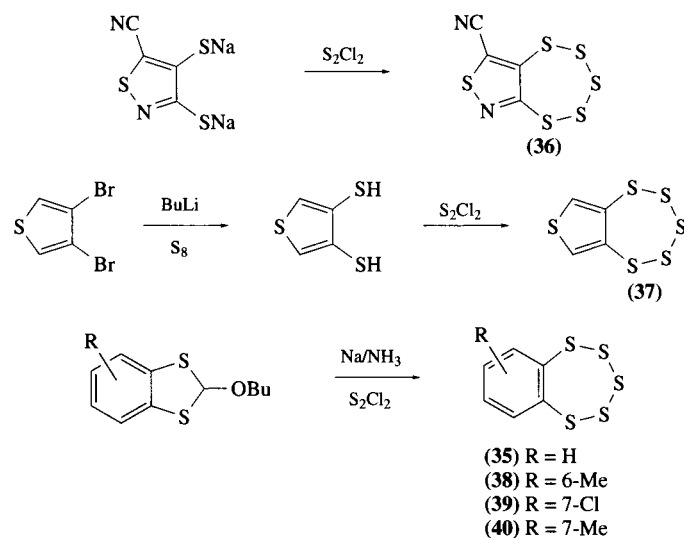


9.17.9.11.2 Type (S—C—C—S + S—S—S)

A series of aromatic and heteroaromatic fused pentathiepins has been prepared by reactions of S₂Cl₂ with vicinal dithiols or their salts. The dithiols can be generated *in situ* (Scheme 31) <80JOC5122, 84JOC1221, 85JA3871>.

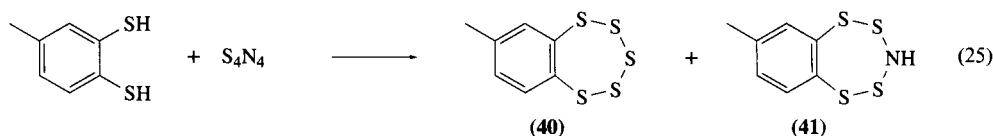
These results suggest that dithiol-sulfur chloride intermediates can readily equilibrate and that the pentathiepin structure may be a thermodynamically favored product.

Benzopentathiepin (35) has also been prepared from benzene-1,2-dithiol and trisulfur dichloride



Scheme 31

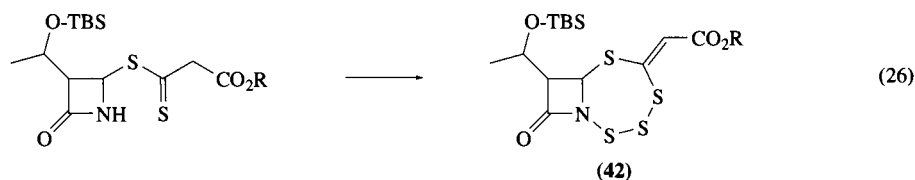
<71TL2125>. When toluene-3,4-dithiol was treated with S_4N_4 , 7-methylbenzopentathiepine (**40**) was obtained. According to the spectral data, the minor product was probably either the 3-aza (**41**) or its 4-aza isomer (Equation (25)) <87JCS(P1)211>.



9.17.9.12 1,3,4,5,6-Tetrathiazepines

9.17.9.12.1 Type ($S-C-S-C-N+S-S$)

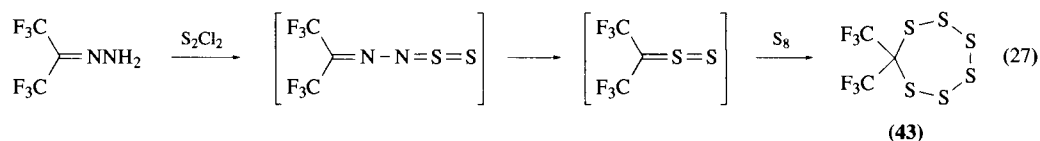
The β -lactams containing tetrathiazepine ring (**42**) were prepared by treating the dithioester with sulfur diphthalimide in the presence of triethylamine <91TL3771>. The products were, however, not rigorously characterized but could be converted to sulfenamide-containing β -lactam (Section 9.17.6) (Equation (26)).



9.17.9.13 1,2,3,4,5,6-Hexathiepanes

9.17.9.13.1 Type ($S-S+S-S-S-S+C$)

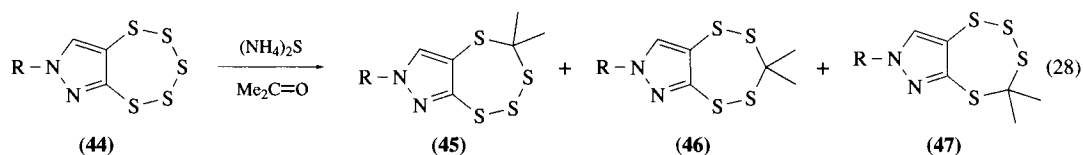
Interestingly, when hexafluoroacetone hydrazone was treated with disulfur dichloride at -23°C , a low yield of the hexathiacycloheptane derivative (**43**) was obtained, presumably via the reaction of an intermediate thiosulfine with sulfur (Equation (27)) <81BCJ3541, 82CR333>.



9.17.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

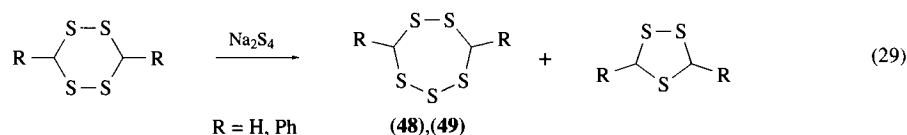
9.17.10.1 Tetrathiepins

Synthesis of the tetrathiepins (45)–(47) is effected by the reaction of pyrazolopentathiepin (44) with acetone in the presence of ammonium sulfide (87JOC2411). In general, a nearly statistical distribution of the ketone fragment in the S-2, S-3 and S-4 sites of the pentathiepin was found (Equation (28)).



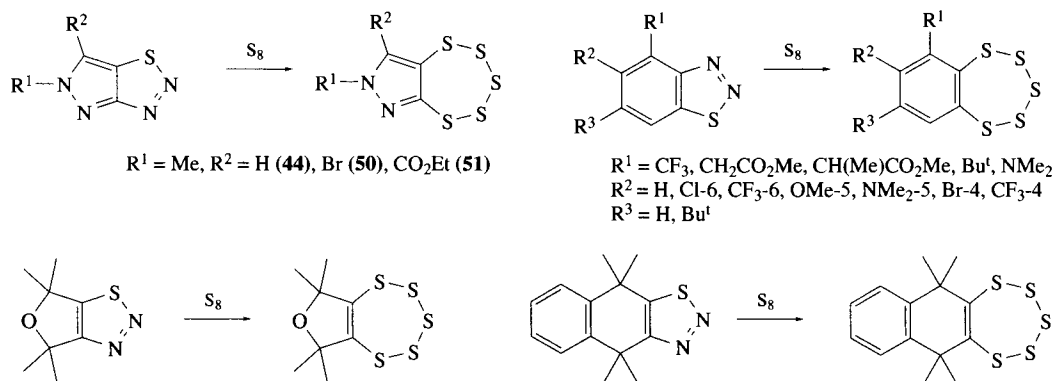
9.17.10.2 1,2,3,5,6-Pentathiepanes

When 1,2,4,5-tetrathianes were treated with ten equivalents of Na_2S_4 in DMF at room temperature, 1,2,3,5,6-pentathiepane (lenthionine) (48) or a *cis/trans* mixture of 4,7-diphenyl-1,2,3,5,6-pentathiepane (49) were isolated in 30% yield. This reaction may proceed through a pathway involving S—S bond cleavage of the tetrathione by nucleophilic attack (Equation (29)) (88CL1517).



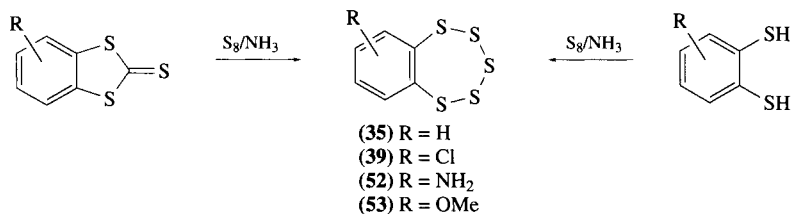
9.17.10.3 1,2,3,4,5-Pentathiepinines

A general route to pentathiepinines is the thermolysis of fused 1,2,3-thiadiazoles with sulfur has been described (Scheme 32) (84JOC1221, 84JOC1224, 85JA3871, 87TL4833, 88CL657, 90TL5323). It appears to be more useful and convenient for the preparation of benzopentathiepinines than the cyclization route proposed by Feher (79ZAAC(452)37).



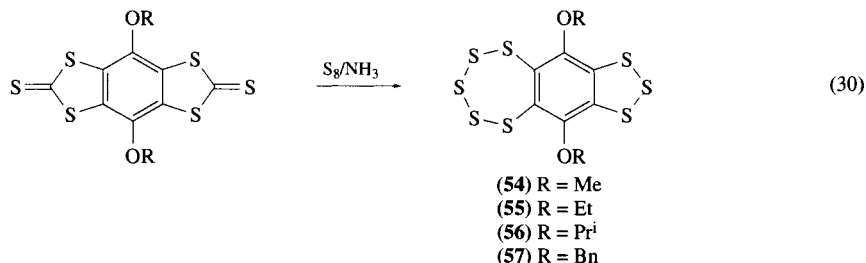
Scheme 32

Another route was proposed by Sato and co-workers. The synthesis of benzopentathiepins (**35**), (**39**), (**52**), and (**53**) was carried out by reactions of corresponding 1,3-benzodithiole-2-thione or 1,2-benzenedithiol with elemental sulfur in liquid ammonia <86CL349, 88BCJ1647, 90YKG797>. Perhydrobenzopentathiepine (**49**) was obtained analogously (Scheme 33) <88BCJ1647>.



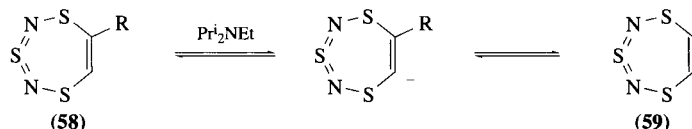
Scheme 33

This method was used for the direct synthesis of new cyclic polysulfides 6,10-disubstituted-1,2,3-trithiolo[5,4*H*]benzopentathiepins (**54**)–(**57**) (Equation (30)) <88TL6291>.



9.17.10.4 Trithiadiazepynes

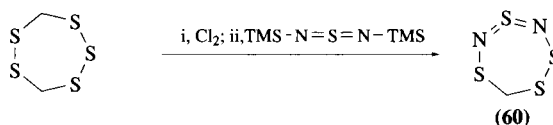
6,7-Dehydrotrithiadiazepyne (trithiadiazepine) (**59**) is readily generated from 6-bromo-trithiadiazepine (**58**) with Hünig's base or sodium methoxide (Scheme 34). Formation of the highly stabilized carbanion and the hetaryne (**59**) was established by deuterium exchange, competition experiments, and generation of (**59**) from 6-chloro, -bromo, -iodotrithiadiazepine <89PS(43)261, 90CC1317, 91JCS(P1)301> (see Section 9.17.5.5).



Scheme 34

9.17.10.5 1,2,4,6,3,5-Tetrathiadiazepines

The tetrathiadiazepine (**60**) was obtained by chlorination of lenthionine in tetrachloromethane at 0°C, followed by cyclization with bis(trimethylsilyl)sulfur diimide to give two products. The first was trithiadiazine (12%) and the second was an orange solid which, on the basis of its mass spectrum, was tentatively assigned structure (**60**) (20%) <90JCS(P1)509>; this presumably arose from incomplete sulfur–sulfur bond cleavage by chlorine (Scheme 35).



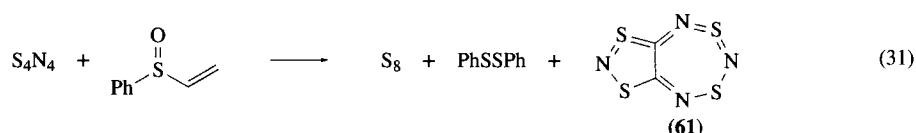
Scheme 35

9.17.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF VARIOUS ROUTES AVAILABLE

9.17.11.1 $1\lambda^4\delta^2,3,5,7\lambda^4\delta^2$ -Tetrathia-2,4,6,8-tetraza-2a-azulene

9.17.11.1.1 Type ($N-S-N-S-N+C-C+S-N-S$)

When S_4N_4 was heated with phenyl vinyl sulfoxide, no trithiadiazepane was formed; the main products were sulfur, diphenyl disulfide and $1\lambda^4\delta^2,3,5,7\lambda^4\delta^2$ -tetrathia-2,4,6,8-tetraza-2a-azulene (**61**) (Equation (31)) <85CC1654>.



9.17.11.2 Critical Comparison of the Various Routes Available

Synthesis of many classes of seven-membered heterocycles with four or more heteroatoms is based on the traditional approach, namely the step-by-step introduction of heteroatoms into the molecule, followed by cyclization (e.g. see Section 9.17.9.5). However a general route to 1,3,5,2,4-trithiadiazepines has been developed. Most of these heterocycles are obtained by the addition of alkynes containing the electron-withdrawing groups to tetrasulfur tetranitride. In spite of some restrictions, this new approach starting with the ring composed wholly of heteroatoms appears to be most useful for the synthesis of heterocycles with a high proportion of heteroatoms <88RHA204>. It also allows the synthesis of 1,3,5,2,4,6-trithiatiazepines. Owing to the high stability of these sulfur–nitrogen containing ring systems, the conversion of the substituents is also a useful synthetic method (see Section 9.17.7.2).

The direct and general route to 1,2,3,4,5-pentathiepins and pentathiepanes is the interaction of elemental sulfur with fused 1,2,3-thiadiazoles or 1,3-dithiol-2-thiones, alkenes, and *o*-dihalobenzenes at elevated temperatures or in the liquid ammonia.

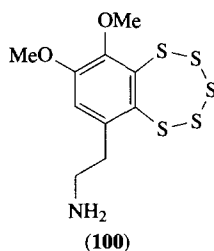
Furthermore, a wide range of cyclic polysulfides has been isolated from the natural products (see Section 9.17.12).

9.17.12 IMPORTANT COMPOUNDS AND APPLICATIONS

Seven-membered cyclic polysulfides are of great interest owing to their diversity in nature and their biological activity. The most known of which is 1,2,3,5,6-pentathiepan lenthionine (**48**) <66TL573, 81TL1939>.

From the intact cells of the sulfur-metabolizing hyperthermophilic archaea *Thermococcus tadjuricus* and *Thermococcus acidaminovorans*, several mono- and disubstituted 1,2,3,5,6-pentathiepanes were isolated. Furthermore, 7-methyl- and 7-*i*-butyl-1,2,3,4,5,6-hexathiepanes were detected by LC–MS <93MI 917-01>.

A novel benzopentathiepin (**100**) was isolated from *Lisso clinum* Vareau <91JA4709>. Later, analogous compounds were synthesized in eight steps from vanillin <94JOC5955>.



Lenthionine (**48**) and varacin (**100**) exhibit antifungal activity; varacin also exhibits cytotoxicity toward human colon cancer HCT <81TL1739, 91JA4709>.

The influence of sulfur compounds (including the 1,2,3,5,6-pentathiepane) on wine quality has been discussed in detail <93MI 917-01>.

Different 1,2,3,4-tetrathiepanes were detected by MS in garlic oil <92MI 917-01>.

1,2,3,4,5-Benzopentathiepin is used as a sulfurization reagent (see Section 9.17.5.6).

A brief total synthesis of 2,3,5,7,9-pentathiadecane 2,2-dioxide exhibiting the bactericidal, fungicidal, and neoplasm inhibitory activity, is reported from 1,2,4,6-tetrathiepane <94JOC2273>.

1,2,3,4,5-Pentathiepins and pentathiepanes are used as antifogging agents in photographic materials <90JAP02157745, 90JAP02256046>.

9.18

Eight-membered Rings with One Nitrogen Atom

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9.18.1 INTRODUCTION

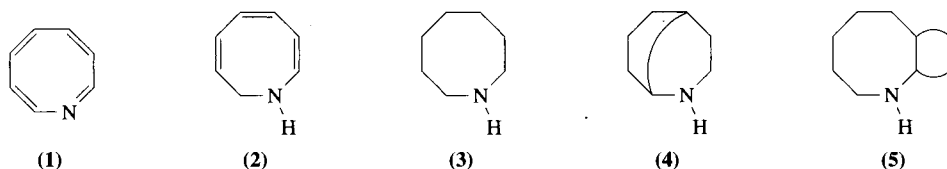
Medium-sized nitrogen heterocycles are an extremely important class of compounds. The term "medium ring" is usually used to refer to alicyclic compounds with a ring size of from 8 to 11. The primary concern of this chapter is eight-membered azaheterocycles, azocines. Azocines are a diverse class of compounds, that frequently occur as biologically active compounds as well as being widely used in synthetic chemistry. Although foundations providing pioneering work on azocines had been started in the 1920s and 1930s <26HCA249, 33LA(504)94>, only limited systematic or comparative studies of azocines as a class have been done. Azocines have received more attention because of their increasing usefulness both as synthetic intermediates and as therapeutic agents. Reviews cover the following topics: a comprehensive account <82CHEC653>, a systematic overview <82AHC(31)115>, and syntheses <85YKG603, 87MI 918-01, 89MI 918-01, 91T9131> of azocines and their derivatives. In order to avoid repetition as well as to cover all the relevant literature available, some sections such as experimental, theoretical, and thermodynamics are grouped together in some instances.

9.18.1.1 Scope

This chapter details the nomenclature, thermodynamics, reactions, and synthesis, and summarizes the experimental structural methods and applications in the following order: (i) unsaturated, partially saturated, fully saturated monocyclic azocines, (ii) benzazocines, and (iii) dibenzazocines. The nitrogen bridged systems and unique compounds are not given detailed treatment owing to space limitations.

9.18.1.2 Structure and Nomenclature

Eight-membered rings with one nitrogen atom can be classified broadly into five categories: unsaturated, partially saturated, fully saturated, bridge-head, and fused ring systems (1)–(5). The most commonly used systematic nomenclature for eight-membered heterocyclic compounds is the Hantzsch–Widman system <83MI 918-05>. According to this system, the compound (1) with four noncumulative double bonds is named azocine, with the prefix "aza" indicating the nitrogen atom, followed by the stem "ocine" indicating the ring size and unsaturation. The nitrogen atom takes the atom number one. Partially saturated systems are expressed by the prefixes dihydro-, tetrahydro-, hexahydro-, and octahydro- with azocine. For example, (2) is named 1,8-dihydroazocine. The fully saturated system (3) is named "azocane" or "perhydroazocine". The names azacyclooctane and heptamethyleneimine have also been used in the literature. The most prevalent term is 'azocine' with suitable prefix(es).



9.18.2 THEORETICAL METHODS

Since the theoretical aspect of heterocycles is a new addition to this series, it is discussed here in greater detail. Although eight-membered aza heterocycles have been known since 1906, theoretical studies on these systems only occurred from 1960. The conformational property of eight-membered aza heterocycles is also of utmost importance in understanding their synthesis and reactions.

A comparative calculation study was performed for cyclooctanone (**6**), octahydroazocine (**7**), and hexahydroazocin-5-one (**8**) using MM2 and MNDO. For discussion purposes, the proposed graphical representation of possible conformations by Dunitz and Prelog ^{<60AG896>} is used (Figure 1). The most symmetrical heterocycle possesses a crown conformation and there are boat-chair (BC), chair-chair (CC), boat-boat (BB) and other forms. In most cases, the position of the individual ring atoms is not equivalent; therefore, additional conformations have to be taken into account. Moreover, twisted forms of the above-mentioned conformations might be more stable than the more noticeable conformations. The calculated heats of formation, ΔH_f , are summarized in Table 1.

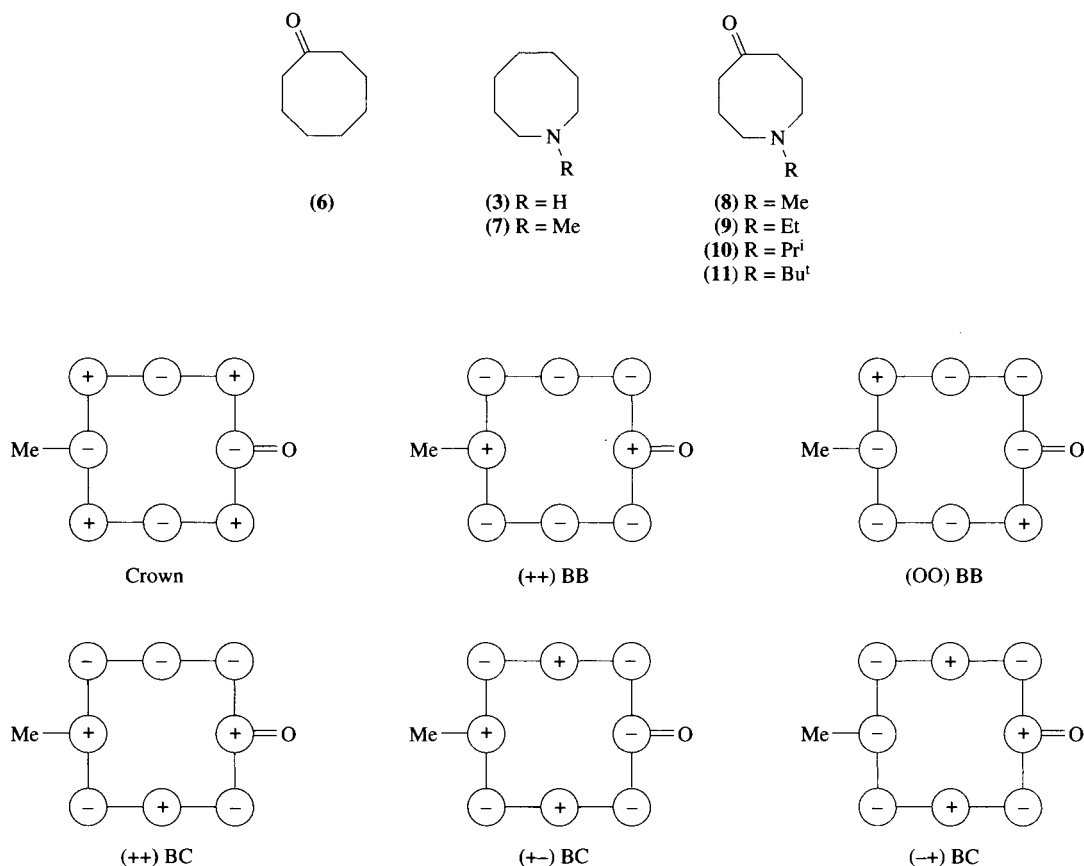


Figure 1 Graphic representation of possible conformations.

Table 1 Heats of formation (kJ mol^{-1}) by the MM2 method.

Conformation	Compounds		
	(1)	(3)	(4)
Crown	-239.9	-43.4	-155.9 (-169.4 ^a)
(+ + BB)	-236.6	-51.6	-172.8 (-154.4 ^a)
(OOBB)	-225.7	-36.0	-151.2
(+ + BC)	-246.7	-51.2	-171.3 (-163.9 ^a)
(+ - BC)	-239.8	-46.7	-162.7
(- + BC)	-235.9	-56.2	-169.5
(OOBC)	-241.2	-46.4	-162.3

^aMNDO results.

The most stable conformer for (**6**) is (+ +)BC and for (**7**) is (- +)BC. These calculated results for (**6**) and (**7**) are in good agreement with other calculations and stereospecific measurements ^{<72T1173, 74T1629, 75JOC369, 77CC939, 78JCP(69)268, 81T3981>}. For (**8**), three conformations are found to be rather close in energy: (+ +)BB, (+ +)BC, and (- +)BC. Hence, (**8**) forms an equilibrium of

three conformers; however, this is not in accord with spectroscopic findings. By NMR spectroscopy, the BC form exists in aprotic solvents and the BB form may exist in strong hydrogen bonding solvents <79CHE699>. Because transannular interactions are an important parameter in determining the conformational properties, MNDO calculations have been executed for higher reliability. The results (Table 1) show that the most stable conformer is that of the crown (5.5 kJ mol^{-1}), in which it is more stable than the (+ +)BC form. There is further argument based on dynamic NMR data, estimating an upper limit of 30 kJ mol^{-1} for the transannular interaction between amino and carbonyl groups in an eight-membered ring <76JCS(P1)913>. Compared with the standard energy of a N—C single bond, 292 kJ mol^{-1} , this value corresponds to a virtual bond order of 0.10. This interaction is neglected by both theoretical methods. Transannular interactions will be favored, when the two functional groups are in close proximity, allowing significant orbital overlap. The results on distance between the two functional groups exclude the crown form, since it has the greatest value (393 pm), even though it is favored by the MNDO method. But the (+ +)BB and (+ +)BC forms have values of 276 pm and 286 pm, respectively, which are rather low. MM2 calculations for (9)–(11) showed that the (+ +)BC conformation was the most stable conformer. The results of x-ray and MM2 calculations revealed that transannular amide resonance in (11) is possible: if all atoms except hydrogens are fixed at their experimental position, an additional steric energy of 11.8 kJ mol^{-1} is calculated, and that has to be compensated by transannular attractions. This energy indicates a N—C bond order of 0.04 <87JOC3362>.

Using a novel NMR shift reagent, for example cobalt(III)meso-tetraphenyl porphyrin (CoTPP), the conformation of (3) is found to be a mixture of many conformations. Theoretical and experimental results revealed ring current shift for (3) <90MRC343>. Electronic structure and conformational properties of the amide linkage were studied in lactams based on MNDO calculations and photoelectron spectroscopy <85MI 918-01>.

Molecular connectivity is a simple and useful method for quantitating the structure of heterocycles. Molecular connectivity for 56 *N*-bridged compounds was calculated and correlated with the octanol–water partition coefficient. Steric effects caused deviations from the LFER (Linear Free Energy Relationship) <83MI 918-01>.

Reduction of 3,8-dimethyl-2-methoxyazocine (DMMA) in HMPA with sodium metal leads to the formation of dianion radical and was detected by ESR. The coupling constants are in good agreement with INDO calculations. It is interesting that the vast majority of the spin density is on positions 2, 4, 6, and 8 of the ring system. The introduction of the nitrogen in the ring system of cot appears to have the same effect upon the spin density as putting an electron-withdrawing group on the eight-membered ring <83JA6078>.

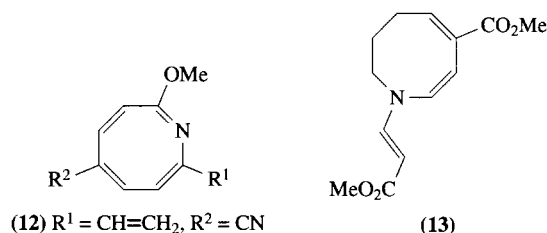
9.18.3 EXPERIMENTAL STRUCTURAL METHODS

Various experimental methods have been used to elucidate the structures of eight-membered rings with one nitrogen atom, to study their conformational properties or to understand their molecular interaction with biological molecules. A brief account is provided on the available methods.

9.18.3.1 X-ray Diffraction

X-ray diffraction studies on (12) revealed that the dimensions of the molecules are as expected. The conformation of the ring showed atoms N(1), C(2), C(5), C(6) planar and C(3), C(4), C(7), C(8) coplanar both within $0.02 \text{ \AA}$. The two planes are $0.81 \text{ \AA}$ apart and approximately parallel (angle of intersection $2.2(1)^\circ$) <85CC85>.

The structure of hydroazocine (13) was confirmed by x-ray diffraction analysis along with ^1H NMR results <87CC1296>.



X-ray diffraction data confirmed the structure of the (*S*)-enantiomer of methyl 5-hydroxy-3,11-di-2 pyridyl-4,5-dihydro-1*H*,3*H*-2,6-methano-6-benz[*c*]azocine carboxylate of the camphanic ester <88ZN(B)901>. The relative configuration, in similar such systems, was determined by ^1H and ^{13}C NMR <89AP(322)21>.

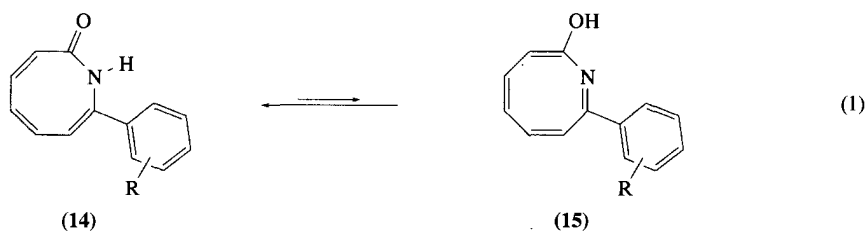
X-ray diffraction studies on dibenz[*b.g*]azocine and dibenz[*b.g*]azocinone have been reported <83AX(C)768, 87JOC2980>.

9.18.3.2 NMR, IR, and UV Spectroscopy

Proton NMR data on fully unsaturated tautomeric azocines (**14**) and (**15**) are provided in Table 2 (Equation (1)) <90JHC1323>.

Table 2 Proton NMR results.

Compound R	NMR (CDCl_3)		IR (KBr) cm^{-1}	UV/Vis (CH_3CN)		
	(ppm)	(No. of protons) Assignment		ν	max (nm)	ϵ
H	6.72m	(1) H-5	1660	C=C	310	1960
	7.06m	(1) H-4	3300	N—H		
	7.20dd	(1) H-7				
	7.32m	(1) H-6				
	7.38–7.50m	(5) Ar-H				
	7.75dd	(1) H-3				
<i>o</i> -OCH ₃	9.25b	(1) N-H				
	3.90s	(3) OCH ₃	1600	C=C	324	1680
	6.70m	(1) H-5	1670	C=O	420	418
	6.95m	(3) Ar-H, H-4				
	7.22dd	(1) H-7				
	7.32m	(1) H-6				
	7.51m	(2) Ar-H				
	7.75dd	(1) H-3				
	9.25s	(1) N-H				



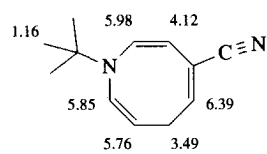
Carbon-13 and ^1H NMR chemical assignments <87TL2517> for a few hydroazocines are designated in Structures (**16**)–(**19**) (where “a” represents ^1H NMR and “b” represents ^{13}C NMR). For other hydroazocines, ^1H NMR data was reported <81JCR(S)306, 82MI 918-01, 82T1579, 83TL5731, 86AJC687, 86JOC3652, 87JOC2929, 88JOC2226, 90SL584, 91JCR(S)46, 94JCS(P1)3557>.

Conformational analysis of perhydroazocine (**3**) was accomplished using a novel cobalt(III) porphyrin shift reagent (see Structures (**3a**) and (**3b**)) <90MRC343>. The structure of the *N*-benzyl derivative of perhydroazocine was elucidated by ^{13}C NMR <81AJC2307>. Natural abundance of ^{17}O NMR data for 30 lactones and 36 lactams in acetonitrile at 75°C was reported <89H(29)301, 89H(29)307>.

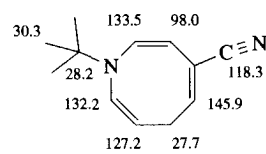
Using ^{19}F NMR data, direct fluorination on heptamethyleneimine was interpreted <90JFC(50)15>.

Proton NMR results and discussion have been provided for benzazocine derivatives <83TL413, 84H(22)355, 84H(22)1771, 84JA5378, 84JMC816, 84JOC953, 86JCS(P1)1533, 86JCS(P1)1977, 87S727, 88JOC5355, 89JCS(P1)1931, 89T5917, 90H(31)1769, 90JCS(P1)1083, 90JCS(P1)1091, 91H(32)2089, 91JCS(P1)353, 91JHC1625, 92OS(70)139, 94H(38)751>.

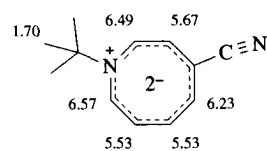
Eight-membered Rings with One Nitrogen Atom



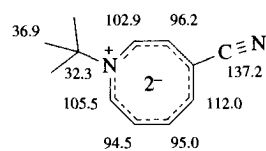
(16a)



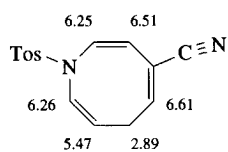
(16b)



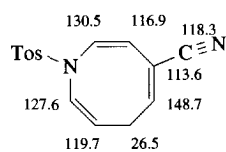
(18a)



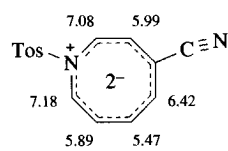
(18b)



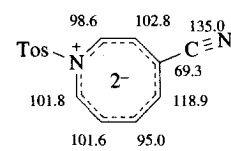
(17a)



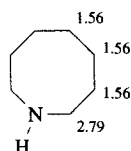
(17b)



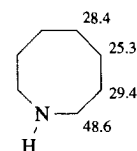
(19a)



(19b)



(3a)



(3b)

NMR results facilitated the structural elucidation of dibenzazocines <73JCS(P1)205, 84JCS(P1)2013, 85H(23)159, 85H(23)895, 87JOC2980, 88JHC161, 94JOC148>.

The NMR technique detected anions of *N*-methyl-1-benzazocinide and indicated the extensive charge delocalization in 1-benzazocindiide, and dibenz[*b,g*]azocindiide <82AG803>.

9.18.3.3 Mass Spectrometry

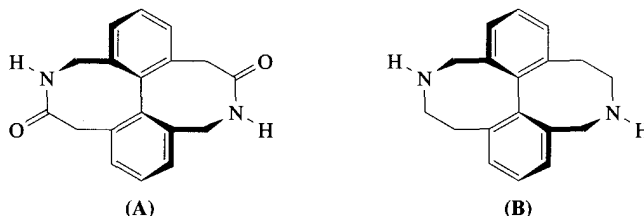
A series of *N*-tosylated azacycloalkanes was studied using mass spectrometry. The $[M + H]^+$ ions of chosen compounds decomposed in the time frame of metastable peak observation, along with three main competitive unimolecular channels common to all ring sizes: (i) rupture of the S—N bond to give the $\text{MeC}_6\text{H}_4\text{SO}_2^+$ ion (m/z 155) and the neutral amine; (ii) ring rupture leading to a common peak at m/z 184, corresponding to the $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NH}=\text{CH}_2$ ion; and (iii) formal loss of the *p*-toluenesulfonic acid. Correlations were found between ionic energies and ring size for the first pathway, and between strain energy and ring size for the second pathway <89OMS(24)291>.

9.18.3.4 Other Techniques

The absorption and fluorescence properties of *N*-substituted azacycloalkanes have been reported <85JCS(P2)1063>.

The liquid crystal method is a sensitive method in studying the stereochemistry of optically active

substances, and sometimes complementary to CD spectroscopy. Conversion of nematic liquid crystals to a cholesteric mesophase may be achieved by adding a small quantity of optically active molecules. Investigation of the nematic phase of (A) and (B) was accomplished and their absolute configurations were expressed in terms of helicity (i.e., R (A) and R (B) had nematic phase, +58 and +19, 8 E₇; biaryl helicity, P, and cholesteric helicity, P) <87T1425>.



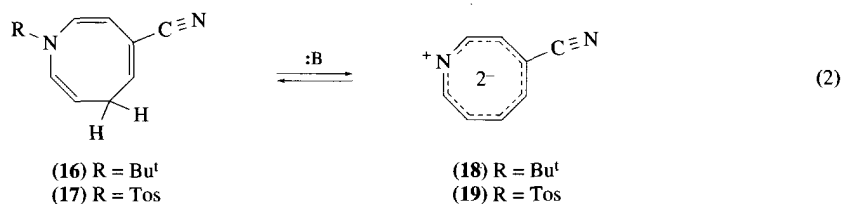
Separation of nitrosoperhydroazocine as well as its α -substituted derivatives from other nitroso-azaheterocycles was accomplished by HPLC using cyclobond I column and a mobile phase of methanol/water <86JLC1783>.

Using cyclic voltametry, the electrochemical properties of the enamines of the cyclic ketones with perhydroazocines as well as with other cyclic amines were studied. The anodic peak potentials depend upon the ring size of the amine reacted ($5 < 7$; $8 < 6 < 1$ -methyl piperazine < morpholine) <88JCS(P2)369>.

9.18.4 THERMODYNAMIC ASPECTS

9.18.4.1 Azocines

"Aromaticity" and availability of the nitrogen lone-pair electrons are always questions of interest in π -excessive heteroannulenes. Addition of two electrons to the completely unsaturated azocine (1) or removal of proton from a dihydroazocine (2) can lead to a dianion or monoanion, respectively, each of which is a 10π -electron system, corresponding to " π -equivalent" and " π -excess" analogues of cyclooctatetraene. Both of these processes have been demonstrated <82CHE653>. Dianions (18) and (19) were formed, respectively, by reacting (16) and (17) with Schwesinger's strong base, nonionic phosphonimine $R_3P=NCH_3$ (pK_a 27.5 in CH_3CN) (Equation (2)). Proton and ^{13}C NMR data indicated efficient enamine resonance with the butadiene rather than the ethylene section of the molecule and thus (16) exists in quasi-half-chair conformation. Contrastingly, the dianions (18) and (19) exhibited planarity or diatropicity <87TL2517>.

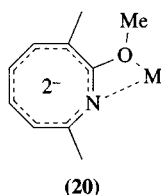


The stability of potassium salt of cot dianion is due to solvation and lattice effect. Substitution of a nitrogen atom for one of the carbon atoms in the eight-membered ring system resulted in an increase in the energy of the THF solvated dianion, relative to the metal and neutral and organic compound, due to an increase in the electron-electron repulsion in the dianion <84JPC5417>.

9.18.4.2 Hydroazocines

Alkoxyazocines exist in tub conformation without conjugative stabilization, but its dianions, obtained by electrochemical or chemical reduction, exist in aromatic planar conformation <71JA161, 71JA168>. The existence of 3,8-dimethyl-2-methoxyazocine (DMMA) dianion radical (20) along with its electron distribution and thermodynamic stability were reported for the first time in 1983 <83JA6078>. Reduction of DMMA in HMPA with metal sodium or potassium yielded an anion

radical, but in THF resulted in only a diamagnetic solution that is devoid of an anion radical. Both anion and dianions are associated with cations in THF while there is no association with cations in HMPA; this absence of ion association makes it possible to detect $\text{DMMA}^{\cdot-}$. Thermodynamic stability of DMMA dianion in comparison with related systems was studied by calorimetry. Thermodynamic parameters for disproportionation for $\text{DMMA}^{\cdot-}$ in the absence of ion association is $\Delta H_{\text{disp}}^{\circ} = +7.0 \pm 1.0 \text{ kcal mol}^{-1}$; $K_{\text{disp}} (0^{\circ}\text{C}) (1.3)10^5$ and for $\text{cot}^{\cdot-}$ is $\Delta H_{\text{disp}}^{\circ} = +4.6 \pm 0.7 \text{ kcal mol}^{-1}$; $K_{\text{disp}} (0^{\circ}\text{C}) (7.5)10^2$. K_{disp} for $\text{DMMA}^{\cdot-}$ is higher than for $\text{cot}^{\cdot-}$ because of ion association in such solvents. The stability of dianion is enhanced by the cation sandwich (20) between nitrogen and oxygen atoms in the solid state. The crystal lattice energy of solid dianion salts appears to play a more dominant role in controlling the heat of formation from the neutral molecules and sodium metal than do aromaticity considerations and the effect of the nitrogen upon the aromatic character of the dianion <83JA6078>.



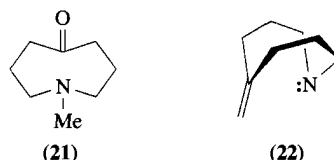
Conformational behavior of 1-alkyl-1,2,3,4-tetrahydroazocin-2-ones was studied by using dynamic ^1H NMR. The T_c (-60 to 40°C) and $\Delta G_c^{\ddagger}$ (10.3 – $10.9 \text{ kcal mol}^{-1}$) values were reasonably explained as being due to the ring inversion associated with rotation of the $\text{N}-\text{C}$ α -bond. The temperature-dependent chemical shifts were due to population changes in the chiral azacinone ring systems, where steric hindrance due to the 3-substituent plays a major role <82JOC1564>.

9.18.4.3 Perhydroazocines

It is well known that conformational effects influence a variety of regiochemical and stereochemical reactions. A rational approach has been initiated to control these transformations for synthetic purposes. Lithiation studies on the *N*-benzyl lactam along with other medium-sized azaheterocycles showed variation to the site of metallation (α to the carbonyl group or α to nitrogen) and is due to their conformations. *C*-Alkylation had occurred only on the α -carbon to nitrogen unlike in five-, six-, nine-, eleven-, and thirteen-ring azaheterocycles. For the eight-membered ring, the minimum conformational energy may not allow H_A or H_B to assume the alignment and thus metallation by benzylic proton is kinetically favored <87JA4405>.

Transannular interaction is a unique feature of medium-sized heterocycles. The chemistry of such compounds with two functional groups in appropriate position(s) may be dominated by transannular interaction(s). The HeI photoelectron spectral technique was used to study the transannular interaction and conformation in cycloaminoketone and cycloaminoalkene. In the lower energy region (10 eV) of the PE spectra, two ionization bands were found for the amino ketones; one for n electrons on the amino group (n_N) and the other for n electrons on the carbonyl oxygen group (n_O). It was not possible to identify the bands due to the ionization of the $\pi\text{C}=\text{O}$ electrons. The results (large shift) indicate that n_O ionization can be considered as an indicator of transannular interaction(s) for aminoketones. Aminoalkene (22) is isoelectronic with aminoketone (21). Aminoalkenes are much better suited for PE spectroscopy, since both interesting MO's n_N and $\pi\text{C}=\text{C}$ are accessible in the lower energy range of the spectrum. For aminoalkenes, the degree of interaction is measured by the shifts of the n_N and $\pi\text{C}=\text{C}$ orbitals. In total, the results indicate that considerable n/π interactions occur in eight-membered rings. This is consistent with IR results ($\text{C}=\text{O}$ frequency is 20 – 30 cm^{-1} lower than cyclic ketone) indicating that the partial single bond character of the $\text{C}=\text{O}$ is due to the transannular amide resonance. In aminoalkene, $\text{C}=\text{C}$ stretching vibration is located at 1625 cm^{-1} indicating a weaker $\text{C}=\text{C}$ bond due to the transannular interaction with the amino group. This transannular interaction may be due to the preferred conformation (22), which brings close contact between the two functional groups. Such a transannular aminoalkene interaction in an eight-membered azaheterocycle was reported for the first time in 1986 <86JOC592>. Transannular interaction in medium-sized azaheterocycles was studied by ^{13}C and ^{17}O NMR spectroscopy. In the aminoketone, chemical shifts of ^{13}C and ^{17}O of the carbonyl group changed to 11 ppm (^{13}C) or 81 ppm (^{17}O) relative to the corresponding cycloalkanone. The observed effects ΔC and ΔO were

linearly correlated $\langle 88\text{JCS(P2)2119} \rangle$. The ionization potential of the lone-pair electrons of nitrogen was determined for *N*-tolylsulfonyl azacycloalkanes by gas phase ultraviolet spectroscopy. The ionization potentials (IPs) are affected by the strain present in the ring. More precisely, the IPs reflect changes of hybridization of the *N*-lone-pair electrons upon varying the ring size, whereby a lower or higher energy is required for the ionization process of the cyclic compounds relative to a series of open-chain alkylamines $\langle 86\text{JCS(P2)667} \rangle$.

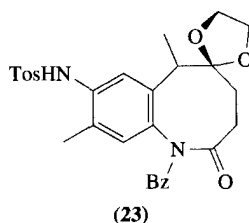


Ruthenium tetroxide (RuO_4) oxidation of *N*-alkyllactams proceeded regioselectively depending on the size of the lactam ring, except for the seven-membered ring. Four- and eight-membered *N*-methyl and *N*-ethyl lactams were oxidized at the exocyclic α -carbon adjacent to nitrogen to produce the *N*-acyllactam and *NH*-lactam. Regioselectivity was confirmed in the oxidation of substrate having a tertiary carbon at the oxidation position $\langle 87\text{CPB357} \rangle$.

Hydrolysis of the enantholactam in 0.5–65% H_2SO_4 at 59.5–94°C indicated that two mechanisms are operating: (i) via complexation of the lactam with H_3O_2^+ , and/or (ii) via a complex of the protonated lactam with a water molecule $\langle 83\text{ZV777} \rangle$.

9.18.4.4 Benzazocines

Ketal (**23**) consists of two stereoisomers. X-ray crystallography and ^1H NMR data indicate a twist-boat chair conformation is thermodynamically favored over the twist-boat. The energies of activation for the interconversion were estimated to be 26.6 kcal mol $^{-1}$ (twist-boat chair to twist-boat conformation) and 25.2 kcal mol $^{-1}$ (twist-boat to twist-boat chair conformation) at 25°C $\langle 84\text{JA5378} \rangle$. Conformational studies on similar such ketals have been reported. These conformational isomers were easily separated by chromatography and their structures were elucidated by x-ray analysis. In refluxing benzene, the pseudoaxial conformer isomerized to the thermodynamically more stable pseudoequatorial conformer $\langle 88\text{JOC5355} \rangle$.



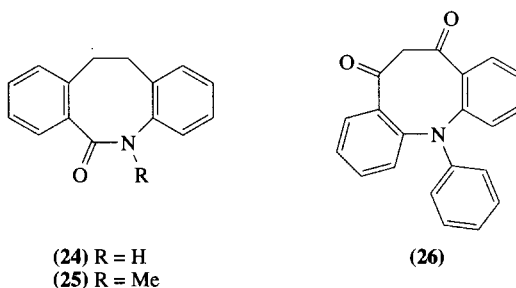
9.18.4.5 Dibenzazocines

Conformational studies on dibenzazocines were performed to understand the molecular interaction between the compounds studied and the biological molecules.

Conformational studies on [*c.e*] and [*c.f*] systems are discussed based on ORD and NMR spectral data, respectively $\langle 82\text{AHC(31)115} \rangle$.

Dibenz[*b,f*]azocine derivative exists in three possible conformations, chair, boat, and twist-boat in solution but in solid state, it has been shown to assume only one conformation, the chair form $\langle 73\text{JCS(P1)205} \rangle$. Proton NMR spectral data supported the half-tub conformation of the tetrahydroazocine ring and the quasi-equatorial configuration of the 8-hydroxy group of 8-hydroxy-5,6,7,8-tetrahydrodibenz[*c,e*]azocine $\langle 89\text{CPB870} \rangle$. The conformational behavior of the *N*-substituted dibenz[*b,f*]azacinone (**24**) in solution by dynamic NMR studies suggested that it exists in an inverted boat-boat form $\langle 74\text{CS52} \rangle$. NMR line shape analysis is a powerful technique for solving the subtle problems posed by compounds like the dibenzazocinones. The temperature dependence of NMR spectra and the computer simulation of Eu(fod)_3 induced resonance shifts (LIS) are useful in

determining the preferred configuration and conformation of the systems. The temperature dependence studies revealed that the observed kinetic process was due to the inversion of the central octaatomic ring which involves a rigid chair and/or mobile boat and twist-boat conformation with all of the series of possible state geometries. In these systems, ring inversion is a slower process than nitrogen inversion. The total line shape method showed that the free energy of activation indicate that (24) ($\Delta G^\ddagger = 13.9$ kcal) has greater ring mobility than (25) ($\Delta G^\ddagger = 21.2$ kcal). resonance shift and LIS simulation data revealed that the greater mobility of (24) is mainly due to $\Delta S^\ddagger$ and the lower mobility of (25) is due to $\Delta H^\ddagger$. Electronic factors can play an important role in determining the ring mobility of the central octaatomic ring of dibenzazacinone systems <85H(23)895>. Chemical properties of the diketone (26) are significantly influenced by the twist-boat conformation of the eight-membered ring. The methylene protons in the diketone are nonexchangeable because it is energetically prohibitive to form the endocyclic enol <87JOC2980>.



9.18.5 REACTIVITY AND REACTIONS

9.18.5.1 Azocines

Reference should be made to Section 9.18.4.1.

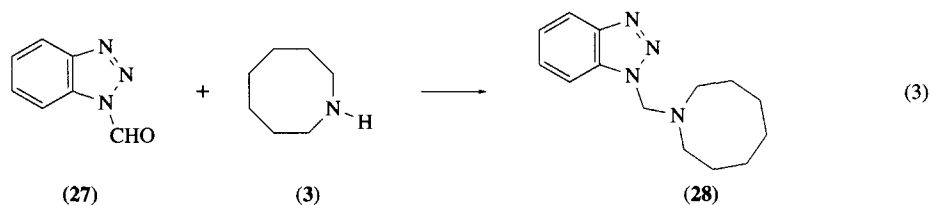
9.18.5.2 Hydroazocines

Highly functionalized pyrrolizidines are obtained via several sequences from *N*-blocked 1,8-dihydroazocines. These sequences allow considerable flexibility in the elaboration of structure and the regiocontrolled placement of substituents <82T1579>. Tetrahydroazocinones have been converted into ethoxytetrahydroazocines with the Meerwein reagent <86AJC687>. Hydroazocine lactams have been shown to also undergo acylation <82GEP(O)3120451>. Via modified Tiemann rearrangement, cyclic amidoxime *O*-methanesulfonate has been transformed into cyclic carbodiimides <83JOC1694>.

9.18.5.3 Perhydroazocines

Perhydroazocines readily undergo nucleophilic substitution to yield *N*-substituted derivatives. *N*-Substituted compounds are synthesized for their applications in pharmaceuticals, agriculture, polymers, etc. *N*-Substitution has been achieved by both acylation and alkylation procedures.

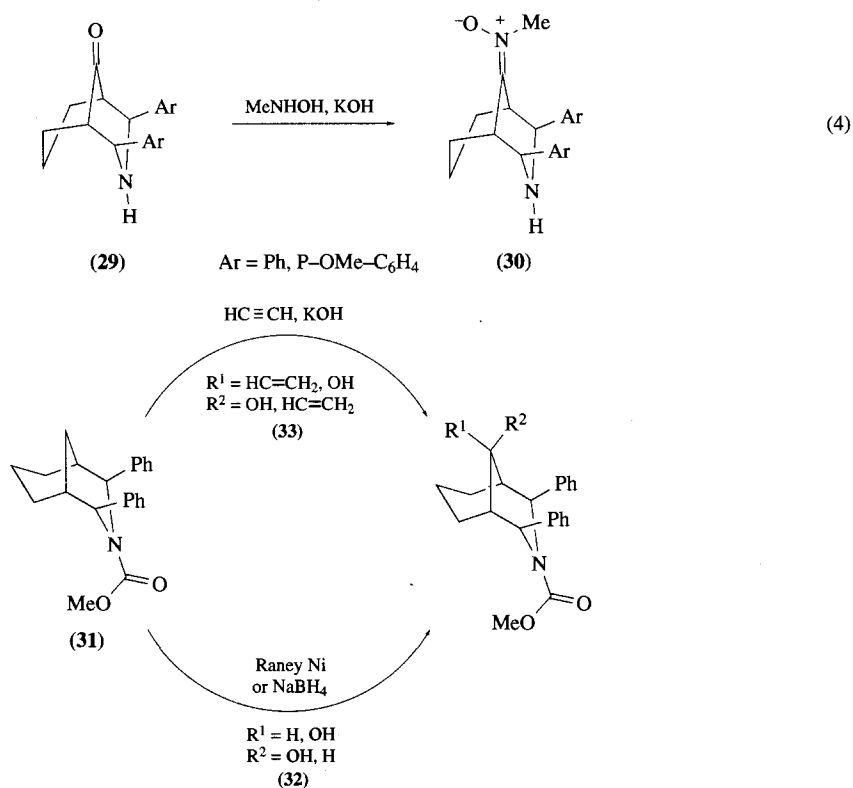
N-Acylation is accomplished by reaction of (3) with (i) acyl chloride <82BRP2081263, 82GEP(O)3240908, 83GEP(O)3301959, 83JMC1433, 86EUP177361, 86EUP179443, 89JAP(K)01319462>, (ii) 1,1-carbonyldiimidazole <85EUP160436>, and (iii) acid anhydrides <85CCA337>. *N*-Alkylation is accomplished by reaction with the corresponding halides (I, Br, Cl) <82GEP(O)3120451, 88AP(321)57, 89MIP9009996, 91JMC2624>, or by Mannich reaction (Equation (3)) <82MI 918-02, 85EUP163537>.



Electrochemical oxidation of cyclic amines resulted in bicyclic compounds <85CJC1170>. Oxidation of perhydroazocine with aqueous $\text{Na}_2\text{S}_2\text{O}_8$ in the presence of AgNO_3 gave 1-formylperhydroazocine <82JCS(P1)3031>. The tri- and tetranuclear clusters of $\text{Ru}_3(\text{CO})_{12}$, $[\text{HRu}_3(\text{CO})_{11}]^-$, and $[\text{H}_3\text{Ru}_4(\text{CO})_{12}]^-$ catalyzed the carbonylation of perhydroazocine to give its formamide. The reaction works with only CO or with a mixture of carbon dioxide and hydrogen <89JOM(368)103>.

Oxidation of *N*-substituted and unsubstituted azocines ($\text{R} = \text{H}, \text{Me}, \text{Ph}$) by RuO_4 gave the corresponding lactam, whereas similar oxidation of benzyl cyclic amine gave mixtures of lactam and benzamide <85G325>. *N*-Substituted azocine(s) undergo (i) rearrangements assisted by mercury acetate <90AP(323)47>, and (ii) Beckman rearrangement of oxime sulfonates assisted by organo-aluminum reagent, offering a new route to obtain α -alkylated amines <83JA2831>. Amino groups present in the side chain of the *N*-substituted azocine underwent protection with phthalimide, deprotection by hydrazinolysis, and acylation with L^- or $\text{DL}^- \text{H-pyroGlu-OC}_6\text{Cl}_5$ to provide the azocine derivative <82MI 918-03>. *S*-Alkylation of *N*-substituted azocine has been reported <83JAP(K)5821674, 83JAP(K)5821675>. Hydrogenation of α -functionalized azocine or nitromethylene derivative with Pd/H gave pyrazine but with Rh-catalyzed reduction gave piperazine <87IJC(B)107>.

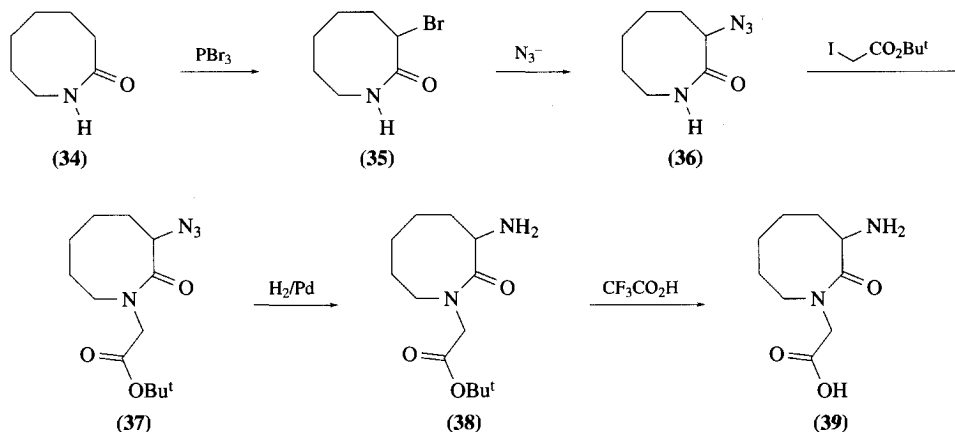
The carbonyl group in the azocinone system (29) reacted with MeNHOH in the presence of KOH to afford the nitron (30) (Equation (4)) <86MI 918-01>. Azabicyclanone derivative (31) underwent reduction with H_2 over Raney nickel or NaBH_4 in dioxane affording a mixture of epimeric alcohols (32) <88IZV71>. Under Favorskii conditions, (31) reacted with ethyne to give alcohols (33) (Scheme 1) <88IZV76>.



Scheme 1

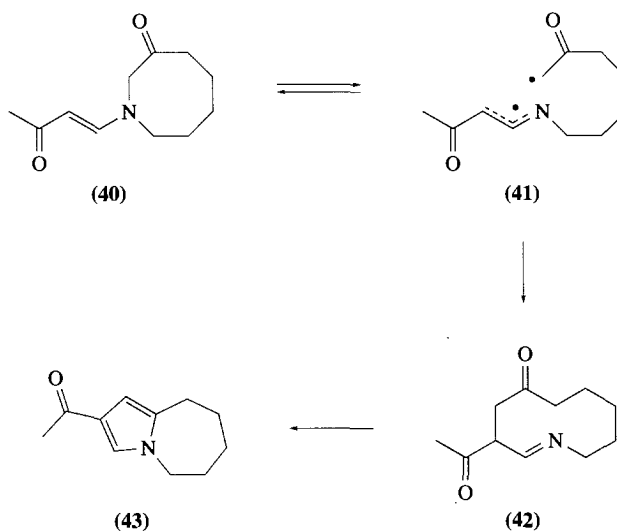
The nitrogen atom in enantholactam can also undergo acylation. Subsequent reactions of *N*-acylated enantholactam yield biologically important compounds <81MI 918-01> or a facile route to

large-membered bi- and tricyclic compounds via an aza Wittig reaction <84CB1513, 91JOC1535>. The α -carbon of the lactam (**34**) was functionalized to obtain the racemic eight-membered lactam (**39**). The racemic mixtures were resolved via its pyroglutamic salts (Scheme 2) <86JMC251>.



Scheme 2

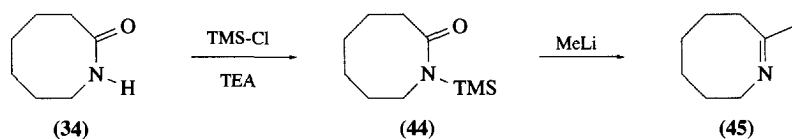
A novel photochemical transformation of β -keto vinylogous amide into the unexpected product 3-acylpyrrole rather than the expected [2 + 2] product has been reported <93TL7697>. Excitation of the vinylogous chromophore (**40**) leads to homolysis to form the stabilized biradical (**41**), which can either regenerate (**40**) by ring closure or form the ring-expanded ketoimine (**42**) via cyclization at the terminus of the azaallylic radical. The ketoimine (**42**) can then undergo a ground-state transannular cyclization, after dehydration, to give the unexpected product (**43**) (Scheme 3) <93TL7697>.



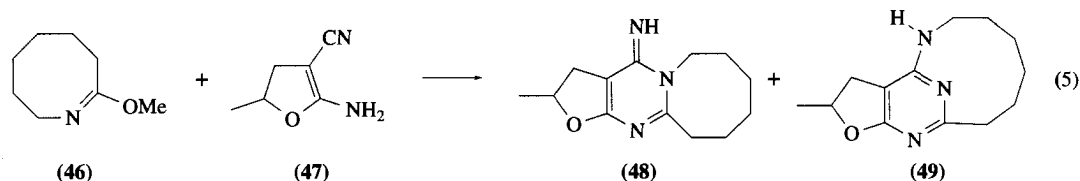
Scheme 3

Selective nucleophilic additions of alkyllithium reagents to *N*-(trimethylsilyl) lactam (**44**) provided the cyclic ketamine (**45**) in high yield. The only Grignard reagent used, ethylmagnesium bromide, attacked mainly at Si to form the amide anion (Scheme 4) <90JOC3682>. *N*-Butoxycarbonyl enantholactam was cleaved by reacting with Grignard reagents (RMgBr ; $\text{R} = \text{Bu}, \text{Ph}$) to give γ -amino-ketones, which were deprotected with CF_3COOH and cyclized with NaOH to give seven-membered cyclic imines <89JOC228>. Regioselective functionalization of enantholactam was achieved via α -alkylation using lithium hexamethyldisilazide, followed by alkylhalide. β -Alkylation was achieved by reaction of α,β -unsaturated lactam with organocuprates <90SL63>. *O*-Alkylation of enantholactam with Et_2SO_4 or $\text{Et}_3\text{O}^+\text{BF}_4^-$ gave the lactim ether, which on protonation by HCl or HBF_4 afforded the ammonium salts. The salts on hydrolysis yielded γ -amino ethyl ester <88SC1625>. Lactim ether (**46**) condensed with heterocyclic enamionitrile, dihydrofurancarbonitrile (**47**) to give the

heterocondensed pyrimidine (**48**) or pyrimidophane (**49**) via a Dimroth rearrangement (Equation (5)) <86CB1070>.



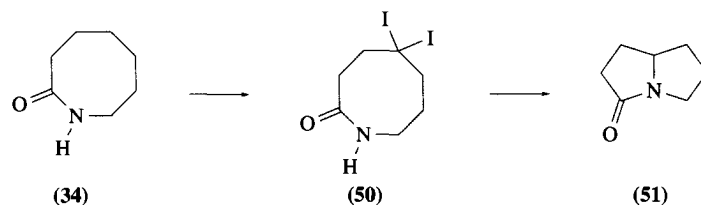
Scheme 4



Anodic oxidation of enantholactam in the presence of halide ions gave the bicyclic compound <87CJC2770>. Ozonolysis on α -substituted and *N*-substituted enantholactams has been reported <83SAP8209141>.

N-Chloroacetyl enantholactam underwent cycloaddition reaction with $\text{MeO}_2\text{CC}=\text{CCO}_2\text{Me}$ and *N*-phenylmaleimide via isomunchnone to give a pyridone derivative <87JOC1599>.

Photolysis of enantholactam (**34**) produced the amidyl radical intermediate in the presence of the hypervalent organoiodine reagent, (diacetoxyiodo)benzene (DIB), and iodine. The radical underwent transannular hydrogen abstraction to afford intramolecularly functionalized 5-oxoindolizidine (**51**). It is noteworthy that the *gem*-diiodide (**50**) is formed through an unexpected double hydrogen abstraction. This result indicated that the first hydrogen abstraction from C-5 resulting in monoiodide is not a propitious step, even though it adopts a conformation which favors cyclization, but the second abstraction of the geminal iodide hydrogen step occurs instead (Scheme 5) <89CC1168>.



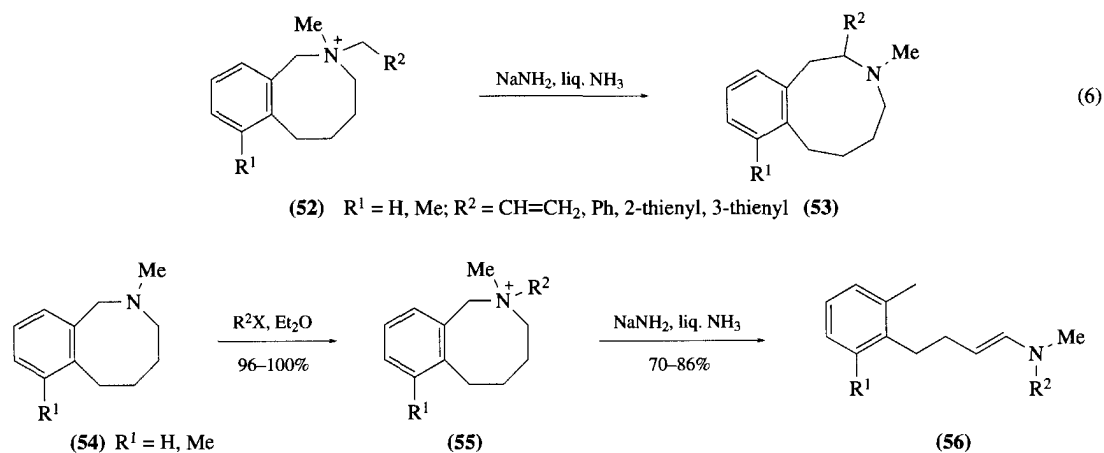
Scheme 5

Modifications of the side chain substituted on nitrogen atom and/or α -C functionalization of the enantholactams have been accomplished to obtain antihypertensive compounds <82EUP49842, 82EUP46289, 84CB1513, 84USP4470988, 85SAP8308227>.

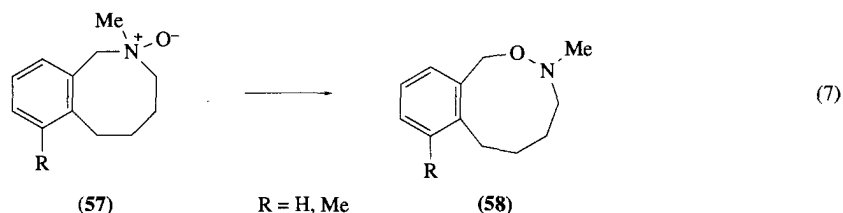
9.18.5.4 Benzazocines

Benzazocines can be easily alkylated by alkyl halides <88MI 918-01>, and acylated by acid chlorides <86MI 918-02, 87MI 918-02>. Benzazocines also underwent oxidation with $\text{NaWO}_4 \cdot 2\text{H}_2\text{O}$ <87JAP(K)62212363>. Benzazonium ylide (**52**) with sodamide in liquid ammonia solely underwent the Stevens rearrangement (1–2 migration) rather than the Sommelet–Hauser reaction (2–3 migration) to afford one carbon ring enlargement product (**53**) (Equation (6)) <89S327>. When the nitrogen atom bears one methyl group and another methyl or ethyl group, (**55**) afforded the ring-opened product, enamine (**56**) (Scheme 6) <87S727>. Thermolysis of 2-methyl hexahydrobenzazocine *N*-oxide (**57**) afforded the ring-enlarged product, methylhexahydrooxabenzazonines (**58**) (Equation

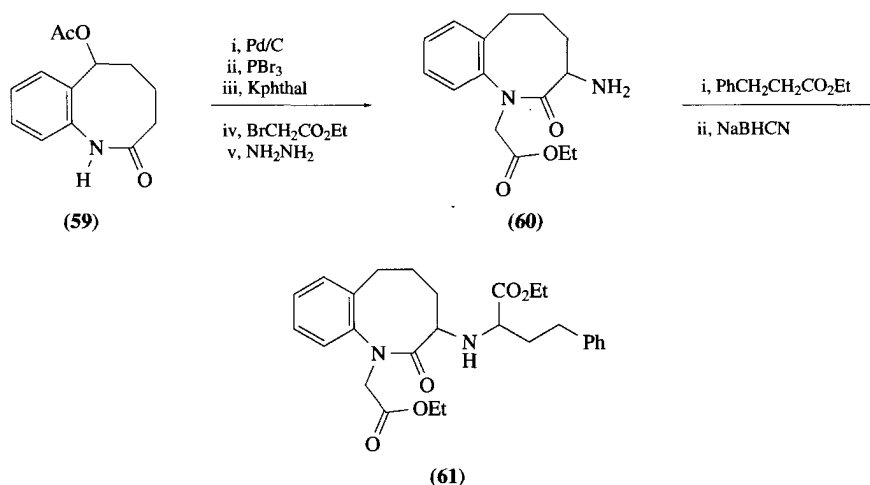
(7)) <89CCC2767>. Modified Tiemann rearrangement of cyclic amidoxime *O*-methanesulfonate afforded the carbodiimide on treatment with NaOH and Aliquat 336 in CH₂Cl₂ <83JOC1694>.



Scheme 6



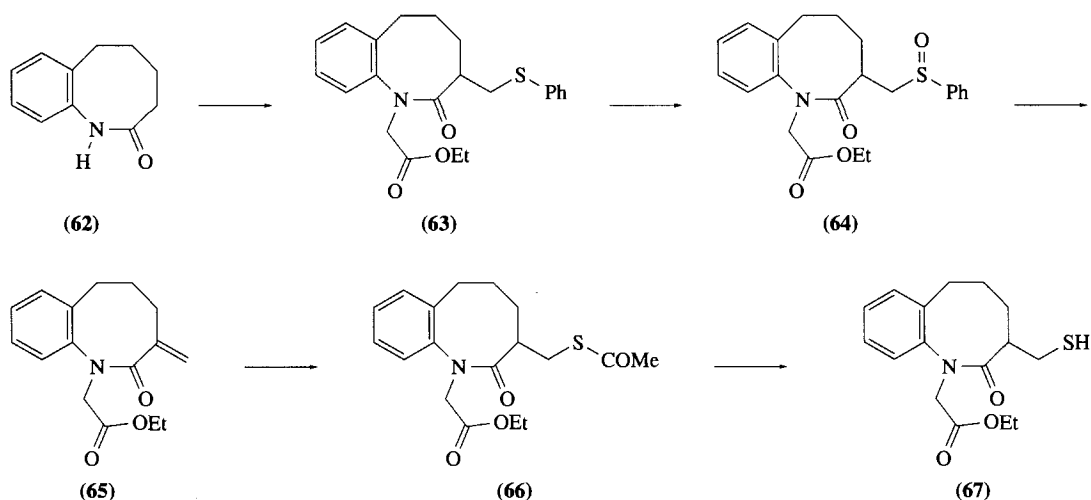
Ring C-alkylation was achieved by exploiting the chiral formamidine leaving group allylic proton pK_a . Subsequent reduction of unsaturation using Rh/C furnished the benzomorphan(+)-metazocine <85JA7974>. The α -carbon was functionalized into an amino group via bromination, phthalimidation, alkylation, or amination to obtain (60) from (59). The introduced amino group was further reductively alkylated and saponified to give (61). Various related derivatives were prepared with a number of "R" groups on the aromatic ring (Scheme 7) <84USP4470988>. A similar strategy was used to prepare benzazacinone and its derivatives <85USP4537885>. *O*-Acylation on the aromatic ring of benzazocine was achieved by Schotten-Baumann *O*-acylation using the corresponding acid chloride <87MI 918-03>. The aromatic ring in benzazocine was functionalized into thiol and was further alkylated <85JAP(K)60169465>. Regioselective *O*-methylation, ketalization, and *N*-tosylation of benzazocine derivatives were achieved in the synthesis of potential intermediates of mitomycin <88JOC5355>.



Scheme 7

The hydroxyl group on the azocinyl ring was oxidized and subsequently cyanated <85JAP(K)6048990>. The amidocarbonyl group on the azocinyl ring was reduced by $(\text{MeO-CH}_2\text{CH}_2\text{O})_2\text{HAlNa}$ <84CZP210993> and was reacted with 1-methylpiperazine <88CPB2386>. The carbonyl group at the 6-position underwent (i) reduction with Grignard and dialkyl lithium reagents <90AP(323)177>, sodium borohydride <88ZN(B)901, 89AP(322)21>, LAH <89AP(322)21>; and (ii) ketalization with 1,2-diol <88JOC5355> and hydrazine in methanol <90USP4973693>. The first example of amide dianion regioselective alkylation by sequential addition of two electrophiles has been reported. Thioethers (**63**) were oxidized to sulfoxides (**64**), which on thermolysis afforded the α,β -unsaturated lactams (**65**). Addition of thiolactic acid and removal of the protecting groups completed the synthesis of 1-(carboxymethyl)-3-(thiomethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazocin-2-one (**67**) from (**62**) (Scheme 8) <84JMC816>.

Tetrahydrobenzazacinone underwent acid-catalyzed cyclization with polyphosphoric acid to afford the novel 1,3-bridged hexahydromethanobenzazocinones <83H(20)1979>.



Scheme 8

9.18.5.5 Dibenzazocines

Treatment of tetrahydromethanodibenzazocine *N*-oxide under basic conditions yielded tetrahydroisoquinolines <84CC1644>. *N*-Alkylation on dibenz[*c.e*]azocine <91CCC2986> as well as nucleophilic addition of alkyl and cyclic amine on the *N*-epoxypropyl substituted dibenz[*c.e*]azocine were reported <91CCC1725>.

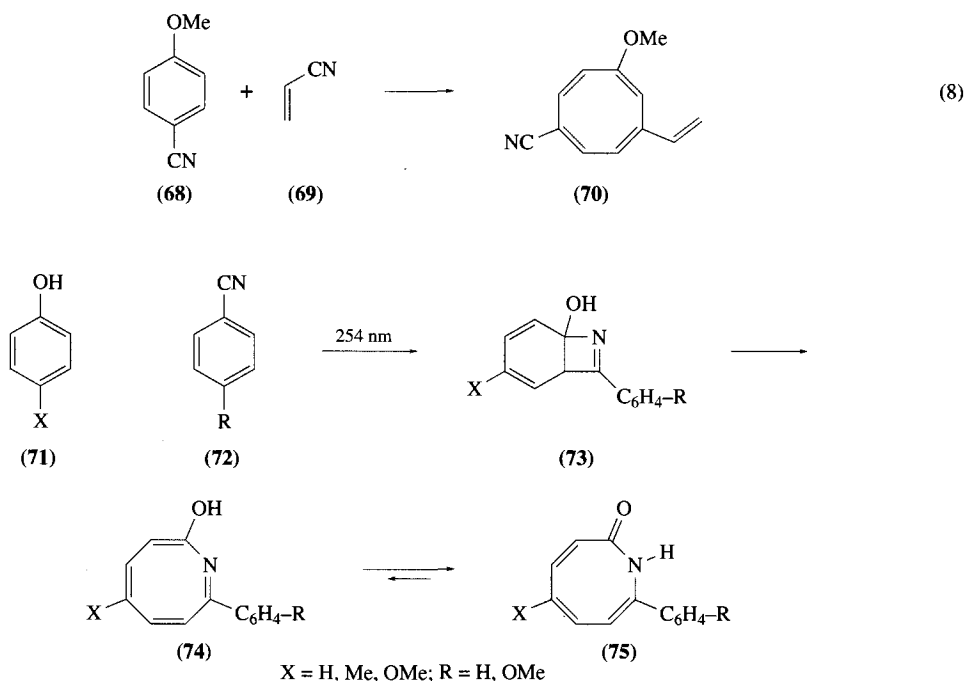
9.18.6 SYNTHESIS

Synthesis of azocines embraces that of azepines and azonines in the use of general methods: Beckmann rearrangement, Schmidt reaction, and intramolecular cyclization. In general, cyclization depends upon the probability of end-to-end encounters. It is determined by the activation energy of the process. In an eight-membered azacycle, energy of activation depends upon (i) Pitzer strain (torsional effect in a single bond), (ii) Baeyer strain (deformation of ring bond angles from their preferred angles), and (iii) transannular (nonbonded through space) interaction which occurs when atoms across the ring are forced into close proximity. These strains will be reflected in the enthalpy of activation for the cyclization. There is a negative $\Delta S^\ddagger$ contribution during the cyclization and this will tend to lower the cyclization rate; thus, accomplishing an eight-membered ring via a cyclization procedure is rather challenging.

Since azocines are a diverse class of compounds, their preparative methods remain specific and often inefficient. The order of discussion is as outlined in the introduction.

9.18.6.1 Azocines

In the literature, synthesis of azocine/azacyclotetraene was achieved by the only route, photocycloaddition $\langle 85CC85, 88T1449, 89JCR(S)110, 90JHC1323 \rangle$. Cycloaddition of a nitrile group into an aromatic ring is uncommon. It may be due to an assumption that arenes involve intramolecular electron transfer via the $S_1 \pi \pi^*$ state. However, formation of (70) along with two *ortho*-photoadducts represents the first example of photocycloaddition of a nitrile group (69) into an aromatic ring (68) (Equation (8)) $\langle 85CC85 \rangle$. This methodology is successful only if the benzenes have both electron-donor and electron-acceptor substituents in the *para* relationship to give azocines. Acrylonitrile, cinnamitrile or 4-hydroxybenzonitrile did not react with phenol. But *para*-substituted methoxy benzonitrile (72) reacted with phenol (71) to yield lactam (75) by initial 1,2-photocycloaddition, followed by ring opening and tautomerization (Scheme 9) $\langle 89JCR(S)110 \rangle$. Studies on the substituent effect of the photocycloaddition of phenol to substituted benzonitriles revealed that, in general, all substituted benzonitriles are less productive than benzonitrile itself. The *para* substitution seems to be better than the others. The photolabilities of these arenes in the presence of phenol vary appreciably. Solvent polarity enhanced the reaction, suggesting the photo-induced electron transfer from the phenol to the cyano compound and that the radical-ion species thus formed either undergo addition or react with oxygen $\langle 90JHC1323 \rangle$.



Scheme 9

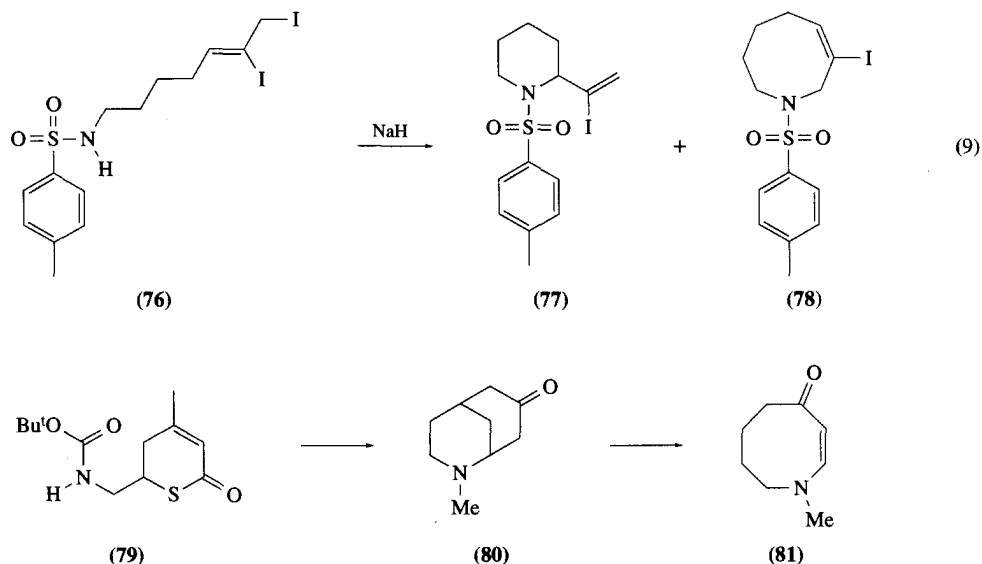
9.18.6.2 Hydroazocines

Generally hydroazocines are prepared via cycloaddition; but depending upon the degree of unsaturation, the preparation can also be achieved by other routes.

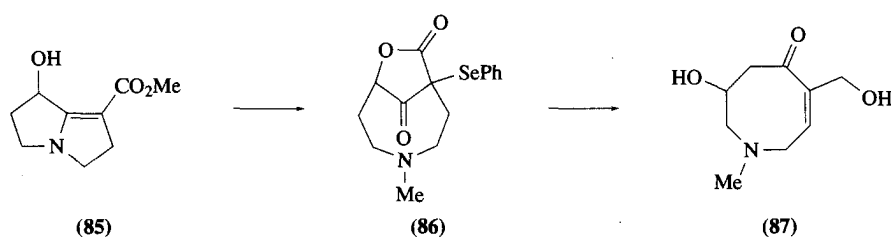
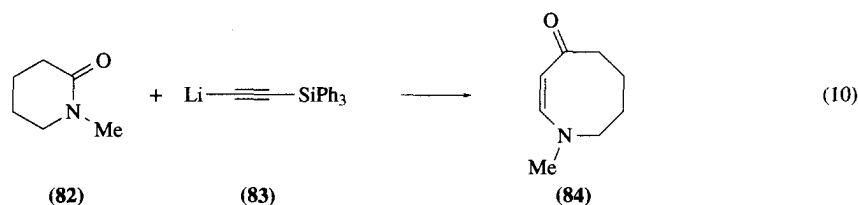
9.18.6.2.1 Hexahydroazocines

Intramolecular cyclization of (76) in the presence of NaH gave *exo* (77) and *endo* (78) products (Equation (9)) $\langle 90SL584 \rangle$. Allene-based electrophile-mediated cyclization afforded *N*-tosyl iodo-hexahydroazocines $\langle 94JCS(P)13549 \rangle$. Photochemical intramolecular cycloaddition of phthalimide in acetone afforded the ring-opened product $\langle 82TL4981 \rangle$. An unstable enaminone azocine derivative (81) was formed after the desulfurization of the bicyclic a-minal (80), which in turn was synthesized from

the Diels–Alder adduct, dihydrothiopyranone (**79**). Azocine (**81**) rearranged to (formylmethylene) piperidone derivative (Scheme 10) <88JOC2226>. Lactam (**82**) underwent a two-carbon insertion with $\text{Ph}_3\text{SiC}\equiv\text{CLi}$ to give (**84**) (Equation (10)) <87JOC2929>. Otonecine (**87**) was synthesized in its racemic form from the pyrrolizinecarboxylate (**85**) via lactone (**86**) in six steps (Scheme 11) <83TL5731>. Biosynthesis of otonecine (**87**) has been reported <91JCR(S)46>.



Scheme 10

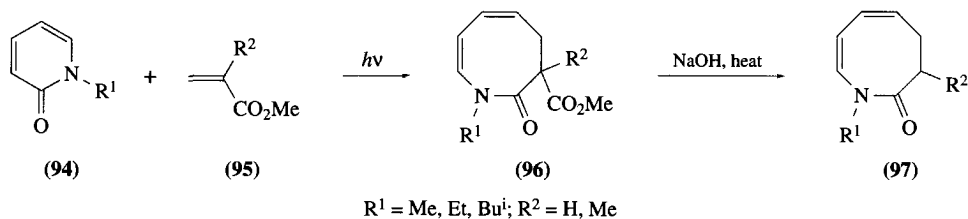
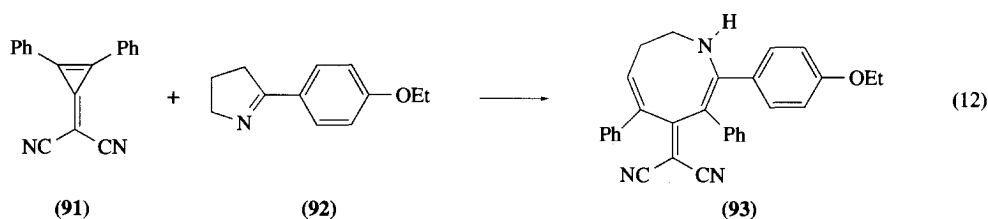
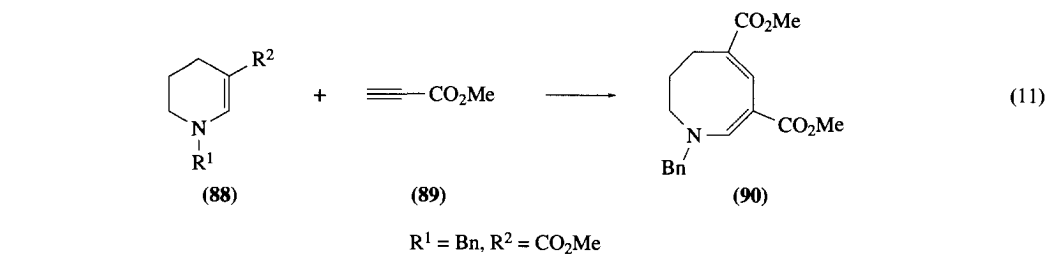


Scheme 11

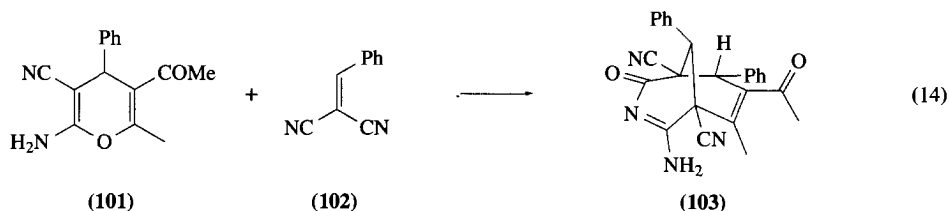
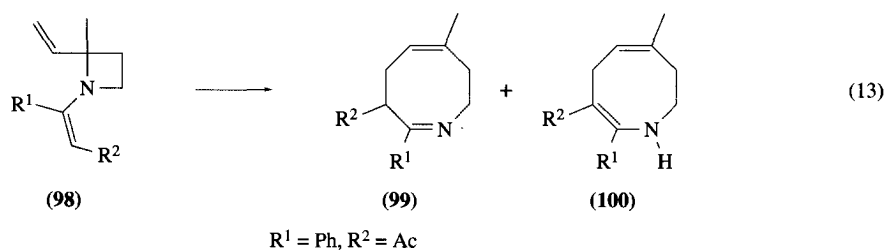
9.18.6.2.2 Tetrahydroazocines

The [2 + 2] cycloaddition of tetrahydropyridine (**88**) with $\text{HC}\equiv\text{CCO}_2\text{Me}$ gave tetrahydroazocine (**90**) (Equation (11)) <81JCR(S)306, 82MI 918-01>. Cycloaddition of fulvene (**91**) with cyclic imine (**92**) gave the azocine (**93**) (Equation (12)) <86S908>. *N*-Alkyl substituted 2-pyridones (**94**) underwent photocycloaddition with methyl acrylate (**95**) to afford the eight-membered unsaturated chiral azacinones (**97**) (Scheme 12) <82JOC1564>. On heating, 1,2-divinylazetidines (**98**) underwent a Cope rearrangement to yield tautomeric mixtures of azocines (**99**) and (**100**) (Equation (13)) <86JOC3652>.

The reaction of acetyl-substituted aminopyran (**101**) with arylidenemalonitrile (**102**) afforded a novel bridge-head azocine (**103**) (Equation (14)). The controversy over its structure was resolved by x-ray crystallography <92T1581>. A one-pot, decarboxylative three-carbon ring expansion of a cyclic secondary amino acid afforded a tetrahydroazocine derivative <87CC1296>.

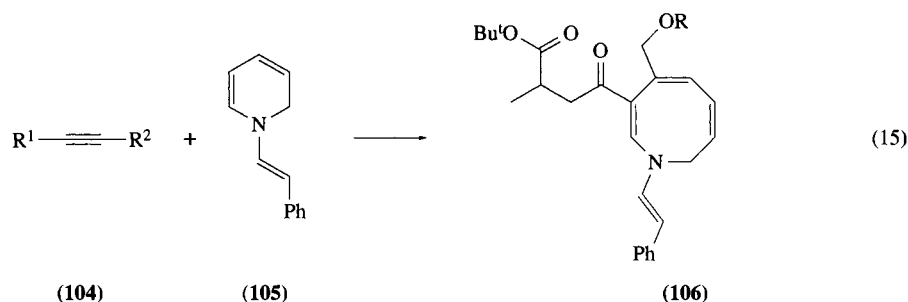


Scheme 12



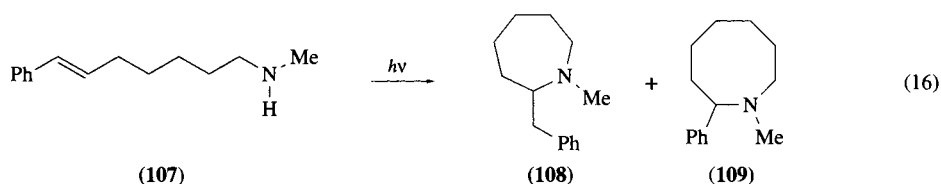
9.18.6.2.3 Dihydroazocines

Unsymmetrically substituted ethynes (**104**) bearing at least one electron-withdrawing group underwent efficient cycloaddition with 1- β -styryl-1,2-dihydropyridine (**105**) to provide 3,4-substituted 1,8-dihydroazocines (**106**) regioselectively (Equation (15)) <82T1579>.

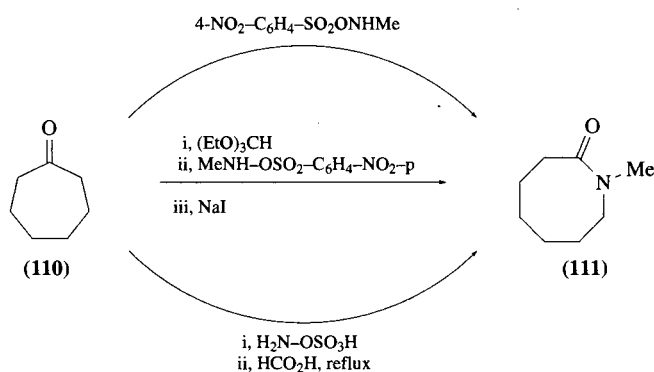


9.18.6.3 Perhydroazocines

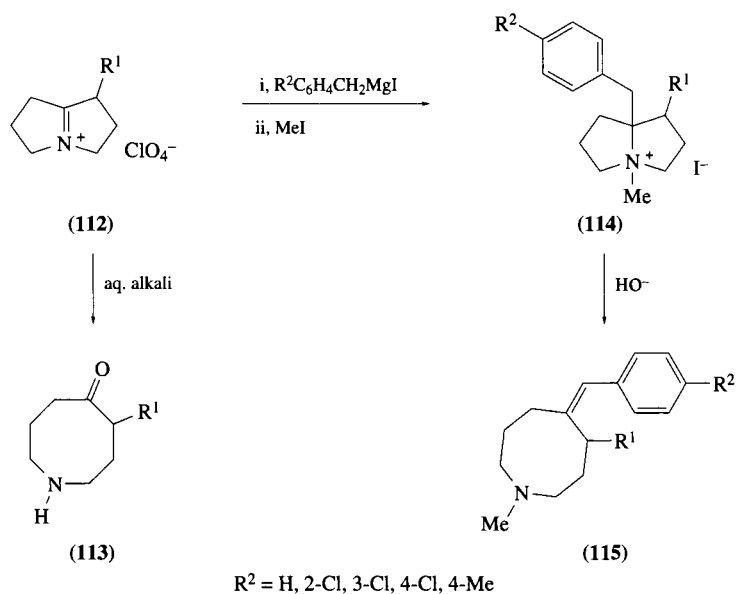
Intramolecular cyclization of suitable starting materials with appropriate reagents afforded perhydroazocines <82G31, 82SC733>. Reaction of *in situ* generated immonium ions with allylsilanes led to intramolecular condensation and desilylation resulting in an azocine derivative; however, the reaction time was five days <86TL5067>. The secondary γ -styryl (*N*-methylamino)alkane (107) underwent intramolecular photochemical addition to yield regioisomeric adducts in which C—N bond formation had occurred either at the α -carbon to give *N*-substituted azocine (109) or at the β -carbon to give *N*-substituted azepine (108) (Equation (16)) <91JA3498>. Lactamization of simple α,γ -aminocarboxylic acid had been reported in the literature via catecholborane <78JOC4393> and $\text{Al}_2\text{O}_3/\text{SiO}_2$ <80TL2443>. More recent successful methods used since the early 1980s, are via dibutyltin oxide <83JA7130>, titanium tetraisopropoxide <88TL3049>, and a high dilution method for activated α,γ -amino acid <83JOC2680, 84CPB3789>. An efficient synthesis of eight-membered lactam from α,γ -amino acids using Et_3Ga has been reported <89CL797>.



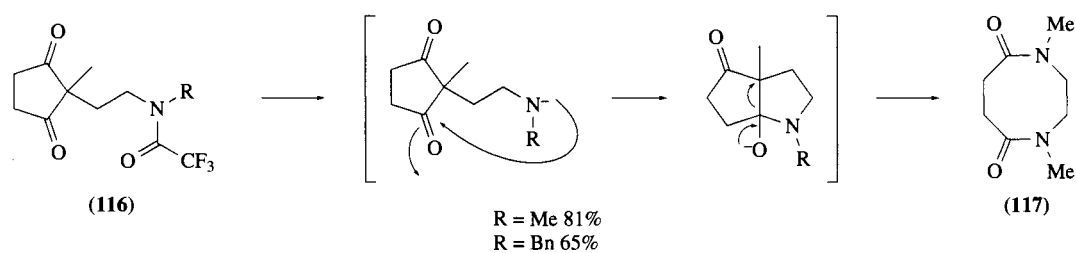
Ring expansion is another route to obtain perhydroazocine derivatives. Insertion of *N*-substituted fragments into azapinone (110) afforded enantholactam (111) (Scheme 13) <85OS(63)188, 89TL4207, 91TL2429>. This is a less well-known methodology. In general, functionalization at the C-5 position was achieved via ring-opening of pyrrolizinium perchlorate (112) to yield (113) and (115) (Scheme 14) <85JCS(P1)2611, 86H(24)2121>. Synthesis of diketone (117) was accomplished by controlled criss-cross annulation. This is a versatile method overcoming difficulties such as high dilution, low overall yield, and a lack of regioselectivity at the cyclization stage (Scheme 15) <83TL4253>. The saturated bicyclic eight-membered lactam, carbocepham, was synthesized by palladium-catalyzed carbonylation of vinyl halide <89H(29)853>.



Scheme 13

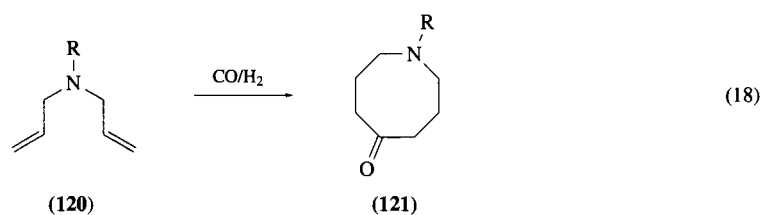
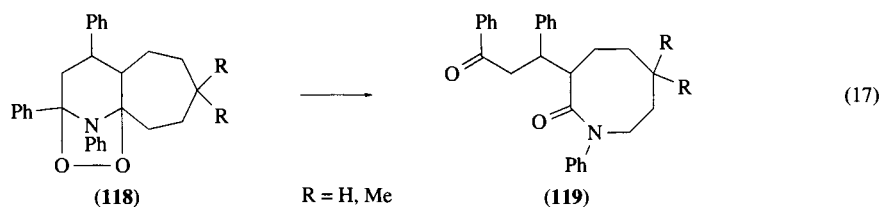


Scheme 14



Scheme 15

Rearrangement by thermolysis of unsymmetrically substituted tricyclic derivatives of 2,6-epidioxypiperidine (**118**) afforded the ketamide (**119**) (Equation (17)) <90KGS109>. Synthesis of *N*-substituted 5-azalactanone (**121**) was accomplished by CO insertion. The xylborane-cyanidation hydroboration protocol proved to be the most useful method with moderate to high yield (Equation (18)) <82JOC1494>.

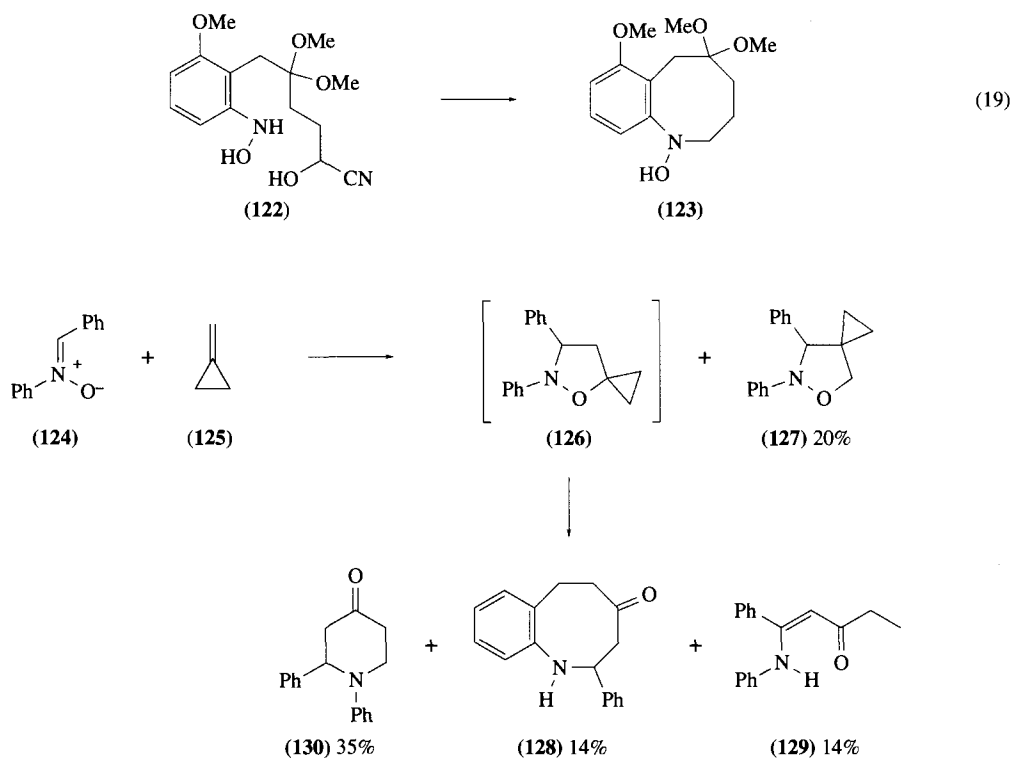


9.18.6.4 Benzazocines

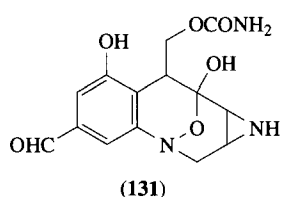
The benzo-fused azocine derivatives are diverse, hence grouping them together and presenting strategic synthetic routes becomes rather intricate. Benzazocine derivatives are mostly formed as unexpected cyclized products, as intermediates, or as one of the "other" products in a reaction. But a desirable benzazocine can be easily separated from other products by flash chromatography.

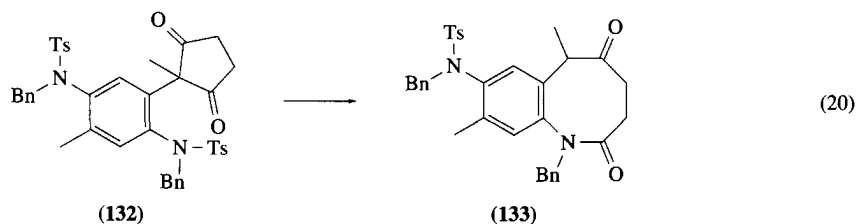
Isolation and structural elucidation of *E*-clausenamide, a benzo-fused lactam, were accomplished from the leaves of *Clausena lansium* <87GEP(O)3700706, 91MI 918-01>.

Intramolecular cyclization is one of the common methods used to obtain benzazocines <86JCS(P1)1533, 86JCS(P1)1977, 88MI 918-02>. Base-catalyzed cyclization of 1,2-bis(2-isocyano-2-tosylethyl) benzene with KOH in ROH (R = Me, Et, *i*-Pr) afforded benzazocines <84JHC611>, but in *t*-BuOH it gave benzazocinone <87CPB3475>. Again, base catalyzed of *N*-phthalimido substituted β -ketoester provided benzazocine trione <94H(38)751>. Cyclization of hydroxylamine derivative (**122**) in MeOH with NaBH₃CN gave (**123**) (Equation (19)) <91JAP(K)03115287>. Thermal rearrangement and cyclization of spirooxazolidines (**126**) provided a straightforward synthesis of benzazocinone (**128**) (Scheme 16) <89T5917>. A novel approach to obtain FR-900482 (**131**) via a ring-forming metathesis reaction has been reported <95TL1169>. Electrochemical removal of the *N*-tosyl group from phenylenediamine derivative (**132**) in the presence of cooperative systems of anthracene and ascorbic acid afforded the benzazocine (**133**) via a criss-cross annulation (Equation (20)) <84JOC953>. A review is dedicated to the synthesis of 1-benzazocinone derivatives by controlled criss-cross annulation <88MI 918-03>. Tetrahydro-1-benzazocin-5-ones are achieved by a Dieckman condensation <83H(20)2051>.

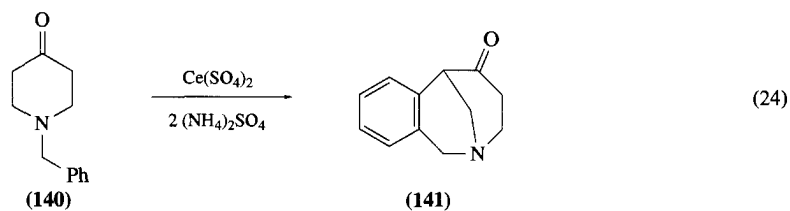
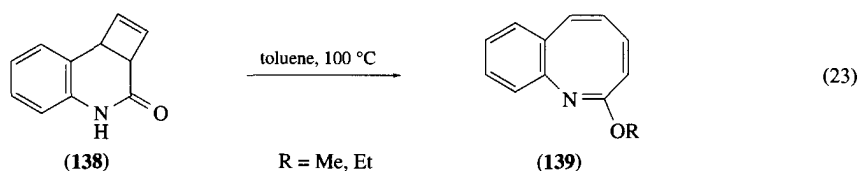
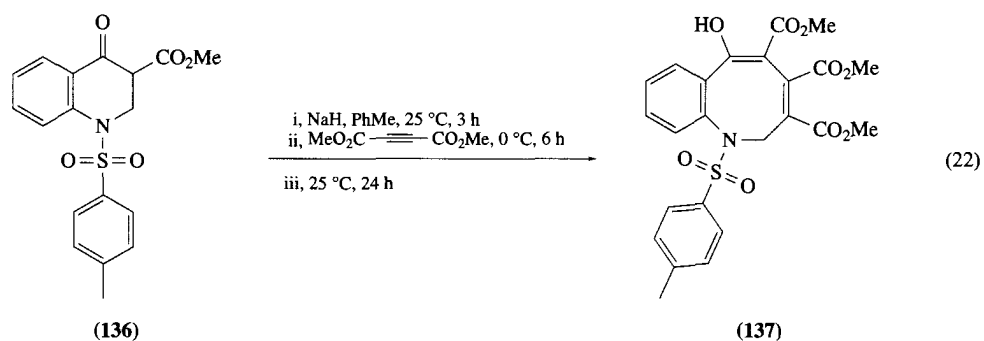
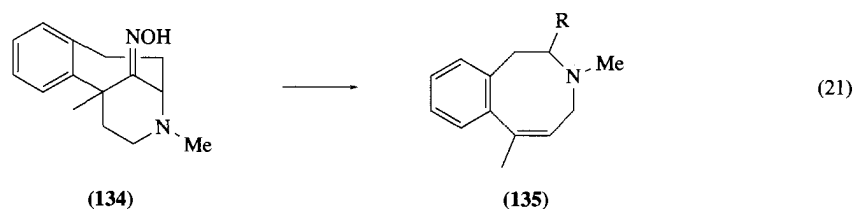


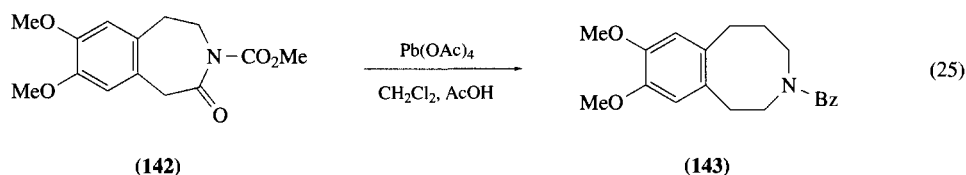
Scheme 16





Numerous investigators have used ring-expansion strategies. Ring expansion was achieved (i) by Beckmann rearrangement of *N*-oxime (**134**) leading to benzazocine (**135**) (Equation (21)) <82JHC941, 83JCS(P1)2053, 83TL413, 90JCS(P1)1083, 90JCS(P1)1091>; (ii) from β -ketoesters (**136**) (Equation (22)) <84JCR(S)246, 86AP(319)1079>, both reactive as well as unreactive β -ketoesters have been discussed <84JCR(S)246>; (iii) by photolytic <85CL727> and thermal <82AP(315)749, 90H(31)1769, 91H(32)2089> rearrangement of tricyclic compounds such as (**138**), resulting in ring expansion to give benzazocine (**139**) (Equation (23)); (iv) from suitable starting heterocycle(s), for example (**140**), with the aid of a variety of reagents, such as cerium sulfate (Equation (24)) <87AP(320)481>, ammonium carbonate <84H(22)1771>, and lead tetraacetate (Equation (25)) <89JCS(P1)1931, 92OS(70)139>; and (v) by oxidative cleavage <84H(22)355>, fluoride-ion induced desilylation <91CPB36>, intramolecular condensation <91JHC1625>, criss-cross annulation <90CC468>, cycloaddition <82CPB3959, 89T5917>, ring opening of oxaziridine with an increase in three atoms <84AJC599>, intramolecular Grew cyclization <85JA7974>, ring contraction <92CPB617>, and ring-closing metathesis of dienes <95JA2108>.

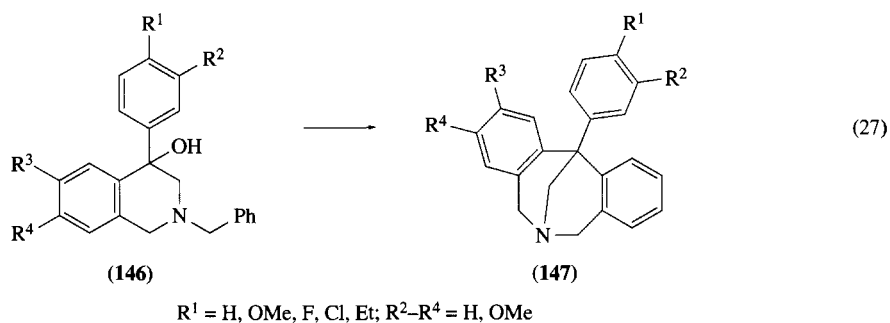
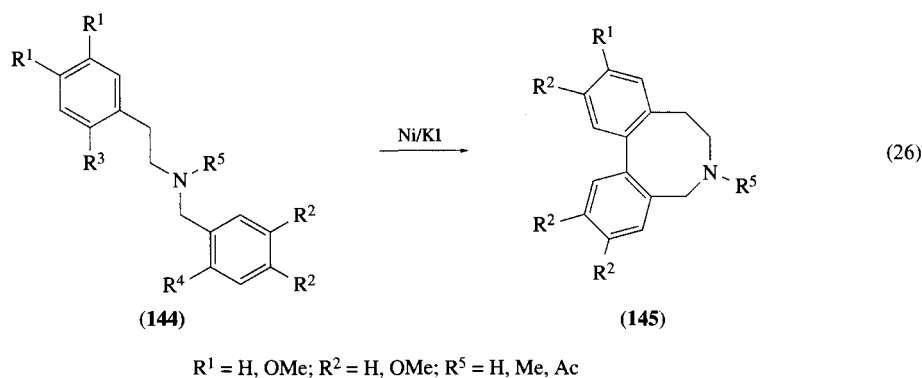


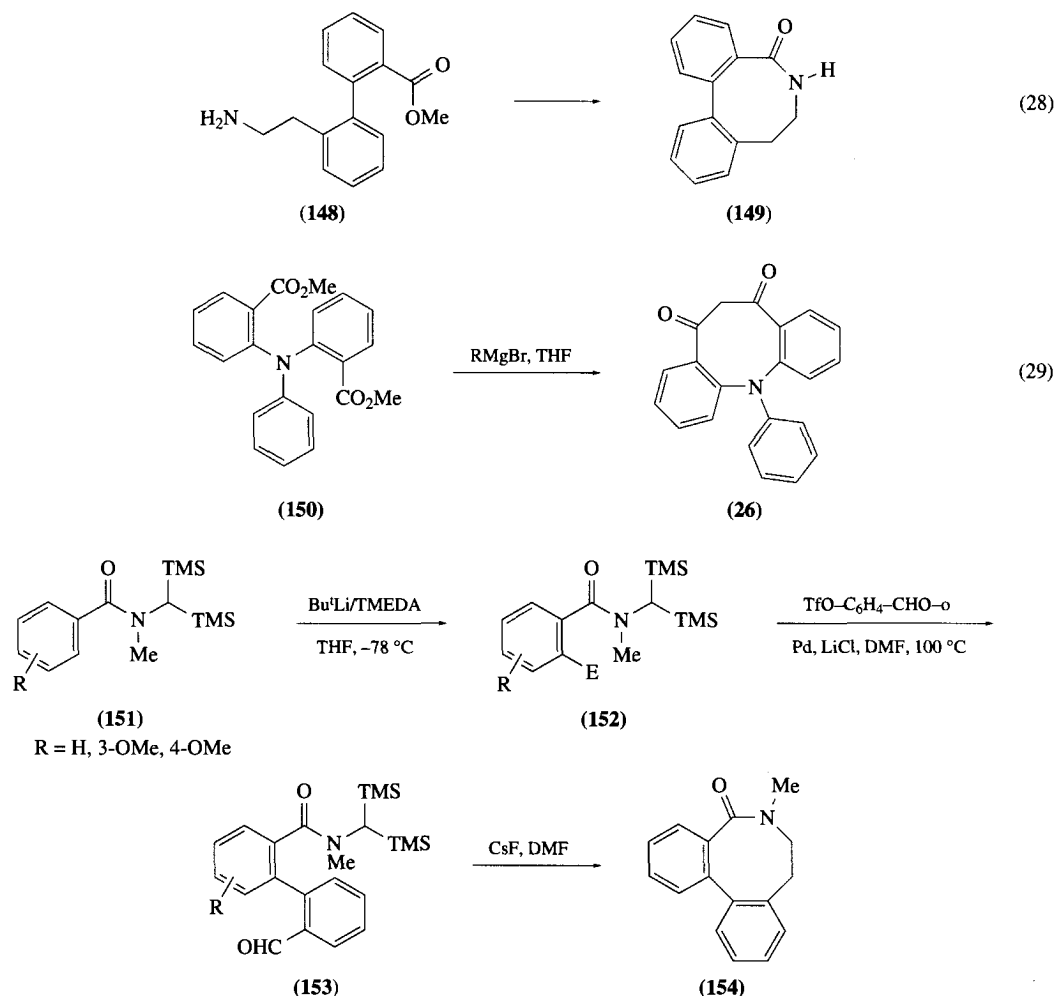


9.18.6.5 Dibenzazocines

Unlike other azocines, dibenzazocines are easily synthesized by the most exploited route, intramolecular cyclization. It is achieved by two approaches: (i) connecting the two phenyl rings always affords the dibenz[*c,e*]azocine, and (ii) connecting the two functional groups (e.g. amine and ester) of two side chains of two participating aromatic rings provides [*c,e*], [*b,g*], and [*b,f*] dibenzazocine systems.

Synthesis of 5,6,7,8-tetrahydrodibenz[*c,e*]azocine derivative(s) (145) was achieved by using KI and a stoichiometric amount of zero valent nickel, generated *in situ* (Equation (26)) <88JCR(S)8, 88JHC161, 89CPB870, 89CPB1744>. Photochemical cyclization of the amine <85CPB1260, 85H(23)159> and intramolecular cyclization of $\text{Ph}(\text{CH}_2)_2\text{NRCH}_2\text{C}_6\text{H}_4\text{NO}_2$ -3 in the presence of $\text{Fe}(\text{CO})_5$ also afforded dibenzazocine derivatives <85TL5815>. An intramolecular Friedel–Craft reaction of isoquinolinol (146) afforded dibenz[*c,f*]azocine (147) (Equation (27)) <92H(34)747>. Intramolecular cyclization was also achieved by connecting the two functional groups such as amine and ester in the side chains of the two phenyl rings (148) at elevated temperature to give (149) (Equation (28)) <83CZP209400, 84JCS(P1)2013, 86CB3165, 91MI 918-02>. A similar approach was successful in synthesizing functionalized dibenzazocine derivatives <88KGS1000>. Intramolecular cyclization involving two ester groups (150) with reagents like alkyllithium or alkylmagnesium yielded dibenz[*b,g*]azocines (26) (Equation (29)) <85ZNB858, 86CB3165, 87JOC2980>. α,α' -Disilylated benzamide (151) constitutes an ortho- and α' -carbanion synthon, which provides dibenzazocines (154) by Peterson alkenation (Scheme 17) <89TL5841>. Synthesis of dibenzazocine derivatives was also achieved by electrochemical oxidation of aromatic ethers <83JCS(P1)2053>, by intramolecular cycloaddition <90JOC2103, 90UKZ749>, and by ring enlargement via Sommelet–Hauser rearrangement of ammonium ylides <94JOC148>. The last is an attractive method for the reason that the rearrangement occurs regioselectively at milder conditions. Photocycloaddition of 6-substituted phenanthridines and electron-rich alkenes, such as *trans*-anethole and $\text{PhOCH}=\text{CH}_2$ gave azocine or azetidene derivatives <82BCJ2190>. Synthesis and properties of dibenz[*b,f*]azocine functional derivatives have been reported <91KGS109>.





Scheme 17

Although several methods are reported in the literature for the synthesis of azocines, the need for a general, versatile, and stereoselective method still remains a challenge.

9.18.7 APPLICATIONS

Eight-membered azaheterocycles have found a wide spectrum of applications as summarized in the following sections.

9.18.7.1 Azocines

The fully saturated azocine (**1**), has not been exploited for application purposes up to 1995. All studies have been done for academic reasons. Applications of partially saturated azocines are not well known and the only system which has found its application is otonecine (**87**). Otonecine is the base portion of the alkaloid emiline which was originally extracted from the plant, *Emilia flammea*. Emiline has hepatotoxic and carcinogenic effects [83CL125, 83TL5731, 89JCR(S)358, 91JCR(S)46].

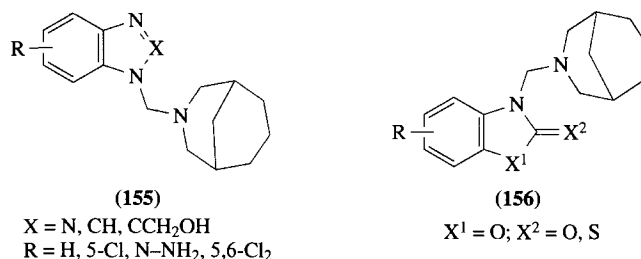
Completely saturated azocines possess numerous applications. *N*-Acylated derivatives of perhydroazocines are used as herbicides [83JAP(K)5821674, 83JAP(K)5821675, 84GEP3238007, 89JAP(K)01319462], as antiarrhythmic agents [85EUP160436, 86EUP177361], and they also possess anti-convulsant activity [88JMC2218].

N-Alkyl or aryl substituted heptamethyleneimines are used as magenta dye image stabilizers

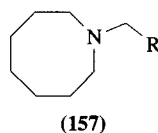
<87JAP(K)62278549>, in treatment of hypertension <85JAP(K)60239458>, central nervous system disorders, diabetes, sexual impotence, and to control appetite <90MIP9015047>.

N- and *C*-substituted heptamethyleneimine exhibit antithrombic activity <90JAP(K)02115197>.

N-Alkynylated perhydroazocines exhibit tremorolytic activity <82MI 918-03>, glutamate blocking effect on neuromuscular junctions <87EUP235942>, antiarrhythmic activity <85JAP(K)60239458, 91MIP9101299>, cognitive performance enhancing activity <86GEP(O)3515093>, and antinociceptive activity <91JMC2624>. *N*-(Alkyldialkoxysilyl) cyclicamine is used as an electron donor for α -alkene polymerization <91EUP410443>. Metallic [Cu(II), Ni(II), Fe(III), Mn(II)] complexes of 2-acetylpyridine thiosemicarbazone showed reduced antimalarial activity but enhanced antileukemic property relative to the free ligands <82JMC1261>. *N*-Nitroso heptamethyleneimine (NHMI) was found to be a carcinogen/mutagen <82MI 918-04, 86MI 918-03, 90MI 918-01>. It is unusual to find so many applications for just two compounds, *N*-substituted derivatives **(155)** and **(156)**: antihypertensive, antidiabetic, gastric secretion inhibition, anticholesteremic, central nervous system depressant, and antidepressant activity <82MI 918-02>. Quaternary salts of perhydroazocine are useful as softeners, conditioners, and/or bactericides in cosmetics, mouthwashes, and textile treating agents <88MIP8802985>, and hair and skin treating formulations with bactericidal properties <89USP4883655>. Azacyclooctanones are effective in stabilizing diazo compounds and materials against precoupling, loss of shelf-life, and image fading <83USP4419432>. Unsubstituted enantholactam is used as an additive for heat resistant ABS resin <86JAP(K)6193158>, in biologically active seed coating composition <85MIP34313>, as an angiotensin converting enzyme inhibitor <83MI 918-02>, a hydrophobic photographic additive <85EGP229514>, a drying inhibitor for aqueous inks <91GEP4001644>, and a discoloration preventing reagent in the photochlorination reaction of *para*-xylenes <82JAP(K)98225>. *N*-Acyl enantholactams have found wider application in polymer synthesis <85JA5817, 86MM1530, 86PP118, 87USP4644050>, to provide improved mechanical properties, heat resistance and decreased flammability <81MIP21000>, reinforced thickness for glass fibers <82CZP193697>, and coating composition on electrically insulating wire <86JAP(K)6100270>, as well as being used as antihypoxic and antiamnesic agents in pharmacological studies <83KFZ1439>. Bicyclic perhydroazocine derivative is used as a capacitor <88JAP(K)63305507>, as well as in treating heart disease <88GEP(O)3704661>.



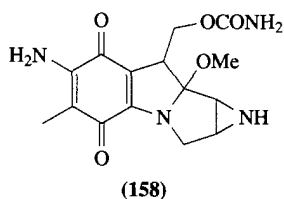
Numerous studies have been done on guanethidine **(157)**. Reviews which focus on guanethidine are <80MI 918-01, 81MI 918-02, 82MI 918-05, 84MI 918-01, 86MI 918-04>. A complete discussion is beyond the scope of this chapter, hence, only the available references are indicated. Since **(157)** is proven to be an antihypertensive agent <83MI 918-03>, studies on hypertension have been done on all systems of mammals: nervous system, ophthalmic system, cutaneous system, digestive system, excretory system, cardiovascular system, pulmonary system, reproductive system, neonatal studies, biochemical studies, and physicochemical studies. Guanethidine sulfates are antidiabetic <81SAP8002161> and used in ointment composition <89JAP(K)01216928>. Platinum(II) and (IV) complexes of guanethidine exhibit antitumor activity <82MI 918-06>.



9.18.7.2 Benzazocines

Benzazocines are a biologically important group of compounds because of their diverse functions. Interestingly, some benzazocines are analgesics <84JAP(K)5913760, 91MI 918-03> and some are

antagonists of analgesics <82CP1128934>. Benzazocine 1,3-diones possess antiarrhythmic activity <88USP4755505>. Benz-fused lactams have been shown to be (i) antagonists of the peptide hormone, cholecystokinin (CCK) <86EUP166353, 87USP4644050, 89JMC1681>, (ii) antagonists of angiotensin converting enzyme <83BBR108, 83BBR161, 84EUP107095, 84JMC816, 85USP4537885>, and (iii) antihypertensives <84SAP8303903, 84USP4474778, 85SAP8309532, 85SAP8503670, 85SAP8503670, 88EUP292840>. Various benzazocines with diverse structures exhibit effects on the central nervous system <82DIS(B)1850, 83MI 918-04, 84MIP54268, 87JAP(K)62212372, 88CPB2386, 90JCS(P1)1091>. A well-known class of antitumor antibiotics, mitomycins (**158**) are benzazocine derivatives <90CC468>. FR-900482 is another antibiotic (**131**), isolated from the bacterial culture, *Streptomyces sandaensis*, which has structural resemblance with mitomycin C (**158**), and FR-900482 is active against mitomycin C and vincristine-resistant P388 cells <89TL6491, 95TL1169>.



9.18.7.3 Dibenzazocines

Dibenzazocines have found major applications in the area of pharmacology. Dibenz[*c,e*]azocine and apogalanthamine analogs have been proven to be adrenergic blocking agents <85CJC1170, 85CPB1260, 85H(23)159, 85MI 918-02, 88JCR(S)8, 88JHC161, 89CPB870, 89CPB1744>. Yet other pharmacological uses such as antihistaminic, antiinflammatory, antiarrhythmic, and anticholinesterase have been mentioned <82AHC(31)115>.

9.19

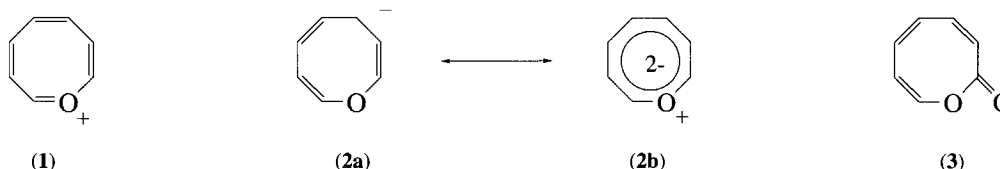
Eight-membered Rings with One Oxygen Atom

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3M Company, St. Paul, MN, USA

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9.19.1 INTRODUCTION

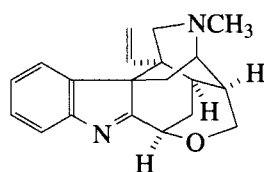
Compounds of this class have been the subject of several hundred chemical papers and a comparable number of biological papers. The abundance of biological literature reflects the occurrence of this ring system in natural products, particularly marine-based natural products. Accordingly, this chapter emphasizes the synthesis, characterization, and structures found in nature. To some extent, this emphasis is dictated by the fact that the constraints imposed by this ring system limit the number of aromatic and antiaromatic systems. For example, neither the parent 8π antiaromatic oxonium (1) nor the 10π aromatic oxocynyl anion, represented by two canonical forms (2a) and (2b), is known. The 8π systems (1) are isoelectronic with cyclooctatetraene and would be expected to be very susceptible to nucleophilic attack. There are, however, examples of both 10π aromatic benzo-annulated oxocynyl anions and 10π aromatic electron withdrawing-substituted oxocynyl anions (see Section 9.19.5). There are also some examples of some highly unsaturated systems having the nucleus shown in (3), which are 10π aromatic systems, counting the exocyclic double bond. Owing to the dearth of aromatic compounds, electrophilic substitution reactions and other reactivity typically associated with aromatic systems are severely limited.



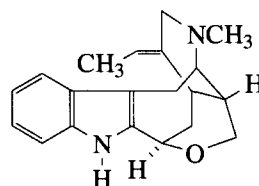
Numerous natural products feature either an oxocane or oxocene sub-unit. As a result, since the early 1980s there has been an extensive effort directed at the synthesis and characterization of these materials. In some cases, oxocanes or related eight-membered ring systems represent the sole heterocycle present in the natural product. Many marine products, particularly those found associated with gorgonian octacorals, fall into this category. The eight-membered cyclic ethers are also found in alkaloids and other complex molecules and are generally fused to other ring systems. In general, the systems that occur in nature possess either a saturated ring or a eight-membered ring with a single double bond in the ring. The most studied systems are the brevetoxins and related compounds, which are the toxic metabolites, produced by the dinoflagellates and the algae, which cause the "red tide" phenomenon. The brevetoxins consist of all *trans*-contiguously fused cyclic polyethers. Two brevetoxin skeletons have been identified and over eight x-ray structural investigations have been carried out on these toxins or chemical modified variants of these toxins (B-90MI 919-01). The structural work has been important in understanding the physiological effects of these toxins (B-90MI 919-02). It is now known that many of these toxins interfere with ion transport in some cell membranes (B-90MI 919-02, B-90MI 919-03, B-90MI 919-04, B-90MI 919-05). For example, brevetoxin B and ciguatoxin target a particular ion channel in plasma membranes causing the channels to open at lower potentials than normal. This results in increased ion permeability and depolarization (B-90MI 919-02). The biogenesis of these materials has been studied by growing the organism in isotopically labeled media. The labeling pattern suggests that the brevetoxin skeleton is not accounted for by the usual polyketide pathway and that further study is required (B-90MI 919-06).

Numerous complex polycyclic alkaloids from the *Gelsemium* species exemplified by koumine (4) and taberpsychine (5), also, contain an eight-membered ring system with one oxygen atom. Koumine is found in the Chinese plant Kou-wen (*Gelsemium elegans*) and is of interest owing to its analgesic and antitumor activity (B-88MI 919-01). The total syntheses of the antipods of (4) and (5), (+)-koumine and (+)-taberpsychine, have been achieved (90JA5220). One of the final steps in this procedure involves formation of the cyclic ether ring system (90JA5220). Koumine has also been prepared from taberpsychine and hydroxytaberpsychine (89JA786, 90H(31)325).

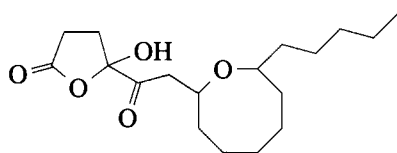
In some cases, the total synthesis has been used to prove or disprove the putative structure of a natural product. A novel oxocane structure (6) was initially proposed for the potent antifungal (–)-gloeosporone. There is little doubt that this assignment was at least partially based on the relatively common occurrence of the eight-membered ring system in other natural products. The total synthesis of (6) demonstrated that this structure was incorrect and the true structure is macrocyclic ether (7) (86TL6133, 88JA6210, 91TL537, 92JCS(P1)95).



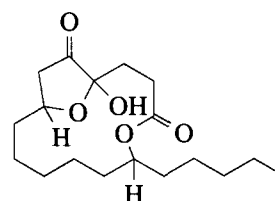
(4) (-)-koumine



(5) (-)-taberpsychine



(6)



(7)

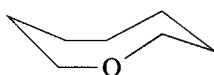
The total synthesis of natural products is also important in verifying the absolute configuration $\langle 88JA2248 \rangle$.

9.19.2 THEORETICAL MODELS

Eight-membered ring systems have been the subject of extensive theoretical effort. The large number of atoms in these systems has limited the study of these ring system by *ab initio* methods; however, a variety of semiempirical and statistical methods has been used to address the various conformational possibilities associated with this ring system. Increasingly, computational studies are found in conjunction with x-ray diffraction and NMR studies and are often used to rationalize the observed conformations and various conformational processes.

9.19.2.1 Oxocane

A molecular mechanics (MM2) study has been reported for oxocane $\langle 92JOC291 \rangle$. As in a previous force field study $\langle 80ZN(B)1479 \rangle$, the BC-3 (8) conformation is calculated to be the lowest energy conformer, favored by 1.1 kcal mol⁻¹ over the BC-1 conformer.



(8)

Barriers for interconversion between BC-3 and its enantiomer, BC-7, have been calculated. Passage through either a BC-5 or a BC-1 conformation, are calculated to be 5.0 kcal mol⁻¹ and 6.7 kcal mol⁻¹, respectively. The small barriers allow for a rapid pseudorotation between BC-3 and BC-7, even at low temperatures, and account for the symmetric spectra. NMR results on oxocane-2,2,7,7-d₄ have allowed a definitive assignment for the ¹H and ¹³C chemical shifts. Lanthanide-induced shift reagents provide compelling proof, that the lowest energy conformations are BC-3 and BC-7.

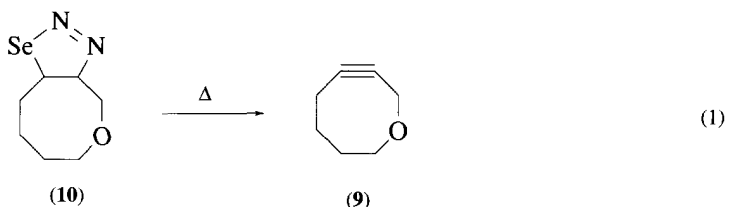
9.19.2.2 2-Oxocanone

A stochastic method coupled with the MM3(92) force field has been used to locate conformational minima in a series of lactones $\langle 93\text{MI } 919-01 \rangle$. For 2-oxocanone, 14 conformers were identified, spanning $10.02 \text{ kcal mol}^{-1}$. Of these conformers, six were in the *Z*-configuration and eight were in the *E*-configuration. The three lowest energy conformers were calculated to be in the *Z*-conformation; the first *E*-conformation is predicted to be $4.0 \text{ kcal mol}^{-1}$ above the lowest energy *Z*-conformer. Dipole moment as well as electronic absorption measurements appear to support a predominantly, but not exclusive, *E*-conformer in nonpolar fluid media. The eight-membered lactone ring system is the smallest lactone ring system, which has sufficient flexibility to allow for the more stable *Z*-configuration to exist in measurable quantities.

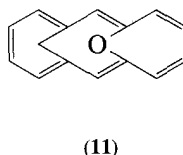
Both Wiberg and Waldron $\langle 91\text{JA}7697 \rangle$ and Allinger *et al.* $\langle 92\text{JA}6120 \rangle$ have studied lactone heats of formation (ΔH_f) using MM3 calculations; however, different parameterization sets were used. Allinger's calculations were done with a more advanced parameterization set which better accounts for the ester functionality. A ΔH_f of $-97.52 \text{ kcal mol}^{-1}$ for 2-oxocanone was calculated which compares favorably with the experimental value of $-98.3 \pm 0.6 \text{ kcal mol}^{-1}$. Strain energies were also considered. The total strain energy was divided into an inherent strain (deformations, dispersive interactions, and electrostatic interaction) and other terms, correcting for population of conformers and low-energy torsion frequencies. The total strain energy for 2-oxocanone was calculated to be $15.57 \text{ kcal mol}^{-1}$.

9.19.2.3 Other Systems

MNDO calculations on 1-oxa-2- and 1-oxa-3-cyclooctyne (**9**) indicate that both these compounds have high strain energies $\langle 90\text{CB}1411 \rangle$. 1-Oxa-2-cyclooctyne is calculated to be 38 kJ mol^{-1} less stable than (**9**). A synthetic procedure for (**9**) was also reported. The critical step (Equation (1)) involves the thermal fragmentation of 6,7,8,9-tetrahydro-5*H*-oxocin[3,4-*d*][1,2,3]selenadiazole (**10**). Cyclopentadienone reacts with 1-oxa-3-cyclooctyne in benzene in essentially quantitative yield. 1-Oxa-2-cyclooctyne could not be isolated from the analogous thermal decomposition of 6,7,8,9-tetrahydro-5*H*-oxocin[3,2-*d*][1,2,3]selenadiazole. Nor could it be trapped by cyclopentadienone, indicating the transient nature of this compound.



The molecular structure of oxy-bridged annulenes has been studied using a range of semiempirical methods including: HF/STO-3G, HF/4-31G, MP2/STO-3G, MNDO, and correlation corrected MNDO $\langle 86\text{JA}4768 \rangle$. The barrier to inversion, at the ether oxygen, of 1,6-methano-8,13-oxido[14]-annulene (**11**) was predicted to be 27 kcal mol^{-1} .



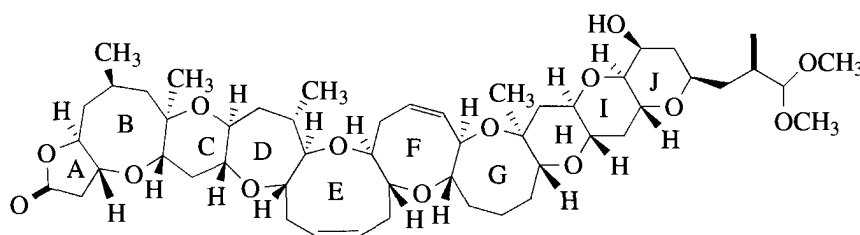
Conformational changes associated with the flipping of the pentamethylene chain in 9,11-diphenyl[5](2,6)-pyranophan-10-one have been observed by NMR methods $\langle 90\text{CB}1587 \rangle$. At room temperature, the conformational rearrangement is facile, however, at 213 K the flipping slows. The barrier for ring inversion between the distorted boat of dibenzo[*b,g*]oxacine-5,7-dione has been reported to be $12.3 \text{ kcal mol}^{-1}$ $\langle 85\text{ZN}(\text{B})858 \rangle$.

9.19.3 EXPERIMENTAL STRUCTURAL METHODS

Owing to the lack of aromatic structures found for this ring system, many of the experimental methods such as electronic absorption spectroscopy, Raman spectroscopy, and infrared spectroscopy are mainly useful in characterizing the substituents attached to the ring. The most useful methods for characterizing compounds of this class are x-ray diffraction, NMR, and mass spectroscopic methods. For many of the natural products, polarimetry is important. The multipulsed NMR techniques have proven particularly powerful in characterizing large molecular-weight natural products.

9.19.3.1 Natural Products

The structures of numerous brevetoxins and structurally similar toxins have been determined (<81JA6773, 82TL2535, 82TL5521, 85TL2865>). Two basic structural types have been identified. The x-ray crystal structure of a chiral 1,3-dioxalane derivative of brevetoxin B was used to confirm the absolute configuration (<86CC1656>). The x-ray structure of brevetoxin A, m.p. 197–199°C and 218–220°C (double melting point), the most potent ichthyotoxin brevetoxin proved problematic. However, the structure of a dimethyl acetal derivative of brevetoxin A (**12**), m.p. 233–235°C, was determined. There are two oxocane and one oxocene sub-units in this molecule. One important feature is a 90° bend at the eight-membered oxygen-containing G ring. In contrast, brevetoxin B, is essentially planar (<86JA514>), in which the G ring possesses the boat-chair conformation. A conformational process associated with this ring system is indicated by NMR; one possibility is a boat-chair-to-crown interconversion. The conformational flexibility has been postulated to account for the greater toxicity of this compound.

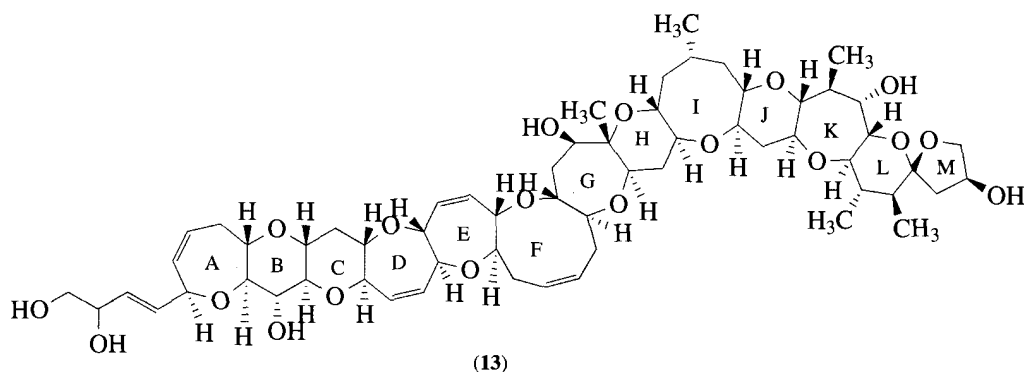


(12)

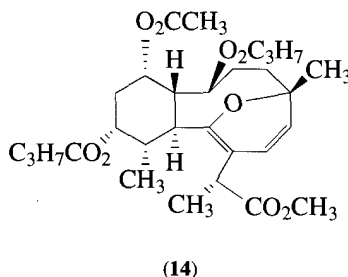
Ciguatoxin is the principal causative agent for the food poisoning referred to as ciguatera. Ciguatoxin has been shown to be a potent ichthyotoxin, ca. 20 times more potent than brevetoxin B (<92MI 919-02>). Ciguatoxin has eluded characterization by x-ray methods, owing at least in part, to the relatively small amount of material available and the difficulty associated with culturing this material. Another complexity is that there appears to be several structurally related forms of the toxins (<84MI 919-01, 91MI 919-01>).

The high-resolution FAB (fast atom bombardment) mass spectrum of one of these fractions designated ciguatoxin-1 (**13**) reveals a parent mass (MH)⁺ at 1111.5843 ± 0.0053, consistent with the molecular formula of C₆₀H₈₆O₁₉. A *tour de force* NMR investigation (<90JA4380>), utilizing 2-D NMR, NOE (nuclear Overhauser effect), and ¹³C NMR methods, has indicated that the structure of (**13**) is comprised of 12 contiguously fused cyclic ethers and a terminating spiroacetal (7/6/6/7/7/9/7/6/8/6/7/6-spiro-5). The NMR of (**13**) is temperature-dependent and conformational changes associated with the centrally located nine- and seven-membered rings are indicated (<90JA4380, 92TL525>). A less-polar toxin, gambertoxin-4b, was also characterized. Gambertoxin-4b has the same basic skeleton as ciguatoxin; however, it is less oxygenated. A terminal *trans*-butadiene group replaces the butenediol at one terminus and the hydroxy group on the terminal spiro-ring is replaced by a hydrogen atom.

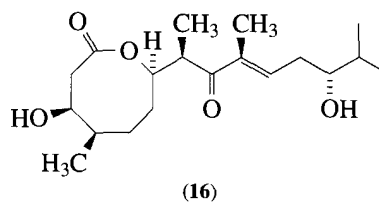
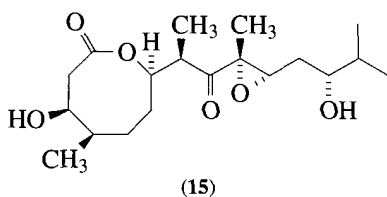
Maitotoxin is associated with the dinoflagellate *Gambierdiscus toxicus*. Unlike the brevetoxins and ciguatoxin, the major physiological effect of maitotoxin is on the Ca²⁺ transport system. In spite of the large molecular weight (3422 Da), the structure of this complex polyether has been postulated on the basis of NMR and FAB MS experiments (<93G367, 93JA2060>). This assignment was accomplished by oxidatively degrading maitotoxin with NaIO₄, followed by reduction with NaBH₄. This process gave rise to two major fractions, designated A and B. The B fragment contained an oxocene unit.



The structure of methyl briareolate (**14**), isolated from gorgonian octocoral, m.p. 165–167°C, $[\alpha]_D^{25}$; +130.9° (c 0.11, chloroform) has been determined by x-ray diffraction and 2-D NMR methods <92TL7761>. The compound is a diterpenoid with the briarein skeleton.



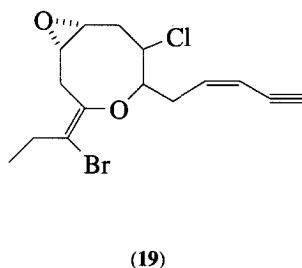
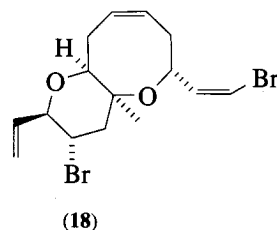
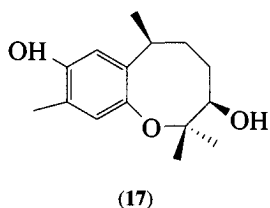
The structure of octalactin A (**15**), m.p. 155–157°C, $[\alpha]_D^{25}$; –14.0° (c 1.80, chloroform), derived from the marine microorganism *Streptomyces* sp., has been determined <91JA4682>. The solid-state structure shows the eight-membered ring to exist in the boat–chair conformation with an *E*-conformation for the lactone. Calculations (MM2) on a trisubstituted eight-membered model compound indicate that the observed boat–chair conformation is one of six conformations within 1 kcal mol^{–1} of the ground state. (**15**) is cytotoxic to several tumor lines; however, the closely related octalactin B (**16**) $[\alpha]_D^{25}$; –12.3° (c 5.60, chloroform), from the naturally occurring sample, exists as a liquid at room temperature and shows no cytotoxicity.



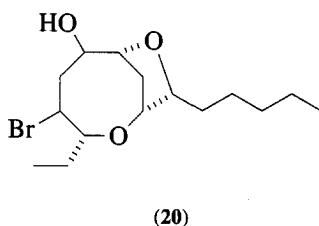
The structure of the sesquiterpene heliannuol A (**17**), m.p. 80–81°C, $[\alpha]_D^{25}$; –55.4° (c 0.30, methanol) has been determined by both NMR and x-ray diffraction techniques <93TL1999>. The structure of microcladallene B (**18**) $[\alpha]_D^{25}$; +96.0° (c 0.50, acetone) has been determined by x-ray diffraction <84CC153>; whereas the structures of related compounds microcladallene A, m.p. 90.5°C, $[\alpha]_D^{25}$; +114.0° (c 0.50, acetone) and microcladallene C, a viscous liquid with $[\alpha]_D^{25}$; +116.7° (c 0.50, acetone), have been deduced on the basis of mass spectral and NMR spectroscopic evidence.

Several metabolites isolated from the red alga *Laurencia venusta* Yamada, which contain a pentyne side chain, have been isolated <83CL779>. The structure of (3*Z*)-epoxyvenustin (**19**), m.p. 72–73°C, $[\alpha]_D^{25}$; –44.1° (c 1.00, chloroform) has been determined by x-ray diffraction methods.

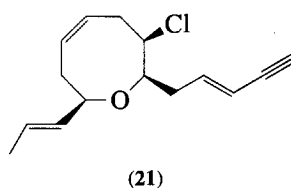
Based on this structure and using other spectroscopic methods, assignments of the closely related (3*Z*)-venustin $[\alpha]_D^{25}$; –103.0° (c 1.14) and (3*Z*)-venustinene, m.p. 38–39°C, $[\alpha]_D^{25}$; –184.0° (c 1.00) have also been made.



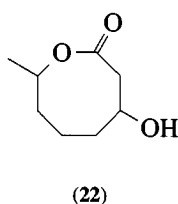
The x-ray structure of (10*R*)-10-bromo-10-deoxyhexahydrolaurefucin (**20**) has been determined; the eight-membered ring ether exists in the boat-chair conformation <83BCJ2523>.



The structure of the alkynic cyclic ether, (+)-laurenyne (**21**), m.p. 78–80°C, $[\alpha]_D^{25}$; +22.64° (c 2.35, chloroform), has been determined <80TL4951>. The absolute configuration was initially proposed to be 2*S*,7*S*,8*S* based on statistical methods and by direct comparison of the Friedel pairs with the Bijvoet ratios. In the late 1980s, (–)-laurenyne, m.p. 78–80°C, $[\alpha]_D^{25}$; –20.0° (c 2.00, chloroform), was synthesized <88JA2248>. This work shows that the absolute configuration of the naturally occurring product must be 2*R*,7*R*,8*R*, the structure indicated in (**21**).

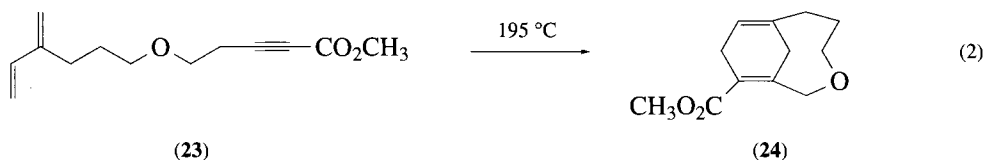


The structure of 4,7-didehydroneophysalin B, which possesses a central eight-membered lactone ring, has been determined <91AX(C)2188>. Several of the sp^3 carbon atoms show significant distortions from the idealized tetrahedral angle geometry. The structure of methyl neoliacinate, a sesquiterpene, has been determined <87CC1861>. The absolute configuration of isoprelaurefucin <86BCJ2953> has been determined by spectroscopic methods. The structure of cephalosporolide D (**22**), a product of fermentation of the fungus *C. aphidicola*, has been assigned <85JCS(P1)843> on the basis of NMR spectroscopic evidence.

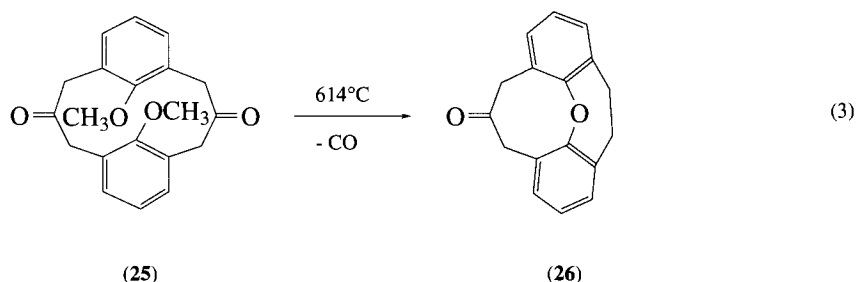


9.19.3.2 Polycyclic Systems

The eight-membered ring in 5,9-dibromo-13-oxatricyclo[8.2.1.0^{2,6}]tridecane is in a distorted crown conformation <87AX(C)1961>. 6-Chloro-10-oxabicyclo[5.2.1]decane-2,3-diol has a structure in which the eight-membered ring possesses nearly mirror symmetry through the plane bisecting the furan unit <90AX(C)1655>. Intramolecular Diels–Alder cycloaddition of (23), shown in Equation (2), results in an interesting highly strained bridgehead diene (24) <90TL6843>. The topological consequence of the cyclic constraint in (24) is to induce significant distortion of the double bonds from planarity.



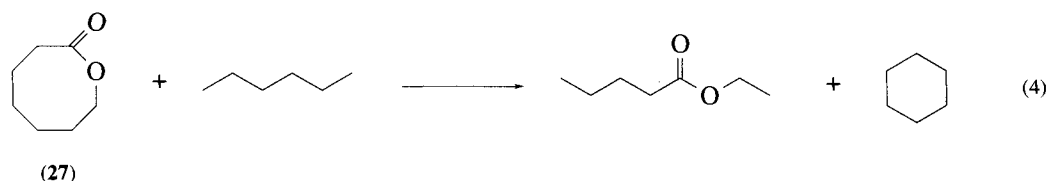
Pyrolysis of dimethoxy[3.3]metacyclophane-dione (25) (Equation (3)) results in the formation of oxa[3.2.1]cyclophane (26), m.p. 185–186 °C. The structure of (26) was determined by x-ray methods; the eight-membered ring oxygen ring has nearly mirror symmetry through the plane defined by the cyclic ether oxygen and the carbonyl group <92CB1283>.



The tub conformation for 9,11-diphenyl[5](2,6)-pyranophan-10-one has been determined by x-ray diffraction methods <90CB1587>. The structure of a novel dibenzo[*c,f*]oxocane spiro compound, derived from the reaction of two benzocyclopropene and diphenylcyclopropenone, has also been reported <90ZN(B)1577>.

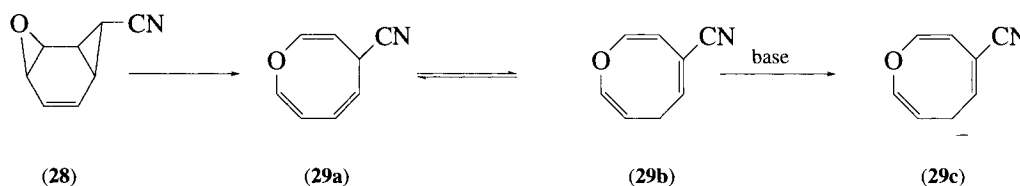
9.19.4 THERMODYNAMIC ASPECTS

There are very few thermodynamic studies on eight-membered ring systems with one oxygen atom. Ideal gas thermodynamic properties for oxocane, as well as other oxygen-containing heterocycles have been compiled <92MI 919-01>. The ΔH_f for oxocane was estimated to be $-225 \text{ kcal mol}^{-1}$ at 298.15 °C. (The estimate was obtained by assuming that the change in enthalpy between cyclohexane and tetrahydro-2*H*-pyran is the same as the difference between cyclooctane and oxocane.) In this same study, a normal coordinate analysis was performed on oxocane; the vibrational spectra was calculated using force constants transferred from oxepane. The estimated error in the frequencies using this approach is 50 cm^{-1} . Wiberg and Waldron <91JA7697> have determined both the enthalpies of hydrolysis and the enthalpies of reduction of various lactones to their corresponding α,ω -alkane diols using calorimetry. Conversion of these to gas-phase values and then applying thermochemical cycles, the enthalpies of formation of the lactone were calculated. For 2-oxocanone (27), the $\Delta H_f(l) = -98.3 \pm 0.6 \text{ kcal mol}^{-1}$. Using the isodesmic reaction (Equation (4)), the strain energy in heptanolactone was calculated to be $12.4 \pm 0.8 \text{ kcal mol}^{-1}$ based on the heats of formation of 2-oxocanone (from reduction). This strain value was the highest for any of the lactones (5–14-membered rings) studied.



9.19.5 REACTIVITY OF FULLY CONJUGATED RINGS

There are very few aromatic or antiaromatic molecules which fall into this ring system. A benzo-annulated oxocinyl anion was previously studied <80AG(E)393>; some aromatic nature (10π system) was inferred from the acidity of the corresponding conjugate acid; however, no significant shielding of the benzenoid protons could be detected by NMR. The cyanooxocinyl anion (**29c**) has been prepared <87TL2513>, conjugate acids of (**29c**) were prepared by the irreversible $\pi 2 + \sigma 2 + \sigma 2$ -cycloreversion of *cis*-oxa-bis- σ -homobenzene. Initially, (**29a**) was formed which rearranged to (**29b**). Structure (**29b**) rapidly polymerizes on exposure to air; however, treatment of (**29b**) with base, under anaerobic condition, resulted in generation of the oxocinyl anion (**29c**) (Scheme 1). The planarity (**29c**) was indicated by comparison of the proton and carbon NMR spectra by comparison to the (**29b**) <87TL2517>. An upper value of 30 was established for the pK_a of (**29b**).



Scheme 1

9.19.6 REACTIVITY OF NONCONJUGATED RINGS

For this ring system, the reactivity is dominated by the reactivity at the carbon atoms in the ring system and therefore this discussion is relegated to the following section.

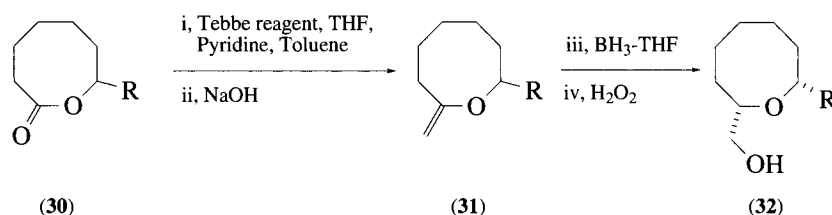
9.19.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Mono-substitution in all but the 5-position in oxocane results in a chiral center, accounting for the optical activity in many natural products. (Substitution at the 5-position for some conformations such as the crown or chair-chair would not give rise to a chiral center; however, for some boat-chair and other less symmetric conformations, a chiral center could be generated. This issue appears not to have been specifically addressed in the literature.) The base-catalyzed isomerization of some 2,8-disubstituted oxocane derivatives has been studied. It has been found that the *cis*-geometry is preferred over the *trans*-geometry <88TL4333>.

9.19.7.1 Reactivity of Lactones at the Carbonyl Group

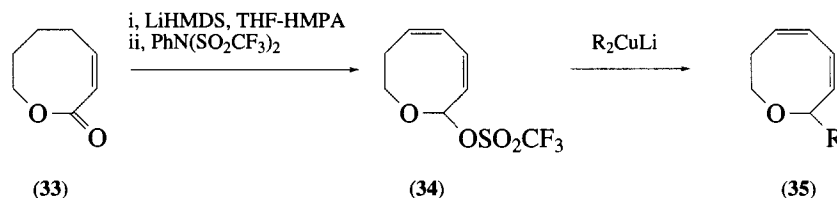
The treatment of 2-oxocanone with $\text{NaBH}_4/\text{BH}_3$ or $\text{LiAlH}_4/\text{AlCl}_3$ in ether does not result in reduction of the carbonyl group; however, the photochemically-induced free radical reduction with HSiCl_3 is reported to proceed cleanly in 44% yield <92JOC291>.

Tebbe reagent, $\text{Ti}(\text{Cp})_2(\mu\text{-CH}_2, \mu\text{-Cl})\text{Al}(\text{CH}_3)_2$ reacts with 8-alkyl-2-oxocanones (**30**) to give the unstable 2-exo-methylenalated species (**31**). Reduction of (**31**) with borane-THF, followed by oxidation with hydrogen peroxide yields the 2,8-disubstituted oxocanes (**32**) (Scheme 2). The predominant product is the *cis*-alcohol (**32**) favored by a ratio of ca. 10:1 over the *trans*-alcohol <86CC565>. This synthetic strategy was applied to the syntheses of both lauthisan and laurenan.



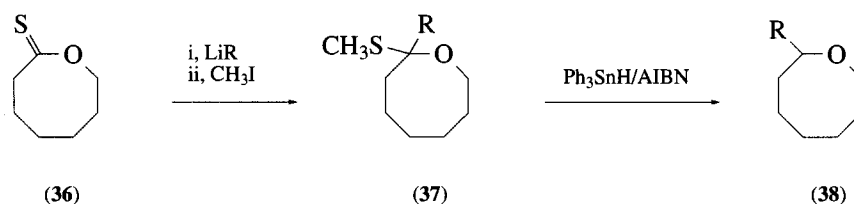
Scheme 2

Attempts to prepare enol triflates by reacting 2-oxocanones with LiHMDS (lithium 1,1,1,3,3,3-hexamethylidisilazane) THF-HMPA and $\text{PhN}(\text{SO}_2\text{CF}_3)_2$ resulted in oligomeric materials, apparently due to a reaction between the carbonyl oxygen and a hydrogen on the C-4 atom <90CL761>. In contrast, the unsaturated lactone (33) can be efficiently converted to the dienol triflate (34) using the above reagents. (34) can then be coupled with lithium dialkylcuprates to give 2-alkyl oxocenes (35) in good yields (61–82%) (Scheme 3). This strategy was employed in a six-step synthesis of the natural product lauthisan.



Scheme 3

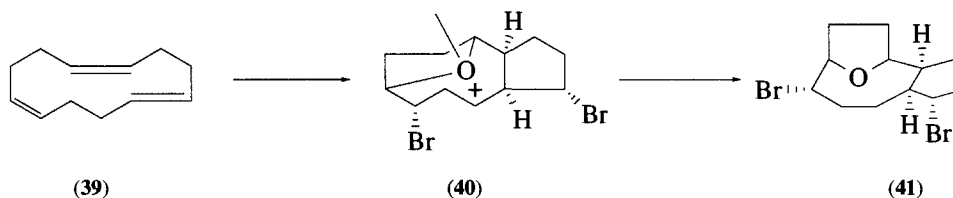
Lawesson's reagent reacts with 2-oxocanone in refluxing toluene to give a 40% yield of 2-oxocanethione (36) <90JA6263>. Reaction of (36) with alkyl lithium reagents proceeds nucleophilically to generate a thiolate, which can be *S*-alkylated with methyl iodide to give (37); the sulfur group can be removed by treatment with triphenyltin hydride and AIBN to give 2-alkyloxocane (38) in high yields (Scheme 4). In related chemistry, the monothioketal, 2-methylthio-2-(1-propenyl)-oxocane (37; $\text{R} = 1\text{-propenyl}$) rearranges when treated with acid to form 2-[2-(methylthio)-propylidene]oxocane <93JOC506>.



Scheme 4

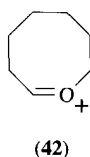
9.19.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO THE RING HETEROATOMS

Hypervalent intermediates are invoked in several reaction mechanisms <88TL2097>. For example, in the bromination of *E,Z,Z*-cyclododeca-1,5,9-triene (39) in methanol, demethylation of a tetrahydrofuranium ion intermediate (40) is postulated in the formation of the novel tricyclic (41) (Scheme 5) <87AX(C)1961>.



Scheme 5

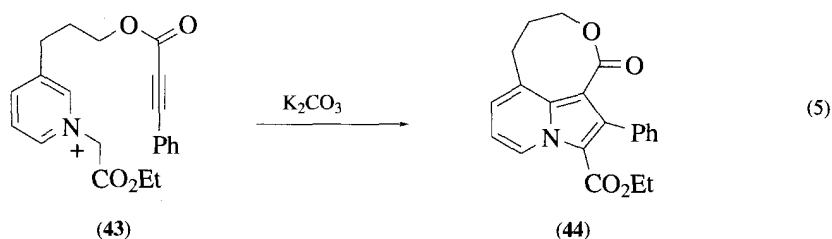
Oxocanyl carbenium ions (42) are strongly indicated in the Lewis acid-catalyzed cyclization of 5-hexenylacetals. The evidence for formation of these species includes: (i) the presence of aldehyde by-products; (ii) the isolation of 2-alkoxyoxocanes (oxocanylacetals); (iii) intramolecular trapped products for some unsaturated acetal derivatives; and (iv) the formation of 2-alkylated oxocanes when alkylaluminum complexes are used as the Lewis acid catalyst.



9.19.9 RING SYNTHESSES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

9.19.9.1 1,3-Dipolar Cyclizations

Salts of 3-[3-(phenylpropynoyloxy)propyl]-*N*-aminopyridinium (**43**) (Equation (5)) undergo dipolar addition to form tricyclic pyrazolo[1,5-*a*]pyridines (**44**) <83H(20)201, 85JSC(P1)379>. *N*-Methoxycarbonylmethyl-3-[3-(phenylpropynoyloxy)propyl]pyridinium salts undergo a similar dipolar addition to give indolizine derivatives.

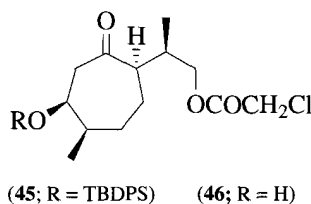


9.19.10 RING SYNTHESSES BY TRANSFORMATION OF ANOTHER RING

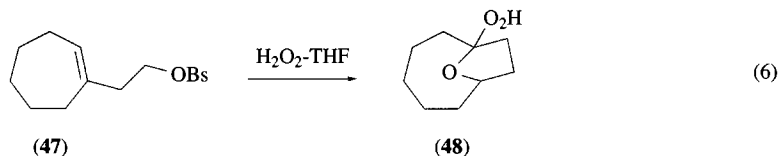
9.19.10.1 Ring Expansions of One Atom

The Baeyer–Villiger oxidation is an important route to 2-oxocanones (see e.g., <94JA8378> in the preparation of octalactin precursors). A variety of reagents can be employed to accomplish this transformation. The reaction of 2-pentyl- and 2-hexylcycloheptanone with $\text{CF}_3\text{CO}_3\text{H}$, Na_2HPO_4 in CH_2Cl_2 resulted in the corresponding 2-alkyl heptanolides in 77% and 68% yields, respectively <86CC565, 88TL4333, 92JCS(P1)83>. Cycloheptanone reacts with permaleic acid, prepared by reacting urea–hydrogen peroxide with maleic anhydride, in 64% yield <93H(36)1075>. Cycloheptanone is transformed into 2-oxocanone in 50% yield by treatment with bis(trimethylsilyl)peroxide and SnCl_4 or $\text{BF}_3 \cdot \text{OEt}_2$ <83BCJ2029>. The oxidation of cycloheptanone to 2-oxocanone by oxygen at room temperature is catalyzed by nickel β -diketonates in the presence of an aldehyde; the yield is 33% <91CL641, 92JAP04275286>. Conversion of cycloheptanone to 2-oxocanone has been accomplished in 23% yield by the reaction of ozone in dichloromethane in the presence of “wet-alumina” <91CL331>. Cycloheptanone has also been reported to be oxidized by sodium perborate to give a 24% yield of 2-oxocanone <91USP4988825>. Many of the above oxidation reactions, which give low-to-moderate yields of 2-oxocanone, are much more effective for other ring systems.

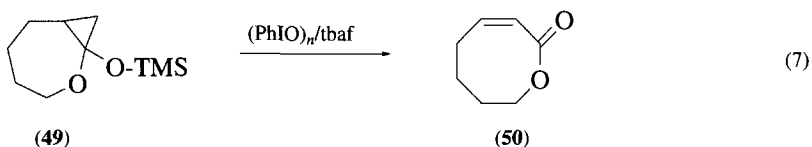
Substitution on the cycloheptanone ring can affect the efficiency of the Baeyer–Villiger reaction. Oxidation of the silyl-protected cycloheptanone (**45**) proceeds in poor yield; however, the oxidation of the deprotected cycloheptanone (**46**) is very efficient <94JA8378>.



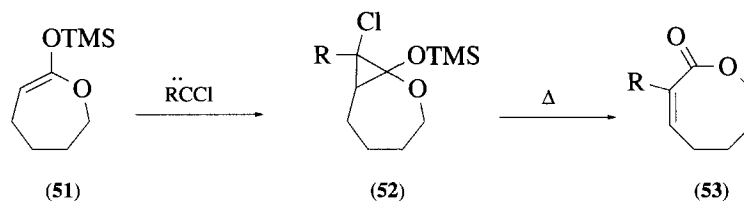
Reaction of cycloheptenylethyl brosylate (**47**) with 1 : 1 90% H_2O_2 -THF results in the formation of an oxa-bridged, hydroperoxy hemiketal (**48**) in 72% yield (Equation (6)) <83JA5709>. This reaction is believed to occur via generation of a cyclobutane-containing intermediate which then undergoes a Criegee-type rearrangement.



Reaction of iodosobenzene and tbaif in dichloromethane with trimethylsilyloxy-2-oxabicyclo-[3.1.0]hexane (**49**) results in a 62% yield of the α,β -unsaturated lactone (**50**) (Equation (7)) <90TL197>.

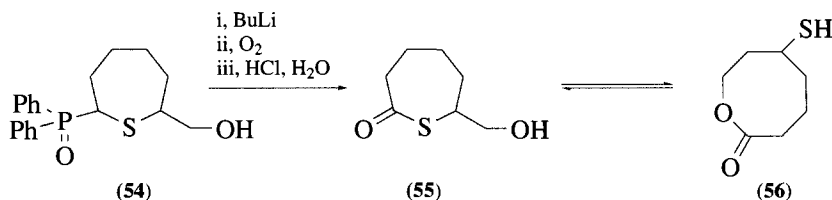


An iterative process for increasing the number of carbon atoms in medium-ring lactones has been developed <90JOC4807>. In this procedure, trimethylsilyl enol ethers (**51**), prepared from lactones, are reacted with chlorinated carbenes to give 1-[(trimethylsilyl)oxy]-2-chlorobicyclo[2.1.0]oxanes (**52**), heating these bicyclic compounds results in a rearrangement to form the α,β -unsaturated lactones (**53**) (Scheme 6). The conversion of seven-membered rings to eight-membered rings occurs in high yield (77–81%).



Scheme 6

The cyclothioether (**54**) can be transformed to a mixture of the seven-membered thiooxepin (**55**) and the thiol-substituted oxocanone (**56**), as indicated in Scheme 7 <82JA2046>. The ratio of (**56**) : (**55**) was 2.5–3 : 1; a true equilibrium constant could not be determined owing to competing decomposition reactions. Apparently, the energy benefit associated with acyl transfer from sulfur to oxygen, resulting in formation of the thiolactone, is sufficient to overcome the strain effects associated with the larger ring system.

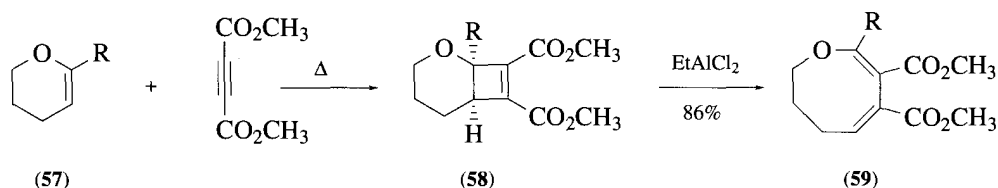


Scheme 7

9.19.10.2 Ring Expansions of Two Atoms

Nicolaou *et al.* have reported <87TL1501> that the bicyclic system (**58**), generated by reacting 3,4-dihydro-2*H*-pyran (**57**) with dimethyl alkenedicarboxylate (Scheme 8), converts to the eight-

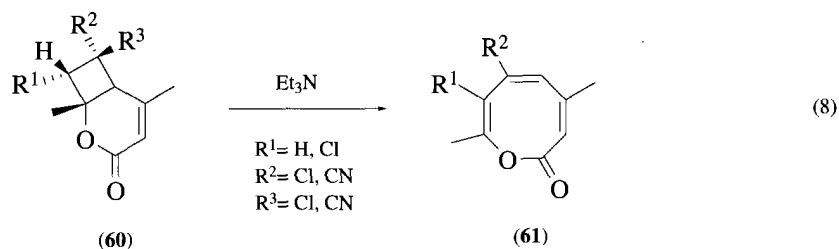
membered oxocyclic system (59) upon heating. Better yields were achieved when a Lewis acid catalyst (EtAlCl_2) was added.



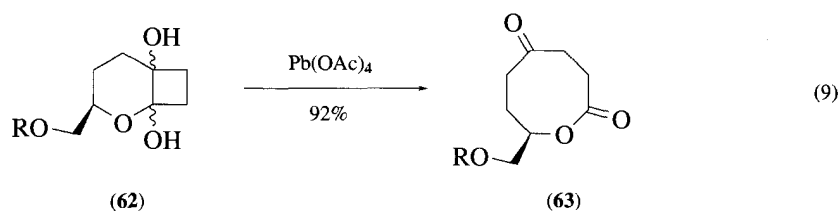
Scheme 8

The reaction of 6-oxo-2,5-diphenyl-6*H*-1,3,4-oxadiazine with cyclobutene results in the loss of nitrogen and formation of an eight-membered ring lactone (85CB2940). Similarly, 5,6-dihydro-2-(triphenylphosphoranylideneamino)-4*H*-pyran-3-carbonitrile reacts with various alkynes to give 7,8-dihydro-6*H*-oxocines (86CB3515).

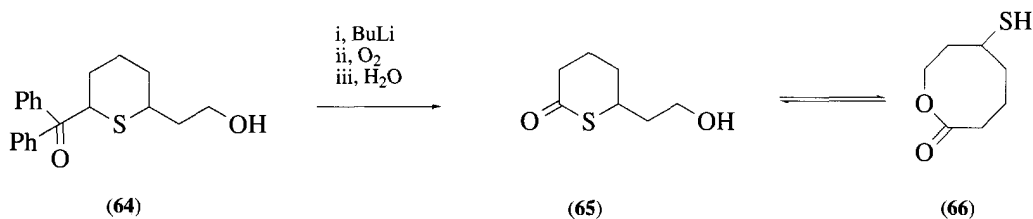
The ring expansion of chlorinated derivatives of 2-oxabicyclooctenones (60) results in monocyclic oxacyclooctatrienones (61) when refluxed with triethylamine ethanol (Equation (8)) (84CL1503). (There is no discussion on the geometry of this potentially aromatic system.) The carbonyl stretch frequency for (61), where $\text{R}^1 = \text{R}^2 = \text{Cl}$, is at 1720 cm^{-1} (KBr). This compares to a carbonyl stretch frequency for 2-oxocanone of 1730 cm^{-1} (film) (92JOC291), suggesting some involvement of the carbonyl in the extended π -system.



Oxidation of 2-oxabicyclo[4.2.0]octane (62) in toluene with $\text{Pb}(\text{OAc})_4$ (Equation (9)) affords the lactone (63) in 92% yield (92TL4345).



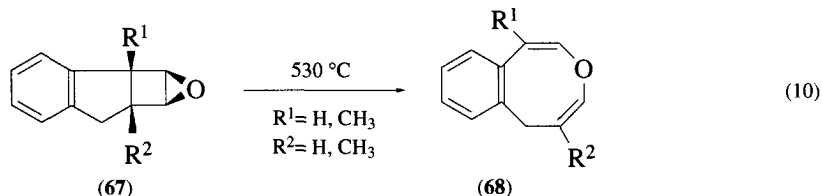
The cyclic thioether (64) can be transformed to a mixture of (65) and thiol-substituted oxocanone (66), (Scheme 9) (82JA2046). The acyl transfer was not as facile for this system as it was for (55) going to (56) (Scheme 7), perhaps reflecting the greater stability of the six-membered ring thiol ester. The formation of substantial amounts of dimeric products was also observed.



Scheme 9

9.19.10.3 Ring Expansions of Three or More Atoms

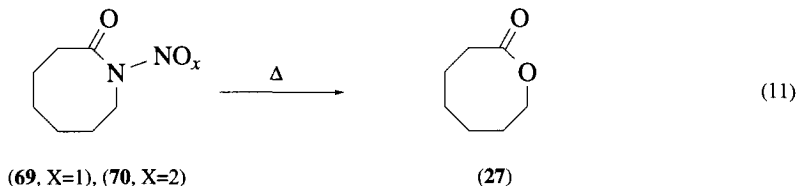
6*H*-3-Benzoxocin (**68**) was obtained in 10–15% yields by flash vacuum pyrolysis of the 8-oxabenzoc[*c*]tricyclo[5.1.0.0^{2,6}] octane (**67**) (Equation (10)) <90H(31)1769>.



The photo-induced cleavage of fused bonds in 2-oxabicyclo[3.3.0]octano-1-ols can result in oxacanones. For example, irradiation of 22-hydroxy-3 β -methoxy-23,24-dinor-5 α -cholan-16-one-16,22-hemiacetal in the presence of diacetoxyiodobenzene and iodine results in efficient conversion to the corresponding lactone system in 82% yield <91JCS(P1)3349>. The reaction proceeds via retro-Claisen rearrangement. Boeckman *et al.* have reported the conversion of a vinylcyclobutanediol to the dihydrooxacene carbaldehyde with Dess–Martin periodinane in CH₂Cl₂ in 88% yield <93JOC1295>.

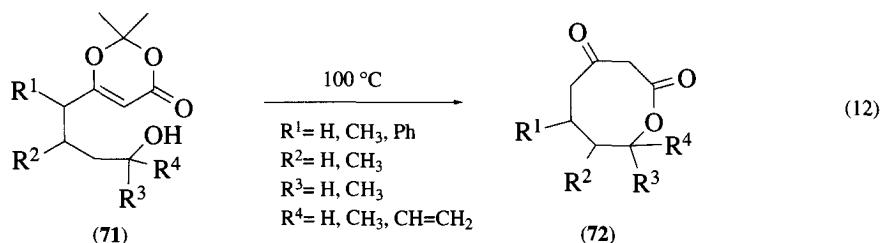
9.19.10.4 Conversion of Other Heterocycles

Nitrosolactam (**69**) and nitrolactam (**70**) react to form 2-oxocanone (**27**) in high yield (>80%) at room temperature in carbon tetrachloride (Equation (11)) <89T863>. Since the nitrosolactones and nitrolactams are ultimately derived from the lactams, this method offers little advantage over traditional Baeyer–Villiger oxidations to achieve these ring systems.



2-Methyl-2-[3-(3'-methoxy-2'-hydroxy)phenyl]pentylloxirane has been reported to undergo a ring opening to produce the 3-hydroxy-3,4,5,6-tetrahydro-2*H*-[1]benzoxocine <88JHC685>. Mass spectral results on the benzoxocine were also reported.

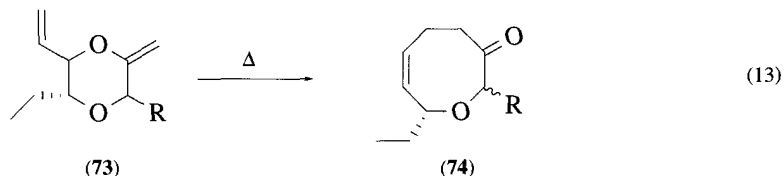
A procedure (Equation (12)), starting with dioxolenones (**71**) to give eight-membered ring β -ketolactones (**72**), has been described <90CC836>. The key step is a thermolysis reaction which results in extrusion of acetone and formation of an acyl ketene which reacts intramolecularly with the hydroxy functionality in >90% yield.



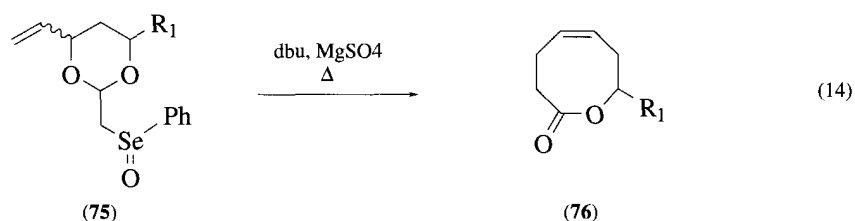
9.19.10.5 Claisen Rearrangement

The Claisen rearrangement is a powerful method for generating various unsaturated oxacanones with a high degree of regio- and stereoselectivity. Owing to this selectivity, several investigators

have incorporated a Claisen-rearrangement step in the synthesis of a variety of natural products. Paquette and Sweeney <90JOC1703> have reported a synthetic scheme to prepare enantiomerically pure lauthisans based on the Claisen rearrangement of (73) to produce (74) (Equation (13)).



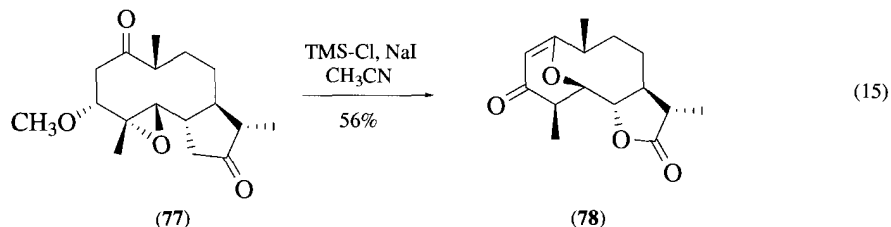
Thermolysis of 1,3-dioxane (75) (Equation (14)) gives the eight-membered ring unsaturated lactone (76) in 84% yield, presumably through a vinyl ketene acetal, which undergoes a Claisen rearrangement <86CC325>.



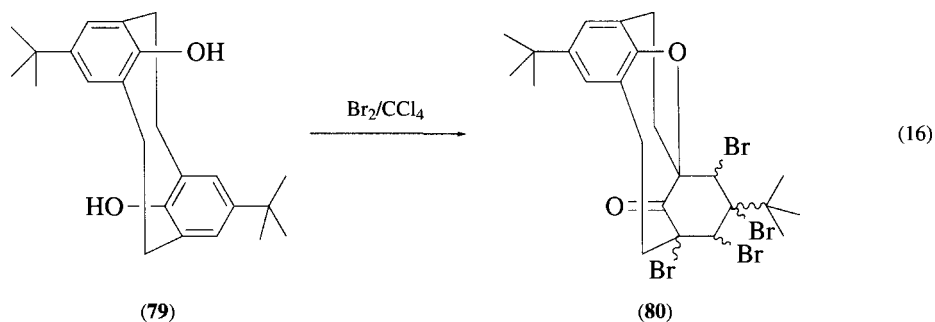
Cis- and *trans*-isomers are generated in a 1 : 1.43 ratio. This reaction was the key step in a concise synthesis of *cis* and *trans*-lauthisan <90T4487>. A Claisen rearrangement of enol silyl ether was also used to produce the gelsemine skeleton <87TL1035>.

9.19.10.6 Ring Contractions

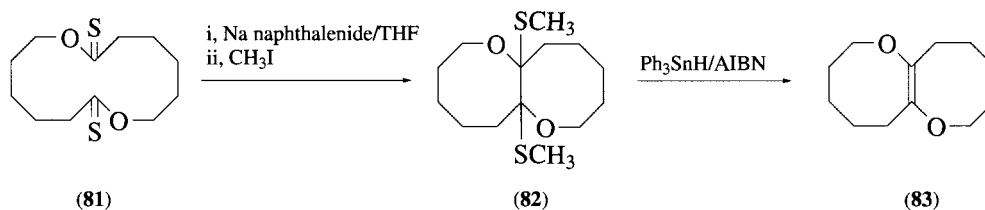
Although eight-membered ring ethers are generally prepared from smaller ring systems or by cyclization reactions, they are also accessible via condensation of larger ring systems. Ger-macronolides containing a pyran ring were obtained by reacting epoxide (77) with iodotrimethylsilane (Equation (15)), generated *in situ* by the reaction of bromotrimethylsilane with NaI in acetonitrile, to yield (78) in 56% <92TL4747>. This transformation involves a number of reactions including a Markovnikov-sense epoxide ring opening, a 1,2-hydride shift and demethylation to form an intermediate hydroxydiketone, followed by hemiketalization and dehydration to form the product.



Another example of an oxidation reaction resulting in the transformation of a larger ring into an eight-membered ring system is shown in Equation (16); the bromination of 5,13-di-*t*-butyl-8,16-dihydroxy[2.2]metacyclophanes (79) results in formation of 5,6'-*t*-butyl-3,8'-ethanospiro[3,4,5,6-tetrabromocyclohexan-2-one-1,2'-chroman] (80) (Equation (16)) <92JOC6368>. This product readily loses bromine to produce other spiro-products which contain eight-membered rings with one oxygen atom. Treatment of (79) with $\text{K}_3[\text{Fe}(\text{CN})_6]$ gives 5,6'-*t*-butyl-3,8'-ethanospiro[cyclohexa-3,5-dien-2-one-1,2'-chroman].



Another example of a ring contraction is shown in Scheme 10. It is postulated that both dithio-carbonyl groups in macrodithiolactone (**81**) are reduced to generate a diradical which couples to form a bicyclic product (**82**), subsequent *S*-alkylation, followed by removal of the sulfur groups complete the sequence. The overall yield of the fused product (**83**) is ca. 50%. Similar schemes have been used to build more complex polycyclic ring systems <90JA3040>.



Scheme 10

In addition, a number of thermolysis reactions, see for example Equation (3), results in ring-contracted products.

9.19.11 SYNTHESSES OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

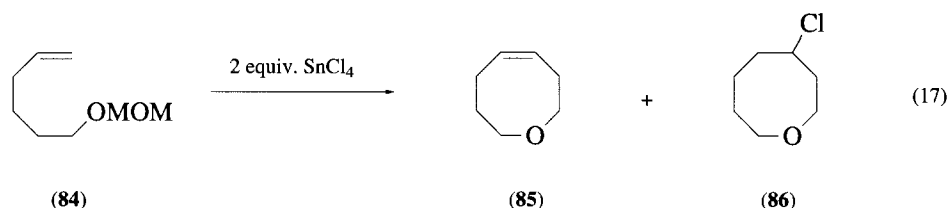
There has been a tremendous increase in the methodology available to assemble medium-size ring systems during the last decade. The impetus for this work is to develop efficient routes to various natural products. In spite of the perceived problems with cyclizing medium-size ring systems, numerous high-yield processes have been developed starting with acyclic precursors.

9.19.11.1 Syntheses of Lactones from Acyclic Precursors

Some efficient preparations of lactones from open chain precursors involve the use of special catalysts. For example, ω -hydroxy esters react at elevated temperatures with ZrO₂ or ZrO₂ treated with TMS-Cl to give 2-oxocanone in 35% <92CL571> and 77% yield <93BCJ1305>, respectively. The use of the silylated ZrO₂ has been the subject of a patent application <93MIP9325308>. This is a direct, relatively high yield route to oxocanone; however, the scope of the reaction and the sensitivity to other functional groups have not been explored.

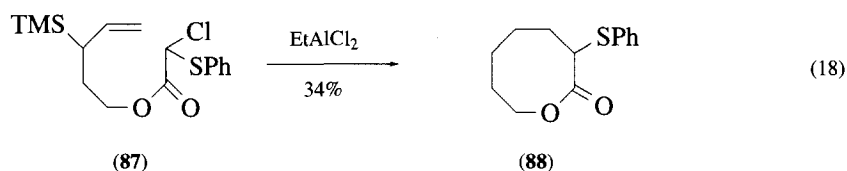
Overman and co-workers <86JA3516, 88JA2248, 90JA4386> have directly cyclized methoxymethylether of 5-hexen-1-ol (**84**) with two equivalents of SnCl₄ at 4°C for 25 min (Equation (17)). An unsaturated product, *cis*-3,6,7,8-tetrahydro-2*H*-oxocin (**85**), and a saturated product, 4-chlorooxocane (**86**), in 20% and 10% yield, respectively, have resulted. The reactions occur with high regio- and stereoselectivity; the only double-bonded species detected is the Δ^4 -oxocene. The previously mentioned oxonium intermediate, (**42**), is believed to be responsible for the formation of the saturated product. Although reactions of this type occur in modest yields, the availability of the starting materials, the regio-selectivity and the flexibility to run these reactions at reasonable concentrations make this route attractive. Laurenyne has been prepared with this ring formation route as a key step <88JA2248>. The ratio of unsaturated products to saturated products increases with increasing

electron-donating ability of substituents ($H < SiR_3 < SR$) placed at the 5-position of the starting 5-hexenyl acetal <90JA4386>.



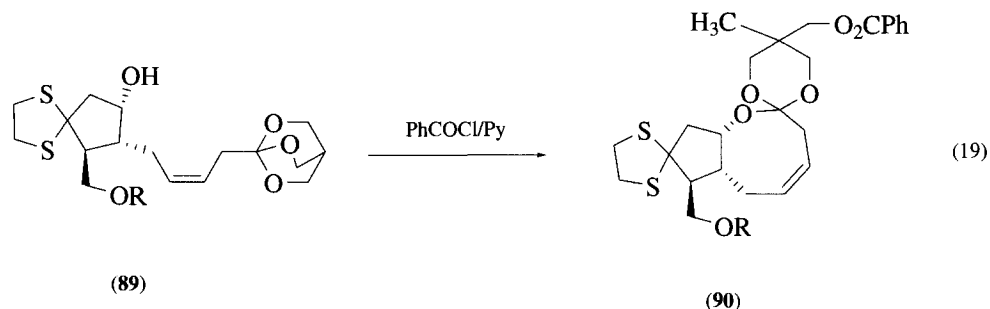
For example, the (methoxyethoxy)methyl ether of 5-trimethylsilyl-5-hexen-1-ol reacts with two equivalents of $SnCl_4$ at $-15^\circ C$ for 9 h to form 4-trimethylsilyl-*cis*-3,6,7,8-tetrahydro-2*H*-oxacin in 51% yield. Another significant aspect of this cyclization is the high yield of *cis*-2,8-disubstituted product formed when there is a substituent in 2-position of the starting 5-hexenyl acetal. Deuterium isotope experiments on the $SnCl_4$ cyclization of 5-(trimethylsilyl)-5-hexenyl acetals to produce 4-(trimethylsilyl)- Δ^4 -oxocene indicate that the reaction occurs by a concerted ene mechanism <90JA4399>.

Another route into medium-size ring systems involves the displacement of silyl groups. For example, aldehydes react with ω -silyloxyallyltrimethylsilane in the presence of $BF_3 \cdot Et_2O$ to yield 2-alkyl-2,3,4,6,7-tetrahydrooxocins <89JOM(373)279> in 55–77% yields. The corresponding reaction with ketones results in poor yields. Aldehydes react with ω -silyloxypropargyltrimethylsilane in the presence of $BF_3 \cdot Et_2O$ to yield 3-vinylidene oxocanes <86T2017>. Allylic silanes have also been shown to undergo acid-catalyzed cyclization to yield the vinyl-substituted oxocanes <91T7689>. Although many silyl- ω -silyloxycarboxylates can be acid-catalyzed to form lactones, eight-membered ring systems are not accessible via this approach, instead dimeric diolides are produced <93CL907>. Silyl enol ethers and acetals can be converted to oxocanones using $TiCl_4$, as a catalyst; a template effect is invoked to account for the stereo- and regiochemistry of this cyclization <83CC705>. Ester (87), prepared by the reaction of 3-trimethylsilyl-4-pentene-1-ol with α -chloro- α -phenylthioacetic acid with triphenylphosphine and diethyl azodicarboxylate, reacts with $EtAlCl_2$ to give 3-phenylthio-oxocanone (88) in 34% yield (Equation (18)) <85TL5191>.



Samarium iodide reacts with 5-oxopentyl bromoacetate in THF solution at $0^\circ C$ for 4 h to form 4-acetoxy-2-oxocanone in 76% yield after acetylation with acetic anhydride and dmap <86TL3889>.

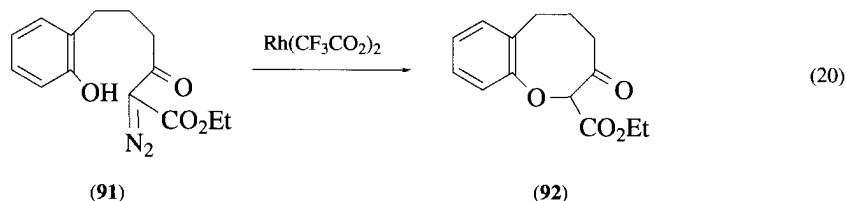
Corey and Shimoji <83JA1662> have described the cyclization shown in Equation (19). Presumably, transesterification of (89) is catalyzed by the presence of pyridinium salts generated in the reaction mixture resulting in the formation of (90). The entropic factors are no doubt mitigated by the presence of the *cis*-double bond in (89). An analogous procedure has been used to prepare intermediates in the total synthesis of major metabolite of prostaglandin D_2 <83JA1662>.



Nicolaou *et al.* have employed a similar strategy using a *cis*-double bond to assist in a lactonization to prepare a variety of 8-alkyl-2-oxocanone derivatives <90JA6263>. A rigidizing ring system can also

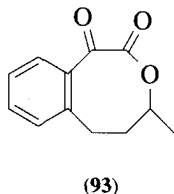
promote cyclization. For example, cholic and deoxycholic acid derivatives undergo intramolecular cyclization when treated with an acyl chlorides (arylsulfonyl chlorides) in pyridine to form 24,12-lactones in moderate yields between 37–56% $\langle 83T2815 \rangle$. Intramolecular Friedel–Crafts reaction of 1-*N*-benzyl-5-phenethyloxy-1,2,3-triazole-4-carboxylic acid, followed by acid cleavage of the benzyl group gives 5,6-dihydro[3]benzoxocin[4,5-*d*]-1,2,3-triazol-11(1*H*)-one $\langle 84JCR(S)400 \rangle$. 5*H*-Dibenzo[*b,g*]oxonine-5,7(6*H*)-diones can be prepared by treatment of 2'-acetyl-2-methoxycarbonyl diaryl ethers with sodium hydride in boiling toluene $\langle 87CB1151 \rangle$.

Another cyclization (Equation (20)), has been developed by Moody and co-workers $\langle 86TL1403, 87TL5351, 89JCS(P1)721 \rangle$. A rhodium-catalyzed cyclization of azo compounds (**91**) results in relatively low yield (24%) of (**92**), presumably via a rhodium carbenoid intermediate.



Treatment of 4-cyclooctene-1-carboxylic acid with phenylselenium chloride in methylene chloride at -78°C gives the intramolecular phenylselenolactone product in 67% yield $\langle 81T4097 \rangle$. The selenophenyl group can be removed either oxidatively or reductively yielding unsaturated and saturated lactones, respectively. Treatment of 3-benzyloxy-hept-6-en-ol with phenylthio-morpholine/triflic acid generates an episulfonium ion, which cyclizes to produce a mixture of predominantly oxepane products; however, 2-phenylthio-3-benzyloxyoxocane is also produced $\langle 91TL2261 \rangle$. An intramolecular Wittig reaction has been used to generate unsaturated eight-membered ring lactones in 28% yield, the predominant product is a cyclic dimeric product $\langle 89TL7393 \rangle$.

7-Octenoic acid can be cyclized to 8-iodomethyl-2-oxocanone in low yield by treatment with bis(*sym*-collidine)iodine(I) salts $\langle 93JOC4 \rangle$. Traces of α -ketolactone (**93**) are produced when 4-(2-iodophenyl)-2-butanol is treated with a palladium catalyst in the presence of CO $\langle 89JMOC145 \rangle$.



Lewis acid-catalyzed type II intramolecular Diels–Alder cycloadditions of 4-methylene-hex-5-enyl acrylate give bridgehead alkene adducts in 85% yield $\langle 83TL657 \rangle$. Although a variety of Lewis acids has been used, diethylaluminum chloride proved to be most effective. The rates of formation of bridgehead dienes from various dienyl esters via type II Diels–Alder cycloaddition has been studied. The location of the oxygen atom has important kinetic consequences. For example, (**94**) reacts 62 times faster than (**95**) at 210°C $\langle 88JA860 \rangle$. Since the entropies of activation are essentially equal, the reactivity differences must be enthalpic in nature. Molecular models suggest that the origin of enthalpic difference is an unfavorable nonbonding interaction between the vinyl hydrogen on the diene and propargylic methylene group in (**95**).



(Alkoxy-carbonyl)methyl radicals, generated by treatment of the corresponding (alkoxy-carbonyl)methyl bromides with tributyltin hydride in benzene and catalytic amounts of AIBN (0.1 equivalent), undergo 8-endo cyclizations $\langle 92JA10981 \rangle$ to generate 2-oxocanones in modest yields. This is not an attractive synthetic route owing to the formation of comparable amounts of reduction and rearrangement products. 4-Pentenyl dichloroacetates and substituted 4-pentenyl dichloro-

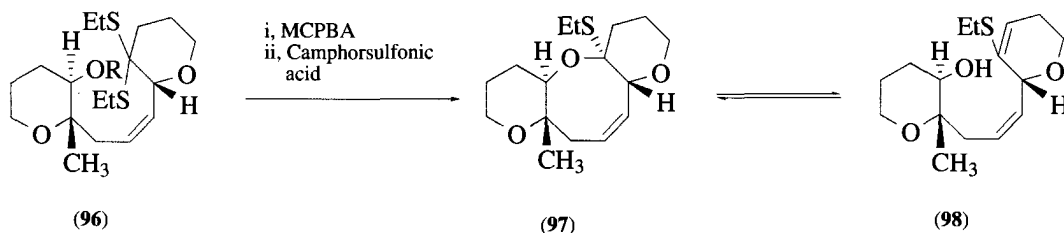
acetates efficiently cyclize to chlorine-substituted 2-oxocanones in the presence of copper(I) (bipyridine)Cl in benzene at elevated temperatures (80–180°C) <92TL5141>. Intramolecular cyclization of ω -trialkylplumbyl and ω -trialkylstannyl ether acetals gives 2-vinyl-3-alkoxyoxocanes in good yields <90JOC6066>.

9.19.11.2 Photochemical Reactions

There have been several accounts of photochemical production of eight-membered ring products containing an oxygen. Invariably, the photochemistry results in aromatic (or hetero-aromatic) substituted or benzo-annulated derivatives. A photocyclization occurs when 2-(indol-3'-yl)ethyl trichloroacetate is irradiated in methanolic acetonitrile to give the pyrrolobenzoxocine in 42% yield. For the corresponding dichloroacetate system, no cyclic products are isolated; however, the products do suggest the intermediacy of analogous cyclic products <92JCS(P1)813>. *Cis*-benzocyclooctenols are generated in low yields by photochemically-induced rearrangement of *o*-(cyclopropylmethoxy)-benzophenones and acetophenones <93JA7914>. These by-products indicate that cyclopropylmethyl radical undergoes rearrangement before cyclization. Photolysis of methyl 8,9-dihydro-5-methoxy-9-oxa-5,8-epoxy-5*H*-benzocycloheptene-6-carboxylate results in the formation of 5-methoxy-2-oxo-3-benzoxocine-6-carboxylate in 20% yield, presumably via a ketene intermediate <91JOC1077>.

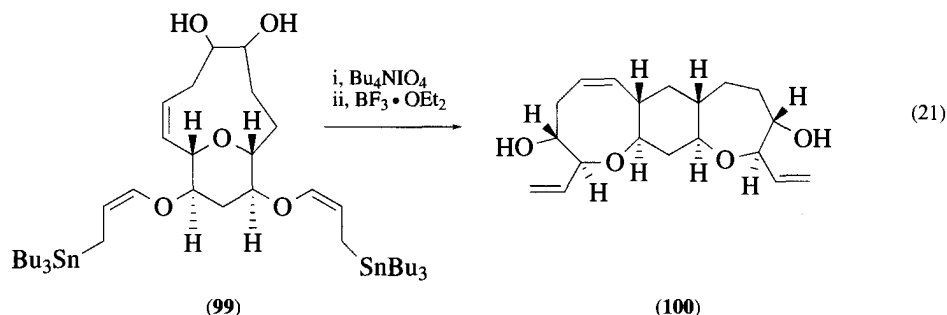
9.19.11.3 Synthesis of Fused Polycyclic Ethers

The presence of fused ring systems in marine metabolites has prompted the development of methods to prepare *trans*-fused polyesters. Scheme 11 shows one approach, where the dithioketal (96) is converted to a mixture of a 6/8/6 ether ring system (97) and an alcohol (98) <82JA2046, 86JA2468, 87JA2504, 89JA5321, 90JA3040, 90JA3696, 90JA6263>.



Scheme 11

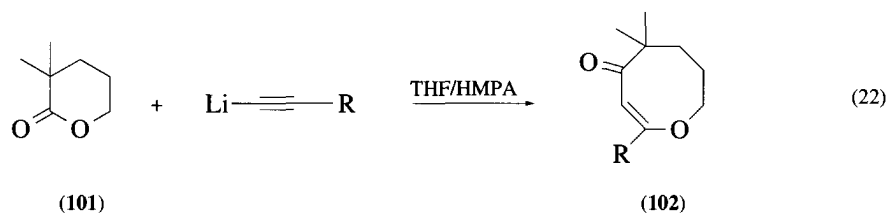
A route into the *trans*-fused oxocene–oxane–oxepan ring systems involves oxidation of the macrocycle (99) with periodate, followed by cyclization with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to give (100) in 63% yield (Equation (21)) <92TL3389>.



9.19.11.4 Synthesis of Oxocanes and Oxocenes

An attractive route into these systems is via ring expansion of readily available six-membered lactone systems. These reactions are desirable because the ring is preassembled and thus entropic

effects are mitigated. Schreiber and Kelly described the synthesis of α,β -unsaturated oxocenes (**102**) starting from substituted δ -valerolactones (**101**) <84TL1757>. The reaction proceeds as shown in Equation (22). The reaction yields are in the range 30–70%.



The previously described work of Carling and Holmes <86CC565>, starting with readily available 2-oxocanones using Tebbe reagent, represents an extremely versatile and clean route into the substituted oxocanes.

9.19.11.5 Enzymatic Reactions

Enzymatic reactions have been used to transform racemic lactones to chiral lactones. For example, pig or horse liver esterase was used to convert the racemic lactones into a mixture of *S*-chiral lactones [$[\alpha]_D^{20}$; +67.8° (c 2.20, THF) (ee95) and their corresponding antipodal *R*-hydroxy acids <89S661>. Laureatin and prelaureatin were prepared by treating 3*Z*,6*S*,7*S*-laurediol with lactoperoxidase in the presence of hydroperoxide and bromide ion in low yields with numerous by-products <90CL1287, 92TL2017>. This transformation was used to explain a plausible biogenesis for these bromooxocanes. Enzymatic treatment of deacetyl laurencin was found to give laureoxanyne as a by-product <90TL4895>; this conversion was used in assigning the structure of laureoxanyne.

9.19.12 IMPORTANT COMPOUNDS AND APPLICATIONS

The great interest, generated by these compounds, is primarily owed to their occurrence in marine and plant metabolism. Many of these compounds have significant cytotoxicity and have been explored as potential therapeutic reagents. By far the most studied materials in this classification are the brevetoxins. These complex polycyclic systems have been the subject of dozens of articles. The acute toxicity of the brevetoxins and ciguatoxins has spurred the development of fast, effective methods for their detection. Several of these methods have been the subject of patents <89USP4816392, 91MIP9116631, 92MIP9209592, 92MIP9211385, 93MIP9307474>. There have been some studies indicating that ciguatoxin and desulfonated yessotoxin possess potent antifungal activity <90MI 919-07>. It seems highly likely that many of these marine-derived compounds and derivatives thereof will be tested for other types of biological activities.

There appear to be very few industrial uses for this class of compounds. The few patents, that do exist, generally relate to synthetic procedures (see Sections 9.19.10.1 and 9.19.11.1 for examples). There are a few examples of synthetic compounds claimed as pharmaceutical reagents. For example, 3-chloro-6,7-dihydro-*N*-methyl-5*H*-dibenz[*b,g*]oxocin-6-amine has been claimed to possess antipsychotic activity without extrapyramidal side effects <89EUP332246>. Also, some benzoxocines have been claimed as serotonin antagonists <92MIP9209592>.

9.20

Eight-membered Rings with One Sulfur Atom

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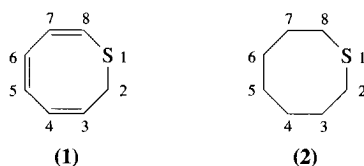
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9.20.1 INTRODUCTION

This ring system was reviewed in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(7)692> and covered the literature up to 1982. This chapter will cover the intervening time through 1994. In general, medium sized ring heterocycles are somewhat hard to make, and there is not a large body of synthetic literature on eight-membered rings with one sulfur atom. Compounds, that are reported, are sparse compared to the more numerous five- and six-membered ring heterocycles.

9.20.1.1 Scope of Chapter

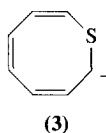
Synthesis of the fully conjugated parent heterocycle, 2*H*-thiocin (1), has not been reported, although there are reported syntheses of the saturated heterocycle, thiocane (2) (b.p. 71 °C/10 torr, 196–198 °C/767 torr; n_D^{20} 0.9910 g cm⁻³) <53M1206>.



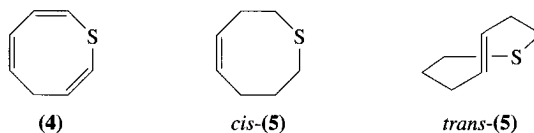
Chapter coverage includes compounds containing ring (1), dihydro-derivatives, tetrahydro-derivatives, and the saturated heterocycle (2) and its derivatives, along with corresponding benzo-fused ring systems and ring ketones. Since some pertinent material overlaps with the previous review <84CHEC-I(7)692>, some published material is repeated when it is appropriate to the discussion.

9.20.1.2 Nomenclature

IUPAC nomenclature <B-79MI 920-01> is generally followed using numbering shown in (1) and (2). The fully unsaturated heterocycle (1) is always named “thiocin”, but nonconjugated *S*-heterocycles are sometimes named as “thiacyclooctene”, and the saturated heterocycle (2) is usually named “thiocane”, or sometimes “thiacyclooctane”. Occasionally, benzo fused ring systems are named as the “thia” analogue of the all-carbon aromatic ring system. There are no aromatic eight-membered ring structures. To achieve aromaticity in an eight membered ring with three C=C’s, two of the eight atomic centers would have to supply either two filled *p*-orbitals or two empty *p*-orbitals, achieving a 10 π electron or 6 π electron system, respectively; this is quite unlikely. For example, *a priori*, anion (3) might be incorrectly thought to satisfy the $4n + 2$ rule for aromaticity, with ten π electrons participating (one sulfur lone pair is assumed to participate). Furthermore, eight-membered rings have great difficulty achieving planar configuration, defeating any incipient aromatic stabilization.

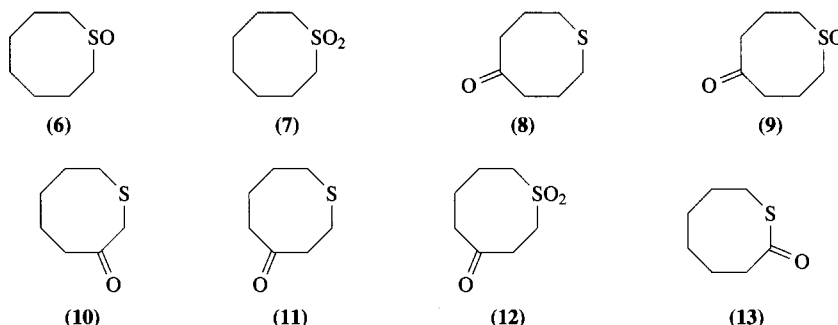


Because (2) has a plane of symmetry through C-5 and S-1, there are only five possible mono-substituted derivatives, neglecting conformational isomers; whereas (1) has no such plane of symmetry and all eight possible monosubstituted derivatives are possible. In addition to conformational isomers (axial-equatorial or *cis-trans*), there is one nonconjugated tautomer of (1), the 4*H*-thiocin (4). There are no reports of ring (4) except for benzo-fused thiocins and a reported spiro compound (see Section 9.20.3.3). For tetrahydro derivatives, particularly 2*H*-3,4,7,8-tetrahydrothiocin (5) for example, there is the possibility of *cis-trans* isomerizations of the double bond.



Oxo-derivatives include the known sulfoxide (6) and sulfone (7), as well as 5-thiocanone (8) (b.p. 120–123 °C/19 torr; m.p. 52–53 °C; ν (CCl₄) 1703, 1408 cm⁻¹; λ (cyclohexane) 226 nm, (water) 242 nm; μ 3.81 D), and the sulfoxide of (8), (9) (m.p. 91–92 °C; ν (CHCl₃) 1750–1710 cm⁻¹) <62JA3701, 81SC231>. Other isomers of (8) are known, such as 3-thiocanone (10) (b.p. 66–68 °C/0.4 torr),

4-thiocanone (**11**) (b.p. 75°C/1.0 torr), and the sulfone of 4-thiocanone, (**12**) (m.p. 133°C) <77CB1069>. However, 2-thiocanone (**13**) is not known. Some benzo-fused derivatives of the parent heterocycles and their oxo-derivatives have been reported.



9.20.2 THEORETICAL METHODS

There are no studies on these ring systems having been reported with the exception of force-field calculations on dibenzo fused dihydrothiocians reviewed in CHEC-I.

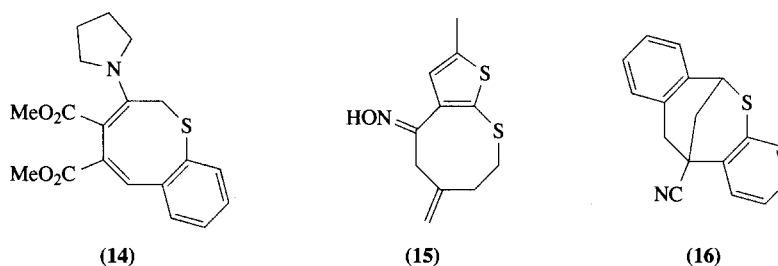
9.20.3 EXPERIMENTAL STRUCTURAL METHODS

Most studies (x-ray diffraction and NMR) have focused on determining the conformation of the eight-membered ring.

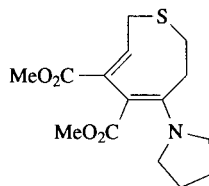
9.20.3.1 X-ray Diffraction Studies

Diffraction data gave information about solid state structures and conformations, which may be significantly different from solution conformations. Possible conformations of eight-membered rings were reviewed in the first edition of this work <84CHEC-1(7)692> and will not be repeated here. Many eight-membered ring compounds seem to show boat-chair conformation, and 5-thiocanone (**8**) is one such example of a thiocane compound <80JOC1224>. Three new reports for nonconjugated thiocians have appeared and, surprisingly, two of the three, (**14**) (m.p. 186°C; *m/e* 359, 327, 326, 300, 171, 96) <81ACR1134, 81ACS197> and (**15**) <93MC114>, show boat-boat conformations. The third report is for the bridged compound (**16**) (m.p. 192–195°C) which is constrained to a boat-boat conformation <87CCC2281>.

One diffraction study was for *cis,trans*-dihydrothiocin derivative (**17**) (m.p. 144–145°C; ν 1710,



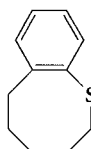
1670 cm^{-1} <84JA1341> which showed a twisted diene conformation <82JA6842>. Conformation of (17) allowed a [1,5] sigmatropic shift to form the *cis,cis*-isomer (m.p. 77–79°C; ν 1720 cm^{-1}) <84JA1341> on heating.



(17)

9.20.3.2 NMR Studies

Proton NMR data for thiocane (2) consists of adsorptions expected for aliphatic, cyclic thioethers: 1.2–1.5 δ for ring protons on carbons not alpha to sulfur and 2.5–3.0 δ for protons on carbons alpha to sulfur <80JOC3613>. Benzo fusion, (18), shifts the protons of the alpha carbon down slightly (3.13 δ), along with the protons beta to ring fusion and beta to sulfur (1.65–1.77 δ) <82ACS(B)561>. Proton spectra for thiocins and their nonconjugated, or partly-reduced, derivatives are typical of unsaturated, nonaromatic, cyclic thioethers.



(18)

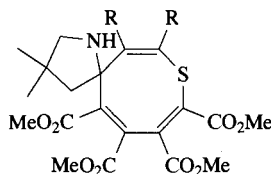
Some benzo-fused, eight-membered ring, methyl-substituted sulfur ylides can show methyl resonance at unusually low values: δ 1.8–2.0 if the ylide methyl group can be shielded by the benzene ring in a predominant conformation <82CC1060, 84CPB4360>. This would be expected to extend to other alkyl group substituted, benzo-fused ylides.

Oxygenation of ring carbons or sulfur brings about expected consequences to proton spectra: increased, proximal deshielding resulting in larger δ values.

Dynamic NMR data was used to assess conformations and symmetry present in solution. It can reveal differences in conformation due to solvent effects, and the activation energy for inter-conversion of conformers can be determined. This area was reviewed in the first edition <84CHEC-I(7)692> and will not be repeated here.

9.20.3.3 Ultraviolet Spectra

There are no studies of simple thiocins or reduced analogues, most being benzo-fused multicyclic ring systems. A spiro compound (19) (m.p. 133–134°C; ν 3420, 1740, 1735, 1720, 1695 cm^{-1} ; m/e 495, 464, 436, 404, 376, 323, 292, 277) shows λ_{max} at 243 nm and 202 nm, $\log \epsilon = 4.24$ and 4.49, respectively <87AP(320)455>. Symmetrical 5-thiocanone (8) exhibits a maxima at between 226 nm and 242 nm depending on the polarity of the solvent used, water solvent giving rise to the higher λ_{max} <60JA4075>.

(19) R = Bu^t

9.20.4 THERMODYNAMIC ASPECTS

9.20.4.1 Physical Properties

Thiocin derivatives are solids with melting points generally between 100–200°C; on occasion, benzo fusion can cause a drop in the melting point to slightly below 100°C. Sulfoxide and sulfone derivatives tend to be even more crystalline than the parent thiocins. Thiocanones have low melting points and may be liquids at ambient temperatures. If materials are purified by distillation, it is usually at pressures under 1.0 torr. Dipole moments are generally not measured, but 5-thiocanone (**8**) has one of 3.8 D <60JA4075>.

9.20.4.2 Solubilities

Thiocins as a general rule are sparingly soluble in alkanes, but are soluble in most other organic solvents, including chlorinated hydrocarbons and benzenoids. Thiocanones are less soluble in the weakly polar solvents than are thiocins.

9.20.4.3 Conformational Studies

This was reviewed in CHEC-I. There have been no further studies except those reported in Section 9.20.3.

9.20.5 REACTIVITY OF FULLY CONJUGATED RINGS

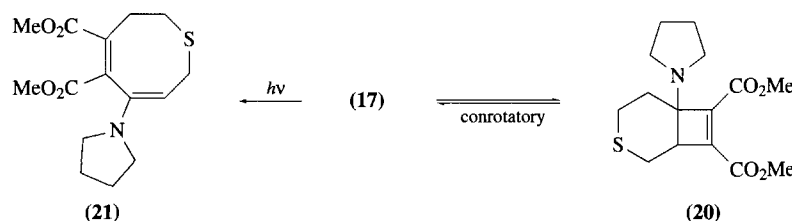
2*H*-Thiocin (**1**) is expected to be a reactive molecule similar to unsaturated, noncyclic ethers. As such, the ring should be readily reactive to a wide range of reagents like electrophiles, nucleophiles, oxidizing agents, reducing agents, free radicals, and strong acids. There are, however, no reports studying the chemistry of (**1**), its benzo-fused derivatives, or other derivatives.

9.20.6 REACTIVITY OF NONCONJUGATED RINGS

In this section, we will treat both reduced or partially reduced thiocins, which may be conjugated but not fully so.

Reactivity of some thiocanes, tetrahydrothiocins, and benzo-fused analogues were reviewed in the first edition. For the most part, reactivity and chemistry of those rings systems are that which are expected from their carbocyclic counterparts, with few exceptions.

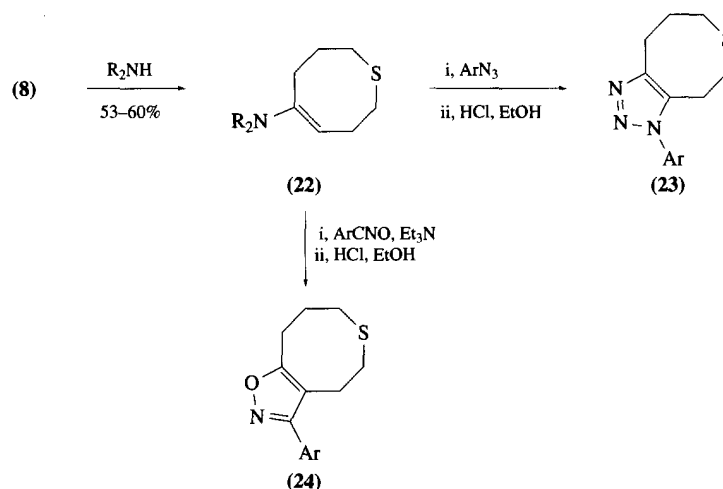
trans-Cycloalkene (**17**), which is in equilibrium with cyclobutene (**20**), undergoes thermal ring opening in a conrotatory fashion in the dark. However, in the presence of light, an unprecedented [1,5] hydrogen shift occurs to give (**21**) (m.p. 77–79°C; ν 1720 cm⁻¹) (Scheme 1) <82JA6842, 84JA1341>.



Scheme 1

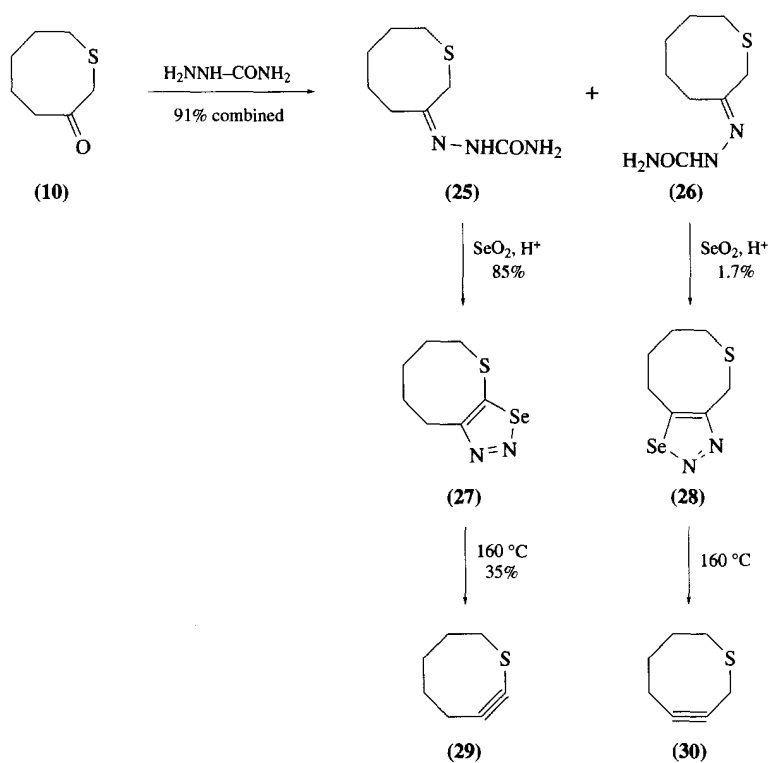
Annelation of rings onto a thiocanone can be accomplished. Reaction of 5-thiocanone (**8**) with a secondary amine forms enamine (**22**) (R = Me; b.p. 80–85°C/0.2 torr; ¹H-NMR (CDCl₃) 4.35 (1 H, m, =CH—)), which in turn can react with aryl azides to generate the tetrahydrothiocino[4,5-*d*]-1,2,3-triazole ring system (**23**) (Ar = 4-nitrophenyl; m.p. 197°C) (Scheme 2) <84JHC1121>. By

reacting enamine (**22**) with an aryl isocyanate instead of an azide, tetrahydrothiocino[4,5-*d*]isoxazoles (**24**) (Ar = 4-nitrophenyl; m.p. 140 °C) can be produced.



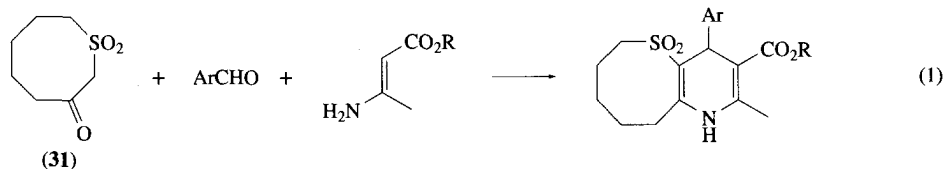
Scheme 2

Annellation of 3-thiocanone (**10**) (m.p. 30 °C; n_D^{20} 1.5073) was accomplished by making the semicarbazone, (**25**) and (**26**) (mixture; m.p. 174 °C; ν (KBr) 3450, 3370, 3150, 2920, 1690, 1580, 1460, 1420 cm^{-1}), followed by oxidation with selenium dioxide to form either tetrahydrothiocino[3,2-*d*]-1,2,3-selenadiazole ring system (**27**) (oil; ν 2920, 2850, 1440, 1330, 1300, 1275, 1250 cm^{-1}) or tetrahydrothiocino[3,4-*d*]-1,2,3-selenadiazole ring system (**28**) (m.p. 62 °C; ν (KBr) 2915, 2840, 1440, 1310, 1270, 760 cm^{-1}) (Scheme 3) <89LA435>. *cis*-Semicarbazone (**25**) gave rise to [3,2-*d*] ring fusion (**27**), and *trans*-semicarbazone (**26**) gave rise to [3,4-*d*] ring fusion (**28**). Both (**27**) and (**28**) could be thermally decomposed to 1-thia-2-cyclooctyne (**29**) (ν 2910, 2840, 2200, 1650, 1435, 750 cm^{-1}) or 1-thia-3-cyclooctyne (**30**), respectively.



Scheme 3

In a variant of the Hantzsch ester synthesis for dihydropyridines <1882LA(215)1>, the sulfone of (10), (31), can behave as a substitute for the normally used acetoacetic ester component (Equation (1)) <94JHC351>.



9.20.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Substituent chemistry is expected from analogous reactions of those substituents on other saturated cyclic hydrocarbons. Presence of the heteroatom in the ring does not confer any unique chemical properties compared to noncyclic analogues.

9.20.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

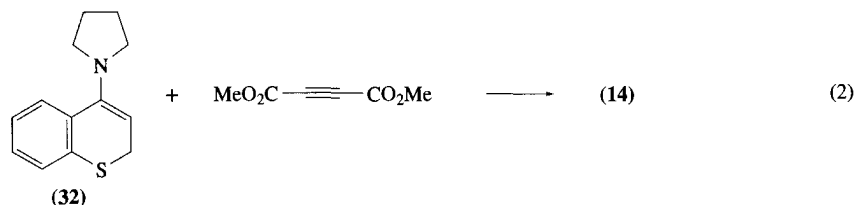
Reported *S*-substituents are restricted to oxygen or alkyl groups. Both have the expected reactivity patterns of sulfones or sulfonium compounds. The presence of a ring formed from two substituents on the sulfur atom does not confer any special reactivity to *S*-substituents.

9.20.9 RING SYNTHESSES

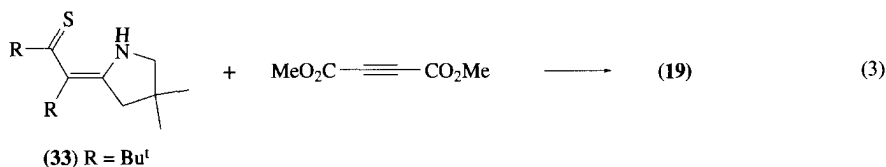
In general, reduced and nonconjugated thiocins are not made from parent thiocins. There are different synthetic approaches depending on the degree of unsaturation in the heterocyclic ring.

9.20.9.1 Fully Conjugated Rings

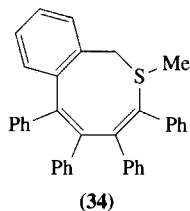
Thiocin derivatives are most often made by addition of alkynes to enamine structures, followed by cyclization. For example, enamine of thiochroman-4-one, (32), gives benzothiocin (14) on addition of dimethyl acetylenedicarboxylate (DMAD) (Equation (2)) <82ACS(B)435>. Use of the enamine from thiochroman-3-one also gives (14) <81ACS(B)197>.



Addition of DMAD to enaminothione (33) gave the nonconjugated 4*H*-thiocin (19) (Equation (3)) <87AP(320)455>.

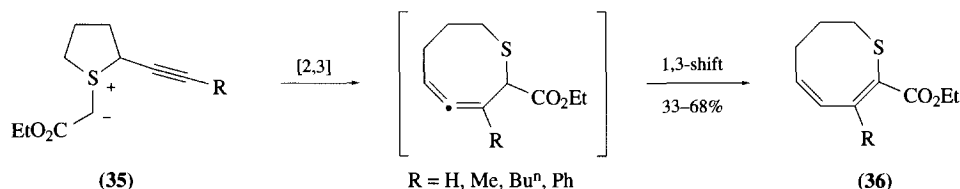


Diphenylethyne can be inserted into a palladium compound to yield the benzothiocin (34) <87JOM(321)C13>.



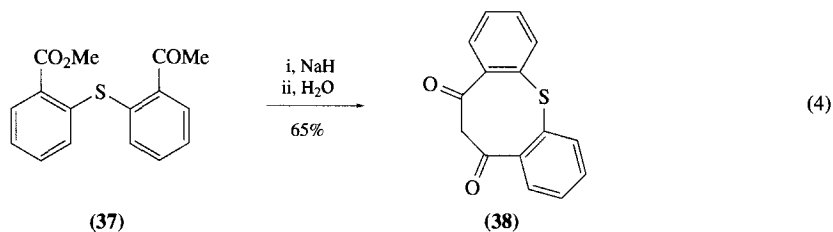
9.20.9.2 Dihydro Derivatives

Like other types of unsaturated ylides, sulfonium ylides having an α -ethynyl group undergo a [2,3]-sigmatropic rearrangement to give a ring expanded product via an allene intermediate. Ylide (35) gave the 2*H*-3,4-dihydrothiocin derivative (36) (Scheme 4) <82H(19)2147>.

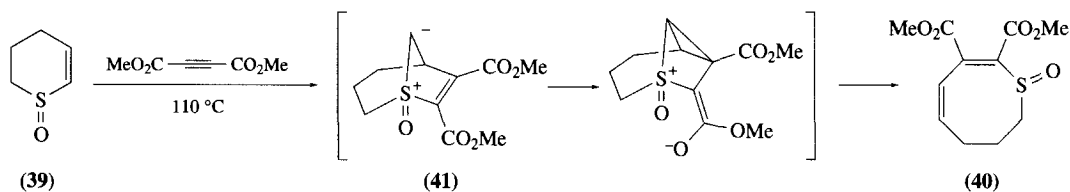


Scheme 4

Diaryl sulfides bearing an acyl group on one ring and an ester group for intramolecular condensation gave the dibenzo-4*H*-5,6-dihydrothicindione ring systems. In an improvement over the use of alkylolithium bases on diaryldiesters, Hellwinkel and Bohnet were able to react sodium hydride, in refluxing toluene, with 2-acetyl-2'-carboxymethyldiphenyl sulfide (37) to give diketone (38) (m.p. 106–108 °C; ν 1690, 1675, 1667 cm^{-1}) in 65% yield (Equation (4)) <87CB1151>.



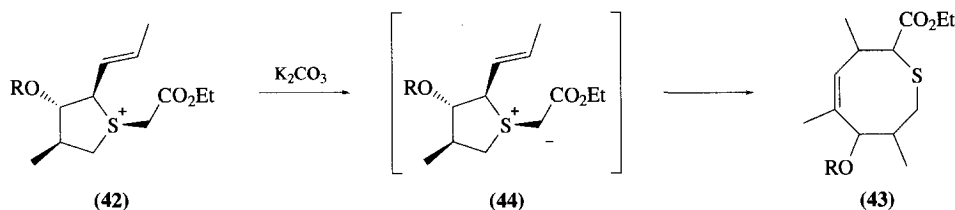
DMAD undergoes [2 + 3] cycloaddition with unsaturated, cyclic sulfoxides, such as (39), to give dihydrothiocin *S*-monoxides, such as (40) (m.p. 108 °C; ν 1060–1045 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 5.82 (1 H, m), 6.57 (1 H, m), 3.85 (3 H, s), 3.68 (3 H, s), 3.30 (2 H, m), 2.38 (4 H, m)), via what is believed to be the bicyclic intermediate (41) (Scheme 5) <80AG849>.



Scheme 5

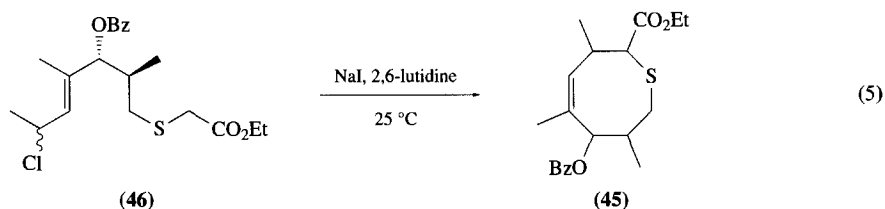
9.20.9.3 Tetrahydro Derivatives

The five-membered ring sulfonium salt (**42**), of specific stereochemistry, can be expanded to 2*H*-3,4,7,8-tetrahydrothiocin (**43**) ($R = \text{CH}_3\text{OCH}_2\text{O}$; b.p. 90–110°C/0.05 torr; ν 1710 cm^{-1}) through ylide (**44**) (Scheme 6), albeit in low (36%) yield <89JA8421>.



Scheme 6

A higher yield (66%) route by the same authors to a similarly-substituted tetrahydrothiocin (**45**) utilized the open chain sulfonium salt (**46**) (Equation (5)). Proposed mechanisms involved a five-membered ring sulfonium ylide identical to (**44**), except that RO was replaced with BzO .



9.20.9.4 Fully Saturated Derivatives

Thiocanes are synthesized by the displacement of a halide from 1,7-dihaloheptane derivatives using NaSH , as a nucleophile. A recent improvement (47% yield) in the synthesis of the parent thiocane (**2**) avoids the need for high dilution and uses NaSH on solid support alumina <92TL7709>. The dihaloheptane chain can contain keto groups. In a variant synthetic scheme, not involving solid support, a lower yield (30%) of 3-thiocanone (**10**) resulted from using NaSH in ethanol solvent <89SC557>.

9.21

Eight-membered Rings with Two Heteroatoms 1,2

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9.21.1 INTRODUCTION

Eight-membered rings with two heteroatoms adjacent to one another have been and remain a comparatively uncommon class of heterocyclic compounds, with a slow but steady trickle of reports on their preparation and reaction chemistry appearing through the years. Interest in this class of compounds, and in eight-membered ring heterocycles in general, frequently appears to have been driven by the desire to explore analogues of the often pharmacologically important seven-membered ring heterocycles. Coverage in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) in which all eight-membered ring heterocycles with one or more heteroatoms were treated in a single chapter, focused primarily on the diaza compounds, the best-known members of this family of heterocycles, with relatively brief coverage of oxygen- and/or sulfur-containing analogues.

Only those compounds with nitrogen, oxygen, and/or sulfur as heteroatoms are covered in this chapter. (Compounds with "unusual" heteroatoms are covered in later chapters in this volume.) Nomenclature for the eight-membered rings with two heteroatoms adjacent to one another follows the standard system, with some permissible variability introduced for the completely reduced compounds. The parent unsaturated systems, of which few have actually been prepared, are 1,2-diazocine, 2*H*-1,2-oxazocine, 2*H*-1,2-thiazocine, 1,2-dioxocin, 1,2-oxathiocin, and 1,2-dithiocin. Reduced analogues may be named as di-, tetra-, hexa-, or, for the diaza compounds, octahydro derivatives of these parent compounds. In some cases, particularly the dioxa and dithia derivatives, the fully saturated rings are more often referred to as the corresponding -anes, 1,2-dioxocane, and 1,2-dithiocane. Benzo and dibenzo derivatives also follow standard nomenclature. Naming of those derivatives which are known, which constitute but a small fraction of the theoretically possible isomers, is introduced as appropriate within the following individual sections. Compounds in which ring heteroatoms are members of another fused ring and bridged polycyclic compounds are not covered in this chapter.

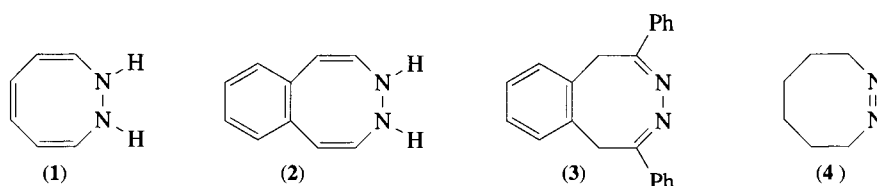
Following a general discussion of theoretical studies of the title heterocycles, each class is discussed separately, with each discussion following the same general format. Where particular classes are not mentioned (e.g. "Reactivity of substituents attached to ring heteroatoms"), this corresponds to cases in which no relevant chemistry has been reported. Comprehensive reviews of the preparation, structure, and reaction chemistry of the diazocines <90AHC(50)1> and of their benzo analogues <87H(26)2477> have appeared in the early 1990s, and since these compounds received relatively complete coverage in CHEC-I, the diazocine section focuses primarily on developments since 1984 in the chemistry of these derivatives. In contrast, coverage of the other classes, which received little attention in the first edition, is meant to be comprehensive. The oxazocines and their benzo analogues have also been reviewed <82H(19)709>.

9.21.2 THEORETICAL METHODS

Theoretical studies of several classes of the title heterocycles have appeared. Although the majority of these studies have focused on the conformational preferences of partially to completely reduced derivatives, several have addressed the stability and potential aromaticity of the parent fully unsaturated derivatives as well. Beyond the brief mention of these theoretical studies provided in this

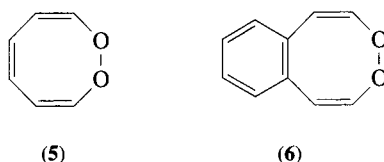
section, further details are more appropriately reported in the relevant sections dealing with the structural and thermodynamic aspects of the subject heterocycles.

Molecular orbital calculations for both 1,2-dihydro-1,2-diazocine (**1**) and 3,4-dihydro-3,4-benzodiazocine (**2**), both potentially 10π -electron systems, provided resonance energies appreciably larger than that of benzene $\langle 60\text{JOC1509} \rangle$. Despite this, however, these results were not considered inconsistent with the failure of nonconjugated compound (**3**) to tautomerize to the corresponding substituted derivative of (**2**) $\langle 60\text{JOC1509} \rangle$. Independent calculational studies of (**1**) and (**2**) were taken to support delocalized bonding in these derivatives $\langle 75\text{MI 921-01, 89AHC(45)185} \rangle$, but assay of their potential aromaticity was inconclusive, with the outcome dependent on the particular criteria of aromaticity adopted. To complicate matters further, semiempirical AM1 quantum mechanical calculations have suggested that (**1**) is, in fact, an antiaromatic system, representing not a stable structure but rather a saddle point on the reaction coordinate leading to ring opening $\langle 91\text{RRC333} \rangle$.

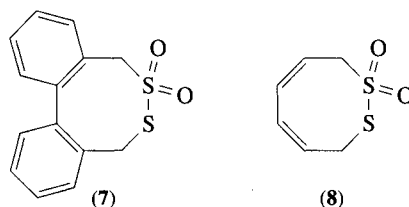


Molecular orbital calculations for the (*E*) and (*Z*) isomers of 3,4,5,6,7,8-hexahydro-1,2-diazocine (**4**) were in accord with both molecular mechanics studies $\langle 88\text{JA7286} \rangle$ and a solid-state structural study of a crystalline derivative $\langle 76\text{CB518} \rangle$, showing the preference of (*E*)-(**4**) for a twist conformation and of (*Z*)-(**4**) for a rather unsymmetrical conformation rather than the alternative chair, boat, or twist forms $\langle 79\text{JA5546} \rangle$.

SC-HMO calculations for 1,2-dioxocin (**5**) and 3,4-benzodioxocin (**6**) have also been reported to suggest delocalized bonding in the 1,2-dioxocin ring, but again establishment of potential aromaticity was not possible $\langle 75\text{MI 921-01} \rangle$. As in the case of 1,2-diazocine, semiempirical AM1 quantum mechanical calculations suggest that (**5**) is antiaromatic, representing a saddle point on the reaction coordinate leading to ring opening to 2,4-hexadien-1,6-dione, which is some $70.1 \text{ kcal mol}^{-1}$ more stable than (**5**) $\langle 91\text{RRC333} \rangle$.



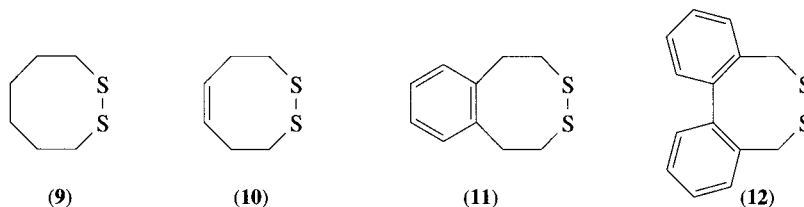
In order to shed light on the initially reported unusual difference in axial and equatorial S—O bond lengths in crystalline 5,8-dihydro-dibenzo[*d,f*][1,2]dithiocin (**7**) $\langle 73\text{AX(B)2272, 74AX(B)2526} \rangle$ (later shown to be an artifact of solution of the structure in an incorrect space group), STO-3G* calculations were carried out for (unknown) model compound (**8**) $\langle 82\text{CJC730} \rangle$. The two S—O bond lengths in the chair-like minimized structure were identical.



Molecular mechanics studies of (*E*)- and (*Z*)-(**4**) supported the *ab initio* results discussed above $\langle 79\text{JA5546} \rangle$. More recent studies of (*E*)-(**4**), using MM2/MO-based molecular mechanics with an improved force field, showed the C_2 -twist form to be more stable than the C_2v -chair by ca. $6\text{--}7 \text{ kcal mol}^{-1}$ $\langle 88\text{JA7286} \rangle$.

Molecular mechanics (MM2(85)) calculations were carried out to assess the strain energy and ring-opening equilibria of a number of cyclic disulfides, including 1,2-dithiocane (**9**), 3,4,7,8-tetrahydro-1,2-dithiocin (**10**), and 1,2,5,6-tetrahydro-3,4-benzodithiocin (**11**) $\langle 90\text{JA6296} \rangle$. In response to

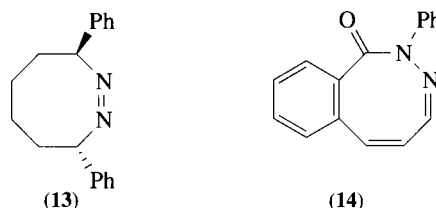
the unexpected chair-like conformation of the dithiocin ring revealed by x-ray diffraction analysis, dibenzo[*d,f*]dihydro-1,2-dithiocin (**12**) was also examined by molecular mechanics calculations, using a parameter set derived from simpler acyclic and cyclic sulfides and disulfides. Although the tub form displays a C—S—S—C dihedral angle much closer to that in simple disulfides than the chair form does, other energy terms lead to a slight thermodynamic preference for the chair form <76JA2741>.



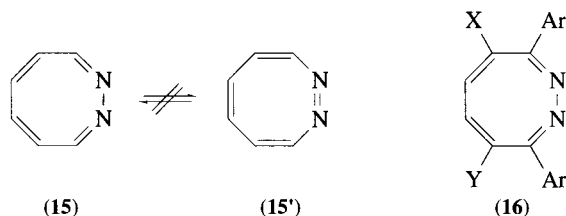
9.21.3 RINGS WITH TWO NITROGENS (1,2-DIAZOCINES)

9.21.3.1 Experimental Structural Methods

Despite the relatively large number of 1,2-diazocines which have been prepared, single crystal x-ray diffraction studies remain scarce. X-ray analysis of (*E*)-3,8-diphenyl-3,4,5,6,7,8-hexahydro-1,2-diazocine (**13**) displayed a crown-type conformation in the solid state <76CB518, 88JA7286>, while the eight-membered ring in unsaturated benzo derivative (**14**) displays the tub shape repeatedly pointed to by various solution studies (*vide infra*) <76AX(B)2314>.



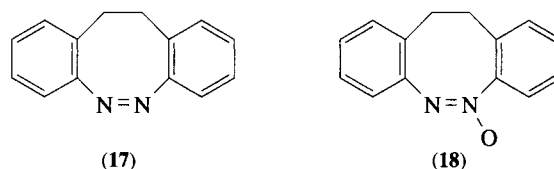
Numerous NMR studies of the diazocines and their reduced analogues have appeared, directed toward conformational analysis and evaluation of bond localization and/or potential aromaticity as well as for routine characterization. Chemical shifts appear largely as expected for compounds displaying related functionality <84TL2577>. Ring protons in potentially fully-conjugated derivatives (**15**) <79JOC1264> (6.03, 6.93 ppm) and (**16**; Ar = Ar' = Ph, X = Y = H, Cl, OAc, OCOPh; Ar = Ar' = Ph, X = OAc, Y = Cl, OCOPh, SPh; Ar, Ar' = 4-Z—C₆H₄, Z = H, Cl, Me, X = Y = Cl) <82CL1579, 86BCJ1087, 87BCJ731, 87CL157> (ranging from ca. 6.5–7.0 ppm, with one at 5.5 ppm.) are rather downfield, but this appears to be due simply to the functionality present rather than to any potential “aromatic ring current” effects. Coupling constants for vicinal protons in unsymmetrically-substituted derivatives of (**16**) are all ca. 4.2 Hz <87BCJ731>.



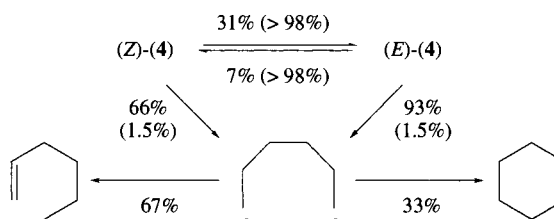
Interestingly, several cases of accidental degeneracy leading to extraordinarily simple ¹H NMR spectra have been reported. Compound (**16**; Ar = Ar' = Ph, X = Y = H), for example, displays a singlet (at 6.49 ppm in CDCl₃) for the four ring protons <82CL1579>, while parent 1,2-diazocine (**15**) shows a broad singlet at 6.93 ppm (2H) and a sharp singlet at 6.03 ppm (4H). Addition of a europium shift reagent splits the latter resonance into an AB quartet. In addition to ruling out

isomeric bicyclic structures for (15), these observations, together with ^{13}C NMR studies, led to the conclusion that this compound exists as the bond-localized 2,4,6,8-tetraene (15) rather than the 1,3,5,7-tetraene (15') <79JOC1264> which, by virtue of the nonplanarity of the ring, must be considered a distinct tautomer of (15) rather than a resonance structure.

1,2-Diazocine (15) displays the anticipated parent ion upon electron-impact mass spectral analysis, as well as significant fragments of m/e 79 (base peak) and 80 (15%) which have been assigned to pyridine and pyridazine, respectively <79JOC1264>. The mass spectral fragmentation more-or-less parallels the thermal decomposition of (15), with both affording pyridine as the major product, although notably the thermal reaction affords benzene rather than pyridazine, while mass spectral analysis does not suggest formation of benzene as a major fragmentation path. These transformations are discussed further below. Unfortunately, only parent ion data was reported for the series of 1,2-diazocines (16) <82CL1579, 86BCJ1087, 87BCJ731>, precluding any further analysis of the mass spectral fragmentation behavior of the fully unsaturated ring system. The thermal reactions of the latter series of compounds however, again forming the anticipated pyridine derivatives as the major products, have been investigated <86BCJ1087, 87BCJ731>. 11,12-Dihydro-dibenzo[*c,g*][1,2]-diazocine (17) also displays the anticipated parent ion ($m/z = 208$), with major fragments of m/z 180 (presumably loss of N_2) and 178 ($\text{M}-\text{N}_2-\text{H}_2$) <85CCC33>. The corresponding *N*-oxide (18), in addition to the parent ion (224), shows significant fragments of m/z 207 ($\text{M}-\text{OH}?$), 206, and, again, 178 <85CCC33>.



Extensive UV spectral studies of 1,2-diazocine derivatives have appeared, focused primarily on the 3,4,5,6,7,8-hexahydro derivatives, of interest for their photoinduced (*E*)/(*Z*) isomerization and fragmentation through loss of N_2 . Additions to the arsenal of studies of these derivatives include picosecond studies of the 354 nm photolysis of (13) and deep UV photolysis of (4). In the former study, (*E*)- to (*Z*)-isomerization was suggested to constitute a minor reaction path, although subsequent C—N bond cleavage from either isomer could lead to the observed extrusion of N_2 <91CPL(178)9>. Photolysis of either (*E*)- or (*Z*)-(4), which were prepared as pure isomers (*vide infra*), at 185 nm, corresponding to the major UV absorption band for both isomers [$\epsilon = 2970$ for (*Z*)-(4), 7880 for (*E*)-(4)], results in significantly different photophysics, summarized in the following scheme, than observed for irradiation at 350 nm, the results of which are presented for comparison in parentheses in Scheme 1 <85CJC1829>.

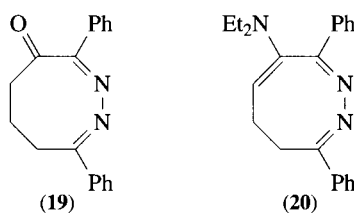


Scheme 1

Many of the 1,2-diazocines, including the parent fully-unsaturated 1,2-diazocine (15) <79JOC1264> and its 3,8-diaryl-4,7-dichloro derivatives (16) <86BCJ1087>, are yellow <85CJC1829>, although the color appears quite sensitive to substituents, as derivatives of the latter, in which one or both chlorines are replaced by nitrogen or sulfur substituents, are all colorless <87BCJ731>. No fluorescence of (13) upon irradiation at 354 nm was observed, leading to an upper limit of 10^{-4} for the fluorescence quantum yield for this compound <91CPL(178)9>.

Unfortunately, only partial IR data has been reported for the latest members of the 1,2-diazocine family; only side-chain carbonyl absorptions were reported for (16) <82CL1579, 86BCJ1087, 87BCJ731, 87CL157>, while 6,7-dihydro-3,8-diphenyl-1,2-diazocin-4(5*H*)-one (19) displays a C=O stretch at

1695 cm^{-1} <84TL2577>. The corresponding enamine (20) shows a typical enamine mode at 1620 cm^{-1} .



Polarographic studies of (17) show two irreversible cathodic waves under either neutral or alkaline conditions; *N*-oxide (18) is reduced in a four-electron cathodic wave under near-neutral conditions <85CCC33>. No further studies of the nature of the reduction products were reported.

No new experimental or theoretical studies of dipole moments of 1,2-diazocines have appeared. However, it is notable that such data contributed to the successful assignment of structures to the (*E*)- and (*Z*)-isomers of the 3,4,5,6,7,8-hexahydro-1,2-diazocine derivatives <72TL4565>.

9.21.3.2 Thermodynamic Aspects

The phase behavior of the 1,2-diazocines, including those newly reported, is largely as expected for molecules displaying similar symmetry and functionality. Each of the substituted 1,2-diazocines (16) is reported to be a crystalline solid <82CL1579, 86BCJ1087, 87BCJ731>, including the comparatively unsubstituted 3,8-diphenyl derivative (m.p. 181–182°C) <82CL1579>, although even in this case, the high symmetry and potential π -stacking opportunities afforded by the aromatic substituents undoubtedly play roles in stabilizing the solid state. Similar effects may contribute in dibenzo derivative (17) (m.p. 110–111°C), which is also reported to sublime at 80–90°C/200–300 Pa <85CCC33>. Compounds (19) and (20) are both solids (m.p. 121°C and 156–158°C, respectively) <84TL2577>, while the parent unsubstituted 1,2-diazocine (15) is a liquid <79JOC1264>, as is unsubstituted hexahydro derivative (4) <85CJC1829>.

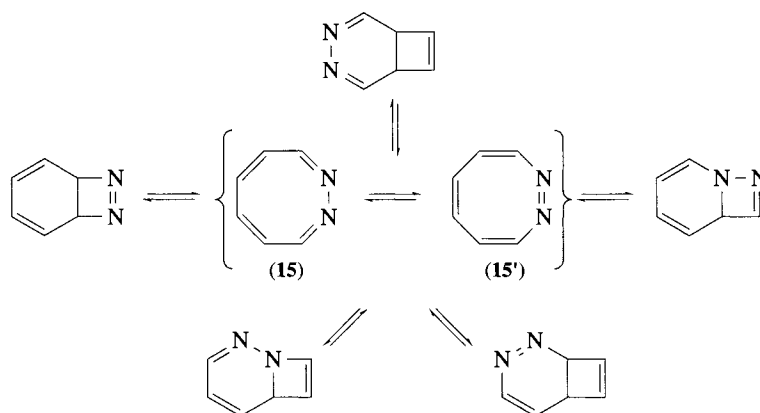
Reported solubilities and chromatographic behaviors <85CCC33, 85CJC1829> continue to follow predictably, with good solubility in many common organic solvents in most cases. A few highly symmetrical 3,8-diphenyl derivatives (16) bearing phthalimide and related functional groups in the 4- and 7-positions are sufficiently insoluble to preclude solution spectral analysis <87BCJ731>. Detection of cyclic azo compounds, including 3,4,5,6,7,8-hexahydrodiazocine (4), in TLC analysis is effected by CuCl in acetonitrile; cyclic derivatives appear as yellow to red spots, while acyclic derivatives are not visualized <87CB251>.

A theoretical study addressed the electronic and geometric structure of 1,2-dihydro-1,2-diazocine (1) (as well as other positional isomers and the corresponding dioxocin analogues) by AM1 molecular orbital calculations <91RRC333>. The singlet, with a nonplanar boat-like conformation (C_s symmetry), is not a minimum but rather a saddle point on the potential energy surface, representing the transition state leading to ring-opening, which is downhill by ca. 21 kcal mol^{-1} . Compound (1) was concluded to be best described as antiaromatic.

Spectral and solid-state structural studies, summarized above, have consistently led to the conclusion that the fully-unsaturated 1,2-diazocine ring is distinctly nonplanar, displaying an apparent preference for a tub-like conformation. As one of the most heavily studied 1,2-diazocines, (4) has been the target of several theoretical conformational studies. MM2/MO-based molecular mechanics studies in the late 1980s, using an improved force field and supported by 6-31G and 6-31G* *ab initio* calculations, show the C_2 -twist conformation of (*E*)-(4) to be ca. 6–7 kcal mol^{-1} more stable than the C_{2v} -chair conformation <88JA7286>. The calculated C—N=N—C dihedral angle of 150° compares very favorably with that determined crystallographically (156°) for the 3,8-diphenyl derivative (13) <88JSP(28)471>, in which additional steric constraints imposed by the phenyl substituents are expected to increase this dihedral angle over that in the unsubstituted compound.

No studies related to tautomerism of 1,2-diazocines have appeared since the late 1970s. Earlier studies of particular note include spectral studies establishing the positions of the localized double bonds in parent 1,2-diazocine (15) <79JOC1264> and kinetic studies of the rate of tautomerism of 3,8-diaryl-3,4,5,6,7,8-hexahydro-1,2-diazocines (e.g., (13)) to the corresponding 1,4,5,6,7,8-hexahydro analogs, supporting formulation of the former as (*Z*)-isomers <69JA3226>. The issue of valence isomerization has been particularly important for the fully-unsaturated 1,2-diazocines, as best

exemplified by the parent compound (15). By analogy with cyclooctatetraene, a number of diazabicyclo[4.2.0]octatrienes might potentially exist in equilibrium with (15) (Scheme 2).

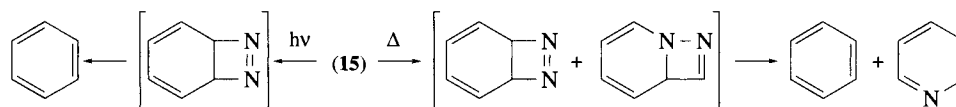


Scheme 2

However, in solution at room temperature, (15) appears not to equilibrate with these structures, which were calculated by group additivity data to be 0–3 kcal mol⁻¹ more enthalpically endothermic than the analogous isomerization of cyclooctatetraene <79JOC1264>. Nonetheless, it seems likely that the thermal and photochemical reactions of (15), as well as its fragmentation upon mass spectral analysis, may occur through the intermediacy of one or more of these valence tautomers, as has also been suggested for related 1,2-diazocine derivatives <86BCJ1087, 87BCJ731>.

9.21.3.3 Reactivity of Fully Conjugated Rings

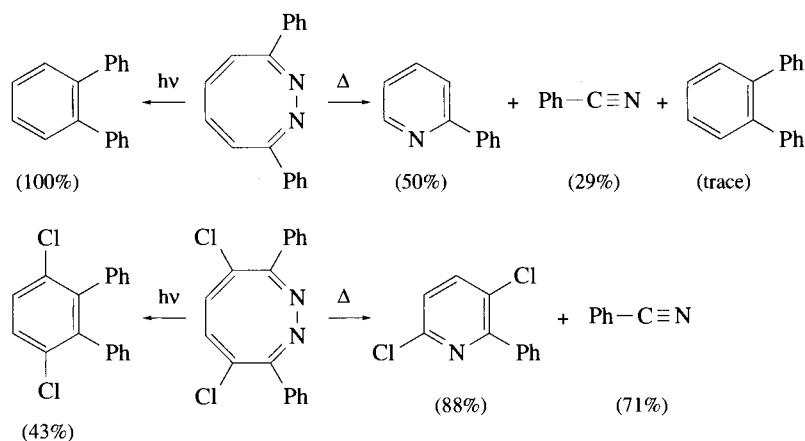
Beyond the few simple substitution reactions summarized below, the dominant chemistry reported for the fully-unsaturated diazocines (15) and (16) involves their thermal and photochemical ring contraction. Both the thermal and photochemical reactions appear to proceed via intermediate formation of bicyclo[4.2.0]octatriene valence tautomers. However, the product distribution differs considerably between the thermal and photochemical reactions. Thus, thermolysis of (15) in dodecane solution at 140 °C affords benzene (43.2%) and pyridine (56.8%); at 175 °C, benzene becomes the major product (55.7% vs. 44.3% pyridine) (Scheme 3). Pyridazine, however, is not formed. In contrast, photolysis in tetrahydrofuran at >300 nm affords only benzene; neither pyridine nor pyridazine are detected <79JOC1264>.



Scheme 3

Thermolysis of 3,8-diphenyl-1,2-diazocine (16; Ar = Ar' = Ph, X = Y = H) in refluxing toluene affords 2-phenylpyridine in ca. 50% isolated yield; benzonitrile (29%) and a trace of the anticipated benzene derivative, *o*-terphenyl, are also formed <82CL1579>. Similarly, 4,7-dichloro-3,8-diphenyl-1,2-diazocine (16; Ar = Ar' = Ph, X = Y = Cl) affords 3,6-dichloro-2-phenylpyridine (88%) together with benzonitrile (71%); none of the benzene derivative is detected <82CL1579>. Trapping experiments appear to lend support to the intermediacy of the bicyclo[4.2.0]octatriene in these reactions <82CL1579>. Similar results have also been reported for other 2,8-aryl derivatives <86BCJ1087>. Again in marked contrast to the thermal results, photolysis of these diphenyl derivatives in solution with Pyrex filtered UV light affords good yields of the benzene derivatives (100% and 43%, respectively) (Scheme 4) <82CL1579>.

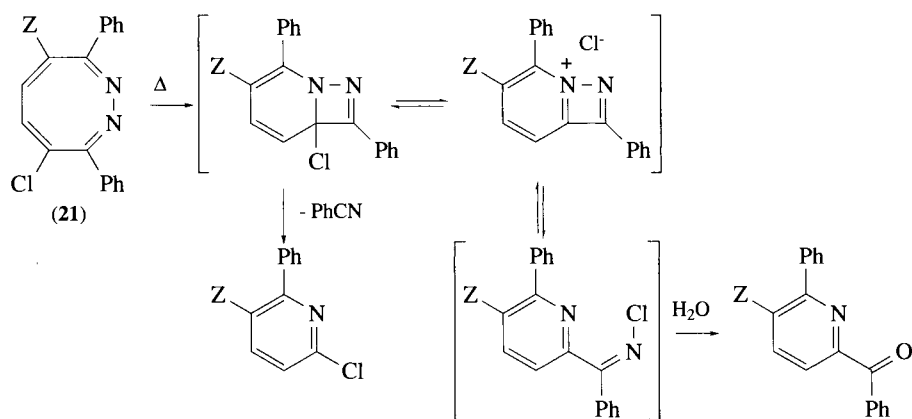
Nucleophilic displacement of chloride substituents in the 4- and 7-positions of the 1,2-diazocine ring provide access to a number of substituted analogues. Thus, treatment of 4,7-dichloro-3,8-diphenyl-1,2-diazocine with silver or lead salts of carboxylic acids affords mono- and diacyloxy derivatives in low to good yield <86BCJ1087>, while treatment with succinimide, phthalimide,



Scheme 4

N-methyl-*p*-toluenesulfonamide, or *o*-benzosulfimide (saccharin) in the presence of silver oxide affords the mono(imido) (**21**; 25–47% yield) and di(imido) (16–36% yield) derivatives, and treatment of the mono(phthalimido) derivative with lead(II) acetate or with benzenethiol affords the corresponding unsymmetrically substituted derivatives (47% yield and 65% yield, respectively) <87BCJ731>.

4-Amino-7-chloro-3,8-diphenyl-1,2-diazocine derivatives (**21**; ZH = maleimide, phthalimide, *N*-methyl-*p*-toluenesulfonamide, *o*-benzosulfimide (saccharin)) undergo similar thermal reactions, although in these cases somewhat more complex product mixtures are obtained (Scheme 5) <87BCJ731>. Both the anticipated pyridine derivatives and 2-benzoylpyridines, apparently arising from hydrolysis upon aqueous workup of intermediate imines formed via ring-opening of azonia species, are obtained as the major products in these reactions, as shown in the following partial scheme. Thermolyses of the corresponding 4,7-diamino diazocines afford the anticipated pyridine derivatives in modest yield <87BCJ731>.

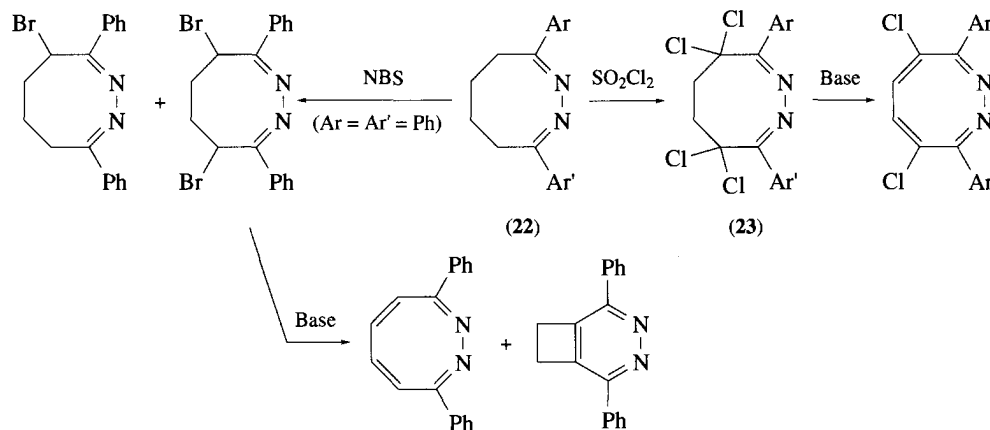


Scheme 5

9.21.3.4 Reactivity of Nonconjugated Rings

3,8-Diphenyl-4,5,6,7-tetrahydro-1,2-diazocine (**22**; Ar = Ar' = Ph) reacts with sulfonyl chloride in methylene chloride, providing the 4,4,7,7-tetrachloro derivative (**23**) in 83% yield <82CL1579>. Other aryl-substituted tetrahydrodiazocines (**22**; Ar, Ar' = *p*-R-C₆H₄, R = H, Cl, Me) react analogously, providing the tetrachloro derivatives in yields of 37–57% <86BCJ1087>. Dehydrochlorination of (**23**) by ethyl sodiomalonate (or NaOH, NaOEt, or DBU) affords the fully unsaturated diazocines (**16**; X = Y = Cl) in 35–81% yield (Scheme 6) <82CL1579, 86BCJ1087>. Free radical bromination of (**22**; Ar = Ar' = Ph) with NBS/benzoyl peroxide affords a mixture of the 4-bromo (22% yield) and 4,7-

dibromo (48% yield) derivatives; dehydrobromination of the latter with NaOH or ethyl sodiomalonate affords (**16**; X = Y = H) (17–28% yield), together with a known cyclobutapyridazine derivative (13–20% yield) <82CL1579>.

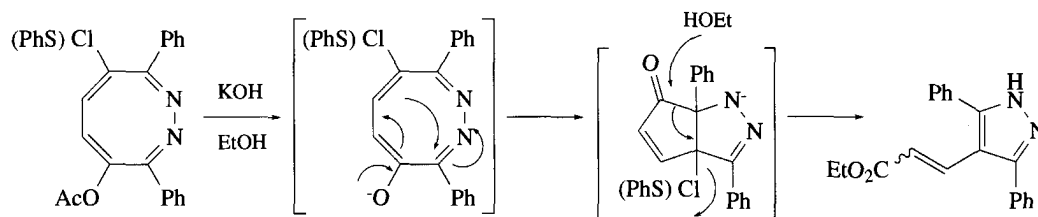


Scheme 6

The 3,4,5,6,7,8-hexahydro-1,2-diazocines continue to attract interest, primarily regarding the issue of photochemical (*E*)/(*Z*) isomerization and photofragmentation. Most recently, the parent hexahydro derivative (**4**) was photolyzed with deep UV (185 nm) light and the results compared to those from more traditional photolysis by 350 nm light <85CJC1829>. These results, together with those of a picosecond study of the photolysis of the 3,8-diphenyl analogue at 354 nm <91CPL(178)9>, are summarized above.

9.21.3.5 Reactivity of Substituents Attached to Ring Carbon Atoms

Alkaline hydrolysis of the acetoxy or phthalimido substituents in several derivatives of (**16**) affords pyrazole derivatives in ca. 60–75% yield, apparently via transannular ring closure, followed by alcoholysis and elimination, as shown for the acetoxy derivatives (**16**; Ar = Ar' = Ph, X = OAc, Y = Cl, SPh). Isolation of the intermediate bicyclic enone upon acidic hydrolysis of the SPh derivative provides strong support for this mechanistic proposal (Scheme 7) <87CL157>.

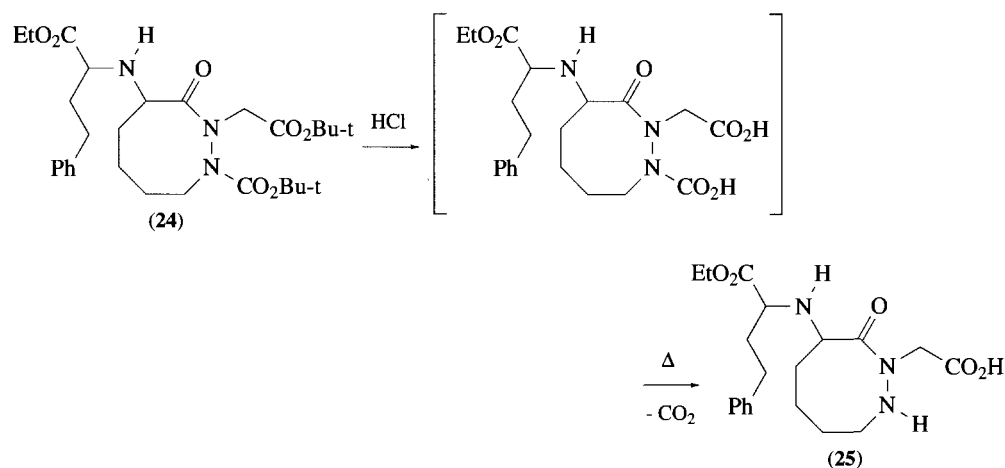


Scheme 7

9.21.3.6 Reactivity of Substituents Attached to Ring Heteroatoms

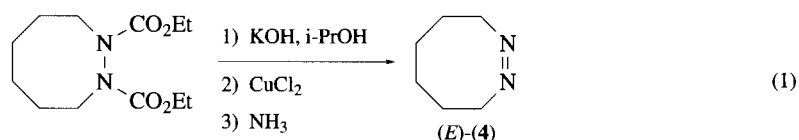
Acidic hydrolysis of *N*-*t*-butoxycarbonyl derivative (**24**) affords an unstable *N*-carboxy derivative, which undergoes facile thermal decarboxylation to (**25**) (Scheme 8) <84USP4465679>.

An improved preparation of (*Z*)-(**4**) through hydrolysis/decarboxylation of an *N,N'*-di(carbo-



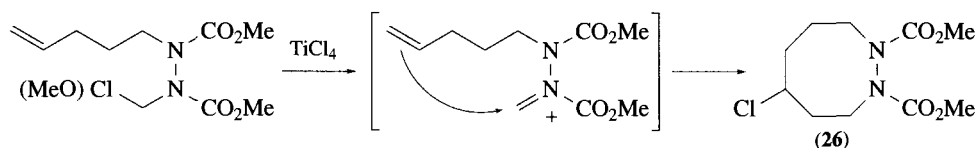
Scheme 8

ethoxy) precursor, utilizing intermediate complexation with CuCl₂ to effect separation, afforded (Z)-(4) in 91% yield after decomplexation with ammonia (Equation (1)) <85CJC1829>.



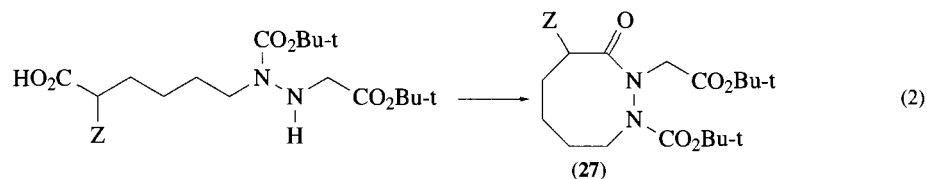
9.21.3.7 Ring Syntheses

In addition to several preparations following now-standard ring-forming procedures, several new preparative routes to the 1,2-diazocines have been reported. In what appears to be the only generation of the diazocine ring system through formation of a carbon–carbon bond, intramolecular delivery of an alkene to a transiently generated hydrazinium ion affords octahydro derivative (26) in 8–15% yield (Scheme 9) <88TL6975>; the analogous reaction affords higher yields of smaller ring diazaheterocycles.



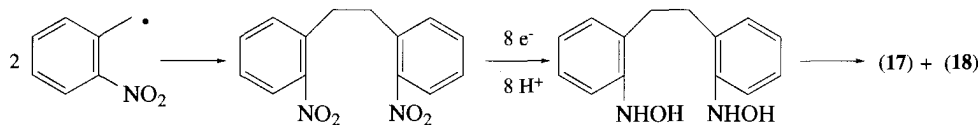
Scheme 9

Formation of a carbon–nitrogen bond, rarely reported as a route to the 1,2-diazocines, affords 1,4,5,6,7,8-hexahydro-1,2-diazocin-3(2*H*)-one (27; Z = phthalimido) (Equation 2) <84USP4465679>.



Controlled potential electrolysis of *o*-nitrobenzyl thiocyanate, under specific pH conditions, affords dibenzo[*c,g*]dihydro derivative (17), together with its mono *N*-oxide (18). The reaction is presumed to occur via dimerization of the initially-formed *o*-nitrobenzyl radical, followed by

electrochemical reduction of the nitro groups to hydroxylamines and intramolecular ring closure via nitrogen–nitrogen bond formation (Scheme 10) <85CCC33>.

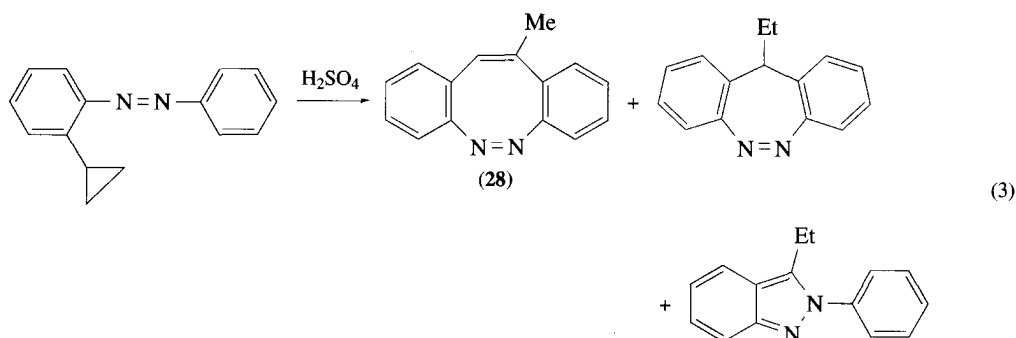


Scheme 10

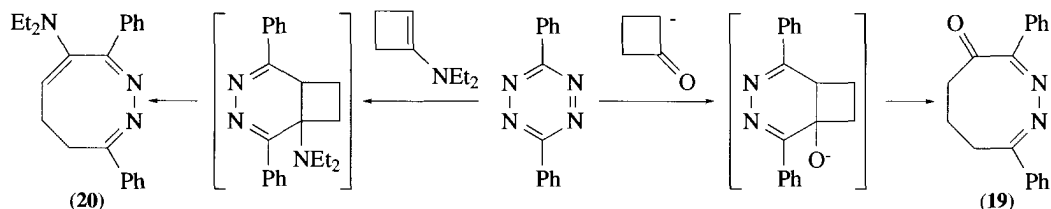
Several new reports utilizing the common strategy of condensation of 1,6-dicarbonyl compounds with hydrazine also appeared, in the context of a selective procedure for the reduction of only one carbonyl group in α,ω -dicarbonyl compounds <90MI 921-01>, and in the preparation of bicyclic initiators for radical block copolymerizations <85USP4532301, 85USP4556512>, as well as in the formation of precursors to fully unsaturated 1,2-diazocines (**16**) <86BCJ1087>.

9.21.3.8 Ring Synthesis by Transformation of Another Ring

Several promising new approaches to the 1,2-diazocine ring system through ring transformation reactions have been reported. Treatment of 2-cyclopropylazobenzene with concentrated sulfuric acid results in cyclopropane ring-opening, followed by electrophilic attack at the adjacent aromatic ring, affording 5,6-dihydro-11-methyl-dibenzo[*c,g*][1,2]diazocine (**28**) in 22% yield, together with modest yields of 7- and 5-membered ring products (Equation (3)) <87KGS1063>. The 11,12-dimethyl derivative is prepared analogously. Use of trifluoroacetic acid as the catalyst gives the pyrazole derivative as the only isolable product (91%).



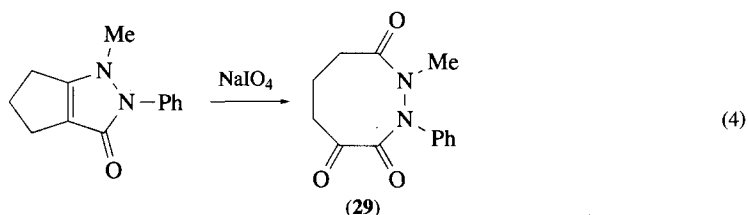
The enolate of cyclobutanone reacts with diphenyltetrazine, purportedly via the intermediacy of a diazabicyclo[4.2.0]octadiene derivative, to afford 6,7-dihydro-3,8-diphenyl-1,2-diazocin-4(5*H*)-one (**19**); the diethyl enamine of cyclobutanone reacts analogously, affording enamine (**20**) (Scheme 11) <84TL2577>.



Scheme 11

In what may foreshadow a versatile and general route to heavily functionalized 1,2-diazocines, as well as to many other larger-ring heterocyclic compounds, oxidative cleavage by periodate of the carbon–carbon double bond of a bicyclic pyrazolone was reported to yield 1,2,6,7-tetrahydro-1-methyl-2-phenyl-1,2-diazocin-3,4,8(5*H*)-trione (**29**) (85%) (Equation (4)); cleavage of larger-ring

analogues gave the corresponding nine- and ten-membered diazaheterocycles <88AP(321)551>. Singlet oxygen was not an effective oxidant for these reactions.

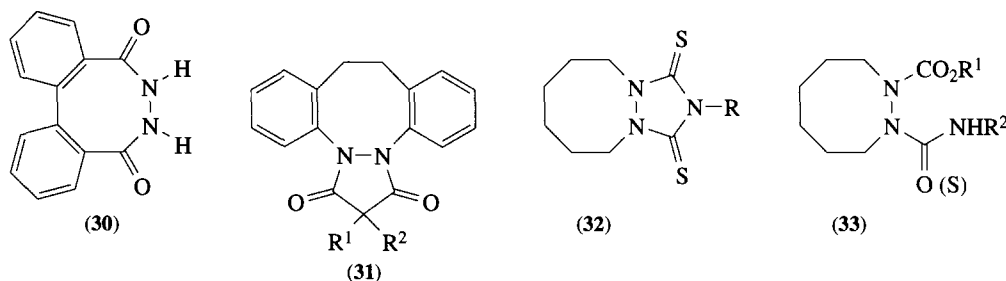


9.21.3.9 Comparison of Synthetic Routes

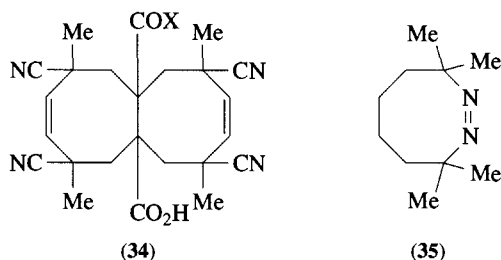
The unimolecular cyclization routes potentially offer some versatility in ring construction, but the facility of the hydrazine/1,6-dione condensations, coupled with the ease with which the resultant heterocycles may be modified, suggests that such condensations will remain a dominant route to the 1,2-diazocines. Ring transformation routes, although chemically and mechanistically interesting, lag behind the condensation route. The cyclobutanone approach may suffer from lack of availability of suitable precursors, while the oxidative ring opening, as noted, may foreshadow a quite general approach to highly-functionalized derivatives.

9.21.3.10 Important Compounds and Applications

Despite the intriguing biological activity of many smaller ring diaza heterocycles, not a great deal of attention appears to have been paid to the 1,2-diazocines. Nonetheless, various derivatives have been noted to display activity as antihypertensive (**25**) <84USP4465679>, analgesic (**30**) <75MI 921-02>, and antibacterial (**31**) <65USP3170929> agents, while others (e.g., (**32**), (**33**)) display herbicidal activity <76JAP7638425, 76JAP7665757, 76JAP7686489, 77JAP7783552>.



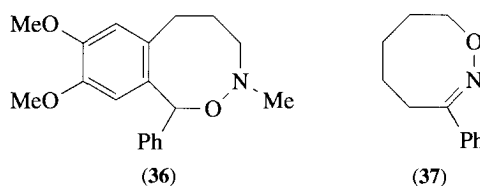
Bicyclic *bis*(1,2-diazocine) derivative (**34**; X = N₃), prepared from the carboxylic acid (**34**; X = OH) derived from oxidation of the corresponding bis(perhydro)diazocine, is reported as an initiator for radical block copolymerization reactions <85USP4532301, 85USP4556512>, while the exothermic nature of the thermal decomposition of hexahydro derivative (**35**) suggests this compound to be a promising heat amplification material for thermal transfer printing applications <82USP454814>.



9.21.4 RINGS WITH ONE NITROGEN AND ONE OXYGEN (2H-1,2-OXAZOCINES)

9.21.4.1 Experimental Structural Methods

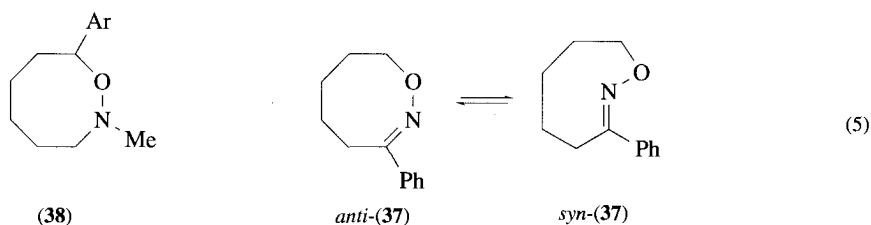
Only one 1,2-oxazocine has been structurally characterized by x-ray diffraction analysis <80AJC1323>. The eight-membered ring in this tetrahydro-1H-2,3-benzoxazocine derivative (**36**) displays a pseudo-chair conformation, with the oxygen and nitrogen atoms, as well as carbons 4 and 5 being substantially out of the defining plane of the benzo group and its attached carbons. (Related conformations are also seen in several 1,2-dithiocins which have also been structurally characterized (*vide infra*).) Bond lengths and angles in (**36**) are as expected, with an N—O bond length of 1.461 Å and the nitrogen pyramidal, with close-to-ideal bond angles at nitrogen (103.1°, 104.8°, and 110.6°).



NMR spectral data for 1,2-oxazocines are largely unreported. Complete ¹H NMR data have been reported only for (**36**) <80AJC1323>, while partial data has been reported for 5,6,7,8-tetrahydro-3-phenyl-1,2-oxazocine (**37**) <81CL1561>. Chemical shifts correlate with those observed in simpler compounds bearing analogous functionality, suggesting no unusual intra-ring effects in these two tetrahydro derivatives, although the observation of distinct resonances ascribed to the protons at C-6 or C-7 of the *syn* isomer formed upon irradiation of the latter compound (*vide infra*) has been reported in support of this proposed photo-induced isomerization. No ¹³C or heteronuclear NMR data has been reported.

The mass spectrum of (**36**) displays the expected parent molecular ion <80AJC1323>. Interestingly, the precursor to this oxazocine displays an identical mass spectrum, suggesting that the Meisenheimer rearrangement (*vide infra*) occurs in the mass spectrometer inlet port. Deuterium labeling has been used to demonstrate a McLafferty-type rearrangement, which is responsible for formation of the base peak ion in the mass spectrum of 3,4,5,6,7,8-hexahydro-2-methyl-8-(3-pyridyl)-2H-1,2-oxazocine (**38**; Ar = 3-pyridyl) <67JCS307>.

Benzo derivative (**36**) displays an absorption maximum at 286 nm (log ε = 3.55), with shoulders apparent at 235 nm, 283 nm, and 290 nm <80AJC1323>. The simpler tetrahydro derivative (**37**) absorbs at 243 nm <81CL1561>. No emission is observed upon irradiation of (**37**) with 254 nm light, but conversion of the stable *anti* isomer to the thermally unstable *syn* isomer (with a half-life for conversion to the *anti* isomer of 20 min at 23°C) is reported to occur from the singlet excited state (Equation (5)). Photoreduction of benzophenone is quenched by (**37**), purportedly due to energy transfer from photo-generated triplet benzophenone to the oxazocine. Interestingly, photo-induced N—O bond scission is not observed for the oxazocine derivative, whereas the corresponding six-membered ring derivative is efficiently cleaved by 254 nm light <81CL1561, 81MI 921-01>.



9.21.4.2 Thermodynamic Aspects

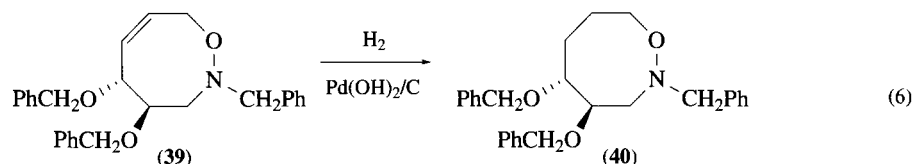
Data concerning the physical properties of 1,2-oxazocines is sufficiently scarce to preclude the drawing of any conclusions regarding the issues responsible for their origin. Benzo derivative (**36**) melts at 106–107°C <80AJC1323>, while the simpler tetrahydro derivative (**37**), in which the oxazocine ring represents the major structural element, is reported to be an oil <81CL1561>.

Compounds (36) and (37) are apparently soluble in more polar solvents, such as chloroform <80AJC1323> and 2-methyltetrahydrofuran <81CL1561>, while the recrystallization of (36) from diethyl ether suggests less polar solvents to be less effective.

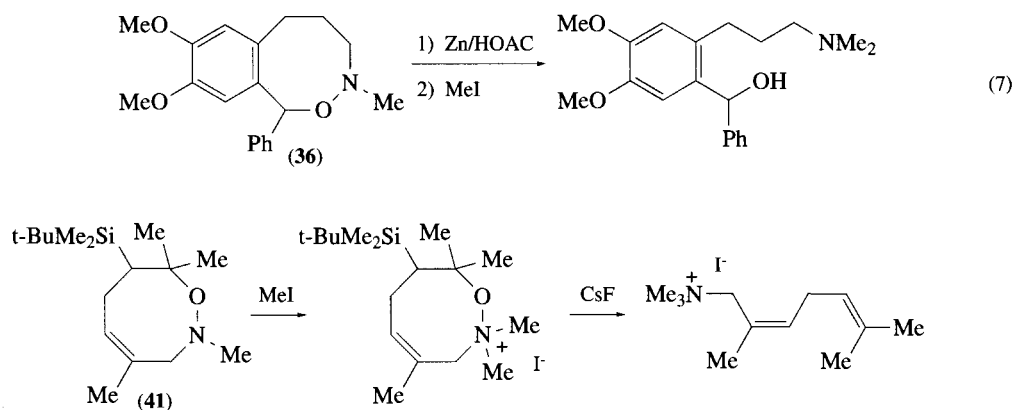
Conformational issues have been briefly addressed, through the crystallographic investigation of benzo derivative (36) <80AJC1323> and through the examination of the photo-induced *syn/anti* isomerization of (37) <81CL1561, 81MI 921-01>. However, the data base of experimentally determined structures is obviously too small to allow one to reach conclusions about conformational preferences for even tetrahydro-1,2-oxazocine, let alone the less-reduced analogues, and no calculational work appears to have been carried out on any oxazocine systems, whether oxidized or reduced.

9.21.4.3 Reactivity of Nonconjugated Rings

All reported reaction chemistry of 1,2-oxazocines concerns tetrahydro derivatives. Photo-induced *syn/anti* isomerization of (37) is discussed earlier in this chapter <81CL1561, 81MI 921-01>. Catalytic hydrogenation of 3,4,5,8-tetrahydro-2*H*-1,2-oxazocine derivative (39) using Pearlman's catalyst affords the corresponding hexahydro derivative (40) (Equation (6)). Curiously, the *N*-benzyl group survives, even though Pearlman's catalyst has been reported to effect selective *N*-debenzylation <90SC1209>.



Ring cleavage, through scission of the N—O bond, has been effected by reduction (36; Zn/HOAc) (Equation (7)) <80AJC1323> and by quaternization followed by fluoride-induced cleavage (41) (Scheme 12) <86TL3611>.



Scheme 12

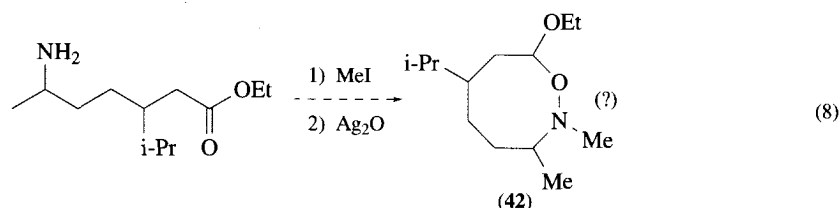
9.21.4.4 Reactivity of Substituents Attached to Ring Heteroatoms

Only the curious immunity of the *N*-benzyl substituent in (39) and/or its reduction product (40) to catalytic hydrogenolysis has been reported <90SC1209>.

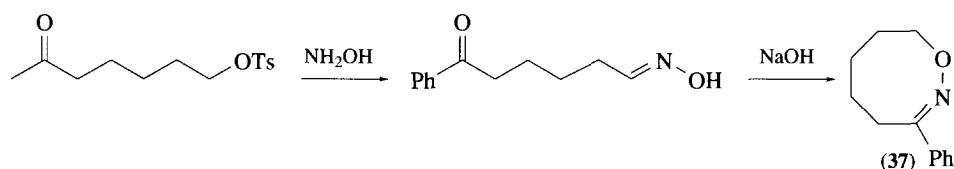
9.21.4.5 Ring Syntheses

Synthesis of the 1,2-oxazocine ring has been effected through both the unimolecular cyclization of appropriate precursors and through the dialkylation of hydroxylamines. Unfortunately, at best

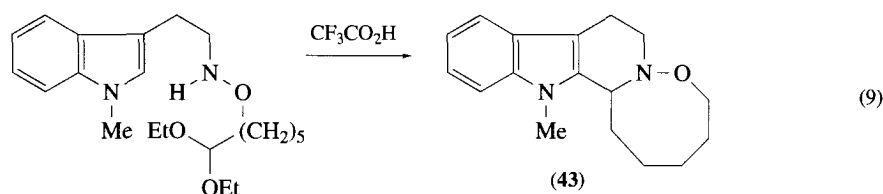
cursory data has been reported for the 1,2-oxazocines prepared by such ring construction reactions, and conclusive proof for the proposed structures is largely lacking. Exhaustive methylation of an amino ester, followed by silver oxide-induced ring closure to hexahydro derivative (42), reported by Wallach (Equation (8)) <02LA(323)323>, represents the first claim of a 1,2-oxazocine synthesis.



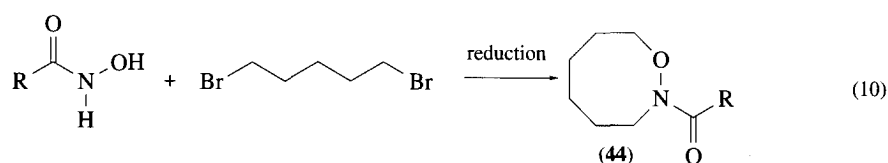
Base-induced ring closure of a keto oxime has been reported to give a 45% yield of (37) (Scheme 13) <81CL1561>, while intramolecular Pictet–Spengler condensation affords a fused-ring hexahydro derivative (43) (Equation (9)) <89TL6809>.



Scheme 13

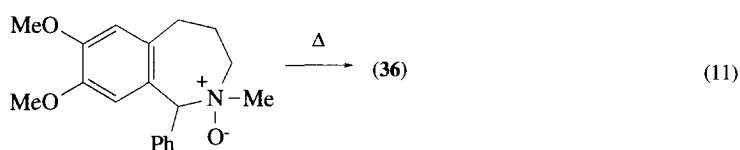


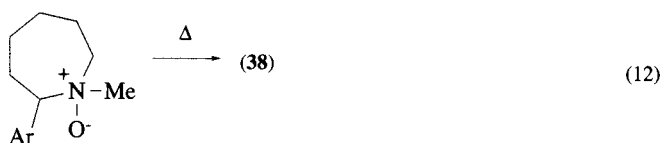
The synthesis of a series of hexahydro derivatives (44; R = Ph, OPh, CH₂OC₆H₄—Cl-*p*, CH₂C₆H₄—CN-*p*, OC₆H₄—SMe-*o*), as well as the *N*-tosyl analogue, through the electrochemical reduction/dialkylation of various *N*-acylhydroxylamines with 1,6-dibromohexane (or 1-bromo-6-chlorohexane) has been reported (Equation (10)) <89JAP01221371, 89JAP01221372, 90JAP02229175>.



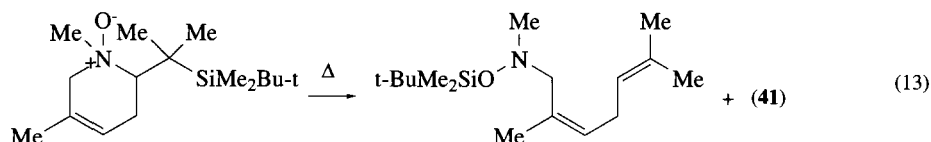
9.21.4.6 Ring Synthesis by Transformation of Another Ring

Meisenheimer rearrangement of azepine *N*-oxides, prepared by *N*-oxidation of the corresponding azepines, has been used to effect the formation of oxazocines (36) (Equation (11)) <80AJC1323> and (38) (Equation (12)) (Ar = Ph, 3-pyridyl) <65JCS1653, 67JCS307>. This rearrangement route can be very effective, with (36), for example, being obtained in 94% yield after heating the *N*-oxide precursor in refluxing acetonitrile for 10 minutes.





Interestingly, a tetrahydropyridine *N*-oxide derivative does not undergo Meisenheimer rearrangement, but rather gives competitive sila-Cope elimination, affording an acyclic diene, and an unusual [1,2] silyl shift, affording (41) in 50% yield (Equation (13)) <86TL3611>.



9.21.4.7 Comparison of Synthetic Routes

Unimolecular cyclization reactions offer potentially versatile routes to various 1,2-oxazocines, with the intramolecular Pictet–Spengler condensation seeming particularly promising. Hydroxylamine dialkylations also appear quite effective, although the reductive conditions required may somewhat limit the functional group tolerance of this approach. The Meisenheimer rearrangement appears quite promising, with, however, the sila-Cope elimination providing perhaps a note of caution regarding synthetic generality.

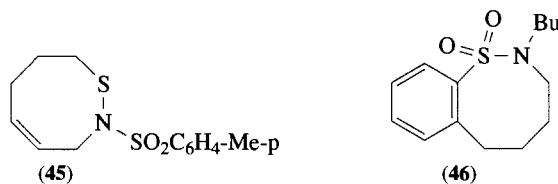
9.21.4.8 Important Compounds and Applications

The *N*-acyl hexahydro derivatives (44), together with a number of smaller-ring analogues, have received patent protection as agrochemical fungicides, providing essentially complete control of *Piricularia oryzae* at ca. 500 ppm and of *Puccinia recondita* at ca. 200 ppm, with no damage to rice or wheat.

9.21.5 RINGS WITH ONE NITROGEN AND ONE SULFUR (2*H*-1,2-THIAZOCINES)

9.21.5.1 Experimental Structural Methods

Proton NMR data has only been reported for 3,6,7,8-tetrahydro-2-tosyl-2*H*-1,2-thiazocine (45) and 2-butyl-3,4,5,6-tetrahydro-2*H*-1,2-benzothiazocine 1,1-dioxide (46) <86CPB3682, 92OPP463>, while ¹³C NMR data has only been reported for (46) <92OPP463>. Chemical shifts correlate with those observed in simpler compounds bearing analogous functionality, suggesting no unusual intra-ring effects in these two tetrahydro derivatives. The 10 Hz coupling constant observed for the vinylic protons in (45), exposed by a homonuclear decoupling experiment, supports the proposed *cis* substitution about the C=C double bond <86CPB3682>. No heteronuclear NMR data has been reported.



Mass spectral analysis of only a single thiazocine (45) has been reported <86CPB3682>. The expected parent ion was observed but, unfortunately, no other data was reported.

Tetrahydrothiazocine (45) displays characteristic bands in its IR spectrum for the sulfonamide group (1150, 1340 cm⁻¹); no other spectral features were reported <86CPB3682>.

9.21.5.2 Thermodynamic Aspects

All the thiazocines for which melting points have been reported up to 1995 are sulfonamides, with this functionality presumably adding substantially to the intermolecular packing forces. Even the simple hexahydro-1,2-thiazocine-1,1-dioxide (**47**) (m.p. 70–71 °C) <56BRP742227> and *N*-tosyl-tetrahydro-1,2-thiazocine (**45**) (m.p. 68–69 °C) <86CPB3682> display respectable melting points, while 3,4,5,6-tetrahydro-1*H*-2,1-benzothiazocine 2,2-dioxide (**48**) melts at an even higher temperatures (160–162 °C) <81CC1087>. Solid-state packing is apparently easily disrupted, as demonstrated by *N*-butyl derivative (**46**), which is an oil <92OPP463>. Loss of hydrogen-bonding capability and introduction of the flexible butyl side chain undoubtedly both contribute to the reduced melting point of (**46**) relative to (**48**), although the issue of heteroatom position within the ring (2,1- vs. 1,2-benzothiazocine) complicates matters.

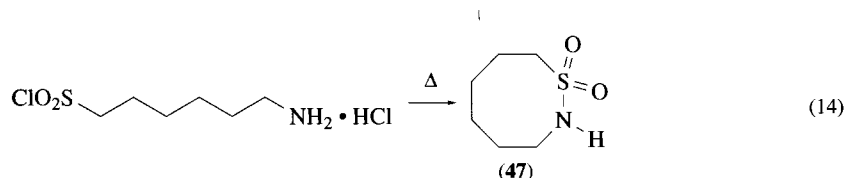


The thiazocine derivatives reported up to 1995, appear to display the solubility anticipated for compounds with related functional groups, with appreciable solubility in polar (diethyl ether <56BRP742227, 92OPP463>, methylene chloride <86CPB3682>, chloroform <92OPP463>) and aromatic (benzene <86CPB3682>) solvents and more sparing solubility in hydrocarbons (*n*-hexane), with the latter used to drive *N*-tosyl derivative (**45**) out of solution <86CPB3682>. Chromatography through silica has been reported to effect purification of (**45**) and (**46**) <86CPB3682, 92OPP463>.

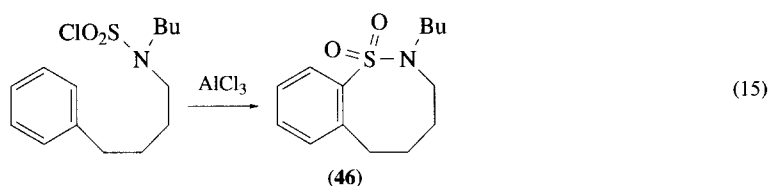
Conformational issues have scarcely been addressed for the thiazocines, with neither crystallographic data nor calculational studies having been reported. In only one case, that of *N*-tosyl tetrahydro derivative (**45**), has any suggestion of such issues been made, with the lack of observed thermal *syn/anti* isomerization cited in support of the stereoselectivity of the rearrangement reaction leading to its formation (*vide infra*) <86CPB3682>.

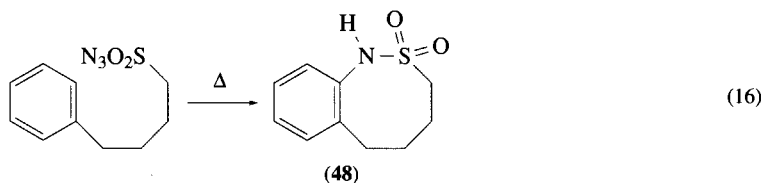
9.21.5.3 Ring Syntheses

All reported syntheses from acyclic precursors of the 1,2-thiazocine ring system have been effected through unimolecular cyclization reactions. The simplest derivative, (**47**), was prepared via lactamization of the corresponding acyclic ω -amino sulfonyl chloride in refluxing toluene (Equation (14)) <56BRP742227>.

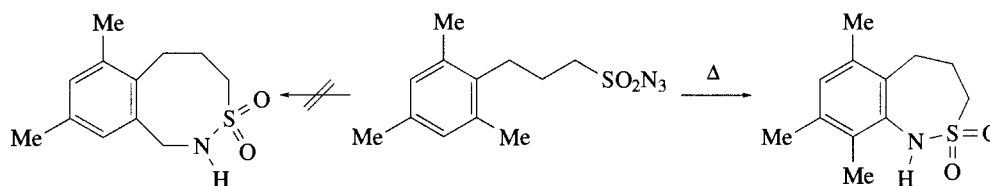


Benzo derivative (**46**) was formed in 7% yield through intramolecular Friedel–Crafts acylation of an acyclic sulfamoyl chloride (Equation (15)) <92OPP463>, while the benzo-2,1-thiazocine derivative (**48**) was formed in 30% yield through the intermediacy of the sulfonyl nitrene, generated thermally from the corresponding sulfonyl azide, which underwent intramolecular insertion into an aromatic C—H bond (Equation (16)) <81CC1087>.





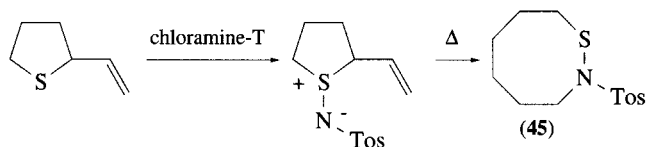
A related nitrene insertion reaction which quite plausibly might have been expected to lead to a benzo-3,2-thiazocine was shown in fact to result in formation of a thiazepine as the result of an unusual rearrangement upon flash pyrolysis (Scheme 14) <84JOC3114>.



Scheme 14

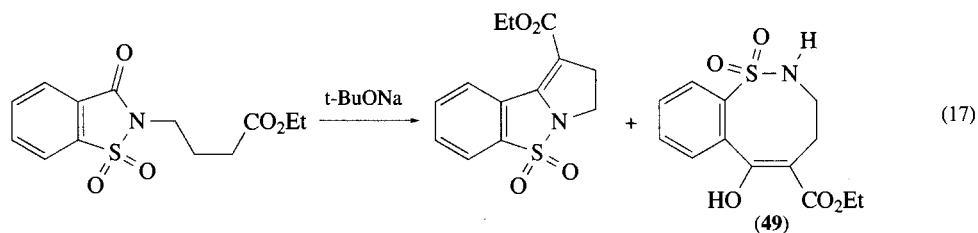
9.21.5.4 Ring Synthesis by Transformation of Another Ring

The Meisenheimer rearrangement pathway to oxazocines suggests an analogous rearrangement route to the thiazocines. Although initial studies confirmed this, with [2,3]-rearrangement of an α -vinyl sulfonium imide leading to *N*-tosyl derivative (45) in 55% yield (Scheme 15) <84H(22)1303, 85JAP6061574, 86CPB3682>, this route appears not to have been applied to the preparation of any other thiazocines.



Scheme 15

Base-induced rearrangement of a carboxyalkyl saccharin derivative has been reported to lead to competitive formation of a tricyclic compound and benzo-1,2-thiazocine (49), with both products arising from a common intermediate and solvent effects dictating the ultimate product obtained (Equation (17)) <92AQ265>.



An earlier report of the formation of a fully-conjugated thiazocine derivative through a "novel ring expansion" reaction between a thiophene sulfimide and dimethyl acetylenedicarboxylate <86JCS(P1)233> was later shown by x-ray crystallographic analysis to be incorrect, with the actual product retaining the thiophene ring <87JCS(P1)2659>.

9.21.5.5 Comparison of Synthetic Routes

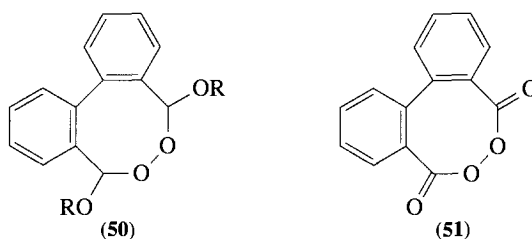
There is clearly room for additional developments in the synthesis of 1,2-thiazocines. Unimolecular cyclizations have been modestly successful, but relatively slight changes in substrate structure can apparently derail these approaches. The Meisenheimer rearrangement route, of success in the oxazocine arena, perhaps offers the greatest synthetic promise, although it has thus far been demonstrated only in a single case.

9.21.5.6 Important Compounds and Applications

Despite the recognition of smaller-ring *N,S*-heterocycles as potentially important materials (e.g., the five-membered ring saccharin, and possible applications of five- and six-membered ring compounds as herbicides, anticonvulsants, diuretics, or sedatives) <92OPP463>, only one thiazocine, (**45**), has received patent protection, as a potential microbiocide, inhibiting fungus-induced tomato diseases.

9.21.6 RINGS WITH TWO OXYGENS (1,2-DIOXOCINS)

The 1,2-dioxocin ring system has received a rather surprising amount of attention, at least in relation to the other compounds discussed in this chapter (with the exception of the 1,2-diazocines). The vast majority of these reports deal with essentially two compounds, namely the 5,8-dialkoxy-5,8-dihydro-dibenzo[*d,f*][1,2]dioxocins (**50**) obtained from the ozonolysis of phenanthrene, and the corresponding 5,8-dione (**51**) ('diphenoyl peroxide'), but a substantial number of other derivatives have also appeared since the publication of CHEC-I in which only a single derivative was reported.

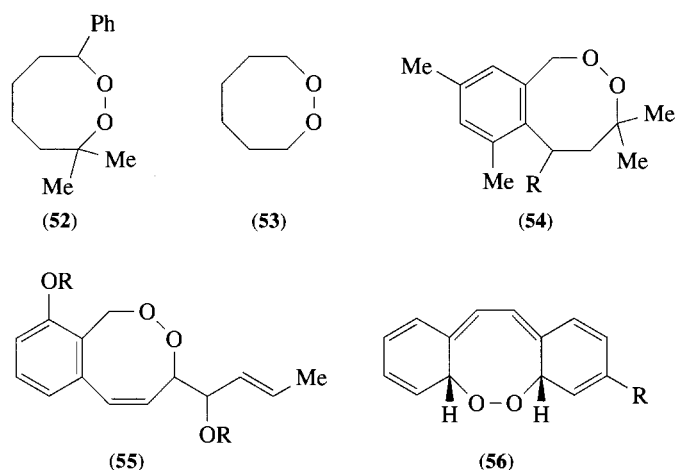


9.21.6.1 Experimental Structural Methods

Although several 1,2-dioxocin derivatives have been obtained in crystalline form, only one appears to have been subjected to single crystal x-ray diffraction analysis. This paucity of structural data may be due to the relative sensitivity of these peroxide derivatives; even in the one structure reported, an extreme drop-off in reference reflection intensities was noted during the course of data collection <76JOC3756>. The crystallographic analysis of *trans*-5,8-dihydro-5,8-dimethoxy-dibenzo[*d,f*][1,2]dioxocin (**50**; R = Me), in addition to demonstrating the *trans* disposition of the methoxy groups, displays a number of interesting features, including a rather short O—O bond, at 1.452 Å and a severe puckering of the dioxocin ring. Interestingly, this conformation places the O—O bond nearly perpendicular to the exocyclic C—O bonds (of normal length, at 1.416 Å), suggesting *n*-to- σ^* donation of electron density from the C—O bonds to the O—O bond, as suggested by *ab initio* SCF molecular orbital calculations for simpler compounds <71JA289>. The dihedral angle between the two aryl rings, at 61.9°, is quite analogous to that in the oxathiocin derivative (*vide infra*).

Proton NMR spectral data has been reported for a number of partially to fully reduced 1,2-dioxocin derivatives <74CL345, 76JOC3756, 79JA4290, 82CB2697, 82CL381, 83LA610, 83LA624, 91ABC2785>. Chemical shifts are largely as anticipated for simpler compounds bearing related functionalities, with protons on carbons bearing oxygen appearing near 4 ppm unless shifted downfield by aromatic substituents. Perhaps surprisingly, the simple 3,3-dimethyl-8-phenyl-1,2-dioxocane (**52**) displays a

chemical shift of 3.66–4.27 ppm for the methine proton $\langle 83\text{LA}610 \rangle$, quite like that in the parent 1,2-dioxocane (**53**) (3.87 ppm) $\langle 79\text{JA}4290 \rangle$ and rather upfield from the analogous protons in benzan-related derivatives (**54**; R = H, Me) (5.2 ppm and AB quartet at 4.75, 5.51 ppm, respectively) $\langle 83\text{LA}624 \rangle$, and (**55**; R = Ac) (AB quartet at 4.50 and 5.25 ppm) $\langle 91\text{ABC}2785 \rangle$. The ^1H NMR spectrum of (**54**; R = H) displays an interesting solvent dependence, with the α -methylene group resolving from a broad singlet in CDCl_3 into an apparent doublet (4.90 ppm, 5.07 ppm) in CCl_4 $\langle 83\text{LA}624 \rangle$. 5,6-Dihydro-dibenzo[*c,g*][1,2]dioxocins (**56**; R = H, Cl, Me), representing a unique structural type, also show a chemical shift of ca. 4 ppm for the α -protons, while the alkenic protons, despite the apparent loss of aromaticity, appear as an unresolved signal near 7 ppm $\langle 82\text{CL}381 \rangle$. The α -protons in (**50**; R = Me) appear at ca. 5.5 ppm, consistent with the acetal functionality present in this compound $\langle 76\text{JOC}3756, 82\text{CB}2697 \rangle$.

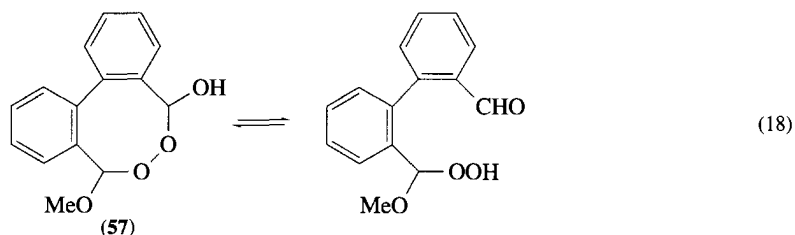


Carbon-13 data has been reported for only a single 1,2-dioxocane (**52**) $\langle 83\text{JCR}(\text{S})282 \rangle$ and two dibenzo derivatives (**50**; R = Me; **56**, R = H) $\langle 76\text{JOC}3756, 76\text{MI}921-01, 82\text{CL}381 \rangle$. Resonances for the α -carbons in (**52**) appear at 81.5 ppm and 85.5 ppm $\langle 83\text{JCR}(\text{S})282 \rangle$, while the dibenzo derivatives display downfield shifts seemingly in accord with their proposed structures, at 120.0 ppm (**56**) $\langle 82\text{CL}381 \rangle$ and 106 ppm (**50**; R = Me) $\langle 76\text{JOC}3756 \rangle$. In the latter case, a $^1J_{\text{CH}}$ of 160 Hz was reported.

Compounds (**50**; R = Me) $\langle 76\text{JOC}3756 \rangle$, (**53**) $\langle 79\text{JA}4290 \rangle$, (**54**; R = H, Me) $\langle 83\text{LA}624 \rangle$, and (**55**; R = Ac) $\langle 91\text{ABC}2785 \rangle$ all display parent ions in their electron-impact mass spectra. Compounds (**50**) $\langle 76\text{JOC}3756 \rangle$ and (**54**; R = H) $\langle 83\text{LA}624 \rangle$ show loss of O_2 as a significant fragmentation pathway, but curiously, closely related derivative (**54**; R = Me) $\langle 83\text{LA}624 \rangle$ does not give such a fragment. For both compounds (**54**), however, the major fragmentation pattern appears to be loss of both O_2 and isobutylene, giving rise to an M-88 fragment as the base peak in the mass spectra of each. The fully-saturated derivative (**53**) $\langle 79\text{JA}4290 \rangle$ displays $(\text{CH}_2)_n$ ($n = 2-5$) as major fragments. No parent ion was observed for (**52**) $\langle 83\text{LA}610 \rangle$, and no fragmentation pattern was reported.

The UV spectrum of (**55**; R = H) $\langle 91\text{ABC}2785 \rangle$, with absorption maxima at 304 nm and 260 nm (in methanol), is dominated by the phenol functionality. Dibenzo derivative (**56**; R = H) $\langle 82\text{CL}381 \rangle$ shows (in ethanol) a strong absorption at 249 nm ($\epsilon = 8300$), with a shoulder at 279 nm ($\epsilon = 2900$) and a weak maximum at 315 nm ($\epsilon = 270$), while dibenzo acetal (**50**; R = Me) $\langle 76\text{JOC}3756 \rangle$ displays a maximum, in methanol, at 236 nm ($\epsilon = 10800$). Diphenyl peroxide (**51**), which undergoes chemiluminescent decomposition, has been the subject of a number of studies $\langle 78\text{JA}4496, 82\text{TI}095, 85\text{JCR}(\text{S})140, 85\text{MI}921-01, 86\text{JOC}2050, 89\text{JA}2633 \rangle$. Since the first detailed analysis of this chemiluminescence $\langle 78\text{JA}4496 \rangle$ appeared, considerable controversy has developed over the mechanism involved, with one report $\langle 85\text{JCR}(\text{S})140 \rangle$ claiming to rule out the originally proposed chemically-initiated electron-exchange (CIEEL) mechanism $\langle 78\text{JA}4496 \rangle$ and another $\langle 89\text{JA}2633 \rangle$ claiming a 10000-fold smaller quantum yield for the chemiluminescent decomposition than originally reported.

Infrared spectral analysis has been used to determine the identity of the functional groups in natural product (**55**) $\langle 91\text{ABC}2785 \rangle$ and to explore the reversible ring opening of (**50**; R = H) $\langle 63\text{JOC}2340, 63\text{USP}3091620 \rangle$ and (**57**) (Equation (18)) $\langle 56\text{JA}3811, 58\text{JOC}1089 \rangle$, with the strong carbonyl stretching band observed for the latter in CHCl_3 or CHBr_3 solution, but not in the solid state, consistent with its interconversion with the acyclic hydroperoxyaldehyde in solution.

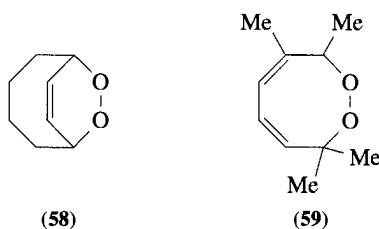


The corresponding acetal (**50**; R = Me) shows an O—O stretching frequency of 915 cm^{-1} , consistent with its peroxidic nature, as well as a C—C—O mode at 1190 cm^{-1} $\langle 76\text{JOC}3756 \rangle$. Diphenoyl peroxide (**51**) displays a single strong carbonyl stretching frequency at ca. 1760 cm^{-1} $\langle 61\text{JA}492, 64\text{JA}4394, 64\text{MI} 921-01, 89\text{JA}2633 \rangle$; the O—O band for (**51**) was not reported. Although spectral features were not assigned for 1,2-dioxocane (**53**) $\langle 79\text{JA}4290 \rangle$ or dibenzo[*c,g*] derivatives (**56**) $\langle 82\text{CL}381 \rangle$, each displays strong absorptions in the 1000 cm^{-1} region which presumably correspond to the O—O stretching mode.

Photoelectron spectroscopic data has been reported for 1,2-dioxocane (**53**) $\langle 79\text{JA}1533 \rangle$. Vertical ionization potentials for the two highest occupied molecular orbitals of 9.29 eV (antisymmetric combination of oxygen lone pair orbitals) and 10.60 eV (antisymmetric combination of C—O σ bond orbitals) were observed. Given the apparent correlation between the difference in ionization potentials for these two orbitals and the C—O—O—C dihedral angle in simple peroxides, this data was used to infer a dihedral angle of 140° for the dioxocane.

9.21.6.2 Thermodynamic Aspects

For those compounds in which the dioxocin ring is not masked by a tangle of attached side chains or functionality, solid-state packing appears to follow standard expectations, with rather symmetrical compounds such as (**58**) m.p. $50.5\text{--}55.5^\circ\text{C}$ $\langle 74\text{CL}345 \rangle$, (**56**; R = H) m.p. $96.0\text{--}96.7^\circ\text{C}$ $\langle 82\text{CL}381 \rangle$, (**50**; R = Me) m.p. ca. 180°C $\langle 56\text{JA}3811, 58\text{JOC}1089, 62\text{MI} 921-01, 76\text{JOC}3756, 82\text{CB}2697 \rangle$, (**50**; R = H) m.p. $105\text{--}106^\circ\text{C}$ $\langle 63\text{JOC}2340, 63\text{USP}3091620 \rangle$, and (**57**) m.p. $116\text{--}117^\circ\text{C}$ $\langle 58\text{JOC}1089, 56\text{JA}3811 \rangle$ being crystalline solids, while less-symmetrical derivatives such as (**52**) $\langle 83\text{LA}610 \rangle$, (**54**) $\langle 83\text{LA}624 \rangle$, and 3,8-dihydro-3,3,7,8-tetramethyl-1,2-dioxocin (**59**) $\langle 62\text{USP}3038906 \rangle$ are liquids, with refractive indices of 1.4803, 1.5291, and 1.4645, respectively.



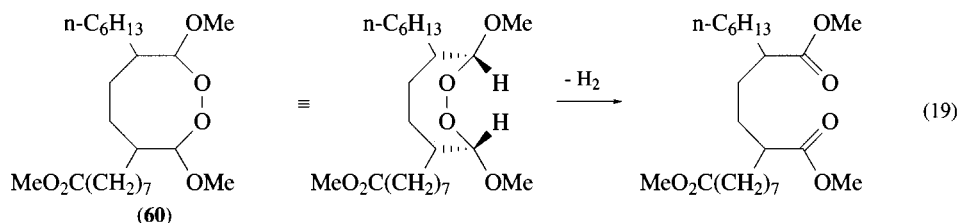
Diphenoyl peroxide (**51**) is nicely crystalline, but decomposes explosively, apparently before melting, when heated to 70°C $\langle 61\text{JA}492, 64\text{JA}4394, 64\text{MI} 921-01, 89\text{JA}2633 \rangle$. A report of the preparation and melting behavior of a full series of dibenzo acetal derivatives (**50**; R = $\text{C}_1\text{--C}_{10}$, benzyl) provides a good look at solid-state packing effects for these derivatives, with the expected drop-off in melting point as the side chains are made longer (from m.p. $172\text{--}174^\circ\text{C}$ for the methyl derivative to a low of ca. $80\text{--}83^\circ\text{C}$ for the *n*-heptyl derivative) $\langle 68\text{MI} 921-01 \rangle$. Interestingly, the *n*-pentyl through *n*-decyl derivatives all melt within a few degrees of each other.

The simpler dioxocin derivatives display normal solubility behavior in the limited range of solvents reported, with apparently reasonable solubility in methylene chloride (**52**) $\langle 83\text{LA}610 \rangle$, chloroform (**52**), (**54**) $\langle 83\text{LA}610, 83\text{LA}624 \rangle$, and carbon tetrachloride (**53**), (**54**), (**58**) $\langle 774\text{CL}345, 9\text{JA}4290, 83\text{LA}624 \rangle$. The dibenzo derivatives are also soluble in methylene chloride (**51**) $\langle 89\text{JA}2633 \rangle$ and chloroform (**50**; R = Me, (**57**) $\langle 56\text{JA}3811, 58\text{JOC}1089, 76\text{JOC}3756 \rangle$, as well as in bromoform (**57**) $\langle 56\text{JA}3811, 58\text{JOC}1089 \rangle$, methyl ethyl ketone (**50**; R = Me) $\langle 56\text{JA}3811, 58\text{JOC}1089 \rangle$, and ethyl acetate (**50**; R = Me) $\langle 56\text{JA}3811, 58\text{JOC}1089 \rangle$, but are sparingly soluble in methanol (**50**; R = Me) $\langle 64\text{JA}4394, 64\text{MI} 921-01, 76\text{JOC}3756, 82\text{CB}2697, 89\text{JA}2633 \rangle$ or 95% ethanol (**50**; R = H) $\langle 63\text{JOC}2340, 63\text{USP}3091620 \rangle$ and insoluble

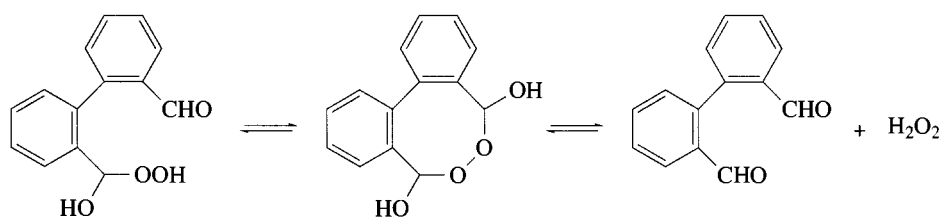
in water (**50**; R = H) <63JOC2340, 63USP3091620>. Liquid chromatography of (**52**) <83LA610> and (**58**) <74CL345> through silica has been reported, as has medium pressure chromatography through Kieselgel at 2.5–3 atm and -25°C (**54**; R = H) <83LA624>. High performance liquid chromatography (HPLC) has been used to separate the products of ozonolysis of phenanthrene, including dibenzo acetal derivatives such as (**50**, R = H) <90MI 921-02>, and the parent 1,2-dioxocane (**53**) has been purified by gas chromatography (Chromosorb W/10% DC 710, 45°C) <79JA4290>.

Although no fully-conjugated 1,2-dioxocins have been prepared, the issue of aromaticity in the parent 1,2-dioxocin (**5**) <75MI 921-01, 91RRC333> and in the 5,6-benzo derivative (**6**) <75MI 921-01> has been calculationaly addressed. Unfortunately, conclusions regarding potential aromaticity appear critically dependent on what criteria of aromaticity are adopted. Calculations of π delocalization energies, free valence indices, and superdelocalizabilities suggest that both (**5**) and (**6**) are potentially aromatic <75MI 921-01>, but AM1 calculations lead to the conclusion that (**5**) is antiaromatic, representing a saddle point on the reaction coordinate leading to ring opening to 2,4-hexadien-1,6-dione, which is some $70.1\text{ kcal mol}^{-1}$ more stable than (**5**) <91RRC333>. Although the 1,2-dioxocins are peroxides, many of the derivatives reported display rather high melting points, apparently without noteworthy decomposition (*vide supra*). Thermal sensitivity has been reported only for diphenoyl peroxide, which explosively decomposes when heated to ca. 70°C or upon impact <61JA492, 64JA4394, 64MI 921-01, 89JA2633>.

The conformation of the 1,2-dioxocin ring in (**50**; R = Me) has been revealed by x-ray structural analysis <76JOC3756>, as discussed above. A few other hints about the conformational preferences of the partially or fully-saturated ring system may be gleaned from several other reports. Thus, the solvent-dependent NMR spectrum of (**54**; R = H) <83LA624>, discussed above, is in accord with a nonplanar ring, the slow decomposition of (**60**) at room temperature has been explained by a concerted intramolecular elimination of dihydrogen from a tub-like conformation (Equation (19)) <70JA51>, and the PES study of 1,2-dioxocane (**53**) suggests a C—O—O—C dihedral angle of 140°C <79JA1533>. Along the latter lines, study of a homologous series of cyclic peroxides has been suggested of relevance to the question of the importance of geometric constraints on the properties and chemistry of the peroxide bond, although no follow-up analysis of such matters has been presented <79JA4290>.

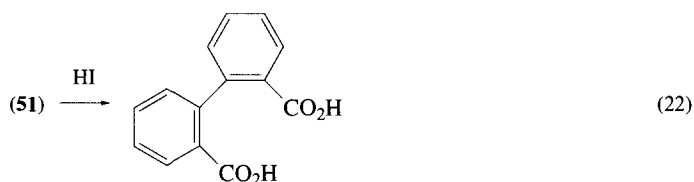
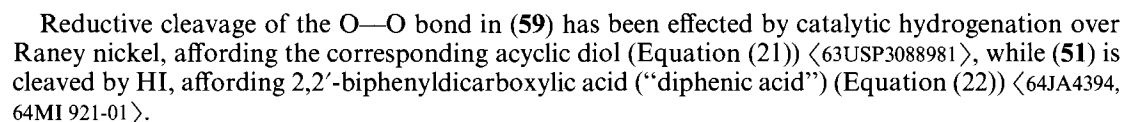


Ring-chain tautomerism, in the form of aldehyde/hemiacetal equilibrium, has been reported for (**57**) <56JA3811, 58JOC1089>. The hemiacetal exists as such in the solid state, with no carbonyl stretching band observed in the IR spectrum, but when dissolved in chloroform or bromoform, equilibration with the hydroperoxyaldehyde form (*vide supra*) apparently is facile, as evidenced by the appearance of a distinct carbonyl stretching band. Solution molecular weight analysis suggests that the aldehyde may also undergo bimolecular hemiacetal formation, apparently affording a cyclic dimer, but no definitive structural proof for this dimer beyond the elevated molecular weight determined for the monomer has been reported <56JA3811>. Related ring-chain tautomerism has also been inferred for bis(hemiacetal) derivative (**50**; R = H) (Scheme 16) <63JOC2340, 63USP3091620>.



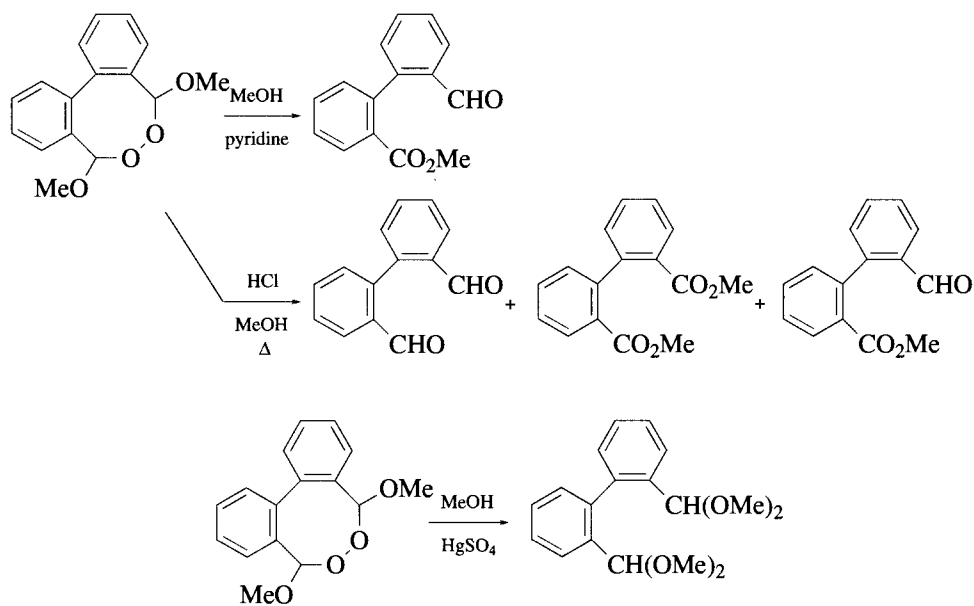
Scheme 16

The chemistry of the peroxide bond has featured prominently in the reported reaction chemistry of 1,2-dioxocin derivatives. Diphenoyl peroxide (**51**) readily oxidizes triphenylphosphine and trimethylphosphite to the corresponding *P*-oxides, in the process being reduced to diphenic anhydride (Equation (20)) <61JA492, 64JA4394, 64MI 921-01>. Compound (**56**; R = H) also oxidizes triphenylphosphine; the fate of the dioxocin in this case has not been determined, but alcohol and/or epoxide derivatives appear to be formed <82CL381>.

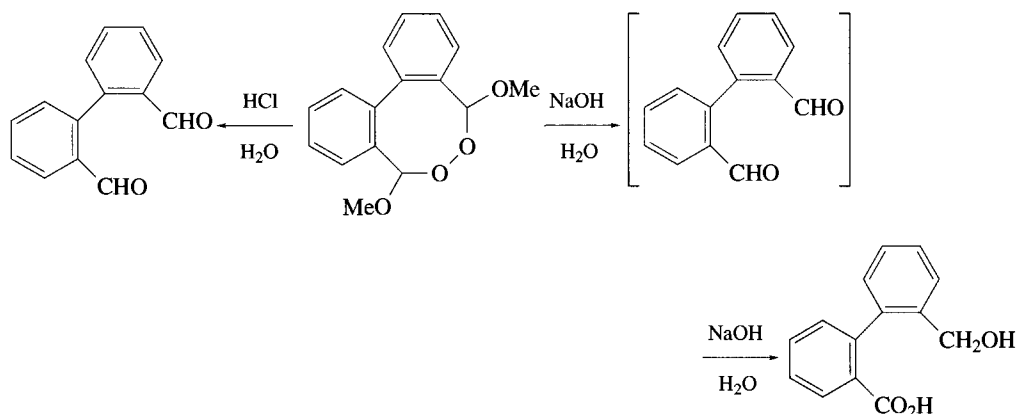


Hydrolysis of (**50**; R = Me) with aqueous HCl affords the corresponding dialdehyde in quantitative yield (<69MI 921-01, 69MI 921-02>), while treatment with aqueous NaOH affords 2'-hydroxymethylbiphenyl-2-carboxylic acid, apparently through initial formation of the dialdehyde followed by a base induced intramolecular Cannizzaro reaction (Scheme 18) (<63JOC2340, 63USP3091620, 69MI 921-01, 69MI 921-02>).

Treatment of (**50**; R = Me) with basic hydrogen peroxide affords 2,2'-biphenyldicarboxylic acid, presumably through oxidation of the first-formed aldehyde (<58JOC1089, 56JA3811>).

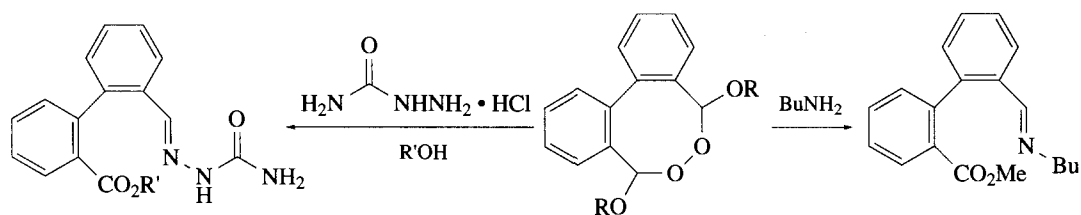


Scheme 17



Scheme 18

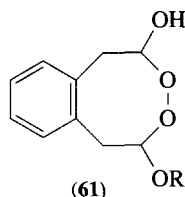
Interception of the ring-opened tautomers of (50) by amines has also been reported. Thus, treatment of (50; R = Me) with butylamine in ethanol affords the methyl ester of 2-carboxybiphenyl-2'-carbaldehyde in the form of its Schiff base <83CZP209400, 91MI 921-02>; this has been used as a key step in the formation of 5,6,7,8-tetrahydrodibenz[*c,e*]azocine. Similarly, treatment of (50; R = Et) with semicarbazide hydrochloride in the presence of aqueous NaOH and alcohols affords the analogous Schiff bases, with the carboxylate present in esterified form (Scheme 19) <81MI 921-02>.



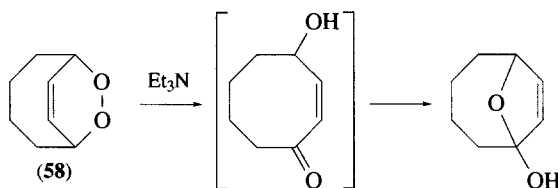
Scheme 19

The reaction chemistry of diphenoyl peroxide (**51**) has been studied primarily in the context of attempts to understand the processes responsible for chemiluminescence. Electron transfer from an excited state donor (e.g., singlet pyrene) to the peroxide has been proposed to generate the radical anion, which either annihilates while in the solvent cage or diffuses out of the solvent cage, allowing chemiluminescent decomposition to ensue <78JA4496, 82T1095>. With no substantiating data provided, it has been claimed that diphenoyl peroxide decomposition proceeds via an intermediate dioxirane <85JCR(S)140>.

Reduction of tetrahydro derivatives (**61**; R = H, Me), presumably to alcoholic products, has been reported to be effected by a number of chemical reagents <75MI 921-03, 77MI 921-01>. Unfortunately, the inaccessibility of these studies precludes reporting of any further information.



Treatment of (**58**) with triethylamine in refluxing methylene chloride results in rearrangement, apparently via the unsaturated ketol, to a bicyclic hemiketal (Scheme 20) <74CL345>.

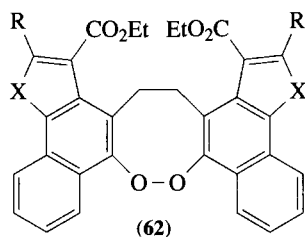


Scheme 20

Compound (**60**), stable at -25°C , undergoes slow decomposition at room temperature, affording primarily dihydrogen, together with traces of CO and CO₂, with dihydrogen claimed to be formed via a concerted unimolecular elimination from a tub-like conformation, as discussed above <70JA51>. Zinc dust reduction of (**60**) affords the corresponding dialdehyde, while thermolysis affords dicarboxystearates and treatment with hydrogen peroxide gives ring cleavage to dihydroxystearic acid <70JA51>.

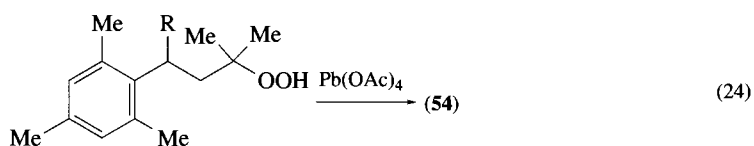
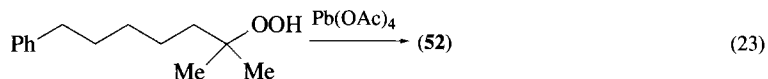
9.21.6.4 Reactivity of Substituents Attached to Ring Carbon Atoms

Reduction of ester side chains to hydroxymethyl groups in several rather complex polycyclic 1,2-dioxocin derivatives (**62**) has been effected by Raney nickel, followed by hydrazine hydrate (X = O, R = Me) and by zinc dust in acetic acid (X = O, R = Ph; X = NMe, R = Me) <61ZOB1902>. No other side chain reactivity has been reported.

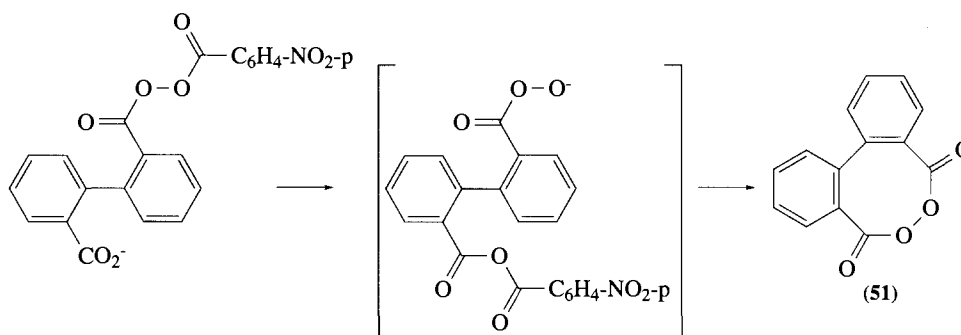


9.21.6.5 Ring Syntheses

Unimolecular cyclization reactions and both nucleophilic and photochemical addition of the O—O unit to appropriate precursors constitute the primary routes which have been reported for the synthesis of 1,2-dioxocins from acyclic precursors. Barton-type cyclization of appropriately-substituted organic peroxides affords low (**52**) (Equation (23)) <83LA610> to modest (**54**) (Equation (24)) <83LA624> yields of cyclic products.

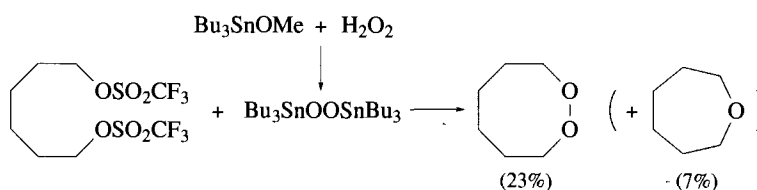


Intramolecular anhydride/peranhydride exchange through *in situ* formation of a peroxy *p*-nitrophenyl anhydride intermediate has been inferred to form diphenoyl peroxide, as evidenced by its chemiluminescent decomposition (Scheme 21) <86JOC2050>.



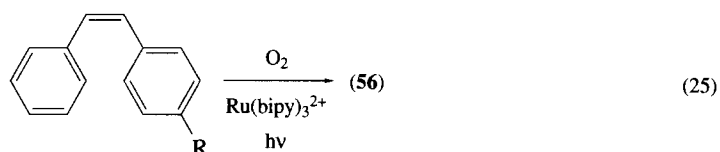
Scheme 21

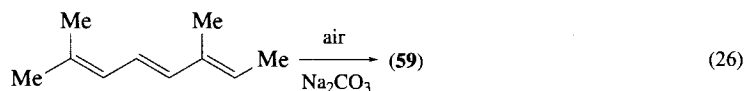
A distannyl peroxide transfer reagent reacts with α,ω -bis(triflates) to afford the corresponding cyclic peroxides, with the parent 1,2-dioxocane (**53**) obtained in 23% yield (Scheme 22) <77JA3500, 79JA4290>.



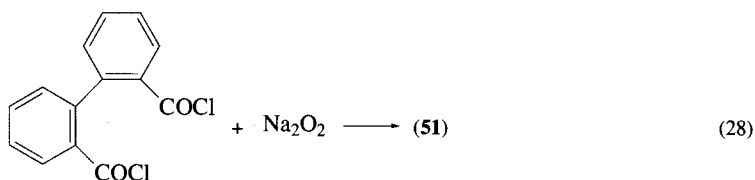
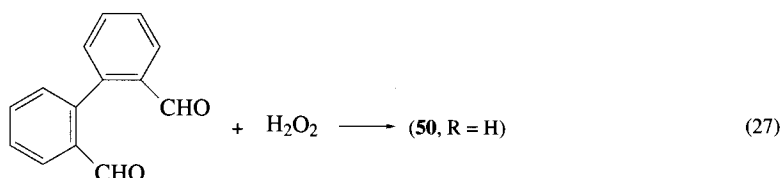
Scheme 22

Photochemical addition of singlet O_2 to *cis*-stilbene derivatives <82CL381> and simple air oxidation of alloocimene <62USP3038906> has been reported to afford low to modest yields of dihydro 1,2-dioxocin derivatives (**56**) (Equation (25)) and (**59**) (Equation (26)), respectively.

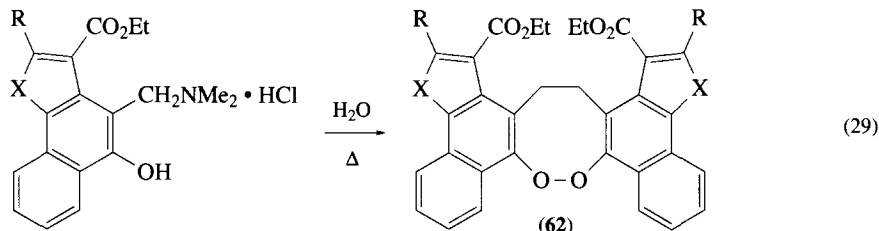




Treatment of 2,2'-biphenyldicarbaldehyde with 15% hydrogen peroxide affords in 90% yield the same compound as is obtained upon ozonolysis of phenanthrene in water (**50**; R = H) (*vide infra*) (Equation (27)) <63JOC2340, 63USP3091620>, thus providing an independent synthesis of this compound, while treatment of diphenoyl chloride with sodium peroxide appears to generate diphenoyl peroxide (**51**) (Equation (28)) <85JCR(S)140>.

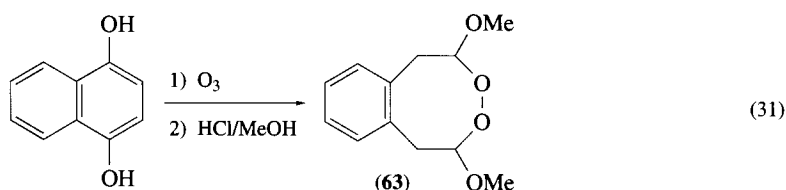
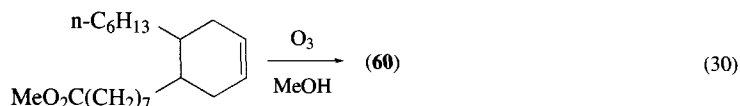


Thermally-induced elimination from a series of dimethylaminomethyl-substituted heterocycles has been reported to be followed by perhaps surprising formal [4 + 4] dimerization, affording polycyclic derivatives (**62**; X = O, R = Me, Ph; X = NMe, R = Me) in unreported yield (Equation (29)) <61ZOB1902>.

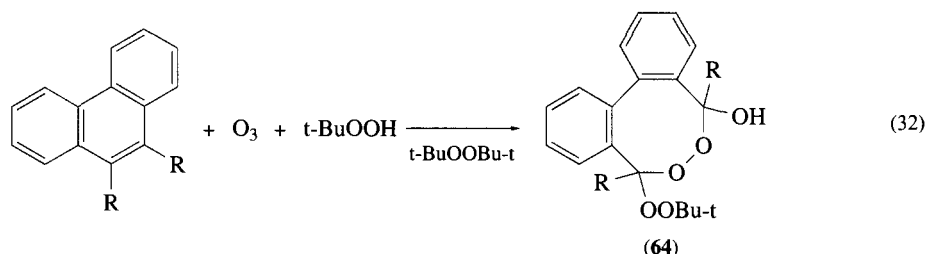


9.21.6.6 Ring Synthesis by Transformation of Another Ring

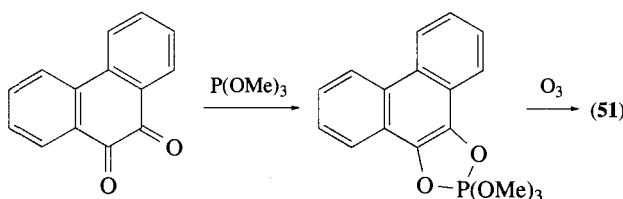
Photoinduced addition of O₂ to cyclooctadiene affords (**58**) in 52% yield <74CL345>. All other preparations of dioxocins by ring transformation reactions involve ozonolyses of appropriate precursors in protic solvents. Thus, ozonolysis of a simple cyclohexene derivative in methanol has been reported to give hemiacetal derivative (**60**) (Equation (30)) <70JA51>. Ozonolysis of 1,4-dihydroxynaphthalene, followed by treatment with methanolic HCl, has been reported to afford (**63**) in 78% yield (Equation (31)) <75MI 921-04>, while slightly modified conditions afford (**61**; R = Me) <75MI 921-04, 77MI 921-01>.



Related ozonolyses of phenanthrene in methanol <56JA3811, 82MI 921-01, 83CZP209400, 84CB16401>, water <63JOC2340, 63USP3091620>, or other alcohols <68MI 921-01>, afford the dibenzo derivatives (**50**) which have received the greatest amount of attention, while ozonolysis of phenanthrene and its 9,10-dimethyl derivative in di(*t*-butyl)peroxide containing *t*-butylhydroperoxide is reported to afford the unusual peroxide (**64**) (Equation (32)) <58USP3009962>.



Ozonolytic cleavage of the adduct between trimethylphosphite and phenanthrenequinone provides diphenoyl peroxide (**51**) in 80% yield (Equation (28)) <61JA492, 64JA4394, 64MI 921-01>.



Scheme 23

9.21.6.7 Comparison of Synthetic Routes

Unimolecular cyclizations appear to provide access to a variety of substituted 1,2-dioxocins, although yields in general appear fated to be rather modest. Singlet oxygen cycloadditions to and ozonolyses of appropriate substrates, when successful, represent attractive routes to the 1,2-dioxocins, but both routes will presumably be rather limited in terms of substrate availability and functional group tolerance. The trimethyl phosphite/quinone adduct route perhaps provides a suggestive hint as to how both synthetic generality and selectivity may potentially be introduced to the ozonolytic preparations.

9.21.6.8 Important Compounds and Applications

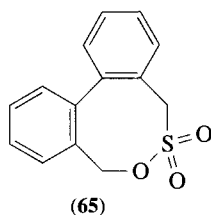
As rather exotic heterocycles, the 1,2-dioxocins have not received a great deal of attention from the perspective of practical applications. Nonetheless, (**59**) has received patent protection as a modifying agent for epoxy resins <62USP3038906> and dibenzo derivative (**50**; R = Me) has been put forth as a key intermediate for the synthesis of dibenzazocines <83CZP209400, 91MI 921-01>. A most interesting benzo-1,2-dioxocin natural product (**55**; R = H), isolated from agar cultures of *Piricularia oryzae*, the causal fungus of rice blast disease, displays phytotoxic and spore germination inhibitory activity toward the fungus <91ABC2785>. The presence of both the potentially reactive peroxide bond and the latent functionalities masked within the various acetal derivatives leads one to suspect that additional practical applications of these heterocycles may be discovered.

9.21.7 RINGS WITH ONE OXYGEN AND ONE SULFUR (1,2-OXATHIOCINS)

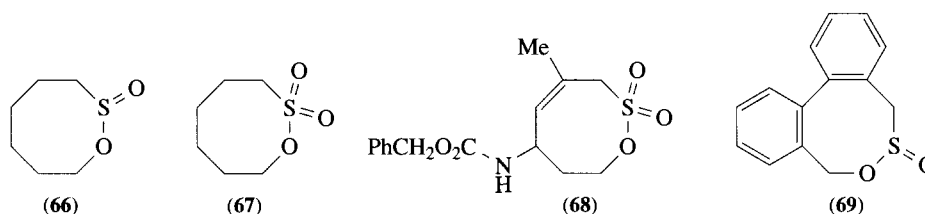
9.21.7.1 Experimental Structural Methods

A single 1,2-oxathiocin has been structurally characterized by x-ray diffraction analysis <83AX(C)289>. The eight-membered ring in this 5,8-dihydro-dibenzo[*d,f*][1,2]oxathiocin derivative

(65) displays a pseudo-chair conformation, similar to that seen in the related dibenzodithiocin and dibenzodithiocin 2,2-dioxide analogues discussed below. Interestingly, the dioxocin analogue (50; R = Me) displays a pseudo-boat conformation (*vide supra*) <76JOC3756>. Bond lengths and angles in (65) are largely as expected, with an intra-ring S—O bond length of 1.550 Å and a dihedral angle between the two aryl rings of 63°. Several notable structural features include a rather large S—O—C bond angle (119.7°) and a C—O bond length appreciably longer than that in the dioxocin analogue <76JOC3756> (1.468 Å vs. 1.416 Å), although direct comparison of the two is not completely appropriate given the peroxyacetal functionality of the latter compound.



Proton NMR spectral data have been reported for 3,4,5,6,7,8-hexahydro-1,2-oxathiocin 2-oxide (66) <76CJC3012> and its 2,2-dioxide (67) <87PS(31)161>, 6-amino-3,6,7,8-tetrahydro-1,2-oxathiocin 2,2-dioxide derivative (68) <87JOC1177>, and 5,8-dihydro-dibenzo[*d,f*][1,2]oxathiocin 2-oxide (69) <78JA1222>. In each case, chemical shifts correlate with those observed in simpler compounds bearing analogous functionality, suggesting no unusual intra-ring effects. The appearance of the methylene protons in (69) as AB quartets is reminiscent of the studies of restricted rotation (and conformational enantiomerism) reported for dihydro-dibenzo[*d,f*][1,2]dithiocin (*vide infra*), but is more simply explained in this case by the presence of the pyramidal S=O center. Carbon-13 NMR spectral data for (67) is also in accord with the proposed structure, with the carbon bearing the sulfur appearing at 50.1 ppm and that bearing oxygen at 73.1 ppm.



The simple hexahydro derivative (66) displays the expected mass spectral parent ion; fragmentation data has not been reported <76CJC3012>. Tetrahydro 2,2-dioxide derivative (68) displays a weak parent ion, fragments consistent with loss of SO₂, and a variety of other fragments <87JOC1177>, while (69) gives, in addition to a very weak parent ion, the M—SO₂ fragment as the base peak, as expected given the facile thermal and photochemical SO₂ extrusion reactions reported for this derivative (*vide infra*) <83CJC757, 78CJC512>. Solution molecular weight determination by vapor pressure osmometry for (67) supports its formulation as a cyclic monomer. Given the potential of the precursors to these and related heterocycles to form cyclic or acyclic oligomers rather than the anticipated 1,2-diheterocins, it is unfortunate that more solution molecular weight data have not been reported.

Although IR spectral data has been reported for oxathiocin derivatives (66)–(69) <87PS(31)161, 76CJC3012, 87JOC1177, 78JA1222>, only the exocyclic S=O stretching frequencies, occurring at ca. 1100 cm^{−1}, have been assigned, and the available data is too sketchy to allow assignment of intra-ring modes such as the O—S stretch.

9.21.7.2 Thermodynamic Aspects

Oxathiocin (68) is an oil <87JOC1177>, while the more symmetrical (67) is a low-melting solid (m.p. 37.0–37.5°C) <87PS(31)161>. Both the dibenzodithiocin 2-oxide (69) and 2,2-dioxide (65) are, not surprisingly, crystalline solids. Crystallographic analysis of (65) revealed one somewhat close intermolecular O—O contact, but the solid-state packing appears to be dominated by simple van der

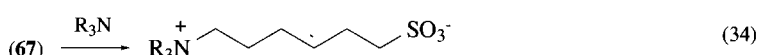
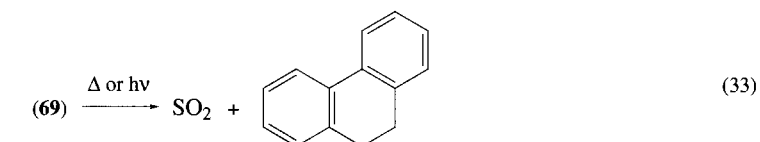
Waals interactions $\langle 83\text{AX}(\text{C})289 \rangle$. Dipole–dipole interactions between such polar molecules might also be expected to be significant in the solid state.

The oxathiocin derivatives reported, all either *S*-oxides or *S,S*-dioxides, display the solubilities anticipated for compounds with related functional groups, with appreciable solubility in polar (chloroform $\langle 76\text{CJC}3012 \rangle$, ethyl acetate $\langle 87\text{JOC}1177 \rangle$), and aromatic (benzene $\langle 87\text{PS}(31)161$, $83\text{AX}(\text{C})289 \rangle$) solvents and more sparing solubility in diethyl ether $\langle 78\text{JA}1222 \rangle$ and hydrocarbons (*n*-hexane) $\langle 83\text{AX}(\text{C})289$, $87\text{JOC}1177 \rangle$. Preparative thin layer chromatography of **(68)** on silica $\langle 87\text{JOC}1177 \rangle$ and filtration of **(67)** through a short column of Kieselgel 60 $\langle 87\text{PS}(31)161 \rangle$ have been reported to effect purification.

In-depth analysis of the conformation of **(65)** was made possible by x-ray crystallographic analysis (*vide supra*). This study, carried out as part of an on-going investigation of the conformations of bridged biphenyl derivatives, demonstrates a pseudo-chair conformation of the oxathiocin ring, analogous to that seen in two dithiocin derivatives but distinct from that of the corresponding dioxocin derivative. Although molecular mechanics studies have been carried out for both simpler dithiocin derivatives $\langle 90\text{JA}6296$, $82\text{CJC}730 \rangle$ and the parent dibenzodithiocin $\langle 76\text{JA}2741 \rangle$, such studies have not been reported for the oxathiocin ring system.

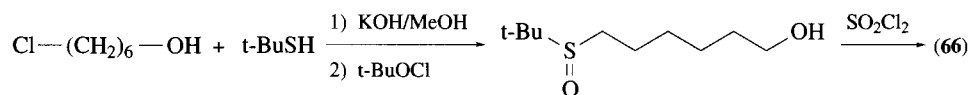
9.21.7.3 Reactivity of Nonconjugated Rings

Oxathiocin 2-oxide **(69)** undergoes thermal (700°C , 0.05 torr) and photochemical (254 nm) extrusion of SO_2 , affording 9,10-dihydrophenanthrene in high yield (Equation (33) $\langle 78\text{CJC}512$, $83\text{CJC}757 \rangle$). Extrusion of SO_2 from **(69)** is also observed upon electron impact mass spectral analysis, with the $\text{M}-\text{SO}_2$ peak representing the base peak in the mass spectrum of **(69)** $\langle 83\text{CJC}757 \rangle$. Beyond this extrusion reaction, only the ring cleavage of **(67)** by ammonia or trimethylamine (room temperature, chloroform solution, 48 h), affording the acyclic betaines ($\text{R} = \text{H}$, Me) (Equation (34)) in unreported and 95% yield, respectively $\langle 87\text{PS}(31)161 \rangle$ and oxidation of 2-oxide **(66)** to the corresponding 2,2-dioxide **(67)** have been reported $\langle 76\text{CJC}3012 \rangle$.



9.21.7.4 Ring Syntheses

The oxathiocin ring, in reduced form, has been prepared through the unimolecular cyclization, in unreported yield, of 6-hydroxy-1-hexanesulfonyl chloride to **(67)** $\langle 87\text{PS}(31)161 \rangle$ and through the sulfonyl chloride-induced ring closure, in 45% yield, of an ω -hydroxysulfoxide to **(66)** (Scheme 24) $\langle 76\text{CJC}3012 \rangle$. Mass spectral analysis of the product of the latter reaction lends support to its formulation as a monomeric oxathiocin, and this in turn strengthens the structural assignment for **(67)** as well.

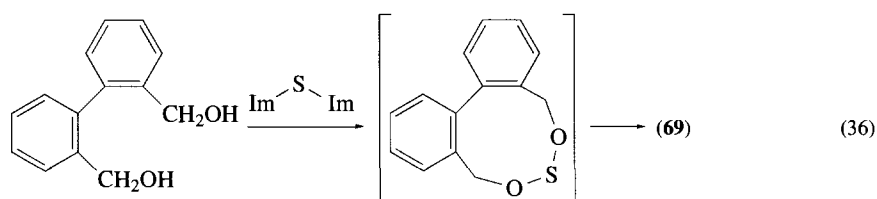
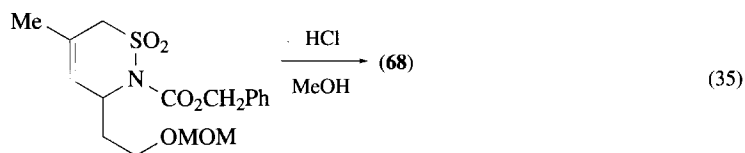


Scheme 24

9.21.7.5 Ring Synthesis by Transformation of Another Ring

Two routes to the oxathiocin ring system, one discovered accidentally, have been reported. In the attempted deprotection of a methoxymethyl ether of a thiazine derivative, an intramolecular

sulfonamide/sulfonate ester exchange results in a rather astonishing ring expansion to (68) (Equation (35)) <87JOC1177>. The synthesis of (69) is effected through the reaction of bis(hydroxymethyl) biphenyl with sulfur atom transfer reagents such as bis(imidazolyl)sulfide, apparently affording an intermediate dioxathia heterocycle which undergoes spontaneous thermal rearrangement to afford the oxathiocin 2-oxide in an overall yield of 91% (Equation (36)) <78JA1222>.



9.21.7.6 Comparison of Synthetic Routes

1,2-Oxathiocins obviously remain exceedingly scarce. Cyclization routes provide access, in modest yields, to the ring system, but may be limited by the inaccessibility of appropriate precursors. The use of sulfur atom transfer reagents to effect the cyclization of diols may represent a more general entry to the 1,2-oxathiocin ring system, but the synthetic potential of this route clearly has scarcely been examined.

9.21.7.7 Important Compounds and Applications

No commercial applications or intriguing biological or chemical properties of 1,2-oxathiocins or their benzo derivatives have been reported up to 1995. Given the potentially significant applications of related heterocycles discussed above and below, perhaps this should be taken as an indication of the importance of more work in this area rather than as a suggestion that such compounds simply do not display significant properties.

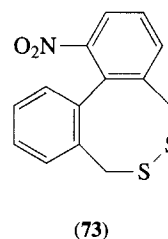
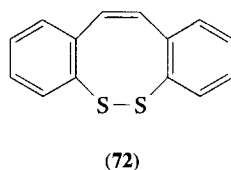
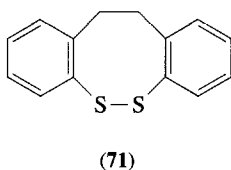
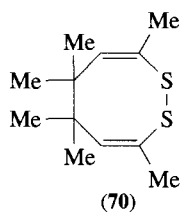
9.21.8 RINGS WITH TWO SULFURS (1,2-DITHIOCINS)

9.21.8.1 Experimental Structural Methods

Both 5,8-dihydro-dibenzo[*d,f*][1,2]dithiocin (12) <72CC985> and its 2,2-dioxide derivative (7) <73AX(B)2272, 74AX(B)2526> have been structurally characterized by single crystal x-ray diffraction analysis. Both display similar metrical parameters, including an S—S bond length of 2.035 Å (12)/2.048 Å (7), C—S bond lengths of 1.835 Å (12)/1.81 Å (7), an S—S—C angle of 104.3° (12)/105.2° (7), a C—S—S—C dihedral angle of 56.4° (12)/47.4° (7), and an aryl–aryl dihedral angle of 67.2° (12)/65.4° (7), resulting in a pseudo-chair conformation for the dithiocin ring in each. Unfortunately, the originally reported structural data for the dioxide should not be over-interpreted given an error in space group assignment made in the original structure determination. Despite the claimed intention of the authors to report the corrected structure, this revised structure appears not to have appeared.

NMR data has been reported for only a few dithiocin derivatives. The ring hydrogens in 5,6-dihydro-3,5,5,6,6,8-hexamethyl-1,2-dithiocin (70), reportedly obtained as an inseparable mixture with the corresponding 1,4-dithiocin, appear at ca. 5.5 ppm, displaying coupling to the *cis*-disposed methyl groups <81T3839>. 11,12-Dihydro-dibenzo[*c,g*][1,2]dithiocin (71) also shows only the anticipated proton resonances for the benzylic protons (3.15 ppm) and in the aromatic region <80ZOR384>. Interestingly, fully conjugated (72) displays resonances only in the aromatic region, with a singlet

at 7.08 ppm assigned to the bridge methine protons $\langle 80\text{ZOR}384 \rangle$. Dibenzo[*d,f*] derivative (**73**), the only dibenzo[*d,f*] derivative for which NMR data has been reported, displays a multiplet at 3.5–4.0 ppm for the benzylic protons $\langle 73\text{JCS(P1)2818} \rangle$, suggesting slow interconversion of nonsymmetrical conformers. As discussed below, analogous behavior has been analyzed in detail for the parent dibenzo[*d,f*] derivative for which, however, full NMR data appears not to have been reported. The parent 1,2-dithiocane (**9**) displays no unusual ^1H NMR resonances; the α -methylene groups appear as a triplet at 2.6 ppm $\langle 89\text{T91, } 92\text{JOC1699} \rangle$. No ^{13}C or ^{33}S NMR data has been reported for any 1,2-dithiocin derivatives.



Mass spectral analysis of dibenzo[*c,g*] derivatives (**71**) and (**72**) revealed the anticipated parent ions; no fragmentation patterns were reported $\langle 80\text{ZOR}384 \rangle$. The fragmentation behavior of 1,2-dithiocane (**9**) has been analyzed $\langle 79\text{JC435, } 92\text{JOC1699} \rangle$. In addition to the parent ion (of 80% intensity relative to the base peak), fragments observed include $\text{C}_n\text{H}_{2n-1}$ and $\text{C}_n\text{H}_{2n-1}\text{S}$. Cyclic sulfonium ion structures were proposed for the $\text{C}_4\text{H}_7\text{S}$ and $\text{C}_5\text{H}_{11}\text{S}$ fragments. Curiously, while $\text{C}_6\text{H}_{11}\text{S}$ ($\text{M}-\text{SH}$) is a significant fragment (20%), the C_6H_{11} fragment appears not to be formed.

Dibenzo[*d,f*] derivative (**73**) is colorless, displaying a UV absorption at 254 nm ($\log \epsilon = 3.81$) in methanol solution $\langle 73\text{JCS(P1)2818} \rangle$. Dibenzo[*c,g*] derivatives (**71**) and (**72**) are also colorless; the absorption bands for the dihydro derivative, at 224 (4.41) and 259 (3.69) nm, are shifted ca. 20 nm to higher energy from those for the fully-conjugated dithiocin, at 247 (4.23), 285 (3.66), and 320 (3.07) nm $\langle 80\text{ZOR}384 \rangle$. Comparison of the UV spectrum of the latter with stilbene led to the conclusion that there is decreased conjugation relative to stilbene. Rather than development of aromaticity through conjugation with the S—S group, apparently the S—S linkage forces a less planar conformation, thereby reducing electronic communication between the two aromatic rings through the alkenic linkage. Both (**71**) and (**72**) display a feature at ca. 300 nm which is apparently due to an absorption localized in the S—S group; indeed, the absence of such an absorption maximum in the UV spectrum of a putative dibenzo[*c,g*][1,2]-dithiocin $\langle 70\text{T1157} \rangle$ alerted later workers to a structural misassignment, with the actual product being a 1,4-dithiocin derivative $\langle 70\text{JA7001} \rangle$. 1,2-Dithiocane (**9**) is a colorless liquid $\langle 57\text{AG713, } 58\text{LA66} \rangle$. Interestingly, the five-, nine-, and ten-membered ring cyclic disulfides are all yellow in color $\langle 57\text{AG713, } 58\text{LA(614)66} \rangle$.

The solution IR spectrum of 1,2-dithiocane (**9**) reveals only C—H stretching and bending modes and an apparent C—S stretching band (at 770 cm^{-1}) $\langle 92\text{JOC1699} \rangle$. The solid-state Raman spectrum of 5,8-dihydro-dibenzo[*d,f*][1,2]dithiocin (**12**), while displaying a number of weak bands in the $470\text{--}620\text{ cm}^{-1}$ region as well as a strong band at 659 cm^{-1} , did not permit unambiguous assignment of the S—S stretching band, expected at ca. $450\text{--}550\text{ cm}^{-1}$ $\langle 76\text{JPC1823} \rangle$; solution analysis was precluded by the comparative insolubility of (**12**).

9.21.8.2 Thermodynamic Aspects

The simpler 1,2-dithiocin derivatives for which data is available, 1,2-dithiocane (**9**) $\langle 57\text{AG713, } 58\text{LA66, } 66\text{USP3284466, } 89\text{T91, } 92\text{JOC1699} \rangle$ and dihydro derivative (**70**) $\langle 81\text{T3839} \rangle$, are liquids, consistent with their relatively nonpolar nature and the absence of any significant intermolecular interactions. 1,2-Dithiocane (**9**) displays a fairly high refractive index (ca. 1.57) $\langle 86\text{TL441} \rangle$. The dibenzo[*c,g*] and dibenzo[*d,f*] derivatives for which data has been reported, in contrast, are rather high melting solids ((**12**), m.p. 133°C (enantiomerically pure) or 161°C (racemate) $\langle 67\text{ZN(B)1296} \rangle$, (**71**), m.p. $192\text{--}193^\circ\text{C}$ $\langle 80\text{ZOR}384 \rangle$, (**72**), m.p. $144\text{--}146^\circ\text{C}$ $\langle 80\text{ZOR}384 \rangle$, (**73**), m.p. $137\text{--}138^\circ\text{C}$ $\langle 73\text{JCS(P1)2818} \rangle$); presumably aromatic stacking interactions are responsible. The significantly lowered melting point of (**72**) vs. (**71**) seems to support the decidedly nonplanar conformation for (**72**) also hinted at by UV spectral analysis. Compound (**12**) is reported to sublime at ca. 100°C under high vacuum $\langle 67\text{ZN(B)1296} \rangle$.

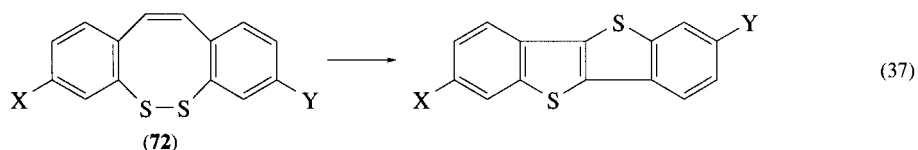
Solubility behavior for the 1,2-dithiocins appears largely as expected, with good solubility in chlorinated hydrocarbons <67ZN(B)1296, 73JCS(P1)2818, 80ZOR384> and aromatics <67ZN(B)1296, 80ZOR384> and modest to sparing solubility in alcohols <67ZN(B)1296, 73JCS(P1)2818, 80ZOR384> and hydrocarbons <67ZN(B)1296>. Liquid chromatography on alumina <80ZOR384>, silica <67ZN(B)1296, 80ZOR384, 86CPB486>, and cellulose acetate <67ZN(B)1296> has been reported for the purification of 1,2-dithiocane (9) and dibenzo derivatives (7), (12), (71), and (72), while gas chromatographic analysis of 1,2-dithiocane has been effected on a 3% OV-1/Diatomite CQ column at 140°C <79JC435>.

A number of the dithiocins have been reported to melt at rather high temperature, apparently without decomposition, suggesting appreciable thermal stability. Theoretical and experimental studies of the stability of the dithiocin ring to reductive ring opening <90JA6296> and to ring-opening polymerization <60TFS1784, 87JA6825> have been reported. Although the cyclic disulfides appear to have reduced ring strain relative to their all-carbon analogues, ascribed to the relative ease of angular deformation at sulfur vs. carbon <60TFS1784>, 1,2-dithiocane is calculated to display a strain energy of ca. 10 kcal mol⁻¹ <57AG713, 58LA(614)66, 90JA6296>. Calorimetry qualitatively substantiates this, with a heat of polymerization for 1,2-dithiocane of ca. 4 kcal mol⁻¹, significantly higher than that of the six- and seven-membered ring cyclic disulfides <60TFS1784>. Interestingly, introduction of double bonds, as in (10) and (11), appears to reduce strain considerably, apparently by relaxing angle and torsional strain and by removing several unfavorable *trans*-annular van der Waals repulsions seen for the saturated ring compound <90JA6296>. However, strain reappears in dibenzo[*d,f*] derivative (12), with calculations suggesting a strain of ca. 18 kcal mol⁻¹ <76JA2741>.

Crystallographic analysis (*vide supra*) revealed a chair-like conformation for the 1,2-dithiocin ring in (7) and (12) <73AX(B)2272, 74AX(B)2526>, and this conformation was qualitatively reproduced by STO-3G* calculations for (unknown) model compound (8) <82CJC730>. Interestingly, (12) exists as separable conformational enantiomers, which have been resolved and are stable to racemization upon sublimation at 100°C or recrystallization from hot solvents <67ZN(B)1296>. The activation energy for racemization has been measured at ca. 27.3 kcal mol⁻¹, with enthalpic terms dominating <67M1323>. Calculations were carried out <76JA2741> in response both to the surprising stability of these conformational enantiomers and to the seemingly curious preference of the dibenzo[*d,f*] derivatives for the chair-like conformation, giving a C—S—S—C dihedral angle of ca. 60°, severely distorted from the 84° dihedral in dimethyl disulfide, whereas a tub-like conformation, with a C—S—S—C dihedral of 90° was anticipated. Calculations show that, although both C—S—S—C and H—C—S—S dihedral angles do indeed favor the tub conformation, the conformation-determining energetics are primarily the C—C—S—S dihedral angle, which disfavors the tub by 2.5 kcal mol⁻¹ and the aryl-aryl dihedral angle, 0.5 kcal mol⁻¹ lower in the chair, which is overall favored by ca. 1.3 kcal mol⁻¹ <76JA2741>. Similar concern regarding the C—S—S—C dihedral angle in 1,2-dithiocane has also been expressed <50JOC865>, though it has also been noted that the flexibility of the ring may be sufficient to reduce the importance of this potential strain <87JA6825>. Indeed, MM2 calculations lead to the conclusion that angle and van der Waals strain are more important than the C—S—S—C dihedral angle in determining the conformational preference of 1,2-dithiocane, for which a “boat-chair” conformation is slightly favored over alternative twist boat-chair and crown conformations <90JA6296>.

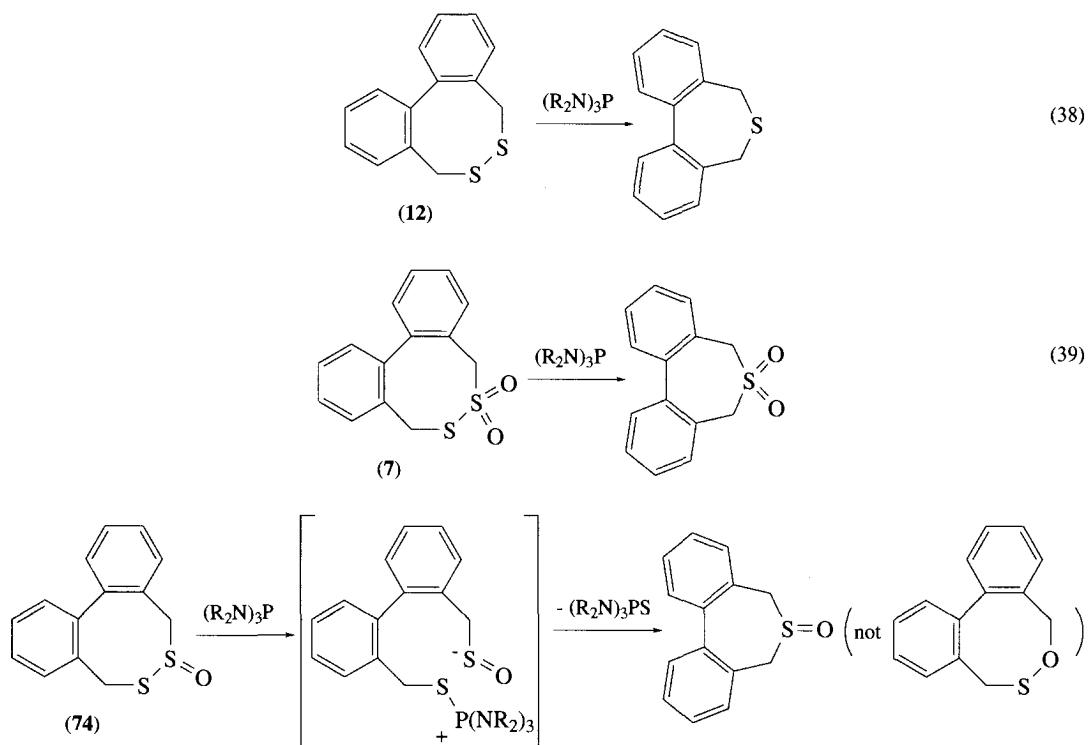
9.21.8.3 Reactivity of Fully Conjugated Rings

Reductive cleavage of the S—S bond in dibenzo[*c,g*] derivative (72) (e.g., using glucose/NaOH), affords the ring-opened dithiol <80ZOR384, 80ZOR430>. In addition, it has been suggested that (72, X = Y = H, Br, Cl, NO₂; X = Cl, Y = NO₂) undergo a curious rearrangement, presumably via either homolytic or heterolytic S—S bond cleavage and subsequent electrophilic attack on the bridging C=C bond, upon treatment with pyridinium perbromide or with bromine in acetic acid or upon attempted recrystallization from high-boiling solvents (Equation (37)) <80ZOR425, 80ZOR430>.



9.21.8.4 Reactivity of Nonconjugated Rings

Reductive cleavage of the S—S bond in (71) has been reported <80ZOR384>, as has desulfurization of (12) and its 2-oxide (74) and 2,2-dioxide (7) by various phosphine reagents, affording dibenzothiepinines (Equations (38) and (39)) <73JCS(P1)2818, 78TL3989>. Interestingly, desulfurization of *S*-oxide (74) affords only the thiepine *S*-oxide, whereas a plausible mechanism suggests that a 1,2-oxathiocin might have been anticipated (Scheme (25)) <78TL3989>.

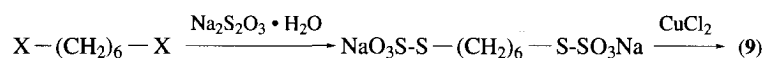


Scheme 25

The S—S bond in 1,2-dithiocane is reported to undergo cleavage by KCN, analogous to but slower than the reactions of acyclic disulfides, affording the potassium salt of 6-mercaptohexanethiocyanate <57AG713, 58LA(614)66>. Polymerization of 1,2-dithiocane to poorly-characterized polymeric disulfides is well-known <60TFS1784, 87JA6825, 89GEP270081, 89T91>.

9.21.8.5 Ring Syntheses

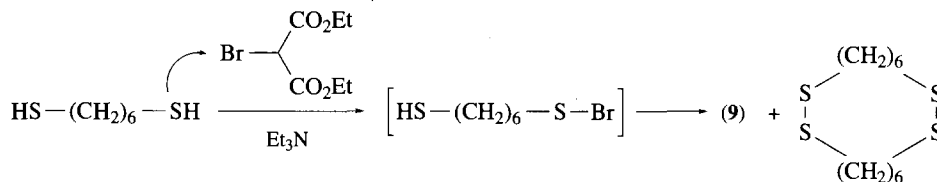
Virtually all syntheses of 1,2-dithiocin derivatives from acyclic precursors have involved unimolecular cyclization reactions, invariably either the oxidative formation (usually using $FeCl_3$) of the disulfide bond from appropriate dithiol precursors used to prepare (9) <57AG713, 58LA(614)66, 73TL655, 85JAP6036456, 86CPB486, 86TL441, 89T91, 90TL3591, 90TL3595, 92JOC1699>, (72) <80ZOR384, 80ZOR430>, (12), and (73) <67ZN(B)1296, 73JCS(P1)2818>) or the cyclization of Bunte salts (Scheme 26) (used for (9) <50JOC865, 57AG713, 58LA66, 66USP3284466>). Yields range from very low to excellent, with the latter seen especially for recently developed reagents specifically designed to effect ring closure (e.g., 95–86% via lead derivatives <73TL655>).



Scheme 26

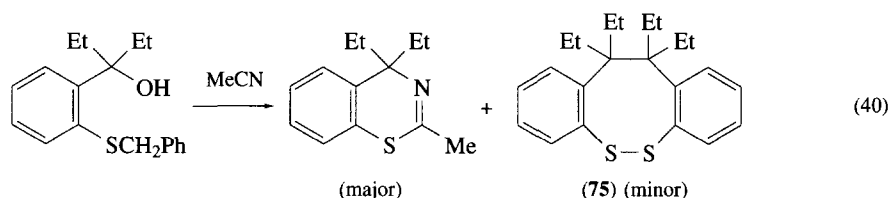
A rather unusual preparation of 1,2-dithiocane from 1,6-hexanedithiol exploits its reaction with diethyl bromomalonate, which is proposed to proceed via nucleophilic attack by the thiol not at

carbon, but at bromine, leading to an intermediate sulfenyl bromide which then couples with the second thiol group; 1,2-dithiocane is formed in 10% yield together with 26% of the cyclic dimeric bis(disulfide) (Scheme 27) <86CPB486>.



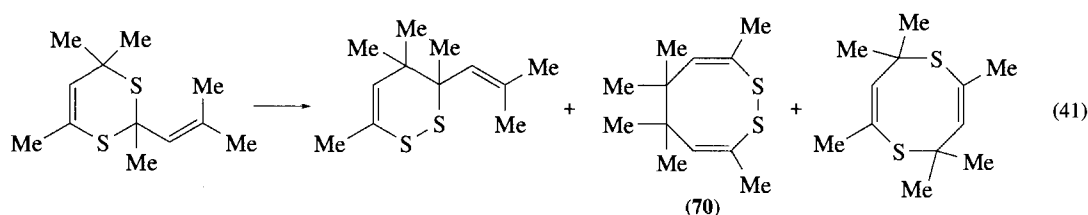
Scheme 27

Dibenzo[*c,g*] derivative (75) was reportedly obtained as a by-product in the reaction of a hydroxy sulfide with acetonitrile (Equation (40)) <74KGS1437, 74MI 921-02, 75KGS1620>. Unfortunately, only limited information is available, precluding any analysis of this unique apparent [4 + 4] route to the 1,2-dithiocin ring system.



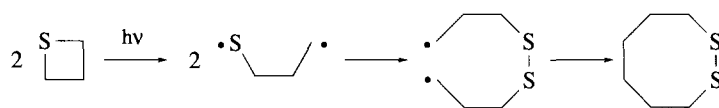
9.21.8.6 Ring Synthesis by Transformation of Another Ring

Beyond the parent 1,2-dithiocane, only a single nonbenzannelated derivative has been prepared by any ring transformation method. Compound (70) was reportedly obtained as an inseparable mixture with a 1,4-dithiocin, in a combined yield of 2.6%, upon thermolysis of a vinyl dithiane at 160°C ; the major product (57% yield) of the reaction was a 1,2-dithiane derivative (Equation (41)) <81T3839>.



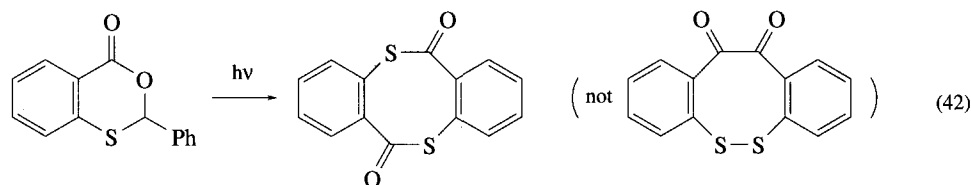
Gas phase photolysis of thietane affords 1,2-dithiocane in low yield (quantum yield 0–0.07%), reportedly via not S—S but rather via C—S bond homolysis, followed by stepwise bimolecular coupling (Scheme 28) <75CJC1744>. The dithiocane is not formed upon photolysis of thietane in either liquid or frozen solution.

A report of the formation of a dibenzo[*c,g*] derivative through photolytic cleavage and dimer-



Scheme 28

ization of 2-phenyl-3,1-benzoxathian-4-one <70T1157> was shown to be incorrect, the actual product being a 1,4-dithiocin (Equation (42)) <70JA7001>.



9.21.8.7 Comparison of Synthetic Routes

The ring transformation routes which have appeared up to 1995 are rather clearly not of preparative utility. Unimolecular cyclizations, then, remain the only viable reported entry to the 1,2-dithiocin ring system, and promising recent developments along these lines suggest some synthetic generality may be possible. Alternative routes, perhaps based on those to the related classes of 1,2-diheterocins, clearly demand additional scrutiny.

9.21.8.8 Important Compounds and Applications

Presumably based on structural analogy with related heterocycles, it has been suggested that cyclic disulfides such as 1,2-dithiocane (**9**) may be useful as antihypertensives and immunity regulators <85JAPP6036456>, but no data has been reported. The polymers obtained by either thermal <70GEP2004305> or chemically-initiated photochemical <89GEP270081> ring-opening polymerization of 1,2-dithiocane, show potential commercial promise, displaying good tensile strength and impact resistance <70GEP2004305> and suggesting possible applications as floor covering, adhesive, coating, and embedding materials.

9.22

Eight-membered Rings with Two Heteroatoms 1,3

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9.22.1 INTRODUCTION

Eight-membered rings with two heteroatoms in a 1,3-relationship remain a comparatively rare class of heterocyclic compounds. The greatest attention appears to have been devoted to the dioxo derivatives, representing cyclic acetals derived from 1,5-pentanediols, and the diaza derivatives, cyclic aminals with structural features in common with smaller-ring, pharmacologically active compounds, while the remaining groups of compounds are scarcely known, and most have been reported since the appearance of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I), in which all eight-membered ring heterocycles with one or more heteroatoms were treated in a single chapter.

Only those compounds with nitrogen, oxygen, and/or sulfur as heteroatoms are covered in this chapter. (Compounds with "unusual" heteroatoms are covered in later chapters in this volume.) Nomenclature for the eight-membered rings with two heteroatoms in a 1,3-relationship follows the standard system, with some permissible variability introduced for the completely reduced compounds. The parent unsaturated systems, of which apparently none have actually been prepared, are 1,3-diazocine, 2*H*-1,3-oxazocine, 2*H*-1,3-thiazocine, 4*H*-1,3-dioxocin, 4*H*-1,3-oxathiocin, and 4*H*-1,3-dithiocin. Reduced analogues may be named as di-, tetra-, hexa-, or, for the diaza compounds, octahydro derivatives of these parent compounds. In some cases, particularly the dioxo and dithia derivatives, the saturated compounds are more often referred to as the corresponding -anes, 1,2-dioxocane and 1,2-dithiocane. Benzo and dibenzo derivatives also follow standard nomenclature. Naming of those derivatives which are known, which constitute but a small fraction of the theoretically possible isomers, is introduced as appropriate within the following individual sections. Compounds in which ring heteroatoms are members of another fused ring and bridged polycyclic compounds are not covered in this chapter.

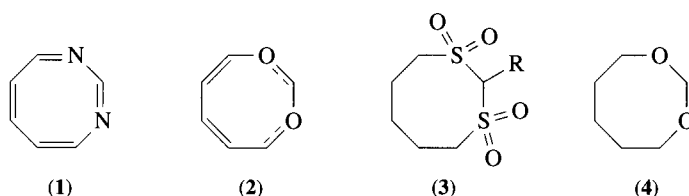
Following a general discussion of theoretical studies of the title heterocycles, each class is discussed separately, with each discussion following the same general format. "Missing" section headings (e.g., "Reactivity of substituents attached to ring heteroatoms") correspond to cases in which no relevant chemistry has been reported. As recent comprehensive reviews of the preparation, structure, and reaction chemistry of the diazocines <90AHC(50)1> and of their benzo analogues <87H(26)2477> have appeared, and since these compounds received relatively complete coverage in CHEC-I, the diazocine section focuses primarily on later developments in the chemistry of these derivatives. The oxazocines have also been reviewed <82H(18)709>. Similarly, the coverage of dioxocins focuses primarily on reports appearing since the publication of CHEC-I. In contrast, coverage of the other classes, which received little or no attention in CHEC-I, is meant to be comprehensive, with complete coverage of the chemical literature dealing with these uncommon derivatives.

9.22.2 THEORETICAL METHODS

Theoretical studies of several classes of the title heterocycles have appeared. Although the majority of these studies have focused on the conformational preferences of partially to completely reduced derivatives or on transition state geometries for intramolecular rearrangement reactions, several have addressed the stability and potential aromaticity of the parent fully unsaturated derivatives as well. Beyond the brief mention of these theoretical studies provided in this section, further details are more appropriately reported in the sections dealing with the structural and thermodynamic aspects of the subject heterocycles.

Molecular orbital calculations for the (unknown) parent fully conjugated 1,3-diazocine (**1**) yielded a single solution, with C_{2v} symmetry and delocalized bonding. (Analogous calculations for 1,4-diazocines afforded two solutions, and the solution was noted to depend upon choice of initial matrix elements.) Resonance energy calculations showed a decrease in antiaromaticity for this derivative relative to cyclooctatetraene <83MI 922-03>.

Calculations for 4*H*-1,3-dioxocin-2,4-diyl (**2**) revealed the singlet state to be a first-order saddle point rather than a stable species, and the triplet state was around 12–13 kcal mol⁻¹ higher in energy <91RRC333>. Molecular orbital studies of deprotonated 1,3-dithiocane 1,1,3,3-tetraoxide and its 2-phenyl analogue (**3**; R = H, Ph), as well as smaller-ring analogues, suggested the phenyl substituent leads to reduced acidity due to steric destabilization of the optimum conformation for anion stabilization by the adjacent sulfonyl groups <83MI 922-02>. The heat of formation and ideal gas thermodynamic parameters of 1,3-dioxocane (**4**) were calculated using a rigid-rotor harmonic oscillator approximation <92MI 922-02>.

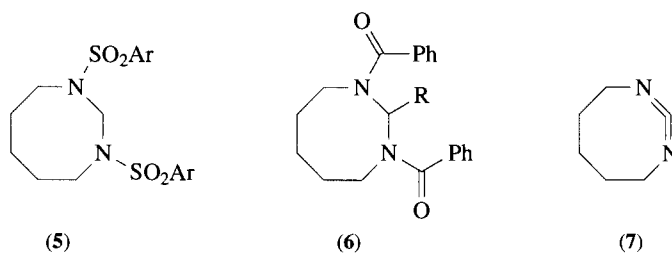


Molecular mechanics have been used to address the favored conformations for [3,3]-sigmatropic rearrangement of (*E*)- and (*Z*)-2-thione derivatives <90TL5471, 91TL1203> and to explore the conformational preferences of dibenzo[*d,g*]dioxocins <89ZOR657, 91JST165, 91ZOB173>, as discussed further below.

9.22.3 RINGS WITH TWO NITROGENS (1,3-DIAZOCINES)

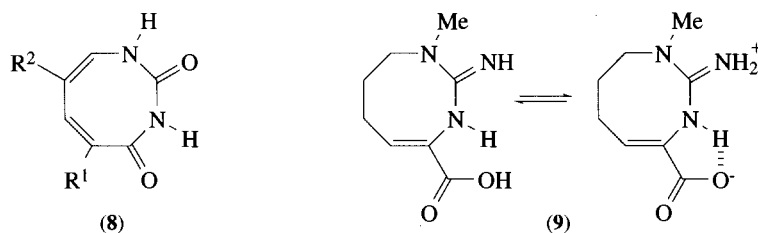
9.22.3.1 Experimental Structural Methods

Despite comparatively heavy interest in the 1,3-diazocines, apparently no crystallographic structural analyses have been reported. Structural proposals have been based primarily upon NMR, IR, and mass spectral analysis, as well as upon method of synthesis. Proton NMR chemical shifts are essentially as expected for molecules bearing similar functionalities. Particularly diagnostic is the appearance of protons at the 2-position of saturated derivatives such as (**5**; Ar = *p*-tolyl, phenyl) at about 4.5–4.7 ppm <83MI 922-02, 84MI 922-02>. Replacement of one of these protons with a phenyl group, as in (**6**; R = Ph) gives a dramatic downfield shift, to around 7 ppm; curiously, an isopropyl substituent (**6**; R = Prⁱ) also is reported to give a large downfield shift (to around 5.8 ppm) <85IZV1612>. Ring methylene groups attached to nitrogen generally fall in the region of 3–4 ppm <83LA1623, 83MI 922-02, 84MI 922-02, 85IZV1612, 85JHC357, 89IZV906, 90JCR(S)319, 93T3781>, even for such unusual derivatives as carbodiimide (**7**) <83JOC1694>.

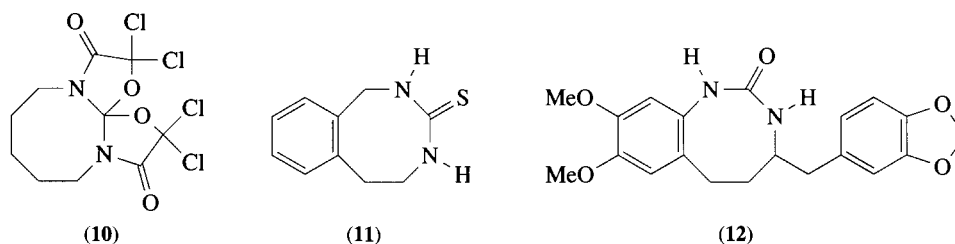


Protons on the ring nitrogen, nearly always found in amide-, urea-, or thiourea-type derivatives, generally fall near 7 ppm <82TL4207, 83JOC2337, 89IZV906, 90JCR(S)319, 90T3781>, while imide protons, as in 1,3-diazocin-2,4(1*H*,3*H*)-diones (**8**) <83JOC2337>, typically are somewhat further downfield, often near ca. 8 ppm <82TL4207, 83JOC2337, 93T3781>. Amino-1,6,7,8-tetrahydro compound (**9**) displays a rather downfield shift for its NH proton; this has been ascribed to formation of an intramolecular hydrogen bond with the adjacent carboxyl group <83LA1623>. Methine protons in unsaturated derivatives such as (**8**) <82TL4207, 83JOC2337> appear at ca. 6 ppm.

Carbon-13 NMR data are consistent with the proposed structures <82TL4207, 83JOC1694, 83JOC2337, 83LA1623, 85JHC357, 86JOC417, 90JCR(S)319, 93T3781>. Methylene groups attached to nitrogen tend to appear near 40 ppm, while the spiro carbon in perhydro derivative (**10**) is reported at ca. 117 ppm <86JOC417>. Virtually all other derivatives, for which ¹³C data are reported, are 2-oxo or 2-thio derivatives, displaying the anticipated downfield shift for the 2-carbon (e.g., 183 ppm for 1,4,5,6-



tetrahydro-2,4-benzodiazocin-3(2*H*)-thione (**11**) <90JCR(S)319>. The chemical shift of this carbon in carbodiimide (**7**) was not reported <83JOC1694>.

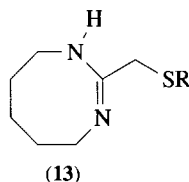


Parent ions have been observed upon electron impact mass spectral analysis for several 1,3-diazocines <82TL4207, 83JOC2337, 86JHC975, 90JCR(S)319>. Data on fragmentation behavior are scarce, but seem to roughly parallel the more detailed information available for the 1,3-oxazocines, discussed below. Thus, (**11**) displays, in addition to the parent ion (as the base peak), a significant fragment due to loss of CSNH₂ (40% peak); formation of *o*-xylylene (93%) is also apparent <90JCR(S)319>. 3,4,5,6-Tetrahydro-1,3-benzodiazocin-2(1*H*)-one derivative (**12**) displays, in addition to the parent ion, a base peak corresponding to loss of the benzyl side chain and CONH <86JHC975>.

Beyond the report of a characteristic band at 2100 cm⁻¹ for carbodiimide (**7**) <83JOC1694>, IR studies have in general merely confirmed the existence of anticipated functional groups <83JOC2337, 83LA1623, 85JHC357, 86JHC975, 90JCR(S)319, 90T3781>, such as the sulfonyl groups of (**5**) <83MI 922-02, 84MI 922-02>.

9.22.3.2 Thermodynamic Aspects

Virtually all of the 1,3-diazocines, for which appropriate data have been reported, are crystalline solids <81IJC(B)672, 82TL4207, 83JOC2337, 83LA1623, 83MI 922-02, 83MI 922-04, 84MI 922-02, 85IZV1612, 85JHC357, 86JHC975, 86JOC417, 87ZC36, 90JCR(S)319, 93T3781>. Given the polar functionality present in many of these derivatives and the presence of both hydrogen-bond donor and acceptor functionalities, their often rather high melting points are not surprising. Those few derivatives lacking polar and/or hydrogen bonding groups, namely carbodiimide (**7**) <83JOC1694> and the (alkylthio)methyl hexahydro derivatives (**13**; R = Et, Pr, Bu) <89IZV906>, are liquids.

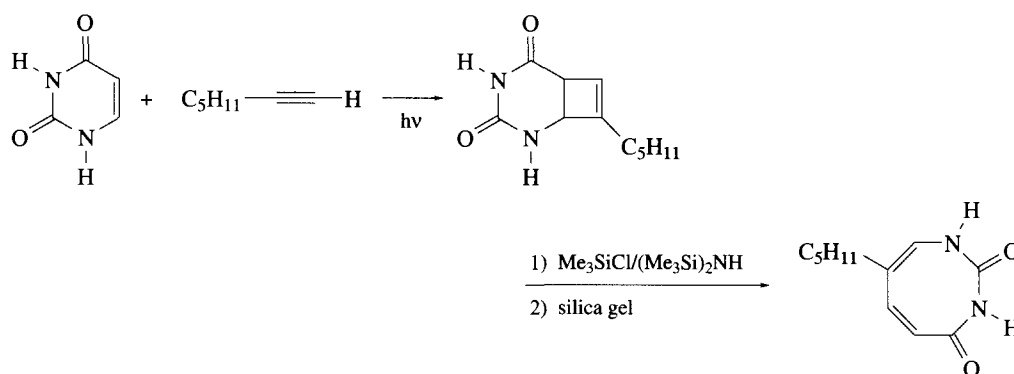


In accord with the anticipated high packing forces expected for many of these polar, hydrogen-bonding derivatives, solubilities of many appear to be rather low, as perhaps most clearly evidenced by the common use of DMSO as a solvent for NMR spectroscopy <83LA1623, 83T3971, 85JHC357, 89IZV906, 90JCR(S)319>. Solubility in chlorinated hydrocarbons <82TL4207, 83JOC2337, 83MI 922-02, 84MI 922-02, 85IZV1612, 85JHC357, 86JOC417, 90JCR(S)319, 93T3781> and recrystallization from methanol or ethanol <83JOC2337, 83LA1623, 83MI 922-02, 84MI 922-02> have been noted in a number of cases. Recrystallization of spirocyclic derivative (**10**) <86JOC417> from hexane and benzo derivative (**12**) <86JHC975> from ethyl acetate has also been reported. Chromatographic purifications on silica have been

reported in a few cases, including *N*-acyl derivative (**6**; $R = \text{Pr}^i$) (benzene/ether <85IZV1612>), spiro derivative (**10**) (1,2-dichloroethane <86JOC417>), benzo derivative (**11**) (chloroform/methanol <90JCR(S)319>), and (**8**; $R^1 = \text{F}$, $R^2 = \text{Bu}$) (CH_2Cl_2 /methanol <83JOC2337>).

As no fully-conjugated 1,3-diazocine derivatives have been synthesized, the issue of potential aromatic stabilization in such compounds has been addressed only theoretically, as discussed above. Conformational studies of 1,3-diazocines and their polyhydro derivatives appear to be completely lacking, other than the theoretical conclusion that the parent unsaturated system (**1**) should be nonplanar, with C_{2v} symmetry <83MI 922-03> and the comment that Dreiding models were used to assay the conformation of the ring in (**6**) <85IZV1612>.

Valence tautomerism of 1,3-diazocines has been demonstrated through the reversibility of their formation from pyrimidinedione-alkyne photoadducts <82TL4207, 83JOC2337>. Thus, for example, photoaddition of 1-heptyne to uracil, followed by silylation and treatment with silica gel affords diazocine (**8**; $R^1 = \text{H}$, $R^2 = \text{pentyl}$) (Scheme 1). Photolysis of (**8**) cleanly converts it back to the starting photoadduct. The mechanism of these rearrangements, as well as the formation of pyridones upon base treatment of the diazocines, discussed below, has been addressed through the study of ^{13}C - and ^{15}N -labeled materials <82TL4207>.

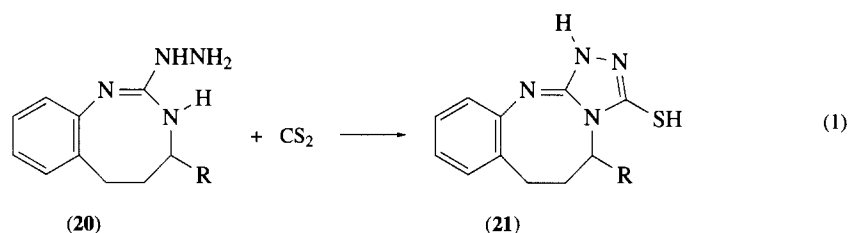


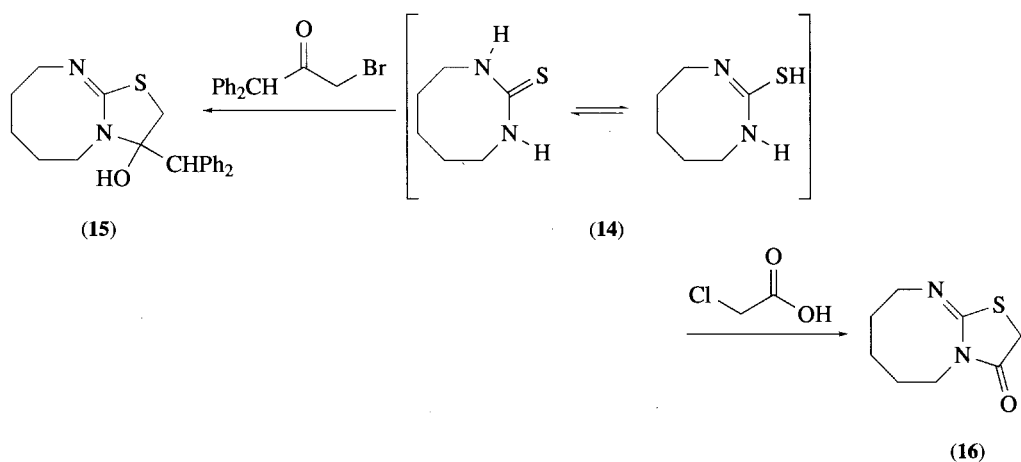
Scheme 1

9.22.3.3 Reactivity of Nonconjugated Rings

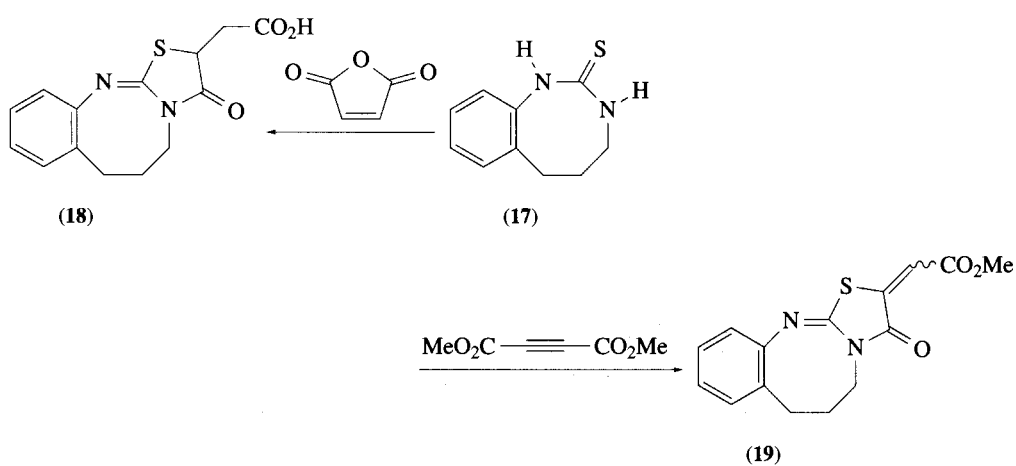
Many of the reported reactions of the 1,3-diazocines represent cyclocondensation reactions mediated by the nucleophilicity of 2-hetero substituents. Thus, perhydro-1,3-diazocine-2-thione (**14**) reacts with α -halocarbonyl compounds such as α -bromoketones <82USP4325955, 82USP4340734> α -bromoesters <87ZC36>, and chloroacetic acid <83MI 922-04>, presumably by initial nucleophilic displacement of halide by the thione, followed by intramolecular nucleophilic attack by ring nitrogen to afford thiazole-type fused ring bicyclic products such as (**15**) and (**16**) (Scheme 2). Somewhat unexpectedly, (bromophenylethylidene)malononitrile afforded only intractable product mixtures, purportedly due to base-induced polymerization of this rather reactive material <90JOC4740>.

Active Michael acceptors, such as dimethyl acetylenedicarboxylate (DMAD) <87EGP251974, 87EGP251983, 87ZC36> and maleic anhydride <87ZC36>, react with 3,4,5,6-tetrahydro-1,3-benzodiazocin-2(1*H*)-thione (**17**), again apparently via initial *S*-alkylation, followed by intramolecular *N*-acylation (Scheme 3). The stereochemistry about the $\text{C}=\text{C}$ double bond in (**19**) appears not to have been established. Similar reaction chemistry of 2-hydrazino derivatives (**20**; $R = \text{H}$, Ph) with CS_2 yields the triazolo-fused products (**21**) in ca. 70% yield (Equation (1)) <89EGP265897>.



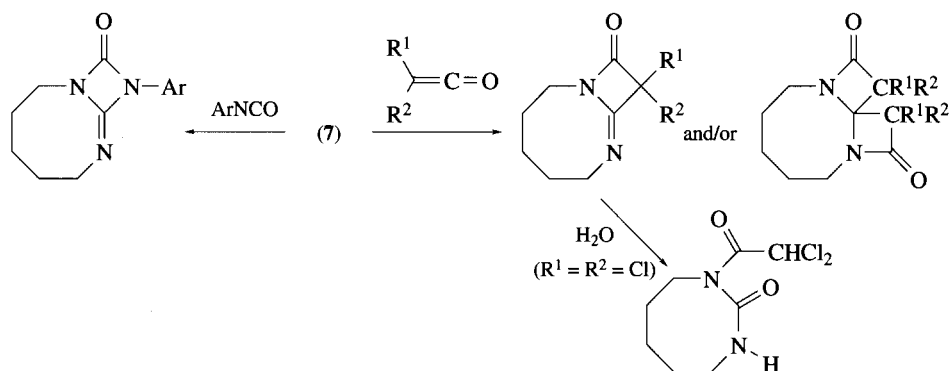


Scheme 2



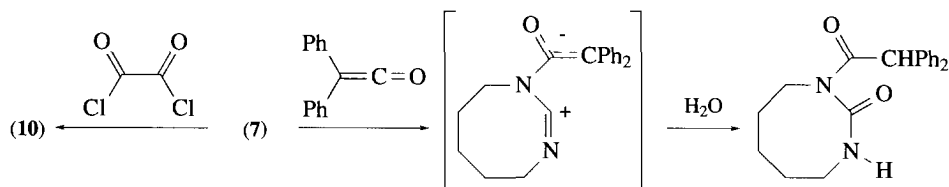
Scheme 3

Desulfurization of thione (14) with yellow mercuric oxide affords the unusual cyclic carbodiimide (7) in >80% yield (83JOC1694); the same compound is also available through the ring expansion reaction discussed below (83JOC1694). The carbodiimide hydrolyzes only slowly (83JOC1694), but undergoes facile [2 + 2] cycloadditions with isocyanates ($\text{Ar} = \text{Ph}$, $p\text{-Cl-C}_6\text{H}_4$) (83JOC1694) and ketenes (85JHC357), with the latter forming either 1 : 1 ($\text{R}^1 = \text{R}^2 = \text{Ph}$, Cl) and/or 2 : 1 ($\text{R}^1 = \text{R}^2 = \text{Ph}$; $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{Et}$) adducts (Scheme 4). Yields of cycloadducts are often high, although that derived from dichloroketene was apparently hydrolyzed by adventitious water to the monocyclic *N*-acyl derivative (85JHC357).



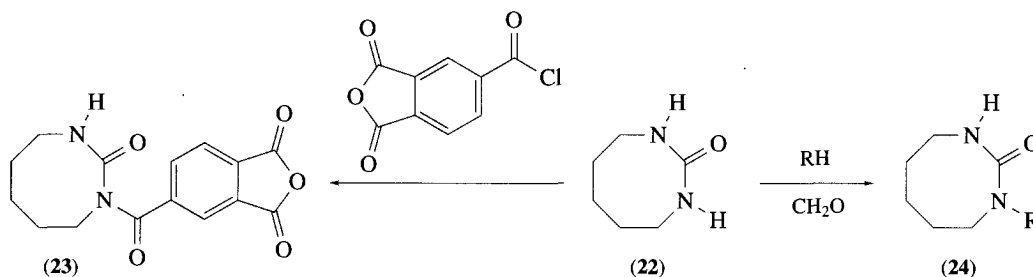
Scheme 4

Interestingly, the diphenylketene derived 1:1 adduct is stable to hydrolysis, but if the reaction forming it is carried out in the presence of traces of water, an *N*-acyl derivative analogous to that from the dichloroketene reaction is obtained, apparently via trapping of an initial zwitterionic adduct (Scheme 5). Treatment of the carbodiimide with oxalyl chloride apparently affords the unusual spirocyclic 2:1 adduct (**10**) (Scheme 5); larger ring carbodiimides, in contrast, afforded only 1:1 adducts <86JOC417>.



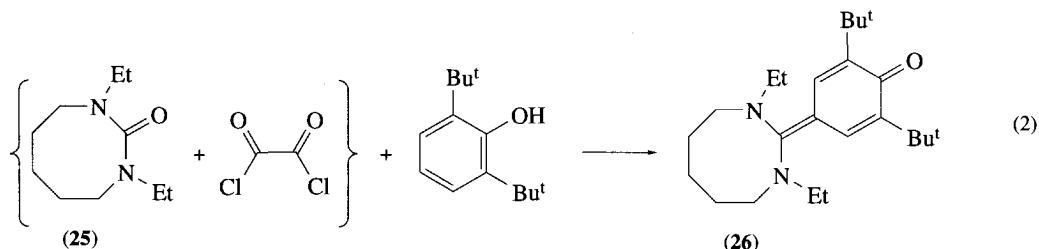
Scheme 5

Hexahydro-1,3-diazocin-2(1*H*)-one (**22**) is monoacylated to (**23**) upon treatment with an aromatic acyl chloride (Scheme 6) <83USP4391751>. Similar nucleophilic behavior is noted in the Mannich reaction of (**22**) with formaldehyde and various secondary amines, affording poor yields (5–9%) of the monoalkylated products (**24**; RH = morpholine, piperidine, pyrrolidine, piperazine) (Scheme 6). Both nitrogens of piperazine apparently react, affording a bis(perhydrodiazocino) product <88MI 922-01>.



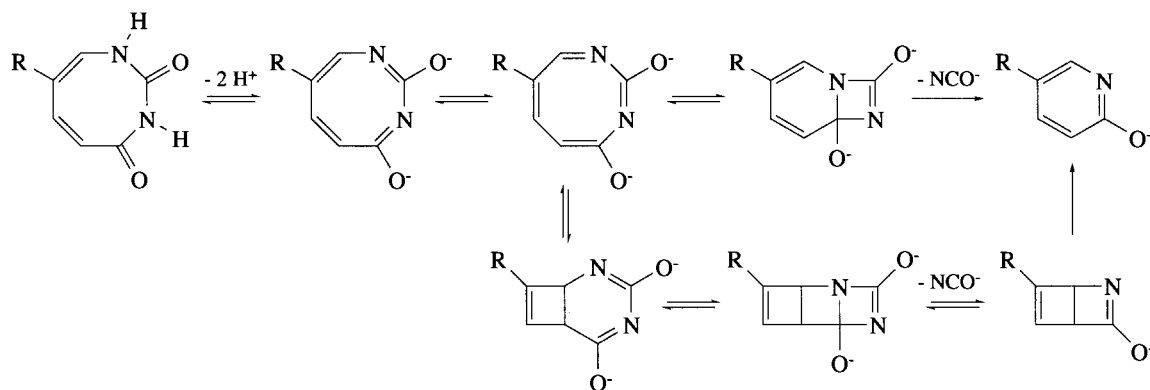
Scheme 6

In a rather curious reaction, 2,6-di-*t*-butylphenol is reported to react with a reagent generated from treatment of *N,N*-diethyl hexahydrodiazocin-2-one (**25**) with oxalyl chloride to afford the *p*-quinone methide (**26**) (Equation (2)) <84MI 922-03>.



Several 1,3-diazocin-2,4-dione derivatives (**8**), prepared by rearrangement of [2 + 2] photoadducts of pyrimidine derivatives, may be reconverted to these starting materials in high yield by photolysis <82TL4207, 83JOC2337>. Treatment of the *n*-pentyl derivative with *t*-butoxide, in contrast, leads to 2-pyridone formation <82TL4207>. Preparation of ¹³C- and ¹⁵N-labeled materials allowed assay of potential mechanistic pathways for this reaction. The favored pathway appears to involve valence tautomerism of the initially formed dianion, followed by loss of cyanate, although alternative formation of an isomeric valence tautomer, followed by passage through a Dewar pyridine-type

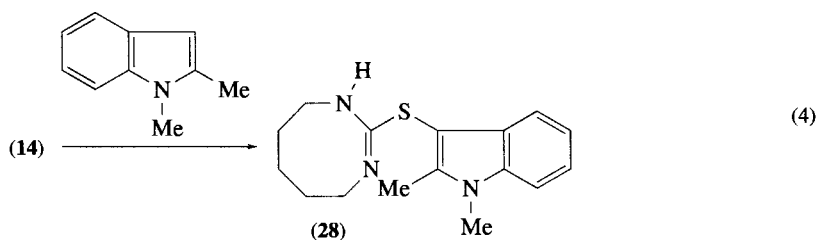
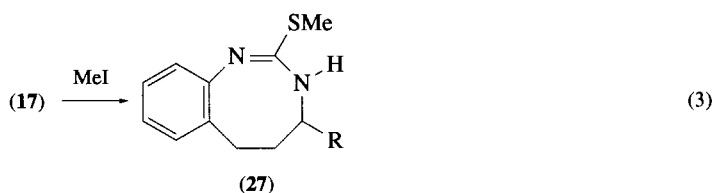
intermediate, loss of cyanate, and conversion from Dewar pyridine to pyridine is not excluded (Scheme 7) <82TL4207>.



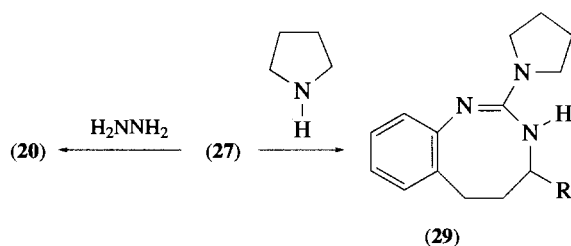
Scheme 7

9.22.3.4 Reactivity of Substituents Attached to Ring Carbon Atoms

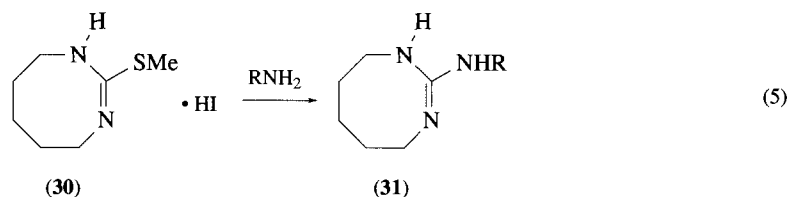
S-Methylation of benzo-1,3-diazocin-2(1*H*)-thione (**17**) affords the corresponding benzotetrahydrodiazocine (**27**; R = H) in unspecified yield (Equation (3)); the 4-phenyl analogue (**27**; R = Ph) is obtained analogously <87EGP251974, 87EGP251983>. Similarly, oxidative coupling of thione (**14**) with 1,2-dimethylindole affords (**28**) in 63% yield (Equation (4)) <81JJC(B)672>.



S-Methylated derivatives (**27**) and (**30**), as their hydriodide salts, undergo nucleophilic displacement of the SMe substituent, allowing access to 2-hydrazino (**20**) (Scheme 8) <88EGP258810> and 2-amino compounds (**29**; R = H, Ph) (Scheme 8) and (**31**; R = Ph₂CHCH₂, Ph₂CHCH₂CH₂) and (Equation (5)) <87EGP251977, 90EUP389765>.

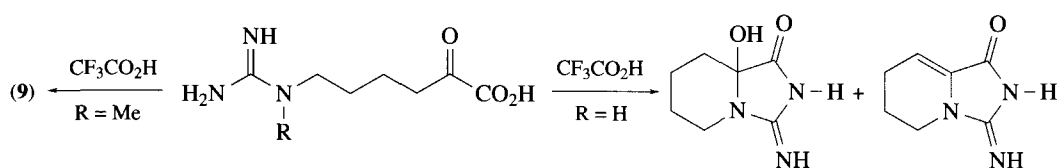


Scheme 8



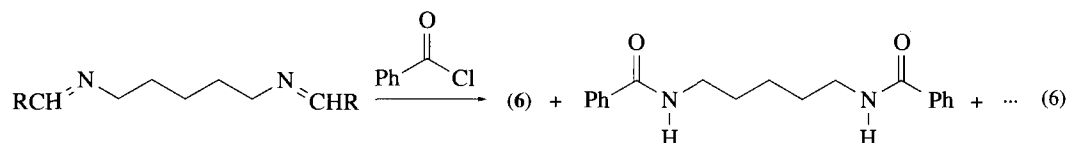
9.22.3.5 Ring Syntheses

Trifluoroacetic acid-mediated cyclization of an ω -guanidino α -ketoacid affords a good yield of the 1,3-diazocine (9) <83LA1623>; however, this route is far from general, as the analogous derivative bearing an N—H in place of the N—Me group cyclized instead to diazabicyclic products (Scheme 9).

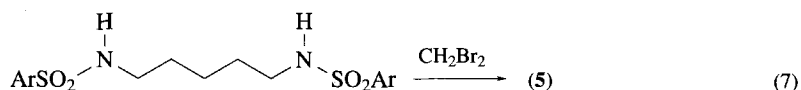


Scheme 9

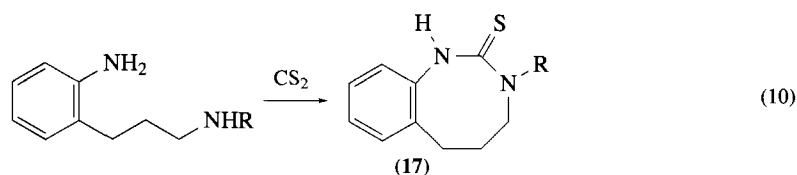
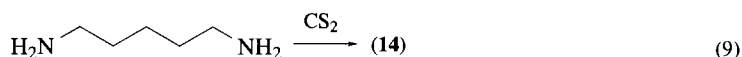
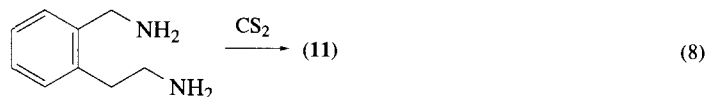
In a rather curious reaction, treatment of bis(imines) with benzoyl chloride effects cyclization, affording (6; R = Prⁱ, Ph) in 30% and 17% yield, respectively (Equation (6)) <85IZV1612>.



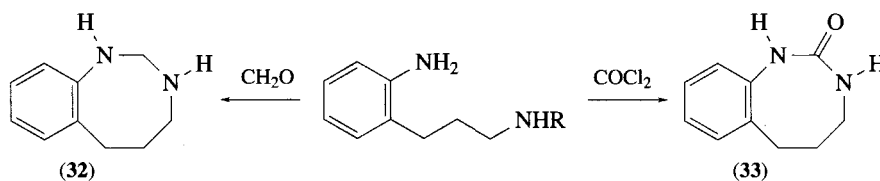
By far the most common approach to the 1,3-diazocine ring system has been and remains dependent on formation of the aминаl functionality through condensation of appropriate one-carbon sources with diamines. Alkylation of α,ω -disulfonamides with methylene bromide affords modest yields (ca. 45%) of perhydrodiazocine derivatives (5; Ar = *p*-tolyl, phenyl) (Equation (7)) <83MI 922-02, 84MI 922-02>.



1,5-Diamines react with CS₂ to provide ready access to thione (14) (Equation (9)) <90JCR(S)319>, benzo-fused analogues (11) (Equation (8)) <90JCR(S)319> and (17; R = H) (Equation (10)) <87EGP251974, 87EGP251983, 87ZC36>, as well as *N*-acyl derivative (17; R = CONHMe) <86EGP235452>.

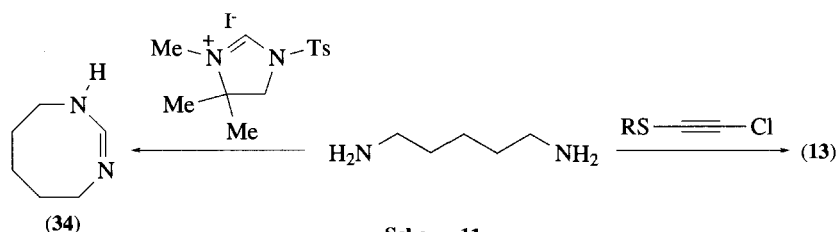


Similarly, formaldehyde condenses to give 2-unfunctionalized 1,3-diazocines (e.g., (32)), while phosgene affords the corresponding 2-ones (e.g., (33)) (Scheme 10) <87H(26)2477>.

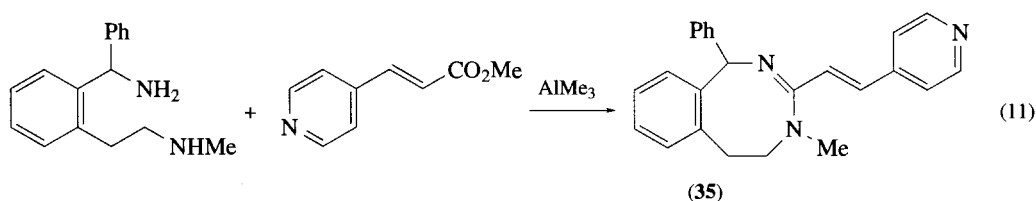


Scheme 10

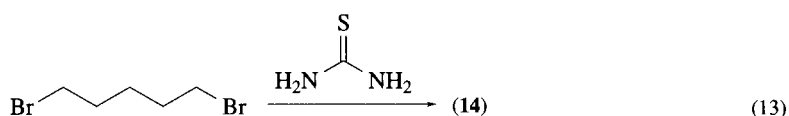
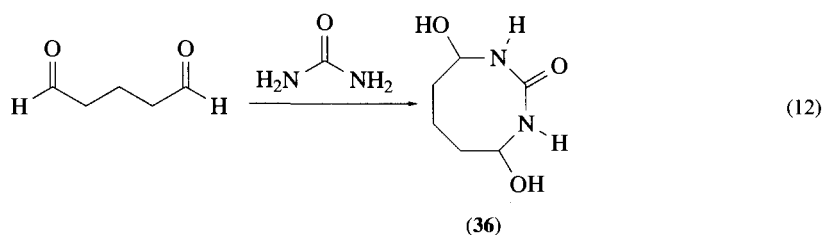
Other dielectrophilic reagents which react with 1,5-diamines to afford 1,3-diazocines include chlorothioalkynes, yielding (13) (Scheme 11) <89IZV906>, imidazolinium salts, yielding hexahydro-1,3-diazocine (34) (Scheme 11) <83T3971>, and esters, affording 1,4,5,6-tetrahydrobenzo-2,4-diazocine (35) (Equation (11)) <92EUP475527>.



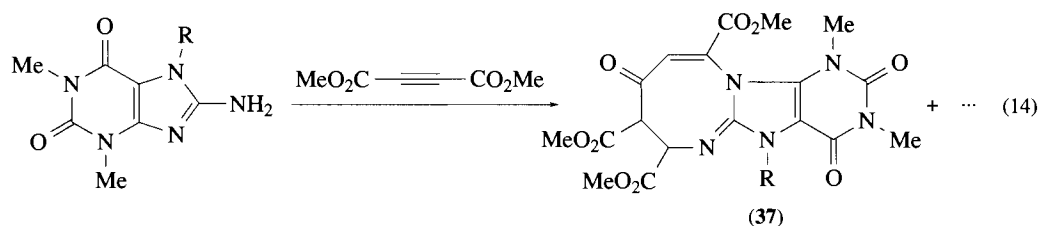
Scheme 11



Condensation of glutaraldehyde with urea is reported to afford 4,8-dihydroxy-3,4,5,6,7,8-hexahydro-1,3-diazocin-2(1*H*)-one (36) (Equation (12)) <84USP4454133>. Dialkylation of thiourea with 1,5-dibromopentane affords 2-thione (14) in ca. 40–60% yield (Equation (13)) <83MI 922-04>.

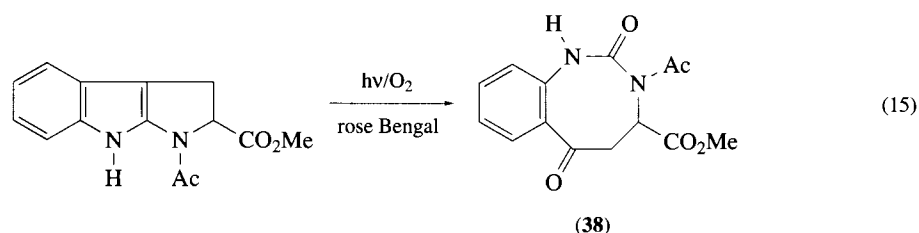


Heavily substituted fused-ring derivatives of 1,3-diazocine (37; R = Pr, Bu, *n*-pentyl, allyl) are reportedly formed in low (10–19%) yield, together with several other products, upon the multi-component condensation of xanthenes with dimethyl acetylenedicarboxylate in DMF; the same reactions in methanol do not afford (37) (Equation (14)) <91CPB270>.

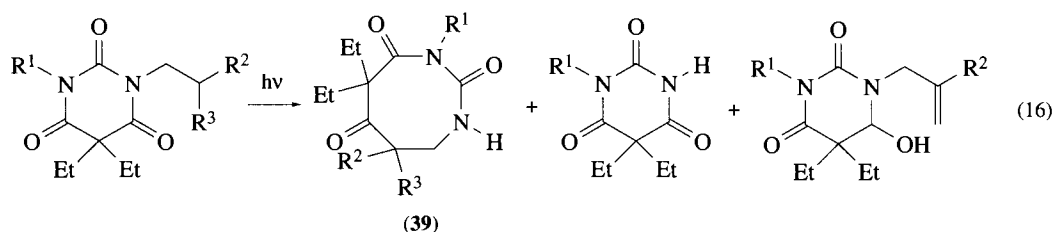


9.22.3.6 Ring Synthesis by Transformation of Another Ring

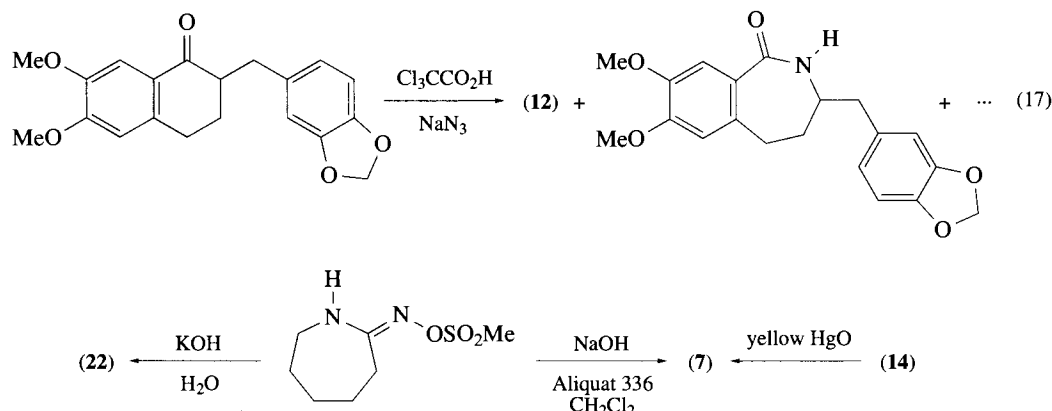
Valence tautomerization of pyrimidine-alkyne photoadducts is mediated by treatment with trimethylsilyl chloride/hexamethyldisilazane, followed by silica gel, affording diazocin-2,4-dione derivatives (**8**) in good yield (*vide supra*) <82TL4207, 83JOC2337>. Oxidative cleavage of a bicyclic diazo compound by rose Bengal-sensitized addition of oxygen affords the benzo-3,4-dihydro-1,3-diazocin-2,6(1*H*,5*H*)-dione derivative (**38**) (Equation (15)) <87H(26)2477>.



Photolysis of barbituric acid derivatives affords, apparently via a Norrish type-II process, low yields of 1,3-diazocin-2,4,6(1*H*,3*H*,5*H*)-triones (**39**; R¹ = R² = H, R³ = Me; R¹ = H, R² = R³ = Me; R¹ = R³ = Me, R² = H) (12–19%), together with several products retaining the barbituric acid ring (Equation (16)) <93T3781>.

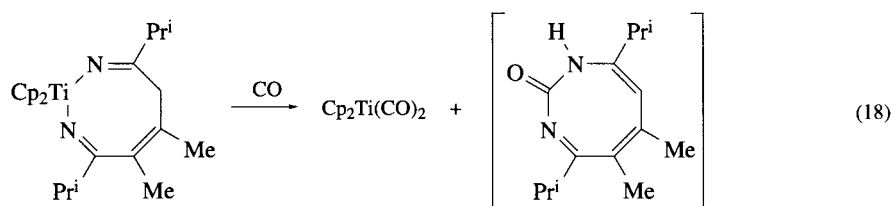


A very low yield (1.2%) of benzodiazocinone (**12**) is obtained as a minor, undesired side product upon rearrangement of the oxime generated *in situ* from a tetralone derivative (Equation (17)) <86JHC975>. The Tiemann rearrangement allows the preparation of perhydro-1,3-diazocin-2-one (**22**) <83JOC1694>, while a modification of this rearrangement provides cyclic carbodiimide (**7**), also prepared by mercuric oxide oxidation of 2-thione derivative (**14**) (Scheme 12) <83JOC1694>.



Scheme 12

Transfer of the organic fragment from a titanocene intermediate to carbon monoxide appears to lead to the corresponding 2-one (Equation (18)) <90MI 922-02>.

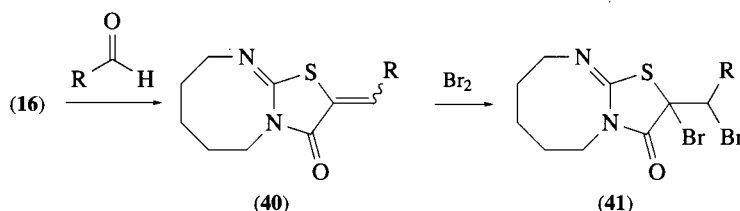


9.22.3.7 Comparison of Synthetic Routes

Unimolecular cyclizations remain scarce and erratic, while cyclization of 1,5-diamines with di-electrophilic reagents remains the primary means of entry to the 1,3-diazocine ring system. Ring transformation routes remain largely unexplored, with typically low yields for those rare cases reported, although the oxidative cleavage route to (38) suggests a potentially versatile and general route particularly deserving of further study.

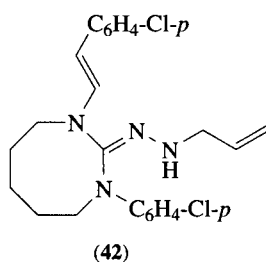
9.22.3.8 Important Compounds and Applications

Perhydro *N*-(piperidinylmethyl)- and *N*-(pyrrolidinylmethyl)-1,3-diazocin-2(1*H*)-one (24) display good to excellent antiviral activity toward orthomyxo and/or pox-type viruses <84MI 922-01, 88MI 922-01>, but are inactive against a variety of other viral types <84MI 922-01, 86MI 922-01>. Dihydroxy derivative (36) has been screened for antibacterial activity <84USP4454133>, as has been the condensation product of the 2-thione with chloroacetic acid (16) and its aldol-derived products ((40), (41); R = Ph, 2-thienyl) (Scheme 13), some of which display activity against *B. subtilis* and *Candida albicans* <83MI 922-04>.



Scheme 13

Ring-opening self-polymerization of *N*-acylated derivative (23) or copolymerization with other monomers affords injection moldable polymers with good glass transition temperatures <83USP4391751>. The 2-amino hexahydro derivatives (31) have been suggested as potential calcium antagonists <90EUP389765>, but no substantiating data has been reported. 2-Thio derivative (28), examined as one of a series of analogues of an active nasal decongestant, "Tinazoline", bearing a five-membered diaza ring, displayed hypotensive activity in cats, but no activity in dogs <81MI 922-02>. Imino derivative (42) was one of many hydrazones examined for insecticidal activity; no data is available regarding activity <87JAP6216921>.

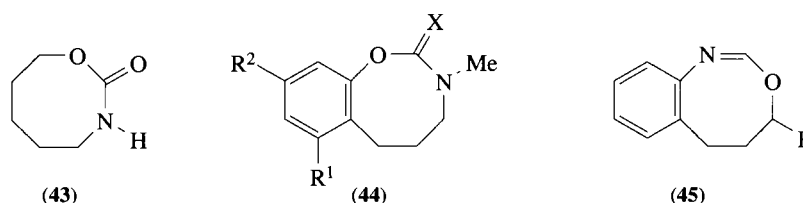


Benzo compound (**35**) displays antiarrhythmic activity <92EUP475527>, while benzothione (**11**) shows moderate affinity for α -adrenoceptors <90JCR(S)319>. Various other benzo derivatives (e.g., (**19**), (**20**)) have been suggested to be useful precursors for potentially bioactive materials <87EGP251974, 87EGP251983, 88EGP258810>.

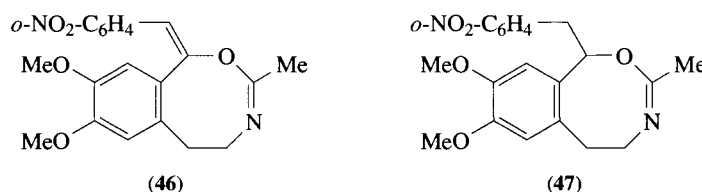
9.22.4 RINGS WITH ONE NITROGEN AND ONE OXYGEN (2H-1,3-OXAZOCINES)

9.22.4.1 Experimental Structural Methods

Although several crystalline 1,3-oxazocine derivatives have been described, no solid-state structural studies have been reported. Structural proposals have been based primarily on method of synthesis and on NMR, IR, and mass spectral analysis. Proton chemical shifts for those compounds analyzed by NMR spectroscopy, 3,4,5,6,7,8-hexahydro-2H-1,3-oxazocin-2-one (**43**) <85BCJ2855>, several 3,4,5,6-tetrahydro-2H-1,3-benzoxazocin-2-thione derivatives (**44**; $R^1 = \text{CH}(\text{NMe}_2)\text{CH}_3$, $R^2 = \text{H}$, $\text{X} = \text{O}$, S ; $R^1 = \text{H}$, $R^2 = \text{CH}(\text{NMe}_2)\text{CH}_3$, $\text{X} = \text{O}$) <90HCA739>, and two 4-alkyl-5,6-dihydro-4H-3,1-benzoxazocines (**45**; $R = \text{Me}$, Et) <78TL2087>, representing three different oxidation states of the heterocyclic ring, are as anticipated for compounds bearing related functionality.



IR spectra of the 2-ones ((**43**) and (**44**); $\text{X} = \text{O}$) display the anticipated urethane carbonyl band at ca. $1700\text{--}1740\text{ cm}^{-1}$ <85BCJ2855, 90HCA739>, while the less-reduced derivatives for which IR data has been reported, (**45**) and 5,6-dihydro-1H-2,4-benzoxazocines (**46**) and (**47**), display intra-ring $\text{C}=\text{N}$ modes near 1655 cm^{-1} <65JCS4014, 78TL2087>.

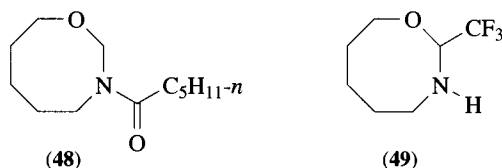


UV/visible spectroscopy of the latter two derivatives was cited in support of the loss of conjugation upon reduction of yellow (**46**) ($\lambda_{\text{max}} = 270\text{ nm}$, $\log \epsilon = 4.20$) to colorless (**47**) ($\lambda_{\text{max}} = 285\text{ nm}$, $\log \epsilon = 3.84$) <65JCS4014>. Insufficient mass spectral data are available for firm conclusions regarding fragmentation patterns to be drawn. Those compounds analyzed, (**43**) and (**44**), show parent ions upon electron impact analysis. Saturated derivative (**43**) appears to lose CO_2CH_2 <85BCJ2855>, while the benzo derivatives, lacking the appropriate CH_2 group for such fragmentation, appear to retain the oxazocine ring upon fragmentation <90HCA739>. Interestingly, the thio analogue (**44**; $\text{X} = \text{S}$) appears to lose COS , while the oxo compounds (**44**; $\text{X} = \text{O}$) do not display analogous loss of CO_2 <90HCA739>.

9.22.4.2 Thermodynamic Aspects

Other than the rather highly functionalized derivatives (**46**) and (**47**) (m.p. 152°C and 223°C , respectively) <65JCS4014>, only (**43**) is reported to be a solid (m.p. $75\text{--}76^\circ\text{C}$) <85BCJ2855>. Other reported derivatives, including (**44**) <90HCA739>, (**45**) <78TL2087>, 3,4,5,6,7,8-hexahydro-3-hexanoyl-2H-1,3-oxazocine (**48**) <68MI 922-01>, and 3,4,5,6,7,8-hexahydro-2-trifluoromethyl-2H-1,3-oxazocine (**49**) <70JMC1212>, are rather high boiling liquids. One might reasonably conclude that intermolecular hydrogen-bonding, probably via formation of dimers, is responsible for the relatively high melting

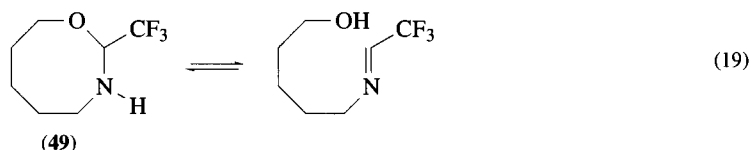
point of (43), given that removal of either the N—H group (e.g., by methylation (44) or acylation (48)) or of the carbonyl group, as in (45) and (49), leads to significantly lowered melting points.



No unusual solubilities have been reported for the 1,3-oxazocines. Most appear soluble in chloroform, judging from its use as a solvent for NMR spectroscopy, while recrystallization of (43) from ethyl acetate <85BCJ2855> and (46) and (47) from ethanol and methanol, respectively <65JCS4014> suggests somewhat lower solubility in these solvents. Liquid chromatography on both silica <90HCA739> and alumina <65JCS4014> has been reported, as has gas chromatographic analysis of (43) (10% Silicone OV-1) <85BCJ2855>.

Conformational aspects have been addressed only briefly, with molecular mechanics calculations suggesting the carbamate group in (44) to be roughly perpendicular to the plane of the benzo group. This near-orthogonality was suggested to be responsible for the acetylcholinesterase-inhibiting activity of (44; X = O), while the lower activity of (44; X = S) was attributed to loss of intermolecular hydrogen-bonding capability <90HCA739>.

Ring-chain tautomerism of trifluoromethyl derivative (49), representing the partial reverse of the reaction used to prepare this derivative, has been noted, with 15% of the open-chain form noted by NMR spectroscopy (Equation (19)) <70JMC1212>. Unfortunately, the solvent, expected to play a key role in governing the position of this equilibrium, was not reported.



9.22.4.3 Reactivity of Nonconjugated Rings

Given their rarity, it is perhaps not surprising that virtually no chemical reactivity studies of the 1,3-oxazocines have been reported. Protonation of benzo derivatives (44) by fumaric acid presumably occurs on the tertiary amino group rather than on ring nitrogen <90HCA739>.

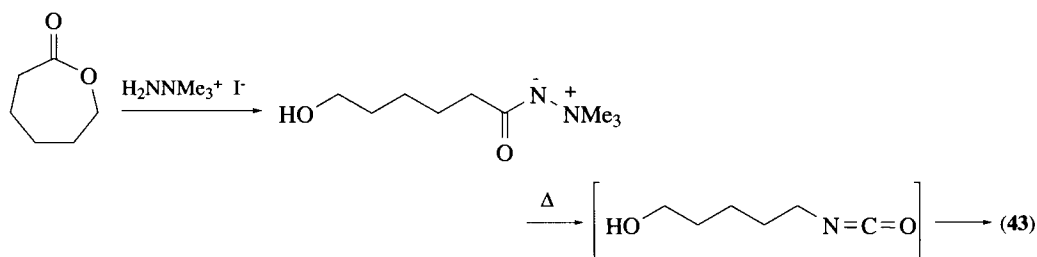
9.22.4.4 Reactivity of Substituents Attached to Ring Carbon Atoms

Reduction of the benzylidene side-chain of (46) upon treatment with formic acid/formamide apparently provides the benzyl analogue (47) in low yield <65JCS4014>.

9.22.4.5 Ring Syntheses

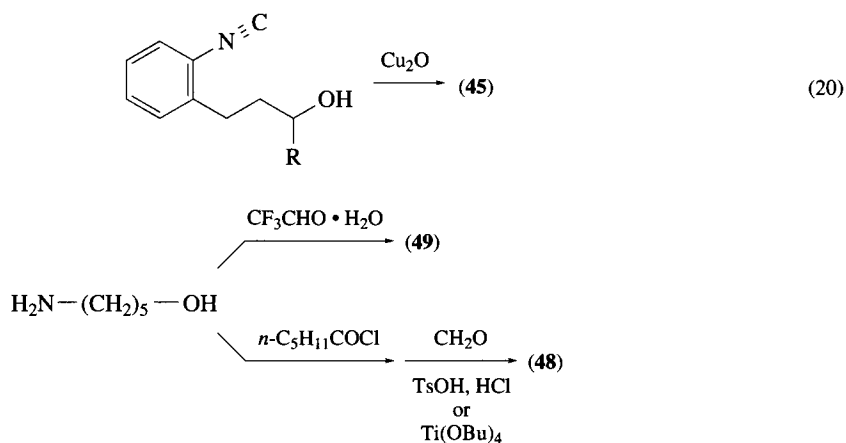
The 1,3-oxazocine ring has thus far been formed via unimolecular cyclization <78TL2087, 85BCJ2855>, hemiaminal formation between acyclic amino alcohols and aldehydes <68MI 922-01, 70JMC1212, 73BRP1321042>, and coupling of amino alcohols with a carbonyl equivalent reagent <90HCA739>. *In situ* formation of 5-hydroxypentane isocyanate via pyrolysis of the corresponding *N*-ammonioamidate provides an 8% yield of the cyclic urethane (43) if carried out under dilute

conditions (1 g/100 mL); higher concentrations lead to the exclusive formation of oligomers (Scheme 14) <85BCJ2855>.



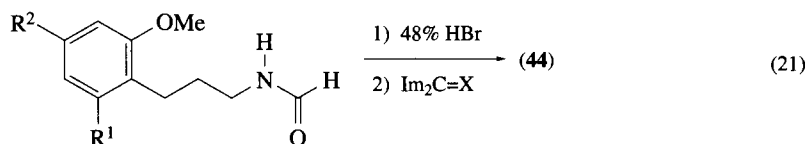
Scheme 14

Copper oxide-mediated alcoholysis of hydroxy isocyanides affords low to moderate yields of benzo derivatives (45) (Equation (20)) <78TL2087>. Aminopentanol reacts with trifluoroacetaldehyde hydrate in benzene, under azeotropic removal of water, to afford (49) in 52% yield <70JMC1212, 73BRP1321042>, while the *N*-hexanoyl derivative of this amino alcohol reacts with formaldehyde, under either protic or Lewis acidic catalysis, to afford a low (9%) yield of (48) (Scheme 15) <68MI 922-01>.

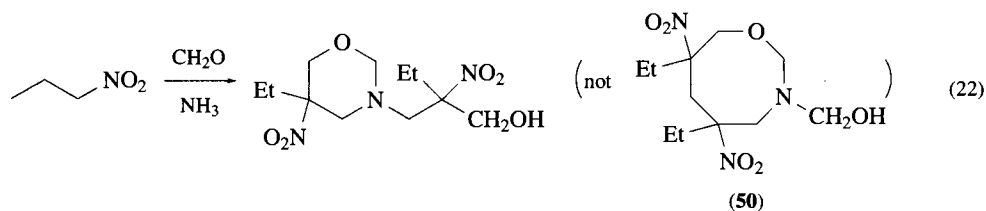


Scheme 15

Coupling of amino alcohols with carbonyl or thiocarbonyl diimidazole affords the corresponding oxo (or thio) oxazocines in 63–76% yield (Equation (21)) <90HCA739>.

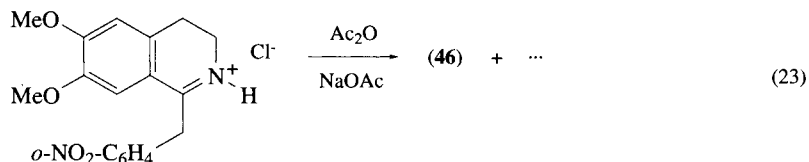


Early reports of the multicomponent formation of *N*-hydroxymethyl derivative (50) were later shown to be in error; the actual products of this reaction were shown to be two stereoisomeric oxazines (Equation (22)) <70JCS(C)1004>.



9.22.4.6 Ring Synthesis by Transformation of Another Ring

In the single reported formation of the oxazocine ring system from a cyclic precursor, acetylation of a dihydroisoquinoline was unexpectedly found to give approximately a 60% yield of benzo derivative (46) (Equation (23)) <65JCS4014>; no mechanism was suggested for this curious transformation.



9.22.4.7 Comparison of Synthetic Routes

While reported syntheses are scarce, they parallel those of the 1,3-diazocines, with unimolecular cyclization routes suffering from low yields while cyclizations of 1,5-amino alcohols with dielectrophiles are more promising. The sole ring transformation route reported, while proceeding in reasonable yield, is presumably not to be expected to represent a general entry into the 1,3-oxazocine ring system.

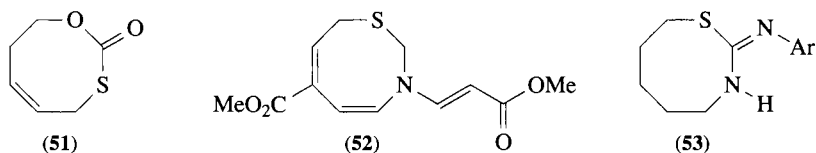
9.22.4.8 Important Compounds and Applications

Compounds (44; X = O) demonstrated the highest anticholinesterase-inhibiting activity of a series of six- to eight-membered heterocycles studied <90HCA739>. *N*-Acyl derivative (48), prepared as part of a study of potential bacteriostatic and fungistatic agents, displayed reduced activity relative to smaller-ring analogues <68MI 922-01>. Trifluoromethyl derivative (49) showed significant anti-inflammatory and CNS depressant activity, while displaying no endocrine stimulatory effects <70JMC1212>.

9.22.5 RINGS WITH ONE NITROGEN AND ONE SULFUR (2*H*-1,3-THIAZOCINES) OR ONE OXYGEN AND ONE SULFUR (4*H*-1,3-OXATHIOCINS)

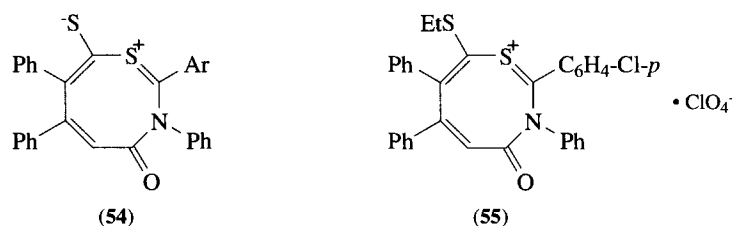
9.22.5.1 Experimental Structural Methods

Little structural information is available for these rare compounds. Proton NMR data have been reported only for 7,8-dihydro-1,3-oxathiocin-2(4*H*)-one (51), which displays no surprising chemical shifts. The (*Z*)-geometry of (51) is suggested by the observed $^3J_{\text{HH}}$ of 11.2 Hz for the methine protons <91CPB1659>. A 3,8-dihydro-2*H*-1,3-thiazocine-6-carboxylic acid derivative (52) is reported to display a ^1H NMR spectrum consistent with fluxional behavior, but no discussion of the conformational changes associated with the fluxional process(es) was presented <87CC1296>. Tautomerization of 2-imino derivatives (53; Ar = *o*-Cl-C₆H₄, *p*-Cl-C₆H₄, 3-Cl-4-Me-C₆H₃, *p*-Et-C₆H₄, *p*-F-C₆H₄, *p*-Me-C₆H₄, C₆H₅) was assayed by the chemical shift of the N—CH₂ group <71CJC971>.



Electron impact mass spectrometry provides the anticipated parent ion for oxathiocin (51) <91CPB1659> and thiazocinium derivatives (54; Ar = C₆H₅, *p*-Cl-C₆H₄) <76JOC818>; (54; Ar = C₆H₅) also displays a significant fragment peak at *M*-93. IR spectroscopy of (51) shows, in addition to the carbonyl stretch at 1700 cm⁻¹, bands at 1100 (C—O—C), 1060, and 965 cm⁻¹ <91CPB1659>, while

the thiazocinium derivatives (**54**) display carbonyl bands at ca. 1650–1690 cm^{-1} and C—N modes at ca. 1600 cm^{-1} <76JOC818>.

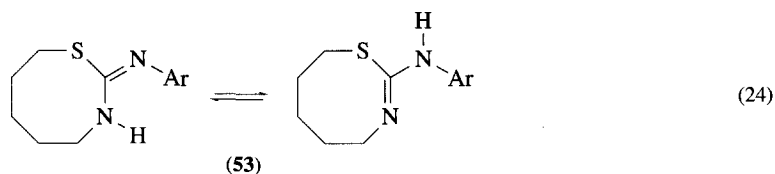


Mesoionic derivatives (**54**) are dark red-brown, with UV/visible maxima near 460 (log ϵ ca. 3.8), 328 (4.0), and 240 (4.4) nm, while the alkylated derivative (**55**) is yellow, with maxima at 428 (3.63), 305 (sh, 3.64), and 244 (4.14) nm <76JOC818>.

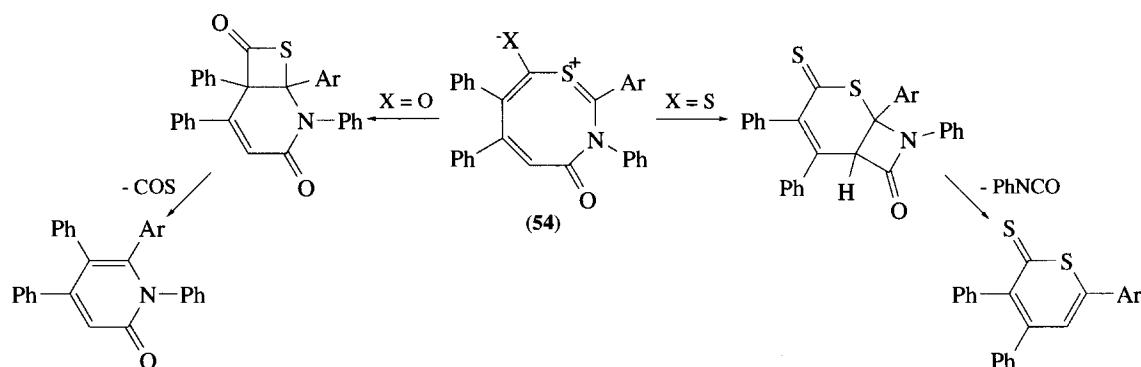
9.22.5.2 Thermodynamic Aspects

The thiazocinium derivatives, (**54**), (**55**), not surprisingly, are high-melting crystalline solids, consistent with their highly polar nature <76JOC818>. The hydrobromide salts of iminothiazocines (**53**) are also solids, with melting points ranging from 94–157°C; properties of the free bases were not reported <71CJC971>. Mesoionic thiazocinium compound (**54**; Ar = *p*-Cl-C₆H₄) was purified by chromatography on silica, eluting with benzene, and it and its analogues appear to be soluble in chloroform and, at least to some extent, in methanol (for UV/visible analysis) and ethanol (for recrystallization) <76JOC818>. The oxathiocin (**51**) also survived chromatography on silica (elution solvent not stated) and is soluble in chloroform <91CPB1659>.

Iminothiazocines (**53**) apparently show some evidence of tautomerism between two isomeric imines (Equation (24)); the exocyclic imine tautomer was tentatively proposed to predominate in solution (solvent unstated) on the basis of the chemical shift for the N—CH₂ group, but the lack of good models for the involved functionalities precluded firm assignment of structures <71CJC971>.



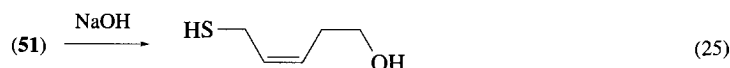
Valence tautomerization has been proposed to account for the formation of pyridone (for X = O) and thiopyranthione (for X = S) derivatives from (**54**) through the following reaction manifold (Scheme 16) <76JOC818>.



Scheme 16

9.22.5.3 Reactivity of Nonconjugated Rings

Hydrolysis of oxathiocin (**51**) with 2*N* aqueous NaOH in methanol proceeds rapidly to afford the corresponding allylic thiol in quantitative yield, with the (*Z*)-configuration of the product helping confirm the proposed (*Z*)-geometry of (**51**) (Equation (25)) <91CPB1659>.

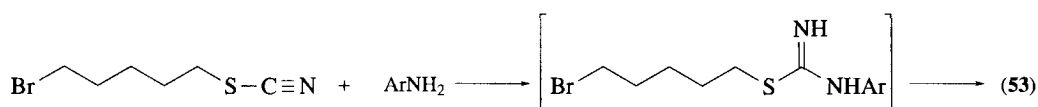


9.22.5.4 Reactivity of Substituents Attached to Ring Carbon Atoms

Mesoionic thiazocinium derivative (**54**; Ar = *p*-Cl-C₆H₄) reacts with triethyloxonium tetrafluoroborate to afford a 74% yield of the side-chain *S*-ethylated derivative (**55**), isolated as a yellow solid after anion exchange with perchloric acid <76JOC818>.

9.22.5.5 Ring Syntheses

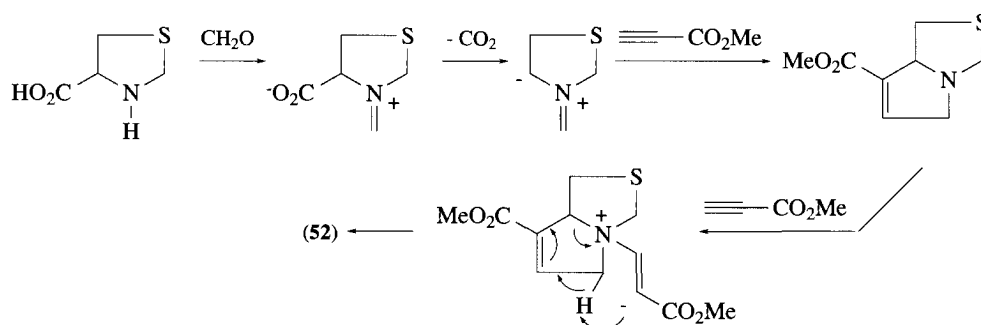
The iminothiazocines (**53**) were prepared via addition of aromatic amines to 5-bromopentane thiocyanate (prepared in turn from 1,5-dibromopentane via formation of the monophthalimide derivative); the initial adduct undergoes intramolecular alkylation to afford the cyclized products in 85–100% yield (Scheme 17) <71CJC971>.



Scheme 17

9.22.5.6 Ring Synthesis by Transformation of Another Ring

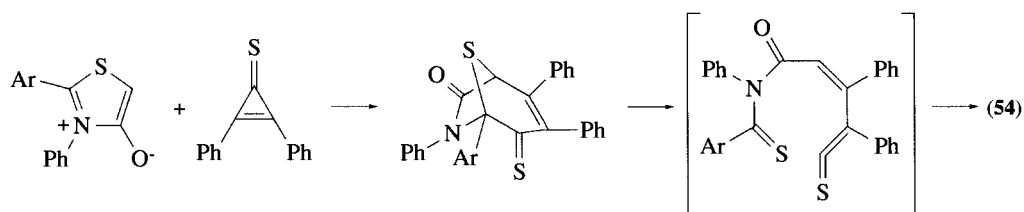
Treatment of 4-carboxythiazolidine with formaldehyde and methyl propargylate affords thiazocine (**52**), apparently via intermediate formation of an azomethine ylide, which then undergoes [3 + 2] cycloaddition with the alkyne, followed by Michael addition to a second equivalent of alkyne and final rearrangement (Scheme 18) <87CC1296>.



Scheme 18

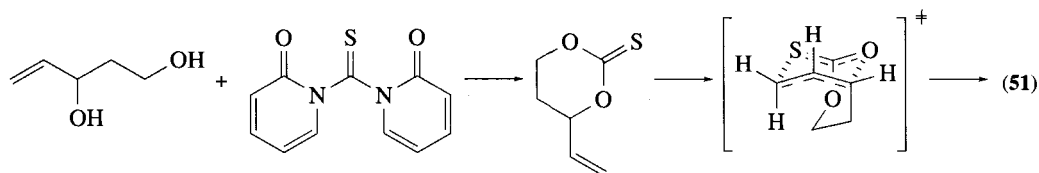
Thiazocinium derivatives (**54**) are formed via thermal rearrangement of bicyclic thiones prepared from 1,2-diphenylcyclopropenethione and a mesoionic *N*-phenyl thiazole derivative (Scheme 19)

<76JOC818>. The corresponding keto derivative does not afford a stable analogue of (54), but instead a pyridone, apparently via valence tautomerization (*vide supra*) <76JOC818>.



Scheme 19

[3,3]-Sigmatropic rearrangement of a vinyl cyclic thionocarbonate affords oxathiocinone derivative (51), with the formation of the (*Z*) product rationalized on the basis of a chair-like transition state for the rearrangement (Scheme 20) <91CPB1659>.



Scheme 20

9.22.5.7 Comparison of Synthetic Routes

Each of the approaches reported thus far to these rare ring systems appears rather promising. The nucleophilic addition/cyclization and [3,3]-rearrangement routes appear potentially well-suited for the rather general preparation of substituted analogues. The azomethine ylide route will presumably be somewhat limited in scope, given the basic reaction motif and its structural requirements, while the bicyclic thione rearrangement route will perhaps be of some use for the preparation of “specialty” compounds related to (54).

9.22.5.8 Important Compounds and Applications

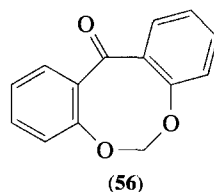
The iminothiazocine derivatives (53) <71CJC971>, as well as their 7- to 13-ring analogues, were all assayed for anthelmintic activity. The 8-ring compounds were inactive, although the thiocyanate precursors to them did display modest activity <71CJC971>.

9.22.6 RINGS WITH TWO OXYGENS (4*H*-1,3-DIOXOCINS)

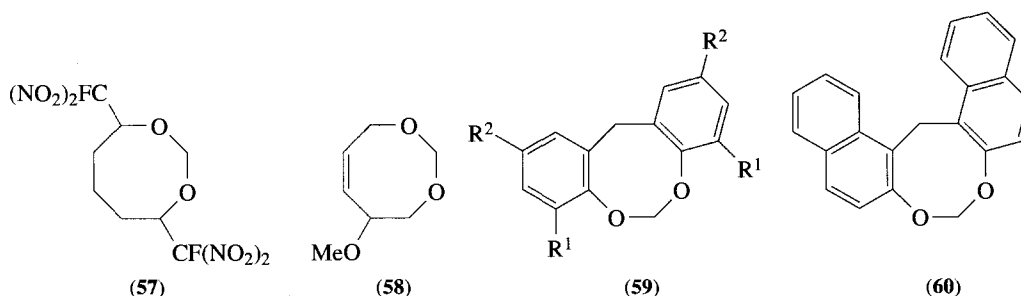
9.22.6.1 Experimental Structural Methods

Single crystal x-ray diffraction analysis of 12*H*-dibenzo[*d,g*][1,3]dioxocin-12-one (56) has been carried out <91JST165>. This apparently represents the only detailed structural study of any 1,3-diheterocin reported. Unfortunately, only partial data was presented. Reported bond angles appear

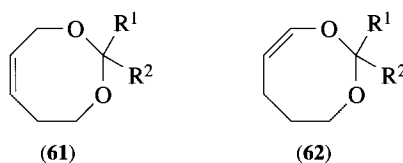
intermediate to those expected for the boat-chair and twist conformers (*vide infra*), while the dihedral angles match reasonably well with those expected for the twist form.



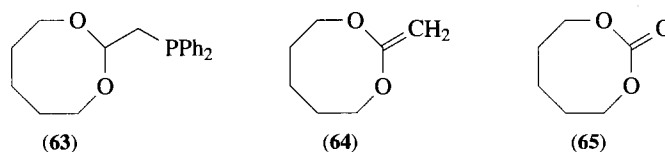
A number of 1,3-dioxocins have been examined by ^1H NMR spectroscopy, generally as part of their routine characterization (83CB2136, 83T1359, 84JOC4060, 86TL1587, 92HCA729). The $\text{O}-\text{CH}_2-\text{O}$ group tends to appear at ca. 4.5–4.8 ppm in unsubstituted derivatives such as 4,8-bis(fluoro-dinitromethyl)-1,3-dioxocane (57) (87JPS(A)805) and (*E*)- and (*Z*)-5,8-dihydro-5-methoxy-4*H*-1,3-dioxocin (58) (82MI 922-01), although it is appreciably further downfield (5.2–5.6 ppm) in dibenzo derivatives such as 12*H*-dibenzo[*d,g*][1,3]dioxocin (59; $\text{R}^1 = \text{R}^2 = \text{H}$; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Cl}$, Me; $\text{R}^1 = \text{Bu}^t$, $\text{R}^2 = \text{Me}$) and the dinaphtho analogue (60) (89ZOR657, 91ZOB173). Other chemical shifts are in accord with the functionality present.



Elucidation of the double bond configuration in (*E*)- and (*Z*)-(58) was critically dependent on ^1H NMR analysis, with (*E*)-(58) showing a $^3J_{\text{HH}}$ for the alkenic protons of 16.5 Hz and (*Z*)-(58) a $^3J_{\text{HH}}$ of 12.0 Hz (82MI 922-01). Similarly, the (*Z*)-2*H*-dihydro-1,3-dioxocins ((61) and (62); $\text{R}^1 = \text{R}^2 = \text{Me}$; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$, Pr^i , Ph) show a $^3J_{\text{HH}}$ of ca. 11 Hz (90TL649). Conformational analysis of several dibenzo derivatives, discussed below, also relied heavily upon NMR spectral analysis, with, for example, the singlets observed for the C-6 and C-12 methylene groups at room temperature (CDCl_3) for dibenzo compound (59; $\text{R}^1 = \text{R}^2 = \text{H}$) resolving into AB quartets at 223K (89ZOR657, 91ZOB173).

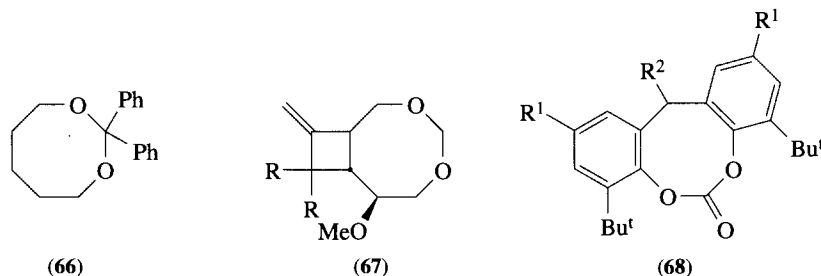


Fewer ^{13}C NMR data have been reported. In all cases, the $\text{O}-\text{C}-\text{O}$ carbon appears at ca. 100 ppm in compounds bearing either no (e.g., (58), (59)) (89ZOR657, 91ZOB173) or simple substitution (e.g., (61)–(63)) (90TL649, 91ZN(B)1519) at this position. 2-Methylene-1,3-dioxocane (64) shows the expected downfield shift (164 ppm) for this carbon (86TL1587), while 1,3-dioxocan-2-one (65) shows a typical carbonate resonance at ca. 150 ppm (92HCA729).



In addition to parent ion data reported for 1,3-dioxocanes (63) and (66) (84JOC4060, 91ZN(B)1519), fragment ions formed upon electron impact analysis have also been reported in a few cases, including (*E*)- and (*Z*)-(58) and their cycloadducts (e.g., (67; $\text{R} = \text{H}$, Me)). These often show rather weak or

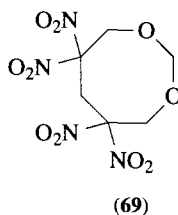
no parent ions $\langle 82\text{MI } 922\text{-}01, 83\text{CB}2136 \rangle$, and loss of CH_2O appears common $\langle 82\text{MI } 922\text{-}01, 83\text{CB}2136, 83\text{T}1359 \rangle$. For 12*H*-dibenzo[*d,g*][1,3]dioxocin-6-ones (**68**; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$; $\text{R}^1 = \text{Bu}^t$, $\text{R}^2 = \text{H}$, Me, Et) loss of CO_2 represents a major fragmentation pathway $\langle 92\text{HCA}729 \rangle$.



Although IR spectral data have been reported for a number of derivatives $\langle 83\text{CB}2136, 83\text{T}1359, 84\text{JOC}4060, 91\text{JST}165, 91\text{ZOB}173, 92\text{HCA}729 \rangle$, specific assignments of vibrational modes are rather rare. The $\text{C}=\text{C}$ mode in (*E*)-(**58**) was observed as a weak band at 1625 cm^{-1} $\langle 82\text{MI } 922\text{-}01 \rangle$, while a very strong band at 1116 cm^{-1} in dioxocane (**63**) was assigned to an antisymmetric $\text{O}-\text{C}-\text{O}$ mode $\langle 91\text{ZN(B)}1519 \rangle$. Focus on the carbonyl stretching mode in (**56**), by both IR and Raman spectroscopy, allowed assessment of its solid-state and solution conformation(s), discussed below $\langle 91\text{JST}165 \rangle$. Based on observed solvent effects on conformational distribution, the higher energy conformation of (**56**) was suggested to be less polar than the lower energy form $\langle 91\text{JST}165 \rangle$. Calculated dipole moments for related dibenzo compounds (**59**), (**60**), using an additive scheme, led to the conclusion that there is a stereospecific dependence of the polarity of the aromatic $\text{C}-\text{O}$ bond on the relative orientations of the aromatic ring and the oxygen lone pair orbitals $\langle 92\text{ZV}607 \rangle$.

9.22.6.2 Thermodynamic Aspects

Phase behavior of the 1,3-dioxocins is largely as expected for molecules displaying similar symmetry and functionality. Many of the simpler dioxocane derivatives are liquids (e.g., (**61**), (**62**) ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Pr}$) $\langle 90\text{TL}649 \rangle$, and (**64**) $\langle 86\text{TL}1587 \rangle$) or comparatively low melting solids (e.g., (**63**), m.p. 40°C $\langle 91\text{ZN(B)}1519 \rangle$; (**66**) m.p. $41\text{--}42^\circ\text{C}$ $\langle 84\text{JOC}4060 \rangle$); even the highly polar polynitro derivatives (**57**) and (**69**) melt at only $128\text{--}9^\circ\text{C}$ and $88\text{--}92^\circ\text{C}$, respectively $\langle 87\text{JPS(A)}805 \rangle$. The dibenzo derivatives for which data have been reported (**59**) and (**68**) are comparatively high melting (typically $> 150^\circ\text{C}$), in accord both with their high symmetry and the potential pi-stacking opportunities afforded by the aromatic substituents $\langle 91\text{ZOB}173, 92\text{HCA}729 \rangle$.



Many of the 1,3-dioxocins appear readily soluble in even nonpolar solvents, with, for example, benzene $\langle 82\text{MI } 922\text{-}01, 83\text{CB}2136, 83\text{T}1359 \rangle$, carbon tetrachloride $\langle 82\text{MI } 145\text{-}01, 83\text{CB}2136, 83\text{T}1359 \rangle$, and chloroform $\langle 84\text{JOC}4060, 87\text{JPS(A)}805, 89\text{ZOR}657, 90\text{TL}649, 91\text{ZN(B)}1519, 92\text{HCA}729 \rangle$ rather routinely used for NMR spectral analysis. Recrystallization from diethyl ether $\langle 84\text{JOC}4060 \rangle$, chloroform $\langle 87\text{JPS(A)}805 \rangle$, hydrocarbons $\langle 91\text{ZN(B)}1519, 92\text{HCA}729 \rangle$, or various mixtures of these solvents $\langle 83\text{T}1359, 87\text{JPS(A)}805 \rangle$ has been reported. Liquid chromatography on silica effected the purification of tetranitro derivative (**69**) $\langle 87\text{JPS(A)}805 \rangle$ and a variety of dibenzo derivatives (**68**) $\langle 92\text{HCA}729 \rangle$, while gas chromatographic purification on a Carbowax 20M column at ca. 140°C of (*Z*)-(**58**) and several of its cycloadducts has also been achieved $\langle 82\text{MI } 922\text{-}01, 83\text{CB}2136, 83\text{T}1359 \rangle$.

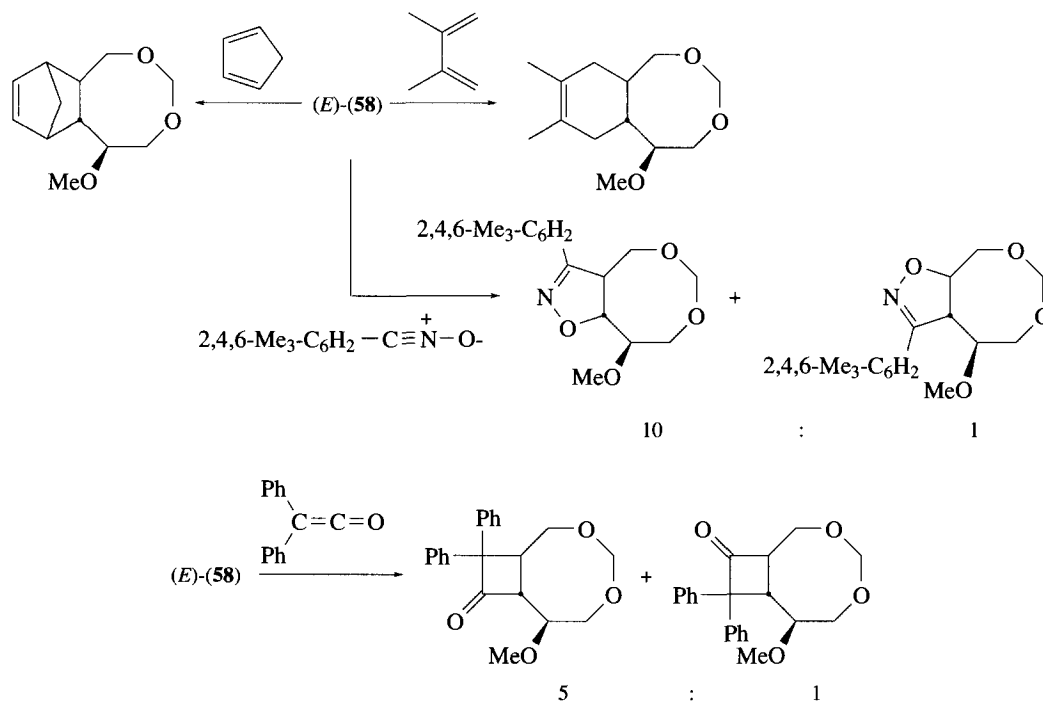
No potentially aromatic (or antiaromatic) derivatives of 1,3-dioxocin (**2**) have been prepared. As discussed above, the potential aromatic stabilization of the fully conjugated compound has been addressed theoretically $\langle 91\text{RRC}333 \rangle$. The ideal gas thermodynamic properties of 1,3-dioxocane,

including heat capacities and formation parameters, were calculated using the rigid-rotor harmonic oscillator approximation <92MI 922-02>.

Only the conformations of dibenzo[*d,g*] derivatives (**59**), (**60**), and (**68**) have been specifically addressed. Variable temperature IR, Raman, and NMR spectral studies, complemented by molecular mechanics calculations, suggest that these dibenzo derivatives favor a boat–chair conformation, with C_s symmetry; boat and twist–boat conformations were ruled out on the basis of the higher symmetry apparent in the ^1H NMR spectra, while the boat–boat form was considered unreasonable due to high steric energy <89ZOR657, 91ZOB173>. Equilibration with isomeric boat–chair conformations occurs with ΔH_{act} of ca. 50–70 kJ mol^{-1} and ΔS_{act} of ca. 0 eu <91ZOB173>. The dinaphtho derivative (**60**) appears also to favor the boat–chair conformation, but is in equilibrium with an alternate conformation, apparently either the twist–boat or boat, with ΔH_{act} of 41 kJ mol^{-1} and ΔS_{act} of -13 eu <91ZOB173>. Placement of an oxo group at the 12-position of the dibenzo[*d,g*]dioxocin ring changes the situation considerably, with the twist form lower in energy than the boat–chair by ca. 1 kcal mol^{-1} . X-ray structural analysis of (**56**) appears in accord with this; although the bond angle data is somewhat ambiguous, dihedral angles are best accommodated by the twist form <91JST165>.

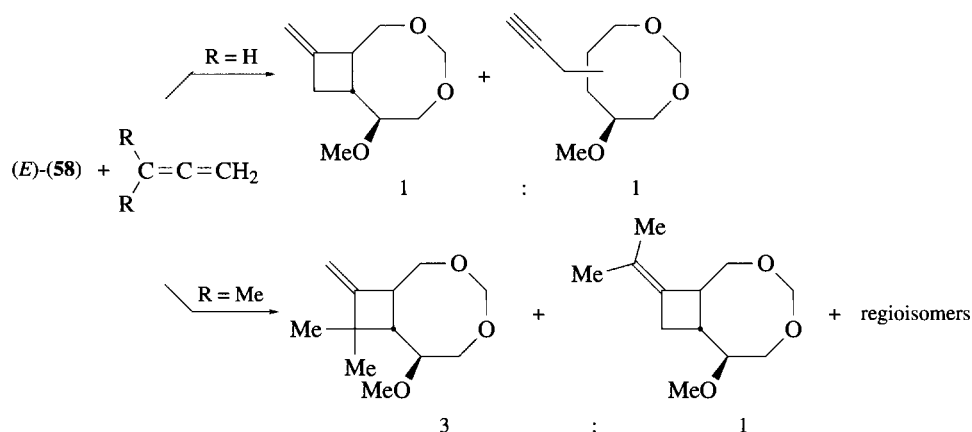
9.22.6.3 Reactivity of Nonconjugated Rings

(*E*)-(**58**) undergoes facile thermal cycloaddition reactions with 1,3-dienes (Scheme 21) <82MI 922-01, 83T1359>, nitrile oxides (Scheme 21) <83T1359>, ketenes (Scheme 21) <83T1359>, and allenes (Scheme 22) <83CB2136>, with the latter showing competitive ene reactions. For each type of reaction, the dioxocin is considerably more reactive than (*E*)-cyclooctene, with rate enhancements ranging from $>20:1$ (for the $[2+2]$ cycloaddition of diphenylketene) to $>1000:1$ (for the $[4+2]$ cycloaddition of 2,3-dimethyl-1,3-butadiene). Stereochemical outcomes are also altered in some cases from those for the cyclooctene reactions; particularly notable is the loss of *endo* selectivity for the addition of cyclopentadiene (from 1.2:1 for (*E*)-cyclooctene to 0.75:1 for (*E*)-(**58**)) and the enhanced regioselectivity of the 1,3-dipolar cycloaddition of mesityl nitrile oxide (from 3:1 for (*E*)-cyclooctene to 10:1 for (*E*)-(**58**)) <83T1359>.



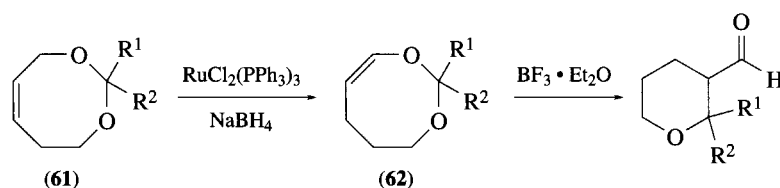
Scheme 21

Treatment of (*E*)-(**58**) with molecular iodine in CCl_4 at room temperature results in the rapid isomerization to the more stable (*Z*)-isomer <82MI 922-01>. A related (*Z*)-5,8-dihydrodioxocin (**61**) is isomerized (in 83% isolated yield) to the corresponding (*Z*)-5,6-dihydro isomer (**62**) upon treat-



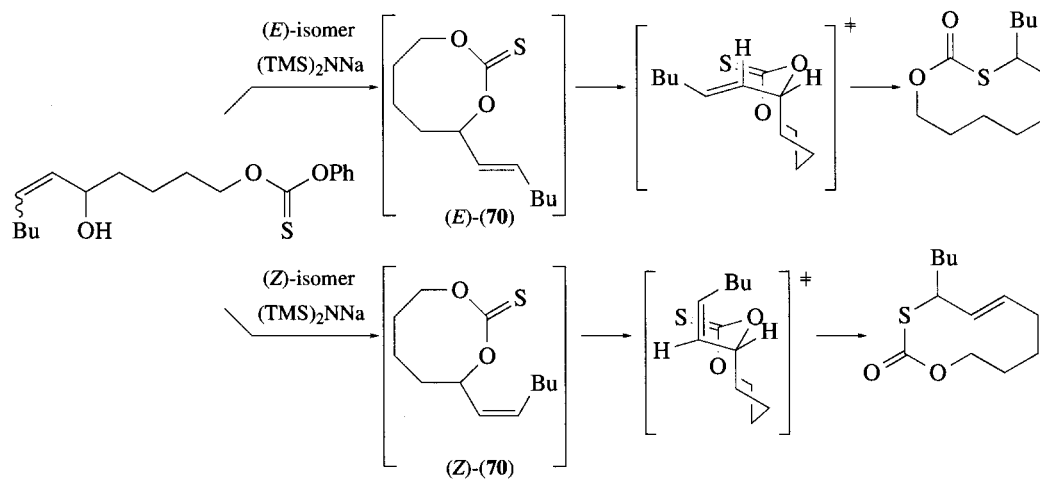
Scheme 22

ment with $\text{RuCl}_2(\text{PPh}_3)_3$ and sodium borohydride in methanol (90TL649). Compound (62) undergoes highly stereoselective rearrangement to a tetrahydropyran derivative upon treatment with BF_3 etherate (Scheme 23) (90TL649).



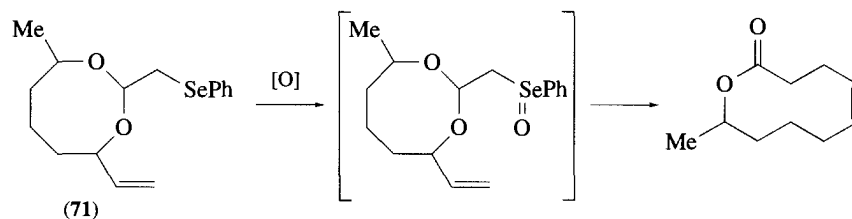
Scheme 23

Presumed intermediates (E)- and (Z)-4-hexenyl-1,3-dioxocan-2-thiones (70), formed through base-mediated cyclization of hydroxy thiocarbonate derivatives, are reported to undergo stereoselective thermal [3,3]-sigmatropic rearrangement (90TL5471, 91TL1203). For the (E)-reactant, molecular mechanics suggests a chair transition state is favored over the boat by ca. 8 kcal mol⁻¹, while for the (Z) isomer, the boat transition state is favored by ca. 10 kcal mol⁻¹ (Scheme 24) (91TL1203).



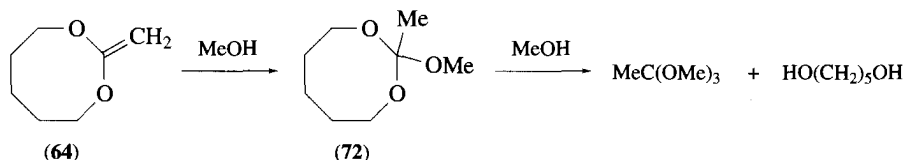
Scheme 24

Similarly, the vinyl 2-phenylseleninyl derivative formed by oxidation of the corresponding seleno compound (**71**) thermally rearranges to afford the γ,δ -unsaturated ten-membered ring lactone (Scheme 25) <83MI 922-05>.



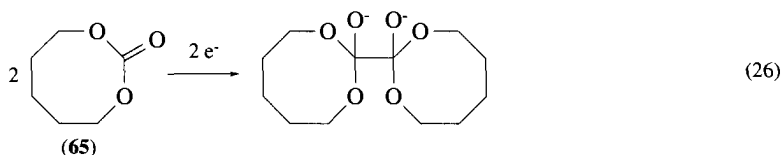
Scheme 25

Methanolysis of 2-methylene derivative (**64**) affords the corresponding ortho ester (**72**); the reaction is considerably slower than for the five-membered ring analogue, and (**72**) is comparatively unstable, decomposing readily to trimethyl orthoacetate and 1,5-pentanediol in the presence of excess methanol (Scheme 26) <86TL1587>.

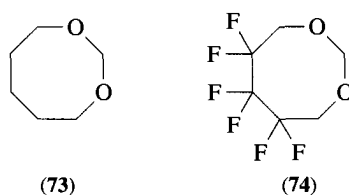


Scheme 26

Chemical (aromatic radical anion) or electrochemical reduction of 1,3-dioxocan-2-one (**65**) is reported to result in dimerization, affording an uncharacterized product of use in the stabilization of polyacetylene as a battery anode material (Equation (26)) <85JAP60126281>.



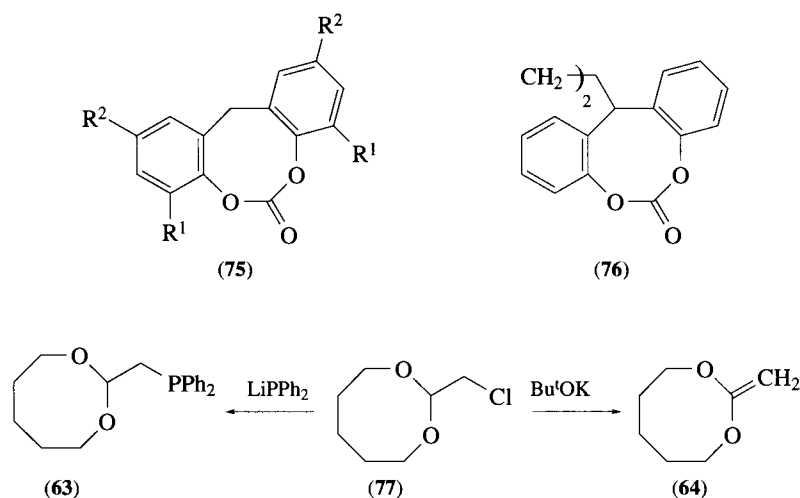
The 1,3-dioxocanes, including the parent 1,3-dioxocane (**73**) <82JAP55916, 82JAP80416, 90MI 922-01> and 5,5,6,6,7,7-hexafluoro-1,3-dioxocane (**74**) <87JPS(A)805, 87USP52503, 91JPS(A)719>, as relatively unstable cyclic acetals, undergo facile ring-opening polymerization or copolymerization, generally under acid catalysis, to afford polymeric materials. Interestingly, (**57**) and (**69**), bearing strongly electron-withdrawing substituents, are resistant to polymerization <87JPS(A)805>.



1,3-Dioxocan-2-ones, such as (**75**; R¹ = cyclohexyl, R² = Me) <91MI 922-02> and bis(dioxocinyl) methane derivative (**76**) <91MI 922-01>, as cyclic carbonates, also undergo ring-opening polymerization or copolymerization, affording polycarbonates. Similarly, the 2-methylene derivative (**64**) undergoes alkene homopolymerization <85JAP60223819, 85JAP60224687> and copolymerization with styrene <89JAP1130976>.

9.22.6.4 Reactivity of Substituents Attached to Ring Carbon Atoms

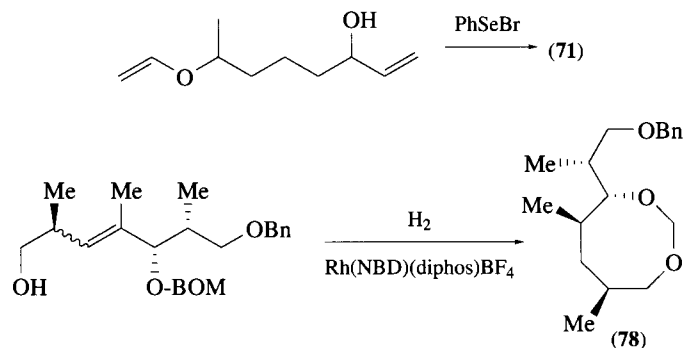
2-Chloromethyl-1,3-dioxocane (**77**) undergoes dehydrochlorination upon treatment with potassium *t*-butoxide, affording the 2-methylene derivative (**64**) (Scheme 27) <85JAP60223819, 85JAP60224687, 86TL1587>. Alternatively, nucleophilic displacement of chloride by diphenylphosphide affords the diphenylphosphinomethyl derivative (**63**) (Scheme 27) <91ZN(B)1519>.



Scheme 27

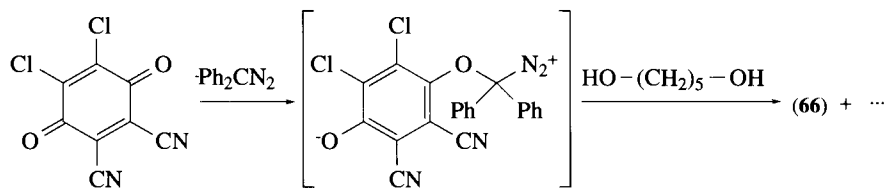
9.22.6.5 Ring Syntheses

Cyclization routes to the 1,3-dioxocin ring system are rather scarce. As shown above, base-mediated *trans*-thiocarbonation apparently gives high yields of 2-thione derivatives (70), which are not observed but rather undergo spontaneous [3,3]-sigmatropic rearrangement (91TL1203). Phenylselenation of a hydroxy vinyl ether affords a 71% yield of the 1,3-dioxocane (71) (83MI 922-05). Presumably unexpectedly, directed hydrogenation of a protected hydroxy alkene is followed by internal ketalization, affording dioxocane (78) in 75% yield.



Scheme 28

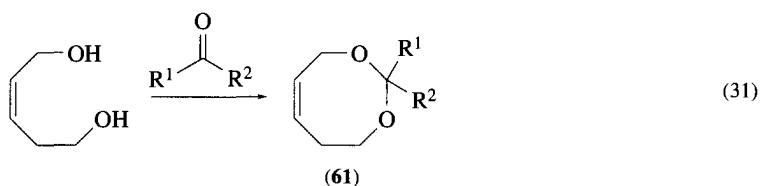
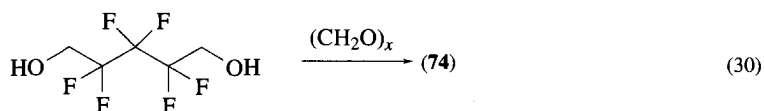
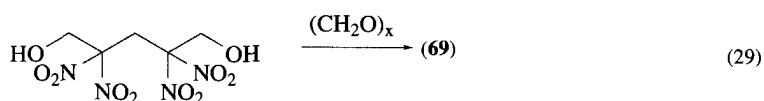
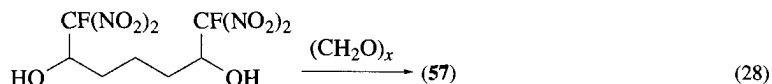
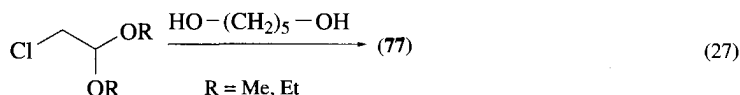
All other reported routes to the 1,3-dioxocin ring system involve condensation of an appropriate one-carbon dielectrophile with 1,5-diols. A low (21%) yield of the 2,2-diphenyl derivative (66) is obtained, together with comparable amounts of a cyclic dimer and an acyclic 2:1 adduct, as well as traces of an apparent cyclic trimer, upon treatment of pentanediol with a reagent prepared *in situ* from diphenyldiazomethane and DDQ (Scheme 29) (84JOC4060).



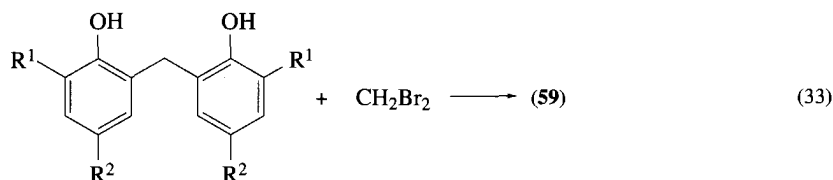
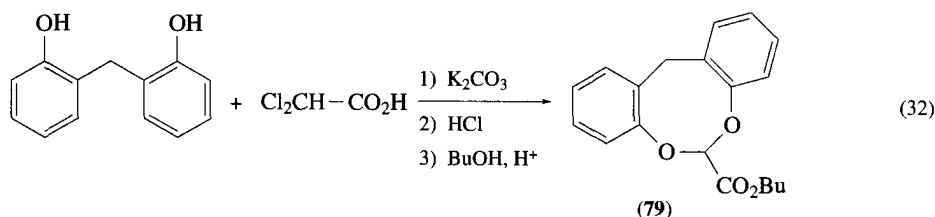
Scheme 29

Trans-ketalization affords a 56% yield of the 2-chloromethyl derivative (77) (Equation (27)) (85JAP60223819, 85JAP60224687, 86TL1587), while treatment of substituted pentanediols with

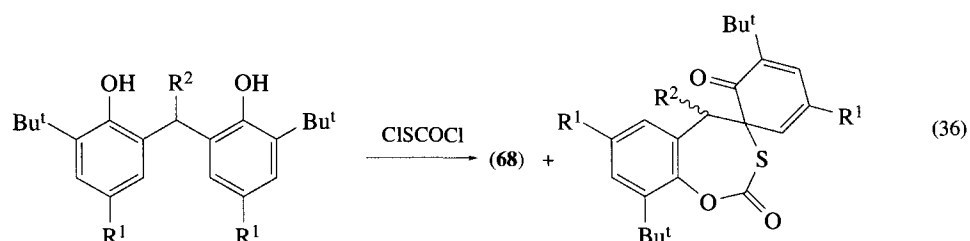
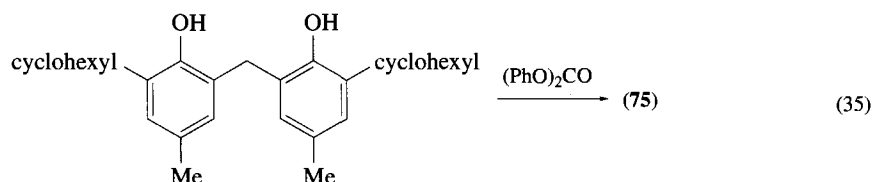
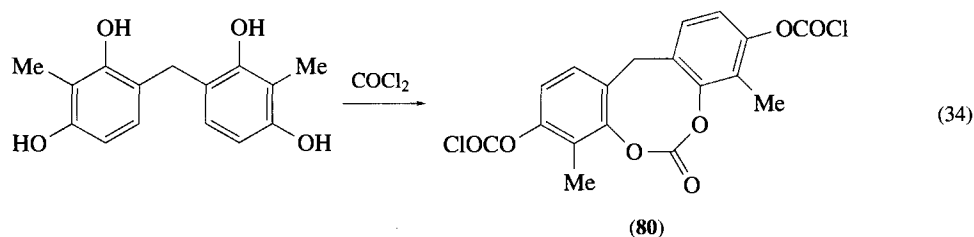
formaldehyde <86USP4593110, 87JPS(A)805, 87USP52503, 91JPS(A)719> affords the corresponding dioxocanes ((**57**), (**69**), (**74**)) in generally good (ca. 80%) yields (Equations (28)–(30)). Aldehydes and acetone react with 2-pentene-1,5-diol, with azeotropic removal of water, to afford the dihydro derivatives (**61**; $R^1 = R^2 = \text{Me}$; $R^1 = \text{H}$, $R^2 = \text{Me}$, Pr^i , Ph) in ca. 70–80% yield (Equation (31)) <90TL649>.



Gem-dihalides also react with 1,5-diols to afford 1,3-dioxocins. Thus far, this approach has been applied only to the synthesis of dibenzo[*d,g*] derivatives such as (**79**) (Equation (32)) and more heavily substituted derivatives, using dichloroacetic acid and its analogues <90USP4976770, 90USP4979978, 91USP4999448>, and (**59**) (Equation (33)) and (**60**), using methylene bromide <91ZOB173>; when reported, yields appear to be moderate to good.

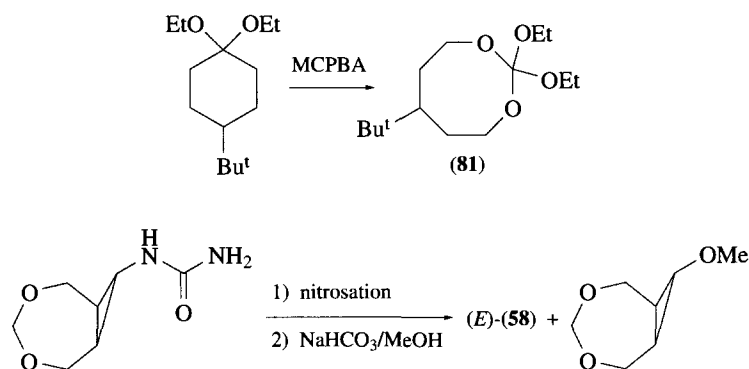


1,3-Dioxocin-2-ones are readily prepared by treatment of 1,5-diols with dielectrophiles such as phosgene (e.g., (**80**)) (Equation (34)) <86EUP186893, 86USP4579896, 88USP4767840> or diphenylcarbonate (**75**; $R^1 = \text{cyclohexyl}$, $R^2 = \text{Me}$) (Equation (35)) <91GEP4015163>. Chlorocarbonylsulfonyl chloride provides low (4–12%) yields of carbonate derivatives (**68**) together with comparable yields of benzoxathiepin derivatives (Equation (36)) <92HCA729>.



9.22.6.6 Ring Synthesis by Transformation of Another Ring

This route to the 1,3-dioxocin ring system is largely unexplored. Double Baeyer–Villiger oxidation of cyclic ketals affords modest yields of the corresponding orthocarbonates, with the cyclohexane derivative affording 2,2-diethoxy-1,3-dioxocane (**81**) in 30% yield <82JA1769> (Scheme 30). Base-induced decomposition/rearrangement of the nitrosoarea derived from a bicyclic dioxepin precursor affords (*E*)-(**58**), which was separated from the bicyclic methoxy product by virtue of its reversible complexation with silver nitrate (Scheme 30) <82MI 922-01>.



Scheme 30

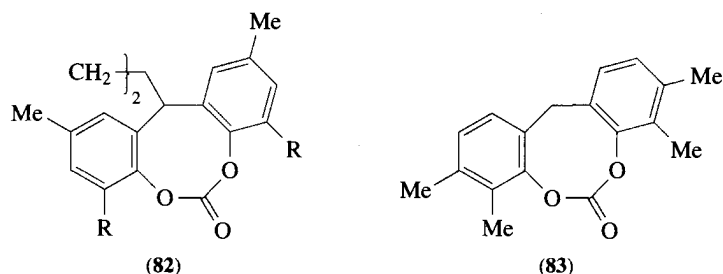
9.22.6.7 Comparison of Synthetic Routes

Unimolecular cyclizations, generally involving intramolecular acetalization reactions, give moderate to good yields of 1,3-dioxocanes despite their requirement for formation of the eight-membered ring. Cyclization of 1,5-diols with one-carbon dielectrophiles and ring expansion reactions provide modest to very good yields, and some generality seems possible. Given the rather sensitive acetal functionality inherent in the 1,3-dioxocins, it is not surprising that its formation is typically effected

late in the synthesis. However, successful synthesis of (58) from an acetal precursor suggests a greater variety of potential precursors may be worthy of consideration in both cyclization and ring transformation approaches.

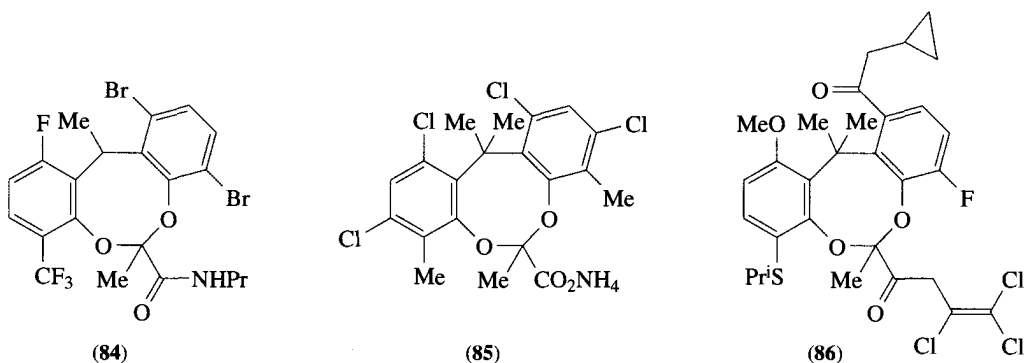
9.22.6.8 Important Compounds and Applications

The homo- and copolymers derived from ring-opening of the cyclic acetal or carbonate functionality of a variety of dioxocin derivatives, including (73)–(75), are of continuing interest <82JAP55916, 82JAP80416, 87USP52503, 90MI 922-01, 91JPS(A)719, 91MI 922-02>. The carbonate-derived materials, in particular, have received attention as cross-linking, drip-proofing and flame-retardant agents for polycarbonates (e.g., (80), (82), R = H, Me) <86EUP186893, 86USP4579896, 88USP4767840>, as heat-resistant polymers for molding materials (e.g., (75; R¹ = cyclohexyl, R² = Me; R¹ = cyclopentyl, Et, R² = H); (83)) <91GEP4015163, 92GEP4109278, 92GEP4109279>, and as high shear sensitivity materials (82, R = H) <91MI 922-01>.



Polymerization of the 2-methylene derivative (64) affords polymers with good heat and alkali resistance <85JAP60223819, 85JAP60224687>, while copolymerization of this compound with styrene affords materials of use in thermal transfer printing applications <89JAP1130976>. Also in the polymer arena, dibenzo derivative (68; R = Me) has been reported to display activity as an antioxidant for polyethylene and Nylon 66, although the apparent requirement for hydrolysis of the carbonate group in (68) (and thus ring cleavage) for formation of the active antioxidant is noted <92MI 922-01>.

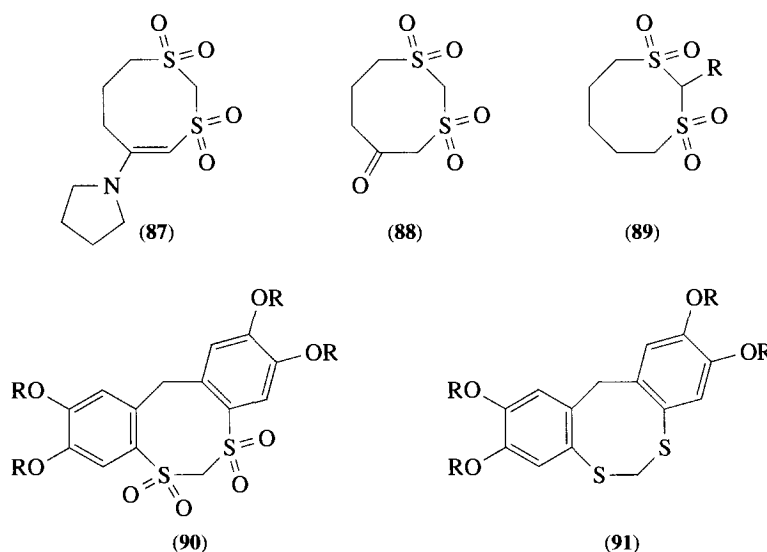
A large number of heavily functionalized dibenzo[*d,g*] derivatives, including (84)–(86) (as representative structures) have received attention as pre- and post-emergence herbicides and plant growth regulators, active against a range of common weeds <90USP4938790, 90USP4976770, 90USP4979978, 91USP4999448>. Miscellaneous other uses noted for 1,3-dioxocin derivatives include insecticidal and acaricidal activity <86EUP196524> and stabilization of polyacetylene as a battery anode material <85JAP60126281>. Compound (78) served as an intermediate in the synthesis of the Prelog–Djerassi lactone, en route to prostaglandins <88TL6901>, while diphenylphosphinomethyl derivative (63) was suggested to be a potential transition metal chelating agent <91ZN(B)1519>.



9.22.7 RINGS WITH TWO SULFURS (4*H*-1,3-DITHIOCINS)

9.22.7.1 Experimental Structural Methods

Structural assignments for the 1,3-dithiocins have been based primarily upon NMR spectral data, supplemented in a few cases with IR and/or mass spectral analysis. Four of the five derivatives examined by ^1H NMR spectroscopy (**87**)–(**91**) are disulfones, with the $\text{SO}_2\text{—CH}_2\text{—SO}_2$ group appearing near 5 ppm ($\langle 83\text{JCS(P1)2735, 89MI 922-01} \rangle$); addition of a phenyl substituent to this carbon, as in 2-phenyl-1,3-dithiocane-1,1,3,3-tetraoxide (**89**; $\text{R} = \text{Ph}$) gives the anticipated shift to still lower field (ca. 6.4 ppm) ($\langle 81\text{BCJ493} \rangle$). The unoxidized derivatives examined, both 12*H*-dibenzo[*d,g*][1,3]dithiocins (**91**; $\text{R} = \text{Me, Et}$), display the $\text{S—CH}_2\text{—S}$ resonance at rather low field (ca. 4–5 ppm) ($\langle 89\text{MI 922-01} \rangle$).



The $\text{S—CH}_2\text{—S}$ resonance in the ^{13}C NMR spectra of (**91**; $\text{R} = \text{Me, Et}$) appears near 47 ppm, while oxidation to the disulfones (**90**) gives the expected shift to lower field (ca. 77 ppm) ($\langle 89\text{MI 922-01} \rangle$). Disulfone (**88**), one of a series of sulfones and sulfonium salts studied by ^{33}S NMR, shows a rather narrow ^{33}S resonance at 298 ppm (vs. CS_2) ($\langle 84\text{OMR250} \rangle$). Compound (**91**; $\text{R} = \text{Me}$), the lone derivative for which mass spectral data have been reported, displays a prominent parent ion upon electron impact analysis; the base peak in the spectrum corresponds to loss of CH_2S (analogous to the loss of CH_2O seen for the 1,3-dioxocanes), proposed to be due to contraction of the eight-membered ring ($\langle 89\text{MI 922-01} \rangle$). IR spectral data available only for (**88**), which shows the expected sulfone ($1335\text{--}1300\text{ cm}^{-1}$ and 1135 cm^{-1}) and ketone (1710 cm^{-1}) absorptions ($\langle 83\text{JCS(P1)1735} \rangle$).

9.22.7.2 Thermodynamic Aspects

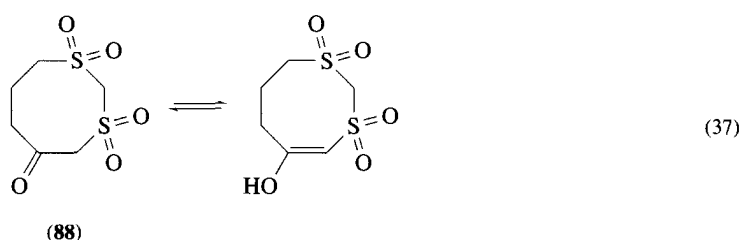
Compounds (**87**)–(**91**) are all quite high-melting solids, as expected given their symmetries and polar functionality. In accord with their anticipated efficient solid-state packing, these compounds appear to be rather insoluble, with DMSO the solvent of choice for NMR studies ($\langle 81\text{BCJ493, 83JCS(P1)2735, 89MI 922-01} \rangle$). The dibenzo derivatives, (**90**), (**91**), crystallized from ethanol, are reported to be relatively insoluble in chloroform, although usable ^1H NMR spectral data were obtained in this solvent ($\langle 89\text{MI 922-01} \rangle$), while the simpler sulfone derivatives may be recrystallized from either ethanol ((**87**), (**89**; $\text{R} = \text{Ph}$)) ($\langle 81\text{BCJ493, 83JCS(P1)1735} \rangle$) or ethyl acetate (**88**) ($\langle 83\text{JCS(P1)1735} \rangle$). No chromatographic analyses or purifications have been reported.

Primary interest in the sulfone derivatives appears to have been in the impact of conformational effects on their acidity ($\langle 62\text{TL515, 81BCJ493, 83MI 922-01} \rangle$). 1,3-Dithiocane tetraoxide (**89**; $\text{R} = \text{H}$) displays a $\text{p}K_a$ of 11 (in H_2O at 25°C), lower than the $\text{p}K_a$'s of the five–seven-membered ring analogues (13.9–11.8). This enhanced acidity has been ascribed to the accessibility of a conformation predicted to give a stabilizing interaction between the anion and the adjacent sulfones in the larger ring ($\langle 62\text{TL515} \rangle$). The decreased acidity of the 2-phenyl derivative (**89**; $\text{R} = \text{Ph}$), with a $\text{p}K_a$ of 12.2, was

ascribed to steric destabilization of the optimal conformation for anion stabilization <83MI 922-01>. This pK_a is dramatically dependent on medium, dropping to 10.7 in the presence of CTAB (cetyltrimethylammonium bromide) micelles <81BCJ493>.

More detailed conformational studies have been reported for the dibenzo derivatives <89MI 922-01>. Sulfone (**90**; R = Me) displays a static "crown" conformation, of C_s symmetry, in $CDCl_3$, while in $DMSO-d_6$, the lowest energy conformations appear to be enantiomeric "twist" forms, interconverting through a 'butterfly-wing' form with an activation enthalpy of 60 kJ mol^{-1} ; the crown conformation appears to be accessed with an activation enthalpy of 74 kJ mol^{-1} . Unoxidized derivative (**91**; R = Me) displays analogous behavior in $DMSO-d_6$, with activation enthalpies of 62 and 67 kJ mol^{-1} .

Keto-enol tautomerism has been noted for keto sulfone derivative (**88**), with ca. 25% enol noted by ^1H NMR in $DMSO-d_6$ (concentration and temperature not reported) (Equation (37)) <83JCS(P1)1735>. The authors note that the corresponding keto thiocin was not reported to enolize, but the conditions for study of the latter compound were not noted, and the tautomerism would of course be expected to be quite dependent on solvent and conditions.



9.22.7.3 Reactivity of Nonconjugated Rings

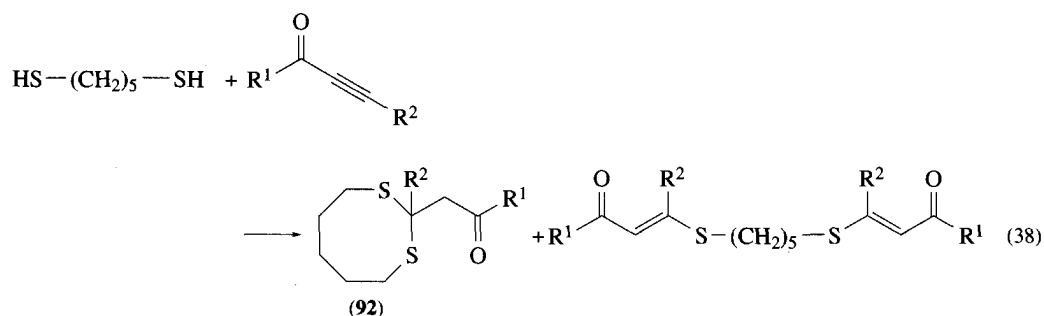
Beyond the deprotonation studies discussed above, only the oxidation of ring sulfurs to the sulfone oxidation state, effected by treatment with either 5% peracetic acid (**91**) <89MI 922-01> or 30% H_2O_2 (**89**; R = Ph) <81BCJ493>, has been reported.

9.22.7.4 Reactivity of Substituents Attached to Ring Carbon Atoms

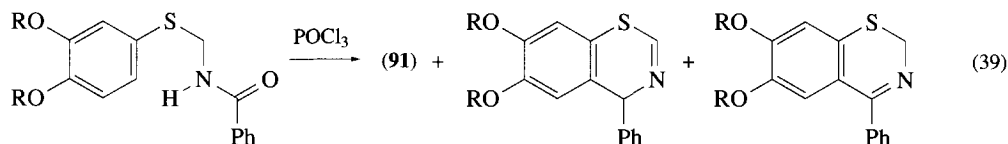
Treatment of enamine (**87**) with 10% HCl for 12 h affords the corresponding ketone (**88**) in unreported yield <83JCS(P1)2735>.

9.22.7.5 Ring Syntheses

Double Michael addition of 1,5-pentanedithiol to acetylenic ketones affords 1,3-dithiocanes (**92**; R = Ph, R^2 = H, Ph; R^1 = 2-thienyl, R^2 = H) in modest (18–23%) yield; the major products (28–42%) of these reactions are the acyclic derivatives resulting from addition of two equivalents of the ketone (Equation (38)) <81MI 922-01>.

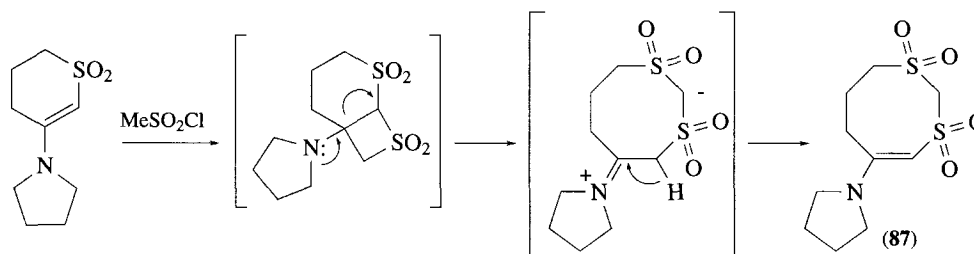


Dibenzo derivatives (**91**) arise in ca. 6% yield through an unknown reaction mechanism upon treatment of phenylthiomethyl amides with POCl_3 ; also formed are the anticipated 1,3-benzothiazines (ca. 45%) as well as 1,5-dithiocin derivatives (1–2%) (Equation (39)) <89MI 922-01>.



9.22.7.6 Ring Synthesis by Transformation of Another Ring

Treatment of a cyclic enaminosulfone with methanesulfonyl chloride in the presence of triethylamine gives a high yield of the ring-expanded enamine (**87**), reportedly through ring-opening of an intermediate bicyclic disulfone (Scheme 31) <83JCS(P1)2735>.



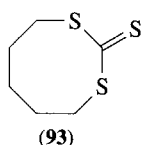
Scheme 31

9.22.7.7 Comparison of Synthetic Routes

The ring expansion route suggests potential applications to more heavily substituted analogues, although the reaction may prove quite sensitive to substituent steric and electronic effects. Cyclization routes are currently inferior, but given the success of several such routes to the corresponding dioxocins, these approaches appear to deserve continued exploration. The double Michael addition, in particular, seems particularly attractive, and may be of use for the preparation of 1,3-dioxocins and 1,3-oxathiocins as well.

9.22.7.8 Important Compounds and Applications

1,3-Dithiocan-2-thione (**93**), in the form of an amine/isocyanate adduct, has been reported as a vulcanization accelerator, inert at normal rubber processing temperatures but active under vulcanization conditions and displaying good scorch resistance and curing time <76GEP2547741>.



9.23

Eight-membered Rings with Two Heteroatoms 1,4

KENNETH M. DOXSEE

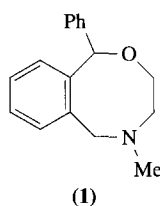
University of Oregon, Eugene, OR, USA

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9.23.1 INTRODUCTION

In contrast to the comparative rarity of eight-membered rings with two heteroatoms in a 1,2- or 1,3-relationship, the 1,4-analogues have been extensively studied. As for the other diheterocins, interest in this class of compounds appears to have been driven in large part by the desire to explore analogues of the often pharmacologically important seven-membered ring heterocycles. The additional level of interest in the 1,4-analogues may stem not only from the relative synthetic accessibility of many of the members of this class of heterocycles, but also from the demonstrated pharmacological activity of a 1,4-diheterocin, the non-narcotic analgesic known as nefopam (1).



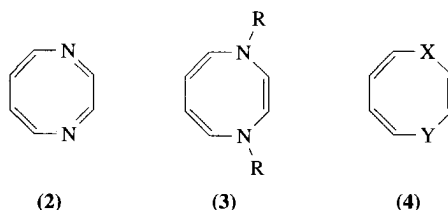
Only those compounds with nitrogen, oxygen, and/or sulfur, as heteroatoms, are covered in this chapter. (Compounds with "unusual" heteroatoms are covered in later chapters in this volume.) Nomenclature for the 1,4-diheterocins follows the standard system, with some permissible variability introduced for the completely reduced compounds. The parent unsaturated systems, many of which have been prepared, generally in substituted form, are 1,4-diazocine, 4*H*-1,4-oxazocine, 4*H*-1,4-thiazocine, 1,4-dioxocin, 1,4-oxathiocin and 1,4-dithiocin. Reduced analogues may be named as di-, tetra-, hexa-, or, for the diaza compounds, octahydro derivatives of these parent compounds. In some cases, particularly the dioxo and dithia derivatives, the fully saturated rings are more often referred to as the corresponding -anes, 1,4-dioxocane and 1,4-dithiocane. Benzo and dibenzo derivatives also follow standard nomenclature. Specific nomenclature is introduced as appropriate within the following individual sections. Compounds in which ring heteroatoms are members of another fused ring and bridged polycyclic compounds are, with few exceptions, not covered in this chapter.

Following a general discussion of theoretical studies of the title heterocycles, each class is discussed separately, with each discussion following the same general format. Within discussions of physical, chemical, and spectral properties, reported compounds have in general been grouped according to the extent of unsaturation of the diheterocin ring, with fully unsaturated ring systems discussed first and fully saturated derivatives last. "Missing" section headings (e.g. "Reactivity of substituents attached to ring heteroatoms") correspond to cases in which no relevant chemistry has been reported. Coverage in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I), in which all eight-membered ring heterocycles with one or more heteroatoms were treated in a single chapter, focused primarily on the *N*-containing compounds, the best-known members of this family of heterocycles, with relatively brief coverage of *O*- and/or *S*-containing analogues. Comprehensive reviews of the preparation, structure, and reaction chemistry of the 1,4-diazocines <89AHC(45)185> and their benzo

analogues <87H(26)2477> and of the 1,4-oxazocines and their benzo analogues <82H(19)709> have appeared, and since these compounds received relatively complete coverage in CHEC-I, the diazocine and oxazocine sections focus primarily on later developments in the chemistry of these derivatives. Coverage of the remaining classes, which received little attention in CHEC-I, is more complete, with appropriate discussion of earlier work as well as later developments, although, given space restrictions, the coverage of earlier studies of these compounds is not completely comprehensive. Finally, comprehensive coverage of the chemistry and pharmacology of nefopam (**1**) is well beyond the scope of this chapter; however, sufficient references to and discussions of the work with nefopam are provided to allow reasonably direct approach to the primary literature dealing with it.

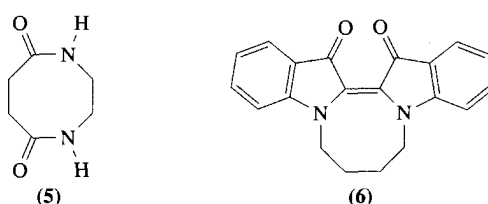
9.23.2 THEORETICAL METHODS

Of the 1,4-diheterocins, 1,4-diazocine is unique in that it has the potential for full π delocalization both as the 8π -electron 1,4-diazocine (**2**) and as the 10π -electron 1,4-dihydro-1,4-diazocine (**3**; $R = H$). Hückel calculations on 1,4-diazocine (**2**) suggested a delocalization energy in excess of that for the 1,3- and 1,5-diazocines <75T295>. In apparent contrast, later PPP-type molecular orbital calculations provided only two solutions, each of C_{2v} symmetry, representing two localized bond structures. From the latter results, it was concluded that 1,4-diazocine (**2**) was antiaromatic, comparable to (planar) cyclooctatetraene and *less* stable than the 1,3- and 1,5-diazocines <83MI 923-01>. More attention has been focused on 1,4-dihydro-1,4-diazocine (**3**) <65RRC1059, 75MI 923-01, 84JOC4475, 91RRC333>, 4*H*-1,4-oxazocine (**4**; $X = O$, $Y = NH$) <84JOC4475>, 1,4-dioxocin (**4**; $X = Y = O$) <65RRC1059, 75MI 923-01, 84JOC4475, 91RRC333>, 1,4-dithiocin (**4**; $X = Y = S$) <65RRC1059>, and their benzo analogues, each representing a potentially aromatic 10π -electron system <78AHC(23)55>.

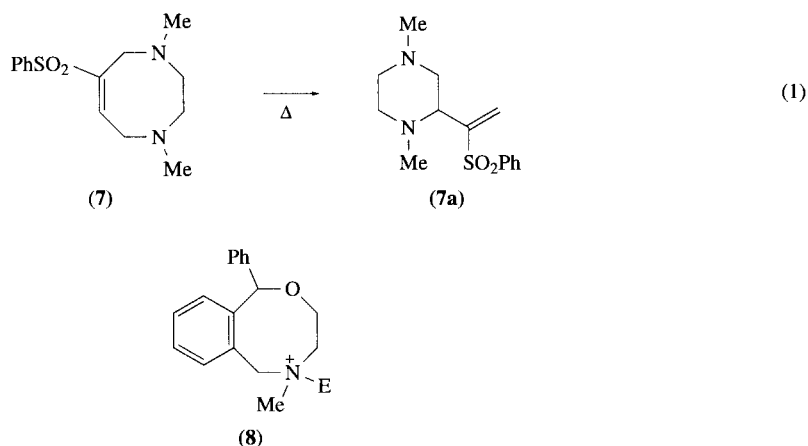


Self-consistent HMO calculations showed significant bond length alteration in 1,4-dihydro-1,4-diazocine and 1,4-dioxocin, indicative of little delocalization <75MI 923-01>. Similarly, semiempirical AM1 calculations, although yielding planar 1,4-dihydro-1,4-diazocine as the lowest energy structure on the singlet potential energy surface, supported a classical structure with no bond delocalization <91RRC333>. 1,4-Dioxocin was also calculated to display localized bonding; in this case, the ground-state conformation was nonplanar. Semiempirical molecular orbital (SINDO1) calculations suggested 1,4-dihydro-1,4-diazocine, 4*H*-1,4-oxazocine, and 1,4-dioxocin to be nearly planar, but again revealed no evidence for bond delocalization <84JOC4475>. Interestingly, this study correctly predicted the conversion of 1,4-dihydro-1,4-diazocine to a nonplanar form upon introduction of an electron-withdrawing substituent. In contrast to cyclooctatetraene dianion, both 1,4-dioxocin and 1,4-dithiocin were shown by Hückel MO calculations to display considerable ring strain, regardless of conformation; nonplanar conformations were predicted for each, with ring strain outweighing any potential stabilization due to delocalization in the planar forms <65RRC1059>.

Semiempirical CNDO-type calculations on diazocinedione (**5**) were carried out in order to assess the nature of its singlet and triplet excited states. These studies, highlighting bond lengthening upon excitation, provide a potential theoretical basis for the transannular ring contractions of such diazocines and their analogues <82ZN(A)232>. MNDO calculations for bridged *cis*-indigo derivative (**6**) suggested that the observed hypsochromic spectral shift in *cis*- vs. *trans*-indigo is not due to the twist of the central alkene in the *cis* form, but rather to enhanced repulsion between the carbonyl oxygens in the charge transfer photoexcited *cis* form <89JCP(91)3431>.



Given the comparatively great attention paid to the potential aromaticity of planar 1,4-diheterocins, surprisingly few molecular mechanics calculations have been reported. MMX calculations demonstrated hexahydro-1,4-diazocine (**7**) (Equation (1)), found to be highly nonplanar, to be less stable than the isomeric piperazine, to which it is thermally converted $\langle 90\text{JOC}4801 \rangle$. The conformational preferences of nefopam hydrochloride, methiodide, and *N*-oxide (**8**; E = H, Me, O⁻) were assayed by MMX methods $\langle 89\text{JCS}(\text{P}2)113, 90\text{CJC}1128, 90\text{MRC}389 \rangle$; these studies are summarized in the discussion of conformations of the 1,4-oxazocines.

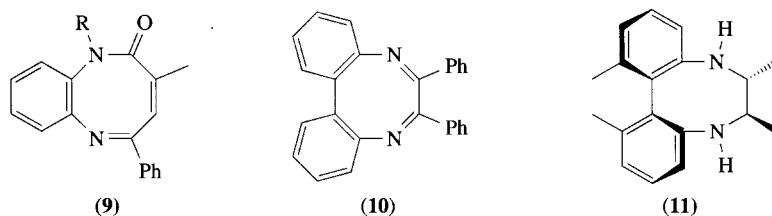


9.23.3 RINGS WITH TWO NITROGENS (1,4-DIAZOCINES)

9.23.3.1 Experimental Structural Methods

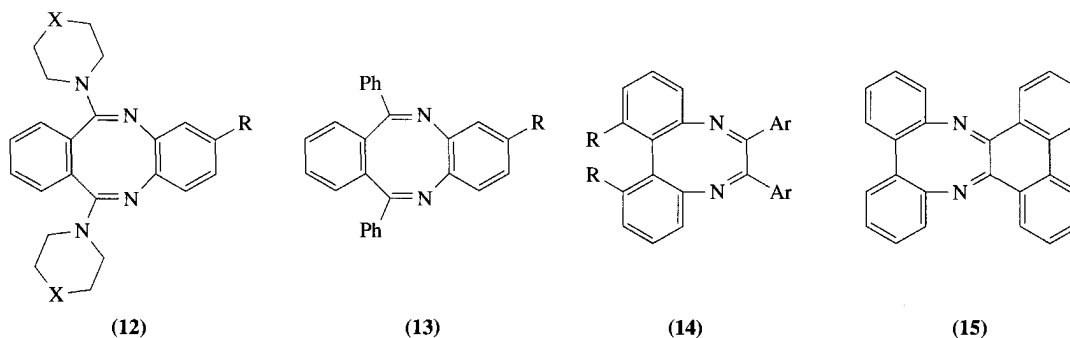
Single-crystal x-ray diffraction analyses have provided unequivocal evidence for the solid-state structures and conformational preferences of several 1,4-diazocines and their benzo and dibenzo analogues, and have also allowed comment on the potential aromaticity of several of these ring systems. The simple unsubstituted 1,4-dihydro-1,4-diazocine (**3**; R = H) $\langle 79\text{AG}(\text{E})964, 79\text{AG}(\text{E})967 \rangle$ and its *N,N'*-bis(trimethylsilyl) derivative (**3**; R = TMS) $\langle 79\text{AG}(\text{E})967 \rangle$ both display a planar diazocine ring, and some π -electron delocalization is suggested by partial bond length equalization. In contrast, monocyclic derivatives bearing electron-withdrawing substituents (**3**; R = MeSO₂, MeO₂C) display markedly nonplanar diazocine rings and completely localized bonding $\langle 79\text{AG}(\text{E})964, 79\text{AG}(\text{E})967 \rangle$.

The single benzodiazocine characterized by x-ray diffraction analysis (**9**; R = Et) displays a tub-like conformation which, although chiral (with both enantiomeric forms found in the crystalline material), does not deviate substantially from mm symmetry $\langle 92\text{AX}(\text{C})897 \rangle$. Observed bond lengths in the solid state do not support delocalization in this derivative beyond that of the amide substructure. 6,7-Diphenyldibenzo[*e,g*][1,4]diazocine (**10**) also provides no evidence for bond delocalization in the solid state, consistent with its nonplanar conformation $\langle 73\text{JCS}(\text{P}2)1929 \rangle$. Bond lengths and angles are unremarkable in markedly nonplanar 5,6,7,8-tetrahydro compound (**11**) $\langle 84\text{JCS}(\text{P}1)2013 \rangle$.

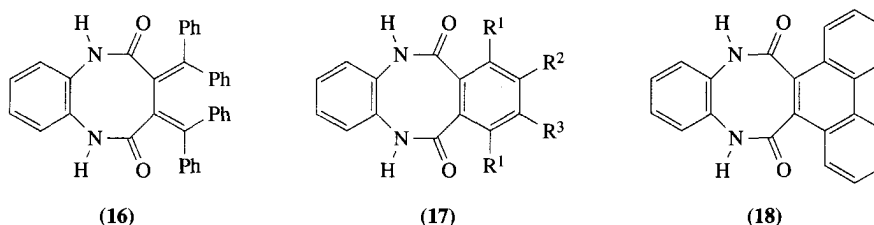


Proton and ¹³C nuclear magnetic resonance (NMR) analyses of a variety of 1,4-diazocine derivative have been reported, in the context of both detailed conformational analysis and assessment of potential aromaticity as well as routine structural characterization. Fully unsaturated 1,4-diazocines appear to be represented only as their dibenzo[*b,f*] and dibenzo[*e,g*] derivatives. A variety of NMR analyses have confirmed or demonstrated the nonplanarity of the diazocine ring in (**12**; X = NMe,

R = H, Me; X = O, R = H) <85H(23)1425>, (**13**; R = Ac, CHO, Prⁱ, PhCH₂) <62JA3591, 76CC276, 77OMR(10)105>, (**14**; Ar = Ph, R = H, Me) <72JCS(P2)2131> and (**15**) <72JCS(P2)2131>.



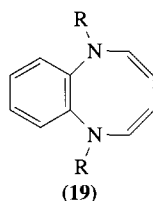
Interestingly, the distortion from planarity is of sufficient magnitude in (**15**) to induce a substantial alteration in chemical shift (shielding) for the protons in the 4- and 5-position from that in phenanthrene itself <72JCS(P2)2131>. Analysis of substituent effects on ¹H and ¹³C chemical shifts in substituted dibenzo[*b,f*] derivatives, such as (**13**), and comparison with acyclic model compounds supports the nonplanarity of these compounds, for which ring inversion is not observable by ¹H NMR analysis even at 150 °C <76CC276>. None of these derivatives bears protons on the diazocine ring, precluding simple assessment of potential aromaticity through observation of ring current effects, although the nonplanarity of these systems certainly argues against any potential delocalization. Oxo derivatives of 1,6-benzo-((**9**; R = Me, Et, PhCH₂) <79JCS(P1)584> and (**16**) <83BCJ3193>) and dibenzo[*b,f*][1,4]diazocines ((**17**; R¹ = R² = R³ = H; R¹ = R³ = H, R² = OMe; R¹ = H, R² = R³ = OMe; R¹ = H, R² = R³ = Br) and (**18**) <69JOC2138, 81JCS(P1)988>), also display NMR properties consistent with distinctly nonplanar structures <73CC571, 74T1903, 79JCS(P1)584>. The nonplanarity of 1*H*-1,6-benzodiazocin-2-ones (**9**; R = Et, PhCH₂) is revealed by the diastereotopicity of the N-CH₂ protons <79JCS(P1)584>, and variable temperature proton NMR analysis reveals no ring conformational changes even at 180 °C for (**17**; R¹ = R² = R³ = H), suggesting an activation barrier of greater than 27 kcal mol⁻¹ for boat–boat interconversion for this derivative <73CC571, 74T1903>.



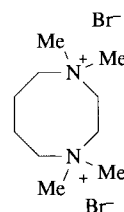
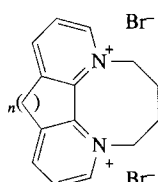
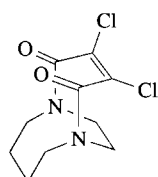
Proton and ¹³C NMR analyses allowed assessment of both conformation and potential aromaticity of 1,4-dihydro-1,4-diazocines as a function of *N*-substituents <79AG(E)964, 79AG(E)967>. Derivatives (**3**; R = H, Me, TMS, CONMe₂) display downfield chemical shifts for the ring protons relative to those predicted for nonplanar, localized bond structures. More dramatically, the ¹³C shifts of these derivatives appear substantially upfield from those in (**3**; R = MeSO₂, CO₂Me). In addition, ³J_{HH} coupling constants for the diene portion of the latter compounds are unequal (³J₅₆ ca. 9 Hz, ³J₆₇ ca. 5–7 Hz) whereas they are nearly equal in the former derivatives (ca. 10.5 Hz), suggesting that the former are planar, with substantially delocalized bonding, while the latter are nonplanar, bond-localized structures. However, 1,6-benzo derivatives (**19**; R = H, Me) <71TL2437> display ¹H NMR properties more consistent with formulation as nonaromatic compounds, although coupling constants in (**19**; R = H) do suggest delocalization.

Obviously there is some ambiguity in these analyses, but nonetheless NMR analysis of potentially aromatic 1,4-dihydro derivatives appears to allow reasonably reliable categorization of derivatives as either planar and aromatic, with delocalized bonding, or nonplanar and nonaromatic, with localized bonding.

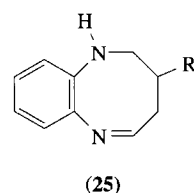
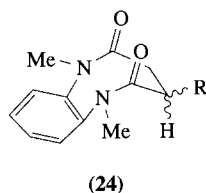
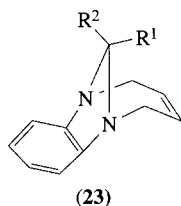
NMR studies of partially- <88JA3979, 90JOC4801, 92JHC1735> to completely reduced <82CPB1579, 88MRC619, 91JOC3063> diazocine derivatives and their benzo <76CJC1135, 84JHC333, 88M233, 92T7467, 90MRC423> and dibenzo <72JCS(P2)1660, 84JCS(P1)2013, 88JOC4745> analogues, in addition to supporting



structural assignments <82CPB1579, 84JCS(P1)2013, 84JHC333, 88JA3979, 90JOC4801, 91JOC3063>, have addressed several conformational issues. Perhaps not surprisingly, bridged compound (20) prefers a conformation providing amide-type delocalization as opposed to the alternative conjugation of the amide carbonyls with the adjacent C=C double bond; use of a chiral shift reagent, which presumably coordinates to the amide carbonyls, resolved this issue <92JHC1735>. The issue of biaryl torsion in polycyclic derivatives (21; $n = 2-4$) and their smaller-ring analogues was assayed by ^1H NMR analysis. Larger torsion angles, leading to decreased delocalization of charge in the biaryl unit, results in greater deshielding of the α -pyridyl proton <88JOC4745>. Octahydro derivative (22) shows axial and equatorial type *N*-methyl groups in its room temperature ^{13}C NMR spectrum; at 90°C , only a single, averaged resonance is observed <88MRC619>.



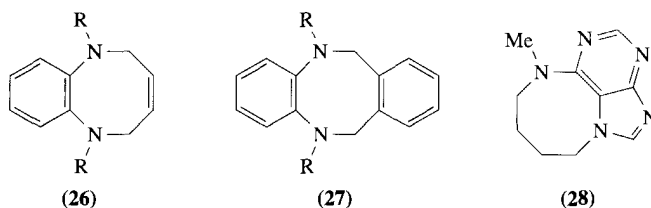
Nuclear Overhauser effect (NOE) and coupling constant analyses demonstrate the preference of bridged benzo derivatives (23; $\text{R}^1 = \text{R}^2 = \text{H, Me}$; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$, $p\text{-Me}_2\text{N-C}_6\text{H}_4$) for the boat-like form shown <90MRC423>. Benzo compounds (24; $\text{R} = \text{H, Me}$) display variable temperature ^1H NMR spectral properties consistent with boat-boat interconversion with an activation barrier of greater than 25 kcal mol^{-1} <76CJC1135>. Doubling of ^1H and ^{13}C resonances for (25; $\text{R} = \text{Me}$) compared to (25; $\text{R} = \text{H}$) led to the conclusion that the former exists in the form of two atropisomers, non-interconverting in solution even at 100°C <92T7467>.



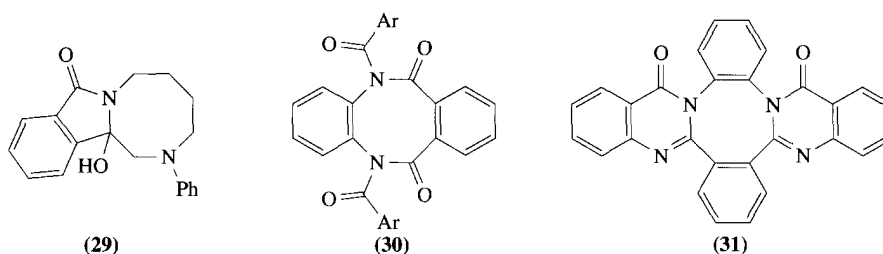
Extensive studies of ^1H and ^{13}C chemical shifts, coupling constants, nuclear Overhauser effects, and dynamic NMR behavior have been reported for tetrahydro-1,6-benzo derivatives (26; $\text{R} = \text{MeSO}_2$, $p\text{-Me-C}_6\text{H}_4\text{SO}_2$) and tetrahydrodibenzo[*b,f*] derivative (27; $\text{R} = p\text{-Me-C}_6\text{H}_4\text{SO}_2$), as well as for the corresponding oxazocines, dioxocins, and oxathiocins <88M233>. Due to the nonplanar conformations of these diheterocins (see below), the ring methylene protons are diastereotopic. Curiously, the aromatic protons *ortho* to the methylene group of the diazocine ring in (27; $\text{R} = p\text{-Me-C}_6\text{H}_4\text{SO}_2$), with this assignment established by NOE analysis, appear rather upfield from the other aromatic protons; the reasons for this shift are not clear. Similar tetrahydrodibenzo[*b,f*] [1,4]diazocines (27; $\text{R} = \text{Me}$, PhCH_2 , Ac) also display rather complex dynamic NMR behavior <73JCS(P1)205, 74T1903, 75CJC3768> consistent with a variety of conformational motions.

One- and two-bond ^{13}C - ^{14}N coupling constants have been reported for (22); the observed values ($^1J_{\text{CN}} = 2.9-3.9 \text{ Hz}$; $^2J_{\text{CN}} \sim 1.5 \text{ Hz}$) are comparable to those seen in simple quaternary ammonium salts <88MRC619>. A single report of ^{15}N NMR analysis of a 1,4-diazocine derivative has appeared;

the diazocine ring nitrogens in (28) appear at ca. 232 and 294 ppm downfield from nitromethane (<84JHC333>).

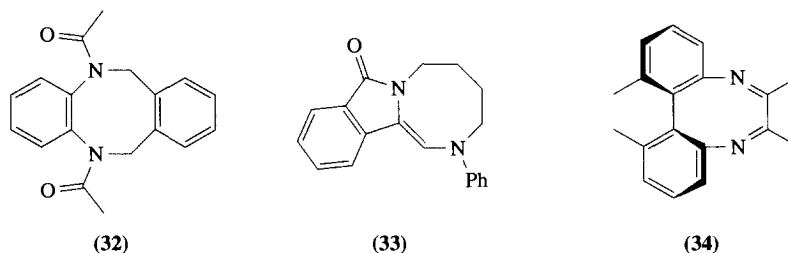


Mass spectral analysis of dibenzo[*b,f*] derivatives, which are unsubstituted on nitrogen, such as (17; $R^1 = R^2 = R^3 = H$; $R^1 = R^3 = H$, $R^2 = OMe$; $R^1 = H$, $R^2 = R^3 = OMe$; $R^1 = H$, $R^2 = R^3 = Br$) and phenanthrene analogue (18) affords M-18 fragments (<81JCS(P1)988>), often as the base peak, consistent with the facile thermal dehydration of these derivatives via transannular ring closure (see below). Seemingly rather closely related benzo derivative (16), however, is not reported to give a simple dehydration fragment (<83BCJ3193>), although one of the two fragments reported in addition to the parent ion (M-Ph₂C₂, M-Ph₂C₂-18) appears to represent dehydration of the other. Loss of the phenyl substituent from benzo derivatives (9; $R = Me, Et, PhCH_2$) represents the major fragmentation for these compounds; in addition, the methyl and ethyl derivatives display M-29 fragments (loss of CHO?) (<79JCS(P1)584>). Not surprisingly, polycyclic derivative (29) displays, in addition to the parent ion, a fragment corresponding to dehydration (M-18) (<82CPB1579>). Bridged derivatives (23; $R^1 = R^2 = H, Me$; $R^1 = H$, $R^2 = Ph, p-Me_2N-C_6H_4$) (<90MRC423>) all give a common fragment ion ($m/z = 157$), corresponding to loss of the bridging group and one hydrogen. Interestingly, the same ion features prominently in the mass spectra of simpler benzodiazocine derivatives (25; $R = H, Me$) (<92T7467>). Similarly, diacylated derivative (30; $Ar = o-N_3-C_6H_4$) (<92JOC6975>) appears to fragment primarily through loss of the *N*-acyl groups, while the fused-ring derivative (31) derived from it is quite robust, yielding only low mass fragments in addition to the parent ion (<92JOC6975>). Parent ions have also been reported for several additional monocyclic (<88JA3979>), fused-ring (<82CPB1579>), dibenzo[*b,f*]- (<85H(23)1425>), and dibenzo[*e,g*][1,4]diazocines (<84JCS(P1)2013>).



The majority of 1,4-diazocine derivatives for which relevant data have been reported are colorless, with their major absorption bands well into the ultraviolet. This appears to hold true regardless of the extent of unsaturation of the diazocine ring, with fully saturated (29) (<82CPB1579>) displaying an absorption band (λ_{max} 253 nm ($\log \epsilon$ 4.34)) at nearly identical energy to that of (9) (<79JCS(P1)584>) (ca. 258 nm (ca. 4.2)). Purine derivative (28) absorbs at slightly lower energy (285 nm (4.18), pH 7); protonation shifts and intensifies this band (290 nm (4.25), pH 1) (<84JHC333>). The 1,4-dihydro-1,4-diazocines (3) are colorless, regardless of planarity or nonplanarity of the diazocine ring (<79AG(E)964, 79AG(E)967>). Ultraviolet spectral properties of the planar structures are similar to those of the cyclooctatetraene dianion, while those of the nonplanar, nonconjugated derivatives are reminiscent of 1,3,6-cyclooctatriene. Conformational analysis of a series of doubly-bridged bipyridinyl systems, including diazocines (21; $n = 2-4$) was achieved in part through UV/visible spectroscopy, which showed a decrease in both wavelength and intensity as the bipyridinyl unit torsion angle increased (<88JOC4745>). Similarly, ultraviolet spectroscopy assisted in the elucidation of the rather complex conformational equilibria of dibenzo[*b,f*] derivative (32) (<72JCS(P2)1660>). Although reported data are extremely limited, more extended conjugation, as expected, appears to shift absorption maxima to lower energy, so that (33) (<82CPB1579>) (384 nm (4.40)) and (18) (<81JCS(P1)988>) are yellow.

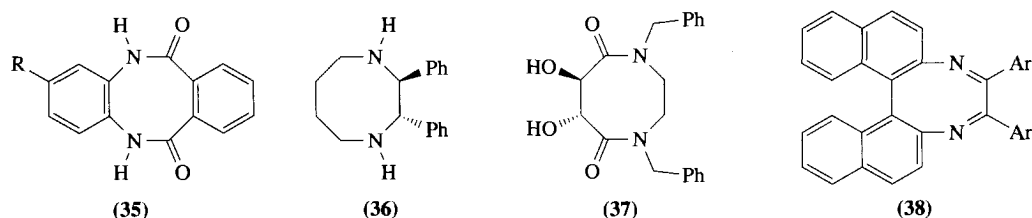
Compound (16) (<83BCJ3193>), bearing analogous functionality to that in (18), displays similar spectral features in the ultraviolet region, but lacks the lower energy transitions responsible for the yellow color of (18). Fully unsaturated diazocine (34) is also reported to be pale yellow, although it



displays no significant absorption above 276 nm (3.50) <84JCS(P1)2013>. Its reduced analogue, (11), displays additional structure in its UV/visible spectrum assigned to benzene ring transitions <84JCS(P1)2013>. Indigo derivative (6) displays an absorption at 610 nm consistent with the presence of a *cis*-type indigo chromophore <89JCP(91)3431>.

The circular dichroism (CD) spectrum of chiral (11) was analyzed and modeled in an attempt to assay the aryl–aryl torsion angle, but the shape of the CD spectrum was found to be virtually independent of torsion angles between 0° and 120° <84JCS(P1)2013>. Protonation of (11), however, not only changes the shape of the CD spectrum, but introduces a change of sign of the spectrum at a critical torsion angle of ca. 90°. Later studies of the twisting power of derivative (11) in biphenyl-type nematic liquid crystals showed this to be a powerful complement to the CD studies, allowing correlation of the absolute configuration of bridged biaryls with the sign of the twisting power <86BCJ1607, 87T1425>. Magnetic circular dichroism studies of 1,4-dihydro derivatives (3; R = H, Me, TMS, MeO₂C) provided complementary data in support of the planarity or nonplanarity of these materials <77MI 923-01, 81JOC3306>.

Often only partial infrared spectral data have been reported for the diazocines, confirming the presence of the lactam functionality in (9) <79JCS(P1)584>, (16) <83BCJ3193>, (29) <82CPB1579>, (33) <82CPB1579>, and (35; R = H, Me, NO₂) <85H(23)1425>, the azido group in (30; Ar = *o*-N₃-C₆H₄) <92JOC6975> and the C=C double bond in (6) <89JCP(91)3431>. More complete infrared data have been reported as part of the routine characterization of a variety of other diazocine derivatives, including saturated (36) <91JOC3063> and (37) <88JA3979>, partially unsaturated (11) <84JCS(P1)2013> and (25) <92T7467>, and fully conjugated (34) <84JCS(P1)2013>, as well as the dioxo derivatives (17) and (18) <81JCS(P1)988>, although no proposed assignments were provided for the observed spectral features.



Several 1,4-diazocines have been prepared in an optically active form and their optical rotations measured, including dione (37), prepared as a chiral auxiliary for asymmetric allylboration <88JA3979>, 6,7-dimethyl dibenzo[*e,g*] derivative (34) and its reduction product (11) <84JCS(P1)2013>, and 6,7-diaryl analogues (14; R = Me, Ar = 2-pyridinyl) and (38; Ar = 2-pyridinyl) <85TL2077>. The dibenzo compounds display quite large specific rotations, of ca. 1400–1600°.

9.23.3.2 Thermodynamic Aspects

For the most part, the 1,4-diazocines are rather high melting, crystalline solids, in accord with the polar and/or *H*-bonding functionalities present as well as the potential for π -stacking interactions in the benzo and dibenzo analogues. As extreme examples of the latter, (18) <81JCS(P1)988> and (31) <92JOC6975> both display melting points in excess of 300°C. Monocyclic diazocines lacking highly polar functionality tend to be considerably lower melting; (3; R = Me) is reported to be a liquid, with a boiling point of 60°C at 1 torr <79AG(E)964, 79AG(E)967>. Several fully unsaturated diazocines display surprisingly low melting points for molecules of their size and apparent symmetry (e.g. (34), m.p. 111.5–112.5°C <84JCS(P1)2013>; (14; R = Me, Ar = 2-pyridinyl), m.p. 80–100°C <85TL2077>); the nonplanarity of these compounds undoubtedly contributes to relatively inefficient solid-state

packing. Even those compounds bearing secondary amine functionalities, such as (**36**) <91JOC3063>, (**11**) <84JCS(P1)2013>, and (**25**; R = H, Me) <92T7467> are rather low melting; apparently *H*-bonding does not substantially stabilize the solid state for these materials. Interestingly, however, the parent 1,4-dihydro-1,4-diazocine (**3**; R = H) is quite high melting (m.p. 196–198°C); unfortunately, although the structure of (**3**; R = H) was determined by single-crystal x-ray diffraction analysis, no discussion of the solid-state packing was presented <79AG(E)964, 79AG(E)967>. Introduction of better *H*-bond acceptor sites, as in the various oxo (lactam) derivatives presented above and below, leads to appreciably higher melting points. As a rather vivid demonstration of a similar effect, (**29**) melts at 207.5–209°C, while its dehydration product, (**33**), from which the capacity for *H*-bonding has been removed, melts at 129–131°C <82CPB1579>. Both the parent 1,4-dihydro derivative (**3**; R = H) <79AG(E)964, 79AG(E)967> and 3-methyl-1,2,3,4-tetrahydro-1,6-benzodiazocine (**25**; R = Me) <92T7467> are reported to sublime readily at 50–60°C and reduced pressure (ca. 0.25–1 torr).

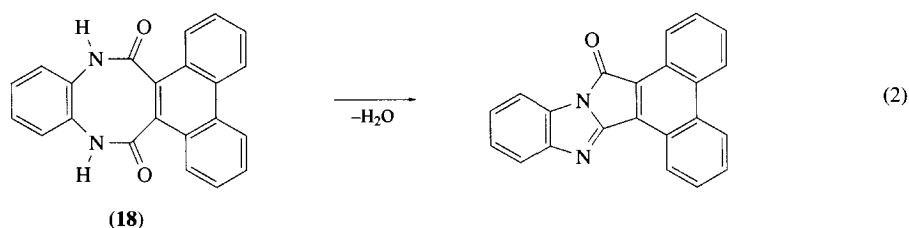
The diazocines display solubility behaviors largely as anticipated for molecules bearing similar arrays of functional groups. Many are soluble in chlorinated hydrocarbons such as CH₂Cl₂ and CHCl₃. Rather hydrophilic derivative (**37**) was reported to have only sparing solubility in CH₂Cl₂ <88JA3979>, but even this compound could be recrystallized from both CHCl₃/Et₂O and aqueous ethanol. Several of the most hydrophobic members of this class of compound to be prepared (**3**; R = TMS) <79AG(E)967>, dibenzo[*e,g*] derivative (**34**) <84JCS(P1)2013>, and bridged derivatives (**23**) <90MRC423> were recrystallized from hydrocarbon solvents <90MRC423>, while many of the more polar derivatives are relatively insoluble in such hydrophobic solvents, which have been used as the poor solvent in recrystallization solvent mixtures <91JOC3063, 92JHC1735>. Modest solubility in alcohols has led to the use of methanol and ethanol as common recrystallization solvents. Several of the more reluctantly soluble derivatives required the use of deuterated DMSO for NMR spectral analysis <81JCS(P1)988, 84JHC333, 88JA3979>. Purine derivative (**28**) is the only water-soluble diazocine to be reported <84JHC333>. A number of diazocines have been successfully purified by chromatography on both alumina <79JCS(P1)584, 85H(23)1425, 91JOC3063, 92T7467> and silica <82CPB1579, 83BCJ193, 92JHC1735, 92JOC6975>, eluting with typical organic solvent mixtures of moderate-to-high polarity.

Two reports have appeared on the electronic structure of fully unsaturated 1,4-diazocine, for which molecular orbital calculations led to only the localized bond structure, of C_{2v} symmetry; planar 1,4-diazocine was concluded to be antiaromatic <75T295, 83MI 923-01>. A considerable amount of theoretical <65RRC1059, 78AHC(23)55, 84JOC4475, 91RRC333> and experimental <79AG(E)964, 79AG(E)967> attention has been paid to 1,4-dihydro-1,4-diazocine and its *N,N'*-disubstituted analogues (as well as to other 1,4-diheterocins, such as 1,4-dioxocin and 1,4-dithiocin; see below). In contrast to the results for several of the positional isomers of these diheterocins, 1,4-dihydro-1,4-diazocine was calculated to be a minimum on the potential surface (whereas other isomers represented saddle points) <91RRC333>. However, bond localization was found, and it was suggested that this compound is actually antiaromatic <91RRC333>. Related studies found similar structures, but concluded that 1,4-dihydro-1,4-diazocine is nonaromatic; interestingly, substituent effects in accord with experimental observations (see below) were revealed by the latter studies <84JOC4475>. Structural and spectroscopic analyses of 1,4-dihydro-1,4-diazocines (**3**; R = H, Me, PhCH₂, TMS, MeSO₂, *p*-MeC₆H₄SO₂, CO₂Me, CONMe₂), as discussed above, as well as the tautomerization issues noted below, led to the conclusion that (**3**; R = H, Me, TMS, CONMe₂) contain planar diazocine rings with delocalized bonding, representing 10 π -electron aromatic systems, while the remaining derivatives are nonplanar and thus nonaromatic <79AG(E)964, 79AG(E)967>. Calculated and experimental magnetic circular dichroism spectra also support these formulations, with (**3**; R = H) calculated to have a structure comparable to the aromatic cyclooctatetraene dianion and (**3**; R = CO₂Me) predicted to be nonplanar <77MI 923-01, 81JOC3306>. Chemical evidence for the aromaticity of (**3**; R = H) is provided by its formation of a charge transfer complex with 1,3,5-trinitrobenzene and its inertness toward *N*-phenyltriazolinedione, a potent dienophile which reacts readily with the nonplanar diazocine derivatives <79AG(E)964, 79AG(E)967>. Benzo and dibenzo analogues of 1,4-dihydro-1,4-diazocine have also been calculated to display appreciable bond-length alteration, consistent with nonaromatic structures <75MI 923-01>.

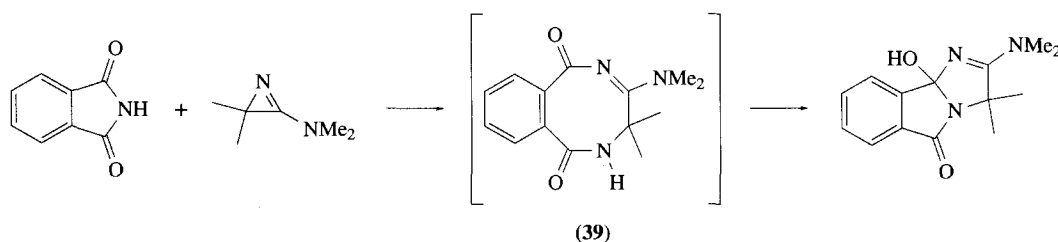
Conformational issues have to some extent been addressed above, given the focus of many of the reported structural, spectroscopic, and theoretical studies on the issues of potential planarity and aromaticity of the 1,4-diazocine and 1,4-dihydro-1,4-diazocine ring. Several interesting additional conformational issues, beyond the realm of aromaticity questions, however, merit discussion. The dibenzo[*e,g*] derivatives, displaying very high barriers to racemization through biaryl bond rotation, have been the subjects of considerable attention. Analysis of the twisting power of (**11**) in nematic liquid crystalline phases was found to allow the assignment of configuration to the biaryl fragment <86BCJ1607, 87T1425>, consistent with x-ray structural analysis of (**11**) <84JCS(P1)2013>; this helical

twist was also demonstrated by an earlier crystal structure of a related derivative (73JCS(P2)1929). These benzo[*e,g*] derivatives display remarkable optical stability, with loss of chirality not clearly documented up to the point of thermal decomposition, at ca. 200–250 °C (63JOC3007, 64JCS2326). Detailed studies of the conformational flexibility of 1,2,5,6-tetrahydro-1,6-benzodiazocine (**26**; R = H) and the dibenzo[*b,f*] analogue (**27**; R = H), as well as several other hetero analogues, have demonstrated the preferred conformation to be the boat form, which represents the average geometry of two twist-boat forms, whose interconversion is rapid even at –120 °C (88M233). Although the energetics of the latter process could therefore not be studied (with an upper bound of $\Delta G_{\text{act}} < 6.9$ kcal mol^{–1}), a boat-inversion process, proceeding through a transition state of unknown structure, was studied as a function of both heteroatoms and solvent. The diazocines display the highest barrier to this inversion, while the analogous dioxocins display appreciably lower barriers. Polar solvents accentuate the barrier, suggesting that the transition state is less polar than the ground-state twist-boat. For the *N,N'*-diacetyl analogue of (**27**), dynamic NMR studies revealed multiple conformational processes. On cooling a solution of (**27**; R = Ac), two of the three possible amide rotamers are frozen out ($\Delta G_{\text{act}} = 16.0$ kcal mol^{–1}). At still lower temperatures, one of these (but not the other) displays a further dynamic process ($\Delta G_{\text{act}} = 13.0$ kcal mol^{–1}) consistent with boat–chair interconversion (89ZC62); the boat is 0.16 kcal mol^{–1} more stable than the chair form at –70 °C. Again, the twist-boat interconversion was not observable even at the lowest temperatures studied. For bridged analogues (**23**), spectral analysis revealed the boat conformation for the diazocine ring to be favored over the alternative chair form (90MRC423). Tetrahydro derivative (**25**; R = Me), interestingly, appears to exist as two non-interconverting atropisomers, in a 3:2 ratio, with no change observed in the ¹H NMR spectrum up to 100 °C (92T7467). 1-Ethyl-1,6-benzodiazocin-2(1*H*)-one (**9**; R = Et) displays a chiral twist-boat-like conformation in the solid state; both enantiomeric forms are present in the crystalline solid (79JCS(P1)584, 92AX(C)897). Dynamic processes of (**9**) in solution appear not to have been examined. The ¹³C NMR spectrum of saturated *bis*(quaternary salt) (**22**) displays axial and equatorial-type *N*-methyl groups in D₂O solution at room temperature; at 90 °C, rapid conformational motions lead to a single, sharp, averaged signal for these methyl groups (88MRC619).

Simple proton-transfer tautomerizations involving the diazocine ring appear not to have been noted. As but one example of an instance where such a tautomerization might have been anticipated, dione (**18**) appears to exist solely as the bis(lactam) (Equation (2)) (81JCS(P1)988). Not surprisingly, 1,4-dihydro-1,4-diazocine does not undergo enamine–imine tautomerization, as expected given the apparent aromaticity of the 1,4-dihydro form (79AG(E)964, 79AG(E)967). Valence tautomerizations of the diazocines, however, are well precedented. For example, sublimation of (**18**) at 200 °C affords a ring-contraction product apparently resulting from dehydration of the initial product of trans-annular ring contraction (81JCS(P1)988). Mass spectral fragmentation patterns suggest similar rearrangement to occur for (**17**) as well (81JCS(P1)988).

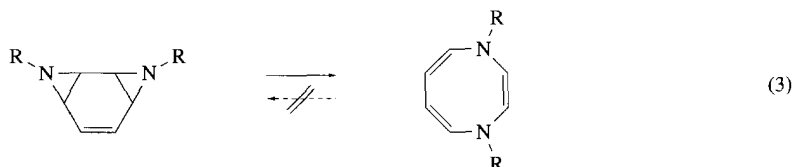


Other diazocinones undergo analogous valence tautomerizations, including (**17**; R¹ = R² = R³ = H) (69JOC2138) and, apparently, (**39**), which was initially reported to be the isolable product of the reaction of phthalimide with an azirene until the ring-contracted structure of the product was determined (Scheme 1) (88C25).



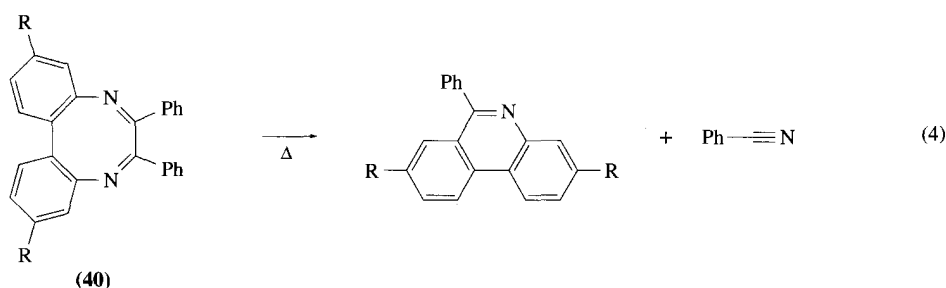
Scheme 1

Similar ring contractions may be at the mechanistic heart of early problems with the attempted preparation of fully unsaturated 1,6-benzo- and dibenzo[*b,f*][1,4]diazocines, which in many cases led instead to valence tautomers. The complete history of these putative diazocines and the controversy surrounding them has been reviewed (89AHC(45)185). In contrast to the dioxocins, whose preparation by valence tautomerization of benzene dioxide precursors is thermally reversible (see below), the thermal rearrangement of diaza analogues to the corresponding 1,4-dihydro-1,4-diazocines appears to be irreversible (Equation (3)) (79AG(E)964, 79AG(E)967).



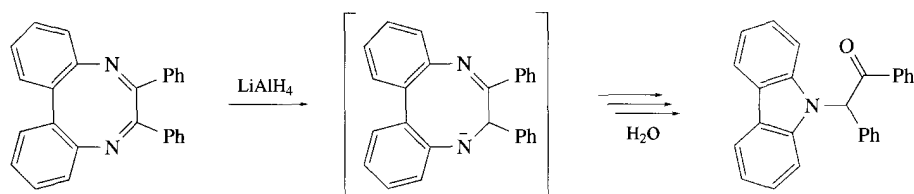
9.23.3.3 Reactivity of Fully Conjugated Rings

Little has been reported regarding the reaction chemistry of either 1,4-diazocine or 1,4-dihydro-1,4-diazocine, both of which should be considered fully conjugated. Reference should be made to CHEC-I (Section 5.19.4.3) for further discussions of the reactivity of both conjugated and partially reduced diazocines. Dibenzo[*e,g*][1,4]diazocines (**40**; R = H, CO₂H, CO₂Me) undergo thermal ring contraction with expulsion of benzonitrile (Equation (4)) (63JOC4290). Thus, attempted racemization of optically active (**40**; R = CO₂Me) led to no loss of optical activity up to its decomposition at 250°C (63JOC3007).



Sulfonamide derivatives of 1,4-dihydro-1,4-diazocine (**3**; R = MeSO₂, *p*-Me-C₆H₄SO₂) are reductively cleaved to the diazocine dianion, which displays the spectroscopic signatures of a planar, delocalized 1,4-diazocine, with charge localized on the nitrogen atoms (79AG(E)967). The dianion reacts readily with methanol to afford the parent 1,4-dihydro-1,4-diazocine (**3**; R = H), and with other electrophiles such as methyl iodide, trimethylsilyl chloride, and methyl chloroformate to form the corresponding 1,4-disubstituted derivatives (79AG(E)967). The parent 1,4-dihydro-1,4-diazocine, in turn, may be deprotonated, although the use of potassium in liquid ammonia to effect this deprotonation may suggest that special care is required (79AG(E)967).

Lithium aluminum hydride reduction of 6,7-diphenyldibenzo[*e,g*][1,4]diazocine (**40**; R = H) affords a ring-contracted product, apparently the result of transannular ring contraction of an intermediate reduction product (Scheme 2) (59JOC306).

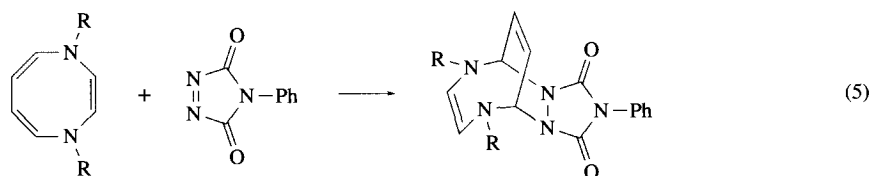


Scheme 2

Catalytic hydrogenation of (*S*)-(+)-dibenzo[*e,g*][1,4]diazocine (**34**) affords the 1,2,3,4-tetrahydro analogue (**11**) as a single stereoisomer (84JCS(P1)2013). Electrochemical oxidation of analogues (**14**;

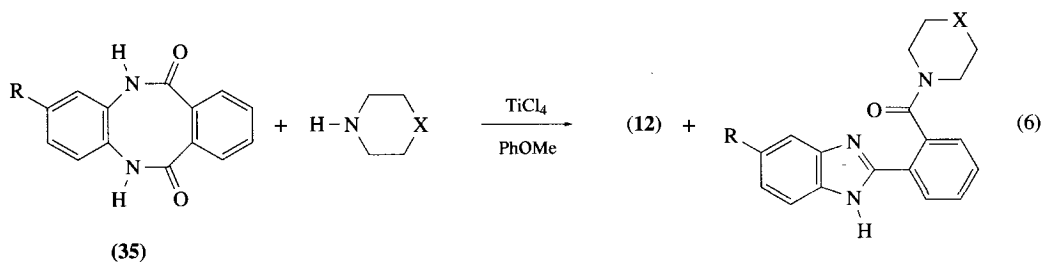
R = H, Ar = Ph, 6-Me-2-pyridinyl; R = Me, Ar = 2-pyridinyl) occurs in two single electron transfer steps, both irreversible on the cyclic voltammetric time scale. The first oxidative process is relatively insensitive to substituent effects, suggesting that the site of oxidation is the 1,4-diazocine ring <85TL2077>.

Nonaromatic 1,4-dihydro-1,4-diazocine derivatives (**3**; R = PhCH₂, CO₂Me) react readily as dienes with *N*-phenyltriazolinedione, affording the corresponding Diels–Alder adducts (Equation (5)) <79AG(E)964, 79AG(E)967>. In contrast, planar derivatives of (**3**) do not react with this dienophile.

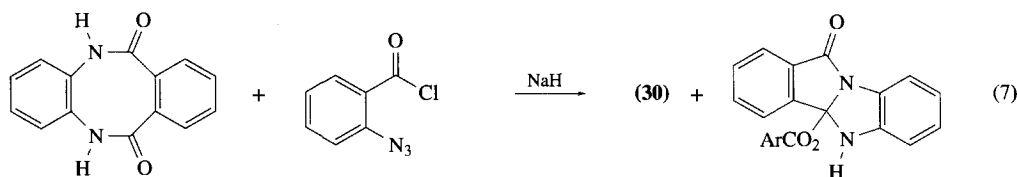


9.23.3.4 Reactivity of Nonconjugated Rings

Diazocines providing a site for transannular nucleophilic attack tend to undergo thermal ring contraction <81JCS(P1)988, 88C25>, as presented in the above discussion of valence tautomerizations. Several additional examples of such transannular attacks appear in the following discussions of reactions of partially saturated diazocines. Treatment of dione (**35**; R = H) with secondary amines and TiCl₄/anisole affords the corresponding diaminodibenzodiazocines (**12**; X = NMe, O, NCO₂Et) (Equation (6)). A ring-contracted benzimidazole product was also formed in the reaction of (**35**; R = Me) with *N*-methylpiperazine, and the benzimidazole was the sole product formed from (**35**; R = NO₂) <85H(23)1425>. Use of POCl₃ in place of the titanium reagent afforded only benzimidazoles.

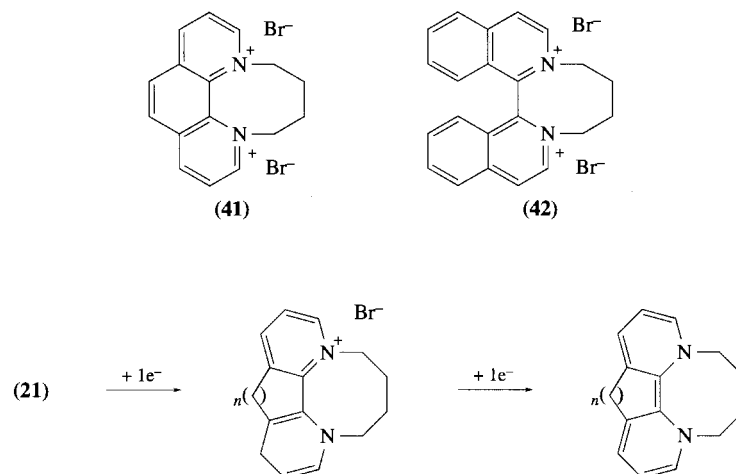


The reaction chemistry of the fully conjugated 1,4-dihydro-1,4-diazocines is discussed above. Transannular ring contraction of dibenzo[*d,f*][1,4]diazocine (**18**), followed by dehydration, occurs upon sublimation at 200°C <81JCS(P1)988>. Analogous thermal reactions, demonstrated earlier for the parent dibenzo[*d,f*][1,4]diazocine <69JOC2138>, are presumably responsible for the appearance of significant M-18 ions upon mass spectral analysis of (**17**) <81JCS(P1)988>. A transannular effect again rears its head in the acylation of dibenzo[*d,f*][1,4]diazocine (**17**; R¹ = R² = R³ = H), which provides comparable yields of the “normal” acylation product (**30**) and that derived from acylation of the transannular valence tautomer (Equation (7)) <92JOC6975>. Reported semiempirical molecular orbital calculations of the singlet and triplet states resulting from photoexcitation of perhydro-1,4-diazocine-5,8-dione are claimed to shed some light on the photochemical ring contractions of such derivatives <82ZN(A)232>.



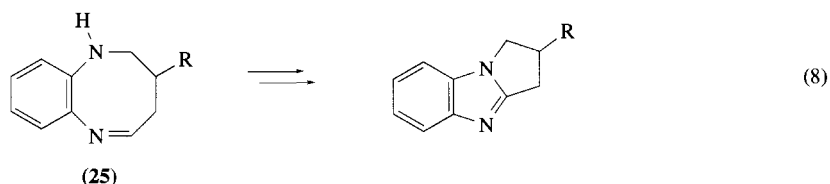
Condensation of 1,2,5,6-tetrahydro-1,6-benzodiazocine (**26**; R = H) with aldehydes and ketones affords bridged aминаl derivatives (**23**; R¹ = R² = H, Me; R¹ = H, R² = Ph, *p*-Me₂N-C₆H₄) in good yield, with the boat conformation and relative positions of bridge substituents indicated above demonstrated by NMR spectral analysis <90MRC423>. Electrochemical reduction of dicationic diazo-

cine derivatives including **(41)** <82IJ117, 83NJC725>, doubly bridged bipyridinyls **(21)** <88JOC4745> and biquinoliny analogues **(42)** <91MI 923-01>, has been extensively studied given the promise of these materials as electron-transfer relays in photocatalytic systems. As the torsion angle between the aryl rings increases, the first and second reduction potentials increase, and the electrochemical reduction steps become less reversible. Both observations are consistent with the anticipated structures of the reduction products, for which co-planarity of the aromatic rings is required for highest stability (Scheme 3) <88JOC4745>.

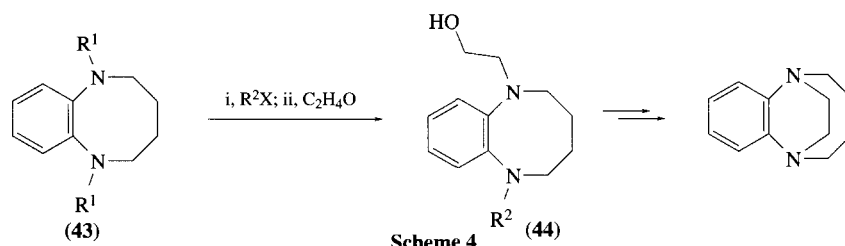


Scheme 3

Simple 1,2,3,4-tetrahydro-1,6-benzodiazocines (**25**; $\text{R} = \text{H}, \text{Me}$) undergo transannular ring contraction (Equation (8)), followed by dehydrogenation, with the latter apparently effected by the rhodium catalyst used for the preparation of **(25)** (see below) <92T7467>. In contrast to the reactions of the analogous dioxocins (see below), 1,3-dipolar cycloaddition of nitrile oxides to **(26**; $\text{R} = \text{MeSO}_2, p\text{-Me-C}_6\text{H}_4\text{SO}_2$) was unsuccessful <88MI 923-01, 88CCC1060>.



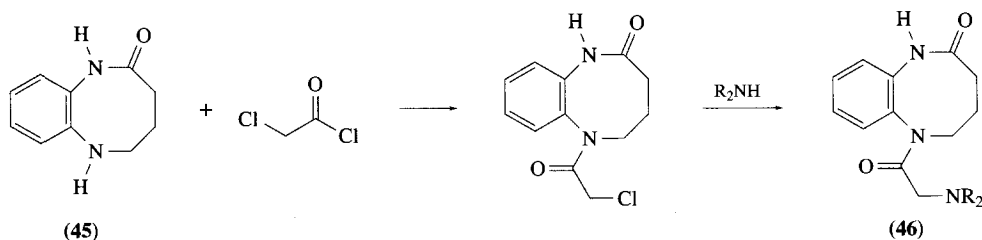
Hexahydrodiazocine (**7**) undergoes ring contraction to the piperazine upon standing in solution at room temperature <90JOC4801>, apparently as the result of transannular conjugate addition. Intermolecular electrophilic reactions of the nitrogens of hexahydrodiazocines also occur readily. Monoacetylation or tosylation of 1,2,3,4,5,6-hexahydro-1,6-benzodiazocine (**43**; $\text{R}^1 = \text{H}$) followed by condensation of the remaining amine-type nitrogen with ethylene oxide, affords hydroxyethyl derivatives (**44**; $\text{R}^2 = \text{Ac}, p\text{-MeC}_6\text{H}_4\text{SO}_2$), which undergo intramolecular alkylation (Scheme 4) <81KGS1538>.



Scheme 4

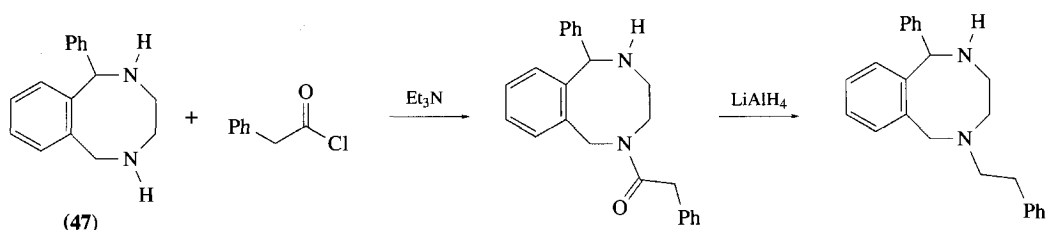
Acylation of the amino group in 2-oxo analogue (**45**) affords the chloroacetyl derivative, which apparently does not undergo intramolecular cyclization, at least under the reported reaction

conditions, but does undergo facile displacement of the side-chain chloride by secondary amines, affording (46; $R_2 = \text{Et}_2$, $(\text{CH}_2)_4$, $(\text{CH}_2)_5$, etc.) (Scheme 5) <87MI 923-01>.



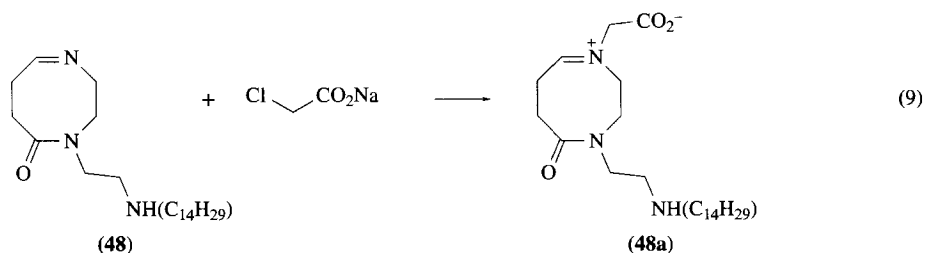
Scheme 5

Similarly, *N*-acylation of 1,2,3,4,5,6-hexahydro-2,5-benzodiazocines such as (47) affords the corresponding amides, which are reduced to the *N*-alkyl derivatives by lithium aluminum hydride (Scheme 6). Several hundred such derivatives were prepared; the following example is representative <83EUP89743, 84JAP(K)5910572, 84JAP(K)5910573>.



Scheme 6

Alkylation of (48) and related compounds affords *N*-carboxymethyl derivatives as inner salts (Equation (9)) <81JAP(K)81154468>. Indigo derivative (6) undergoes photoreduction upon irradiation with visible light in the presence of triethylamine, generating a radical anion (of unknown structure) less stable than that derived from the corresponding $\text{N}-(\text{CH}_2)_3\text{N}$ -bridged derivative <86CE299>.



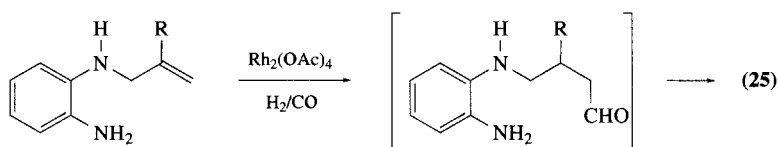
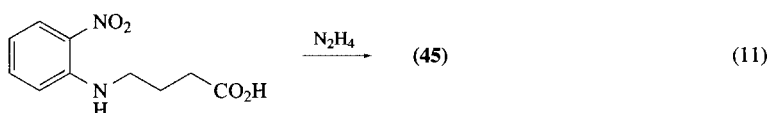
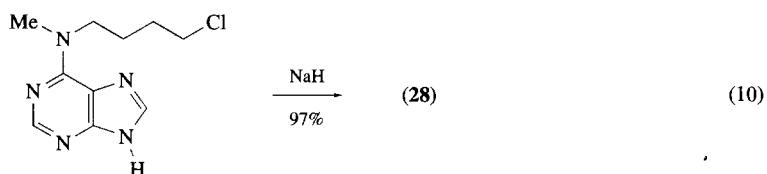
Ring nitrogens of perhydro-1,4-diazocines may also be alkylated <86FRP2567885> and acylated <89JAP(K)01100172>. Acid-catalyzed dehydration of hydroxy compound (29) affords the anticipated enamine (33), apparently in high yield <82CPB1579>.

9.23.3.5 Reactivity of Substituents Attached to Ring Heteroatoms

Reductive cleavage of sulfonamide derivatives of 1,4-dihydro-1,4-diazocine (3; $R = \text{MeSO}_2$, $p\text{-Me-C}_6\text{H}_4\text{SO}_2$) with potassium in liquid ammonia <79AG(E)967> and of 1,2,3,4,5,6-hexahydro-1,6-benzodiazocine (43; $R = p\text{-Me-C}_6\text{H}_4\text{SO}_2$) with sodium/isoamyl alcohol <82CZP195226> has been reported, as has the lithium aluminum hydride reduction of carboxylic amides derived from (47) and its analogues <84JAP(K)5910572, 84JAP(K)5910573, 83EUP89743>. Note, however, that lithium aluminum hydride has been reported to effect the ring contraction of a less-reduced diazocine, as discussed above <59JOC306>.

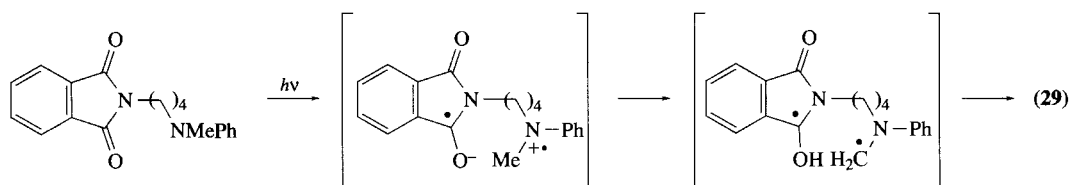
9.23.3.6 Ring Syntheses

Construction of the 1,4-diazocine ring from acyclic precursors has been achieved via intramolecular cyclization as well as by condensation reactions. The latter may in general be presumed to be stepwise reactions, with ring formation the result of intramolecular cyclization as well, but are treated separately for the purposes of this discussion. Intramolecular nucleophilic addition of amines to electrophilic carbon, through alkylation (Equation (10)) <84JHC333>, acylation (Equation (11)) <87MI 923-01>, or imine formation (Scheme 7) <91TL2499, 92T7467> leads to partially reduced diazocines in good to excellent yield.



Scheme 7

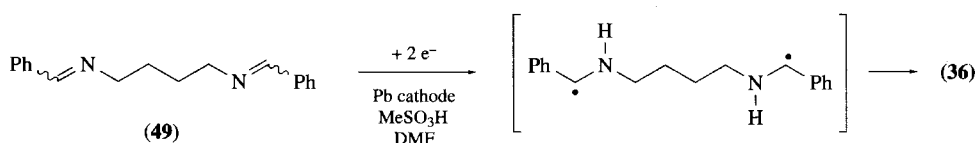
A variety of more unusual C—C bond formation routes has also been reported. Photoinduced remote cyclization of an aminoalkylphthalimide affords a low (6%) yield of perhydrodiazocine (**29**), the formation of which is proposed to occur via intramolecular charge-transfer quenching of the phthalimide triplet state, followed by proton transfer and biradical collapse (Scheme 8) <82CPB1579>.



Scheme 8

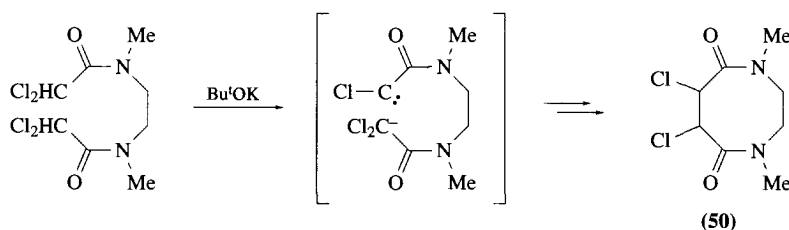
Electrochemical reduction of bis(imine) (**49**) in strongly acidic media affords a 30% yield of *trans*-perhydrodiazocine (**36**), apparently via intramolecular coupling of an intermediate biradical (Scheme 9) <91JOC3063>.

Intramolecular carbene–carbanion coupling affords (**50**) in 34% yield (Scheme 10); additional

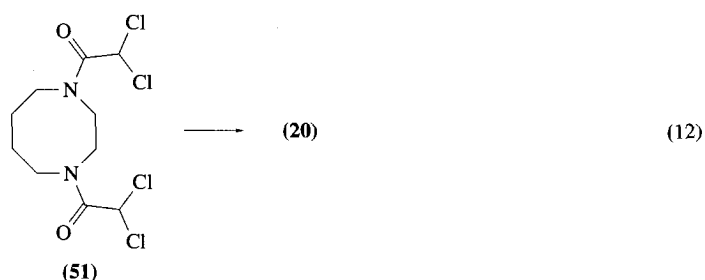


Scheme 9

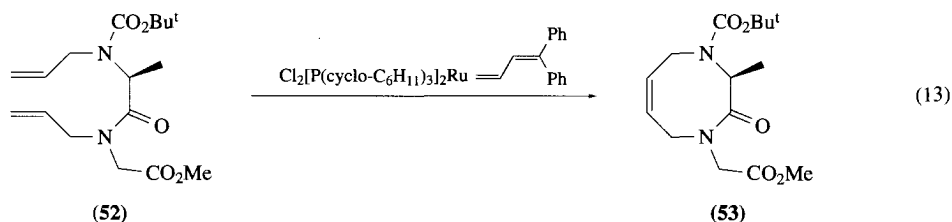
conformational constraint, as in diazocino precursor (**51**), which affords bicyclic (**20**), increases the ring-closure yield to 59% (Equation (12)) <92JHC1735>.



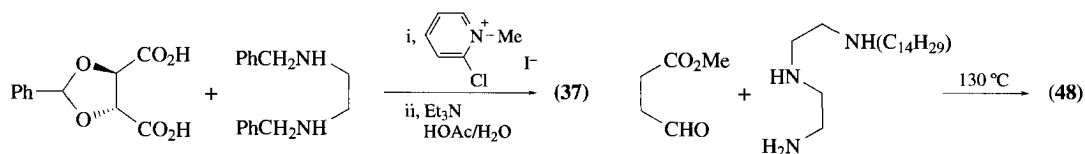
Scheme 10



Ring-closing metathesis of diallyl dipeptide (**52**), using a ruthenium catalyst, affords diazocine (**53**) in 51% yield (Equation (13)) <95JA2108>. Other metathesis-type catalysts were ineffective for closure of eight-membered rings, and the present catalyst fails in the case of acyclic precursors to 1,4-oxazocines or dioxocins.



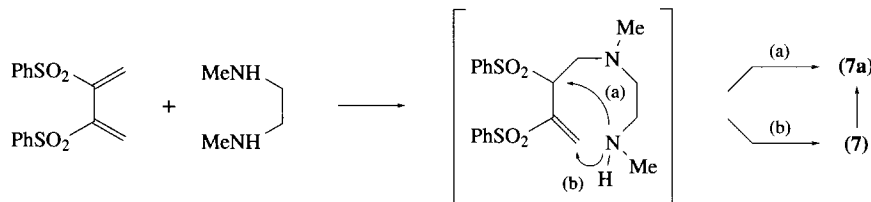
Alkylation of 1,2-diamines by 1,4-dibromobutane affords 1,4-diazocines; this dialkylation route has been successfully applied to acyclic diamines, giving diazocines (**36**) <91JOC3063> and (**22**) <88MRC619>, to indigo, affording the *cis*-indigo derivative (**6**) <86CE299> and to 2,2'-bipyridinyls, giving bridged diquat derivatives (**21**) <88JOC4745>. Yields of the latter, the only cases in which yields were reported, are excellent. Condensation of 1,2-diaminobenzene (*ortho*-phenylenediamine) <69JOC2138> or its substituted derivatives <85H(23)1425> with diethyl phthalate affords 5,12-dihydrodibenzo[*b,f*][1,4]diazocin-6,11-diones (**35**; $\text{R} = \text{H}, \text{Me}, \text{NO}_2$) in modest to good yield. In a variation of this procedure, a protected tartaric acid derivative couples with *N,N'*-dibenzyl-1,2-diaminoethane, affording diazocinedione (**37**) in 43% yield <88JA3979>. Acyclic diamines are also successfully coupled with the methyl ester of succinaldehydic acid, affording (**48**) and its analogues <81JAP(K)81154468> in unspecified yield (Scheme 11).



Scheme 11

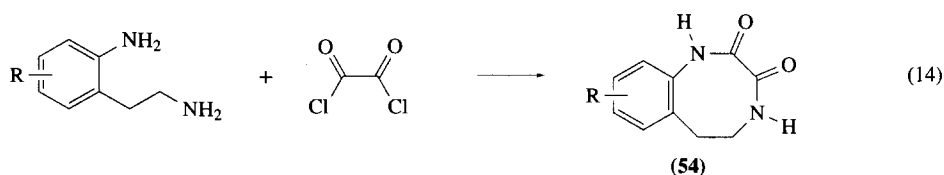
Double conjugate addition of *N,N'*-dimethyl-1,2-diaminoethane with 2,3-bis(benzenesulfonyl)-1,3-butadiene, followed by a facile thermal elimination of PhSO_2H , affords hexahydrodiazocine (**7**), together with the piperazine resulting from alternative nucleophilic displacement of PhSO_2^- from

the product of the first conjugate addition (Scheme 12). The diazocine rearranges thermally to the same piperazine, but kinetic analyses suggest that this rearrangement is not responsible for the piperazine formed in the early stages of the reaction <90JOC4801>.



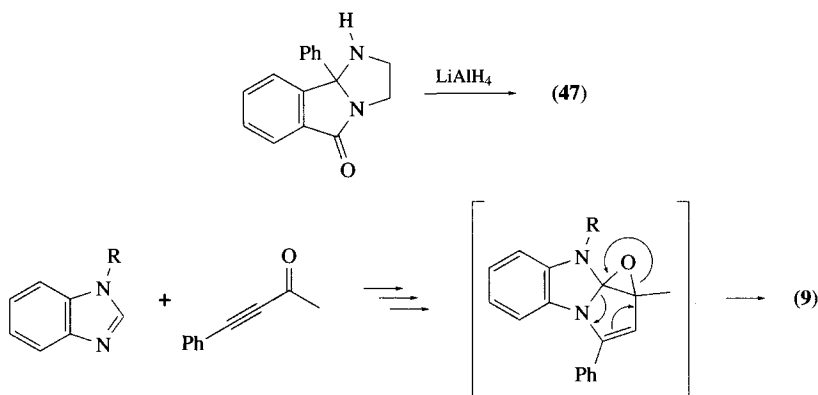
Scheme 12

Condensation of 2,2'-diaminobiphenyls with α -diketones affords dibenzo[*e,g*][1,4]diazocines; this represents the earliest known route to the 1,4-diazocine ring system <1892CB3287>. Applications of this approach have led to tetramethyldiazocine (**34**), prepared in optically active form from the corresponding chiral biphenyl in unreported yield <84JCS(P1)2013> and to pyridinyl derivatives (**14**; R = Me, Ar = 2-pyridinyl) and (**38**; Ar = 2-pyridinyl), again in optically active form but unspecified yield <85TL2077>. Condensation of *o*-aminophenethylamines with oxalyl chloride is reported to afford 1,4-benzodiazocines (**54**; R = H, Br, Cl, alkyl) in good yield (82% for R = H) (Equation (14)) <89EGP274027>; few other routes to this ring system have been reported <87H(26)2477>.



9.23.3.7 Ring Synthesis by Transformation of Another Ring

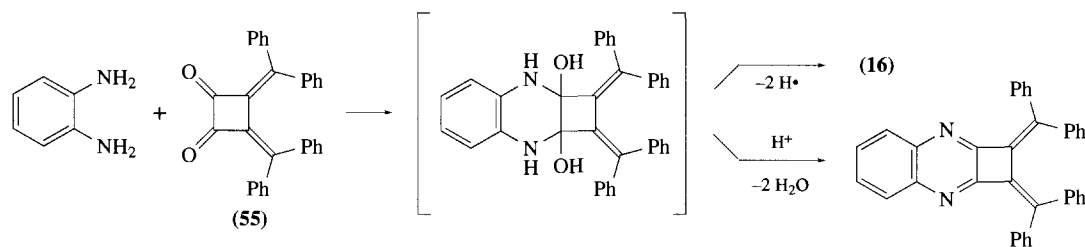
As discussed above, thermal valence tautomerization of benzenediimines affords 1,4-dihydro-1,4-diazocines in high yield <79AG(E)964, 79AG(E)967>. Reductive ring opening of imidazoisindolones affords hexahydro-1,6-benzodiazocines, such as (**47**), in an interesting reversal of the seemingly ubiquitous transannular ring-closure reactions discussed above (Scheme 13) <84JAP(K)5910573>. Ring opening of diazabicyclo[3.3.0]octanes also appears to be responsible for the formation of 1,6-benzodiazocin-2(1*H*)-ones (**9**; R = Me, Et, PhCH₂) in the low-yield ring expansion of benzimidazoles upon treatment with 4-phenyl-3-butyne-2-one (Scheme 13) <79JCS(P1)584>.



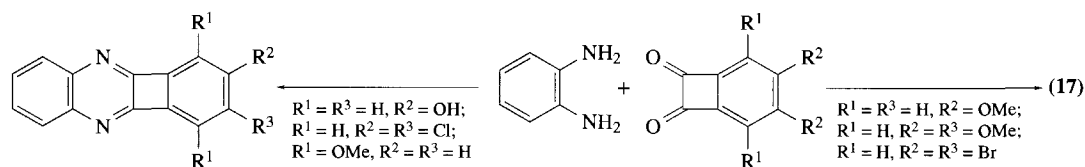
Scheme 13

o-Phenylenediamine reacts with cyclobutanedione (**55**) in the presence of CBrCl₃, as a radical initiator, to afford diazocinedione (**16**) in up to 85% yield, accompanied by a quinoxazine (Scheme

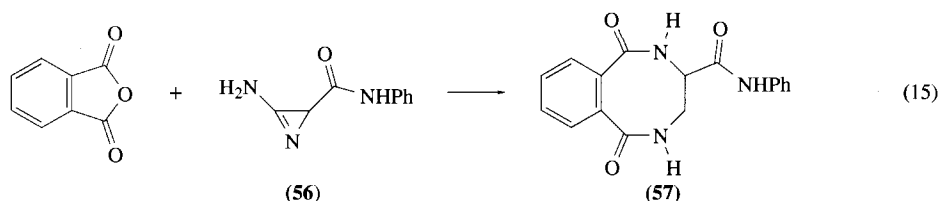
14). The latter appears to be formed as a result of HX generation and is the exclusive product under ionic (protic) conditions <83BCJ3193>.



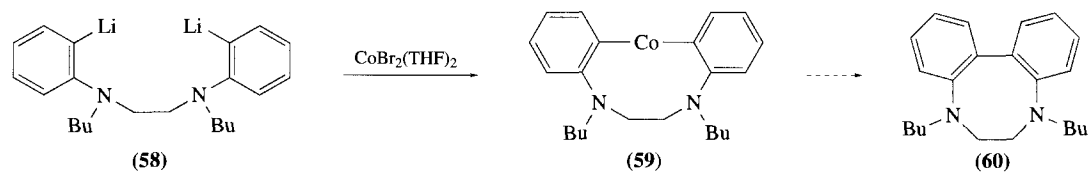
Similarly, condensation of *o*-phenylenediamine with benzocyclobutanediones affords either quinoxazines or diazocinediones (17), with the benzocyclobutanedione substituents exerting rather remarkable control over the course of the condensation (Scheme 15); (18) is prepared analogously <81JCS(P1)988>.



Phthalimide reacts with an aminoazirine derivative to form an imidazoisindolone, presumably via the intermediacy of diazocinedione (39) <88C25>. In a potentially related system, phthalic anhydride reacts with aminoazirine (56) to afford 2,5-benzodiazocine (57) in 70% yield; 2,3-naphthalic anhydride reacts analogously <85KGS848>.



Addition of dilithiate (58) to $\text{CoBr}_2(\text{THF})_2$ affords the sparingly soluble metalacyclic product (59). Mass spectral analysis of (59) shows no parent ion, but rather a significant ion at m/z 322, corresponding to reductive elimination product (60) (Scheme 16) <83ZC443>.



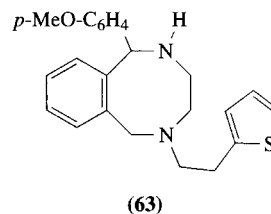
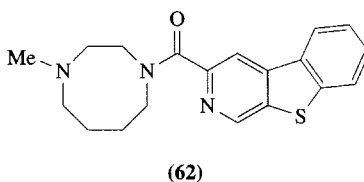
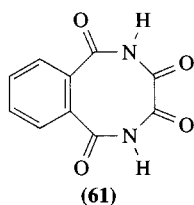
9.23.3.8 Comparison of Synthetic Routes

Most classes of reduced and benzodiazocines are accessible through moderately flexible synthetic routes, although the 1,4-benzodiazocines remain exceedingly scarce and apparently no dibenzo[*b,e*][1,4]diazocines are known. Intramolecular *N*-alkylation or acylation appears to represent a reasonably effective route, from comparatively readily available precursors, of monocyclic- and benzodiazocines in their polyhydro forms, while routes involving C—C bond formation, to

date, would appear to be rather specialized, with perhaps limited generality expected. Diamine alkylation by 1,4-dihalides offers promise, but again will probably be limited to the preparation of polyhydro derivatives. The condensation routes utilizing *o*-phenylenediamine and its substituted derivatives represent an attractive route to 1,6-benzo- and dibenzo[*b,f*][1,4]diazocines, but considerable caution is called for in such approaches, given the already long-standing history of structural misassignments due to the facility of transannular ring contractions of such derivatives. Those routes utilizing cyclobutanediones face additional complications due to their apparently high sensitivity to substituent effects; relatively small changes in reactant structure may lead to quinoxazine rather than diazocine formation. Condensation of 2,2'-diaminobiphenyls with α -diketones provides ready access to substituted dibenzo[*e,g*][1,4]diazocines, and the relative ease of introduction of chirality into these syntheses makes them particularly attractive. The thermal cycloreversion route is effective for the synthesis of 1,4-dihydro-1,4-diazocines, but the relative complexity of the precursors needed to effect these rearrangements will presumably slow the use of this route for their preparation. Similar issues arise in the oxidative cleavage of diazabicyclo[4.2.0]octanes, which has apparently not been further explored since its original report (78T495). Diazabicyclo[3.3.0]octane ring opening, also, may be hampered in this regard, and in some cases, transannular valence tautomerizations may favor the bicyclic system at equilibrium rather than the diazocine. The transition metal-mediated coupling, via reductive elimination, may open access to new diazocine syntheses, but has not yet been carried out preparatively.

9.23.3.9 Important Compounds and Applications

Given their structural analogy to the diazepins and the nonopiate analgesic, benzoxazocine nefopam (see below), considerable attention has been paid to the potential pharmacological activity of the diazocines. Studies have focused on potential activity as amoebicides (85H(23)1425), anxiolytics ((61) (91TH 923-01), (62) (89JAP(K)01100172)), bombesin antagonists (92MIP209626), cardiostonic agents (86FRP2567885), bactericides ((48a) (81JAP(K)81154468)), and analgesics (e.g. (63) (84JAP(K)5910572, 84JAP(K)5910573, 83EUP89743)). The last have also been explored as antitussive, antipyretic, and sedative agents (83EUP89743).



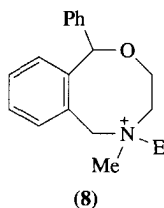
Aminoacetyl derivatives (46), designed as potential anti-implantation birth-control agents, were inactive (87MI 923-01). Interestingly, in addition to their bactericidal activity, (48a) and its analogues are corrosion-inhibiting agents (81JAP(K)81154468). Diquaternary bipyridinyl derivatives, such as (41), have played roles in photochemical water-splitting schemes (82IJ117, 83NJC725), while bridged biphenyl derivatives, in the form of dibenzo[*e,g*][1,4]diazocines (e.g. (11)), have potentially interesting applications in the liquid crystal arena (86BCJ1607, 87T1425). Compound (37) was designed as a chiral auxiliary for the asymmetric allylboration of aldehydes, and its adduct with triallylborane provides excellent enantioselectivity in reactions with achiral aldehydes and high diastereoselectivity in reactions with chiral aldehydes, even in "mismatched" cases (88JA3979). Other applications include the use of 6,11-diphenyldibenzo[*b,f*][1,4]diazocine in electroluminescent devices (91USP5077142), incorporation of related dibenzo derivatives in thermal-transfer recording materials (89GEP(O)3828868), prevention of photofading of inks and fabric and photography dyes with *N*-alkyl perhydrodiazocines (88JAP(K)63205651), incorporation of 1,6-benzodiazocine derivatives in cyan coupling agents for stabilized dye images in color photography (87EUP244697) and the selective chelation of copper(I) ((14) and (38); Ar = 2-pyridinyl, 6-Me-2-pyridinyl) (85TL2077).

9.23.4 RINGS WITH ONE NITROGEN AND ONE OXYGEN (4*H*-1,4-OXAZOCINES)

9.23.4.1 Experimental Structural Methods

The solid-state structure of 3,4,5,6-tetrahydro-5-methyl-1-phenyl-1*H*-2,5-benzoxazocine (nefopam) hydrochloride (8; E = H) was reported for the racemic compound (86AP(319)583, 89JCS(P2)113)

as well as for the optically pure (*S*)-(+) $\langle 89\text{JCS(P2)113} \rangle$ and (*R*)-(-) $\langle 84\text{ACS(B)327} \rangle$ forms (with the latter containing a water of crystallization), as well as for the corresponding racemic methiodide (**8**; E = Me) $\langle 90\text{CJC1128} \rangle$. Bond lengths for (**8**; E = H) were normal, while expanded bond angles at the benzo ring fusion (C(1)—C(11)—C(12) $\sim 126^\circ$; C(6)—C(12)—C(11) $\sim 124^\circ$) were taken to indicate some strain at this ring junction $\langle 89\text{JCS(P2)113} \rangle$. Although several bonds in (**8**; E = Me) were of rather unusual length, the atoms involved were disordered in the solid state, and these metrical parameters are considered to be artifacts of this disorder $\langle 90\text{CJC1128} \rangle$. The primary motivation in these x-ray crystallographic studies was the determination of the preferred conformation of (**8**); these conformational issues are discussed below.



The issue of bond delocalization, irrelevant in the above hexahydro structures, has been addressed by single crystal structural analysis of two *N*-substituted 4*H*-1,4-oxazocines $\langle 84\text{AG(E)309} \rangle$. Oxazocine (**64**; R = *p*-Me-C₆H₄SO₂) displays a markedly nonplanar conformation (see below), with pyramidal nitrogen, while (**64**; R = 3,4,5-(MeO)₃C₆H₂CH₂) is planar, with an average deviation from the ring plane of only 0.021 Å and average intra-ring bond angles of 135.5°. Consistent with these data, and with studies of the diazocine analogues discussed earlier, the planar derivative shows a marked decrease in bond-length alternation within the oxazocine ring, as highlighted by the table of bond lengths (in Å), suggesting significant delocalization in (**64**; R = 3,4,5-(MeO)₃C₆H₂CH₂) (Table 1).

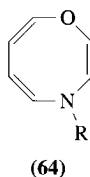


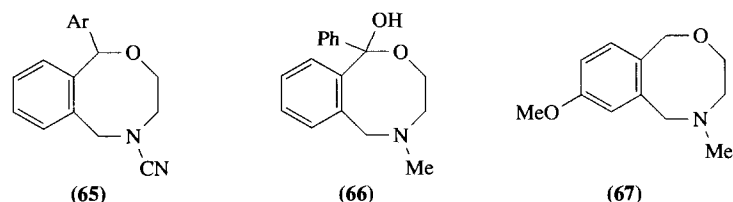
Table 1 Key bond lengths (in Å) in 4*H*-1,4-oxazocines.

Bond	R = ArSO ₂	R = 3,4,5-(MeO) ₃ C ₆ H ₂ CH ₂ ²
O(1)—C(2)	1.362	1.338
C(2)—C(3)	1.293	1.312
C(3)—N(4)	1.421	1.369
N(4)—C(5)	1.412	1.381
C(5)—C(6)	1.328	1.360
C(6)—C(7)	1.527	1.431
C(7)—C(8)	1.296	1.314
C(8)—O(1)	1.385	1.333

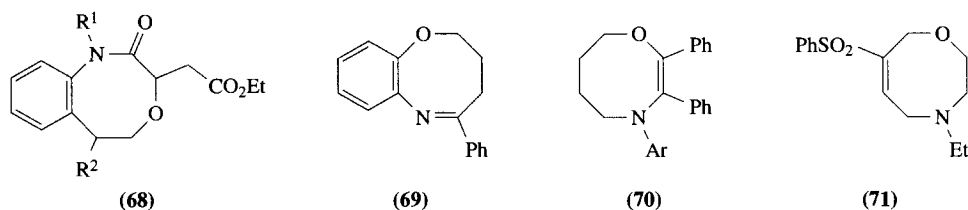
Lattice spacings and relative intensities of the principal peaks in the x-ray powder diffraction pattern of nefopam and several other analgesics have been reported as a potential analytical tool for their assay $\langle 91\text{TAL233} \rangle$.

Nuclear magnetic resonance spectral analyses have been reported for a number of oxazocines and their benzo analogues in a variety of oxidation states. For the fully conjugated 4*H*-1,4-oxazocines (**64**; R = H, CO₂Me, *p*-Me-C₆H₄SO₂, 3,4,5-(MeO)₃C₆H₂CH₂), NMR data appear quite sensitive to ring conformation $\langle 83\text{CB2492, 84AG(E)309} \rangle$. The planar, conjugated structures (R = H, 3,4,5-(MeO)₃C₆H₂CH₂) display shifts in proton resonances from those in the nonplanar compounds (R = CO₂Me, *p*-Me-C₆H₄SO₂) consistent with bond delocalization; especially noteworthy is the downfield shift (by ca. 0.7 ppm) of H-8. Virtually all the ¹³C resonances in these derivatives appear sensitive to ring conformation, differing by as much as ca. 20 ppm in the planar vs. nonplanar forms, although C-3 and C-5 appear relatively insensitive to these effects $\langle 84\text{AG(E)309} \rangle$. Vicinal proton–proton and one-bond proton–carbon coupling constants also track with ring conformation.

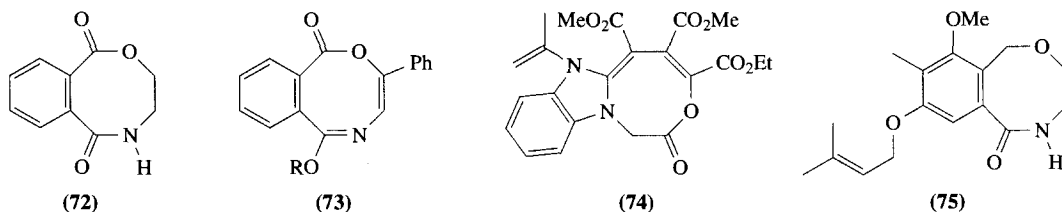
Proton and ^{13}C NMR studies clearly demonstrate the presence of two nefopam hydrochloride conformers in solution $\langle 86\text{JPS}772, 88\text{NJC}953, 90\text{CJC}1128 \rangle$. Detailed analysis of the ^1H and ^{13}C spectra of nefopam *N*-oxide (**8**; $\text{E} = \text{O}$) and the corresponding methiodide and trideuteriomethiodide (**8**; $\text{E} = \text{CH}_3, \text{CD}_3$), aided by DEPT (Distortionless Enhancement by Polarization Transfer) and 2D-NMR (XHCORR $^{13}\text{C}/^1\text{H}$) correlation techniques, allowed the rather complex spin systems and conformational details of these derivatives to be unraveled; shielding and deshielding issues, nuclear Overhauser effects and vicinal coupling constants for the $\text{O}-\text{CH}_2-\text{CH}_2-\text{N}$ protons were of prime importance in these studies $\langle 90\text{MRC}389 \rangle$. Solid-state ^{13}C CP-MAS analyses were also carried out for nefopam hydrochloride $\langle 88\text{NJC}953 \rangle$ and nefopam methiodide $\langle 90\text{CJC}1128 \rangle$ in order to assay solid-state conformations. Interestingly, nefopam analogues bearing *N*-cyano substituents in place of the *N*-methyl group (**65**; $\text{Ar} = \text{Ph}, p\text{-MeO}-\text{C}_6\text{H}_4$) appear to display only single (or rapidly interconverting) conformations; single resonances, falling near 5.8 ppm, are reported for the diagnostic benzhydryl proton in these derivatives $\langle 82\text{AJC}2307 \rangle$. Proton NMR spectral data have also been reported for nefopam degradation product (**66**) $\langle 90\text{MI} 923\text{-}01 \rangle$ and for phenyl-free analogue (**67**), in which the ArCH_2O protons, as expected, are shifted upfield (to ca. 4.7 ppm) $\langle 92\text{CBP}768 \rangle$ from the benzhydryl proton in nefopam.



Various other partially saturated oxazocines have also been examined by ^1H and/or ^{13}C NMR spectroscopy, including 4,1-benzoxazocines (**68**; $\text{R}^1 = \text{Me}, \text{Pr}^i, \text{PhCH}_2, \text{R}^2 = \text{H}, \text{Ph}$) $\langle 86\text{CBP}140 \rangle$, 1,6-benzoxazocine (**69**) $\langle 84\text{JOC}116 \rangle$ and its monocyclic relatives (**70**; $\text{Ar} = \text{Ph}, p\text{-Me}-\text{C}_6\text{H}_4$) $\langle 85\text{BCJ}2399 \rangle$, and several 2,5-benzoxazocines (**67**) $\langle 92\text{CBP}768 \rangle$ and (**71**) $\langle 90\text{JOC}4801 \rangle$ and their oxo (**72**) $\langle 85\text{JOU}1769 \rangle$ and (**73**; $\text{R} = \text{H}, \text{Me}, \text{Et}, \text{Pr}^i$) $\langle 89\text{CPB}1694 \rangle$ derivatives.

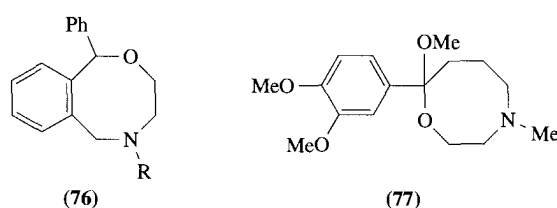


Spectral properties for these structurally diverse oxazocines appear largely as expected for compounds bearing similar arrays of functionality. Observation of a simple AB quartet for the oxazocine ring methylene group in benzimidazole-fused compound (**74**) assisted in ruling out alternative structures for this compound $\langle 92\text{TL}3273 \rangle$, while detailed ^1H and ^{13}C NMR analyses were of central importance in unraveling the structure of porritoxin (**75**), a most unusual fungal toxin isolated from *Alternaria porri* $\langle 92\text{P}2325 \rangle$.



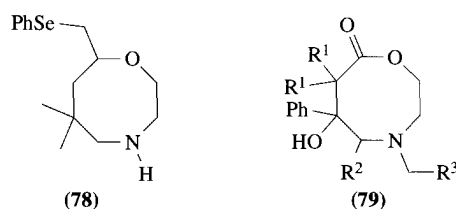
Fully conjugated 4*H*-1,4-oxazocines (**64**; $\text{R} = \text{PhSO}_2, p\text{-Me}-\text{C}_6\text{H}_4\text{SO}_2$) provide parent ions upon mass spectral analysis. In addition to loss of CHO , cleavage of the *N*-sulfonyl group represents the major observed fragmentation, leading to the speculation that the so-derived oxazocine radical cation may display aromatic stabilization $\langle 83\text{CB}2492 \rangle$. In addition to large parent ion peaks, 1*H*-2,5-benzoxazocin-1-ones (**73**; $\text{R} = \text{Me}, \text{Et}, \text{Pr}^i$) all give virtually identical fragmentation patterns, corresponding to loss of the alkoxy group (m/z 248) and formation of *o*-cyanobenzoyl cation (m/z

130) <89CPB1694>. Hydrolysis is suggested to yield (**73**; R = H), the mass spectrum of which displays some features in common with those of the alkoxy analogues <89CPB1694>, but the additional complexity of this spectrum, together with other spectral features (see below) may be in accord with its alternative formulation as a lactam tautomer. Chemical ionization (NH_3) affords the protonated parent ion of nefopam (**1**) as the only abundant ion, while electron impact ionization gives only a trace of the parent ion; the major fragment ion (m/z 179), in addition to the base peak (m/z 58) <86JC379>, corresponds to cleavage of the C=O and C—N bonds of the oxazocine. Analogous fragmentation is observed for *N*-cyano analogues (**65**) <82AJC2307>; this fragment is the base peak for (**65**; Ar = Ph) and is nearly as intense (92%) for the methoxy analogue. Mass spectral analysis of nefopam metabolites such as (**76**; R = H, CH_2OH) <84MI 923-03>, including the use of fast atom bombardment techniques <90MI 923-01>, has also been reported. Saturated oxazocine (**77**) fragments with loss of either the methyl or the methoxy group <85AJC1591>. Parent ions have been reported for a number of other oxazocines, with no fragmentation data provided <84JOC116, 85BCJ2399, 85JOU1769, 85CC363, 87JOC2018, 90JCS(P1)901>.



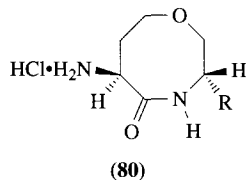
The oxazocines are for the most part colorless, with absorption maxima well into the ultraviolet, whether the ring is completely saturated, as in (**77**) (222 (4.31), 278 (3.51), 283 (3.45) nm) <85AJC1591>, or benzannulated, as in (**69**) (205, 245, 320 nm) <84JOC116>, (**75**) (215 (4.73), 255 (4.07), 292 (3.60) nm) <92P2325>, and (**73**) (ca. 200 (ca. 4.4), ca. 293 (ca. 4.2) nm) <89CPB1694>. Simple tetrahydro derivatives (**70**) display rather low energy absorptions (ca. 355 (ca. 4.0) nm), and might be expected to show some tailing absorption in the visible region; the colors of these derivatives were unfortunately not reported <85BCJ2399>. The fully unsaturated 4*H*-1,4-oxazocines are apparently colorless <83CB2492>, with the exception of the parent compound, (**64**; R = H), which is reported to be pale yellow, with a spectrum resembling that of the dianion of cyclooctatetraene, and the corresponding anion, which is orange–yellow <84AG(E)309>.

Full infrared spectral data have been provided for *N*-sulfonyl 4*H*-1,4-oxazocines (**64**; R = PhSO_2 , *p*-Me- $\text{C}_6\text{H}_4\text{SO}_2$) <83CB2492> and saturated derivative (**78**) <87JOC2018>; the spectra are sufficiently complex to make firm assignment of vibrational modes difficult. Carbonyl stretching modes can be rather diagnostic; e.g. the C-2 carbonyl in fused ring derivative (**74**) is at rather high energy (1773 cm^{-1}), indicative of its enol lactone nature <92TL3273>, while the lactone carbonyl modes in (**79**; R¹ = H, R² = H, Ph, R³ = H, Ph; R¹ = Me, R² = R³ = Ph) are of unexpectedly low energy. The latter has been ascribed to a transannular interaction between the ring nitrogen and the carbonyl group, resulting in a weakening of the carbonyl bond <85CC363, 90JCS(P1)901>, although a similar lactone carbonyl frequency is displayed by dione (**72**) <85JOU1769>, in which the nitrogen might be expected to be more reluctant to engage in such a transannular interaction.



More highly unsaturated derivatives (**73**) display perhaps slightly higher energy lactone modes <89CPB1694>; geometric constraints should preclude transannular interactions in these derivatives. The hydroxy compound (**73**; R = H) does not appear to display a lactam carbonyl band, supporting its existence as the enol tautomer, although the apparent OH stretching band is reported at unusually low energy (2720–2990 cm^{-1}) <89CPB1694>. The typical amide carbonyl stretch displayed by porri-toxin (**75**) assisted in its structural elucidation <92P2325>. The stretching frequencies for the *N*-cyano group in (**65**) <82AJC2307>, the C=C double bond in (**70**) <85BCJ2399> and the imine double bond in (**69**) <84JOC116> all appear normal.

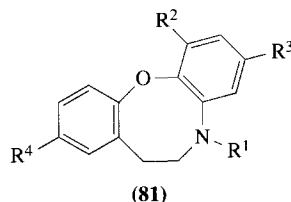
Nefopam and cyclic peptides (**80**; R = Me, Prⁱ, CH₂CHMe₂) have been prepared in optically active form and their optical rotations measured; (*R*)-nefopam hydrochloride (**8**; E = H) displays $[\alpha]_D -119^\circ$ (22°C, c 1, DMSO) <84ACS(B)327>, while the cyclic peptides display rotations ranging from -34.4° to -55.1° (25°C, c 1, MeOH) <87CC474>.



9.23.4.2 Thermodynamic Aspects

As a class, the oxazocines in general appear to be lower-melting than the diazocines. The parent 4*H*-1,4-oxazocine (**64**; R = H) is a low-melting solid (m.p. 32°C) <84AG(E)309>; it and its higher melting *N*-sulfonyl analogues (R = PhSO₂, m.p. 60°C; R = *p*-Me-C₆H₄SO₂, m.p. 112–113°C) <83CB2492> are also reported to deliquesce (and decompose) upon removal from inert atmosphere. Compounds offering no possibilities of intermolecular *H*-bonding tend to be rather low-melting. For example, nefopam (**1**) <82AJC2307>, its simpler analogue (**67**) <92CBP768>, and perhydrooxazocine (**78**) <87JOC2018> are reported to be liquids. However, there are exceptions to this trend, as simple dihydro derivative (**69**) is a crystalline solid (m.p. 96–98°C) <84JOC116>, as is benzoxazocin-1-one (**73**; R = Me) <89CPB1694>. Introduction of more flexible substituents into the latter, however, appears to lower the melting point; (**73**; R = Et, Prⁱ) are both reported to be oils. The corresponding putative hydroxy compound (**73**; R = H) is again a crystalline solid (m.p. 97.5–98.5°C); the similarity of its melting point to that of the methyl ether is perhaps surprising, given that it could well be imagined to participate in intermolecular *H*-bonding in the solid state.

Protonation <84ACS(B)327> and quaternization <90CJC1128> of nefopam, as expected, raise the melting point significantly, consistent with the ionic nature of (**8**; E = H, Me). Microscopic analysis of the melting behavior of nefopam and other drugs has been reported as an analytical technique for their identification <83MI 923-02>. Numerous other solid oxazocine derivatives have been reported as well <82AJC2307, 85AJC1591, 85BCJ2399, 85CC363, 86CBP140, 87CC474, 90JCS(P1)901>. Noteworthy, and reminiscent of similar observations in the diazocine series (see above) is the comparatively low melting point of 2,5-benzoxazocin-1,6-dione (**72**) (m.p. 115–116°C) <85JOU1769>, which, given its symmetry and potential capability for both intermolecular *H*-bonding and aromatic π -stacking, might have been expected to melt much higher. A monumental report of several dozen dibenz-oxazocine derivatives of general structure (**81**; R¹ = H, Me, acyl, etc.; R², R³ = H, X, OMe, alkyl; R⁴ = H, Me, Cl, OH) permits a semisystematic assessment of the effects of substituents on melting behavior. In accord with expectation, replacement of an NH with an NR group lowers the melting point, and introduction of additional flexibility in the NR group (e.g. NMe vs. NPr) results in a further decrease <85JMC225>. Given this, the melting point of potentially rather flexible porritoxin (**75**) (m.p. 115–116°C) is rather respectable, although porritoxin does retain the capacity for *H*-bonding <92P2325>.



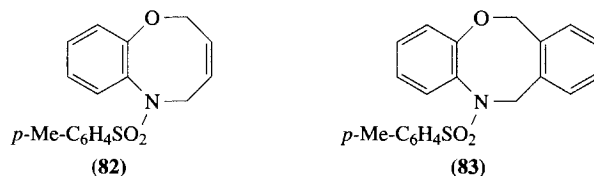
In general, the oxazocines display typical solubility behavior, dissolving readily in chlorinated methanes, with CDCl₃ the near-universal solvent of choice for NMR spectral studies, and, frequently, in methanol or ethanol as well; *H*-bonding may well facilitate dissolution in the latter solvents. Dione (**72**) appears to be rather less soluble, as evidenced by the use of DMSO for ¹³C NMR spectroscopy <85JOU1769>. Lower solubility is apparent in hydrocarbon solvents, although a variety of oxazocines have been successfully recrystallized from low-boiling petroleum ether

<84JOC116, 85AJC1591, 85JMC225>, benzene <90JCS(P1)901>, or hexane <85BCJ2399>. Recrystallization from diethyl <84AG(E)309> and diisopropyl <86CBP140> ethers has also been noted; other crystallization solvents have included ethyl acetate <82AJC2307>, aqueous ethanol <85JMC225>, and CH_2Cl_2 /petroleum ether <83CB2492>. Interestingly, while nefopam hydrochloride (**8**; $\text{E} = \text{H}$) was recrystallized from acetone <84ACS(B)327>, the corresponding methiodide is precipitated from ethanolic solution by the interdiffusion of acetone <90CJC1128>. The hydrochloride is also soluble in aqueous HCl and in CHCl_3 and CH_2Cl_2 <90CJC1128>.

Numerous oxazocines in various oxidation states have been successfully purified by chromatography over either silica <83CB2492, 85JMC225, 85JOU1769, 86CBP140, 87JOC2018, 89CPB1694, 90JCS(P1)901, 92P2325> or alumina <85BCJ2399, 85JMC225, 92CBP768> generally with solvents of only moderate polarity required for elution. The *N*-cyano analogues of nefopam (**65**) required the use of alkaline silica <82AJC2307>, while dihydro-2,6-benzo derivative (**69**) was filtered through magnesium silicate during workup <84JOC116>. Attempted chromatography of oxazocine (**71**) on silica, even under rapid "flash" conditions, resulted in rearrangement <90JOC4801> (see below). Given the regulation of usage of the analgesic nefopam in both human and equestrian sporting events, a number of chromatographic assays for it and its metabolites have been developed; reports include analysis by paired-ion reversed-phase HPLC <88MI 923-02> and gas chromatographic analysis on OV-17 or OV-101 columns <81JC79, 84MI 923-03, 86JC379>.

Semiempirical molecular orbital (SINDO1) calculations for 4*H*-1,4-oxazocine (**64**; $\text{R} = \text{H}$) predicted its planarity, but suggested strong bond length alteration, indicative of little delocalization <84JOC4475>. The aromaticity index for this oxazocine was equivalent to that of the corresponding 1,4-dihydro-1,4-diazocine (**3**; $\text{R} = \text{H}$) <84JOC4475>, despite the suggestion that nitrogen should have a higher tendency toward lone-pair delocalization than oxygen <84AG(E)309>. Crystallographic and NMR spectral analyses demonstrated the planarity and appreciable decrease in bond-length alternation of oxazocine derivative (**64**; $\text{R} = 3,4,5\text{-(MeO)}_3\text{C}_6\text{H}_2\text{CH}_2$) in comparison with the *N*-tosyl derivative (**64**; $\text{R} = p\text{-Me-C}_6\text{H}_4\text{SO}_2$), suggesting significant delocalization in the former <84AG(E)309>. As for the nonplanar 1,4-dihydro-1,4-diazocines, the nonplanar oxazocines react readily with *N*-phenyl- and *N*-methyltriazolinedione (see below) <83CB2492>. Unfortunately, the reactivity (or lack thereof) of the planar, potentially aromatic analogues with these reagents appears not to have been examined; the planar diazocines are inert toward such addition reactions (see above). Many of the 4*H*-1,4-oxazocines are reported to be air- and thermal-sensitive, rapidly yellowing upon air exposure <83CB2492, 84AG(E)309>, but the nature of the apparent decomposition products has not been determined. Molecular mechanics calculations for 2*H*-3,4,5,8-tetrahydro-1,4-oxazocine (**71**), which isomerizes readily to the corresponding morpholine derivative (see below), demonstrated the latter to be ca. 5.9 kcal mol⁻¹ more stable than the oxazocine <90JOC4801>.

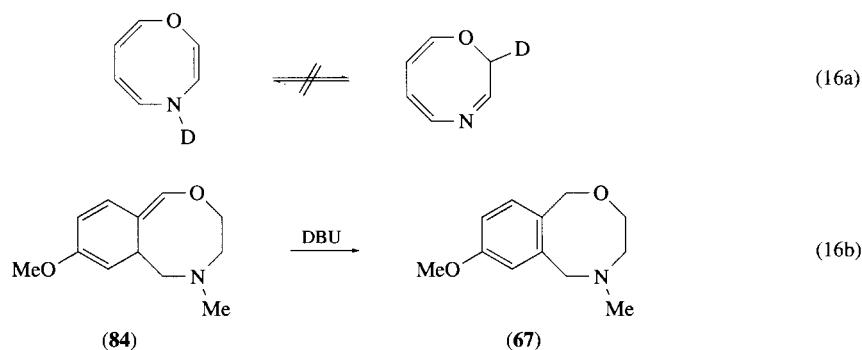
Fully conjugated 4*H*-1,4-oxazocines (**64**; $\text{R} = \text{H}$, Me, $\text{CH}_2\text{CH}_2\text{CN}$, CH_2Ph , 3,4,5-(MeO)₃ $\text{C}_6\text{H}_2\text{CH}_2$) are planar, while derivatives bearing electron-withdrawing substituents on nitrogen ($\text{R} = \text{CO}_2\text{Me}$, CONH_2 , PhSO_2 , $p\text{-Me-C}_6\text{H}_4\text{SO}_2$) adopt nonplanar conformations <83CB2492, 84AG(E)309>. NMR studies of the latter suggest a folded conformation similar to that of the 1,4-dioxocins (see below), although x-ray diffraction analysis of the *N*-tosyl derivative displays a highly irregular conformation displaying considerable torsion about the intra-ring $\text{C}=\text{C}$ double bonds <84AG(E)309>. Dynamic NMR studies of 2*H*-5,6-dihydro-1,6-benzoxazocine (**82**) and the corresponding dibenzoxazocine (**83**) demonstrate the preferred conformation of each to be the boat form, representing the average geometry of two twist-boat forms, the interconversion of which is rapid even at -120°C <88M233>.



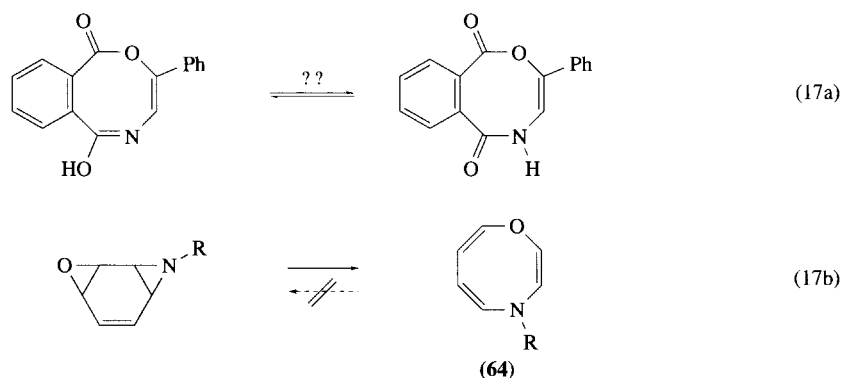
As for the diazocine analogues, the latter conformational process has a sufficiently low activation barrier to preclude its analysis by NMR spectral techniques, but a boat-inversion process, proceeding through a transition state of unknown structure, was studied as a function of both heteroatoms and solvent. Activation energies (ΔG_{act}) for the oxazocines (9.0 and 7.1 kcal mol⁻¹) were intermediate to those of the corresponding diazocines and dioxocins. Again, polar solvents accentuate the barrier, suggesting that the transition state is less polar than the ground-state twist-boat. The conformations of nefopam hydrochloride <84ACS(B)327, 86JPS772, 86AP(319)583, 88NJC953, 89JCS(P2)113> and the

corresponding methiodide $\langle 90CJC1128, 90MRC389 \rangle$ and *N*-oxide $\langle 90MRC389 \rangle$ (**8**; E = H, Me, O) have been discussed in detail. X-ray crystallography displays a single conformation of nefopam hydrochloride in the solid state, with a boat- (flattened-chair) conformation of the oxazocine ring similar to the boat-chair conformation of cyclooctane. However, solution NMR studies in both aqueous acid and in CH_2Cl_2 clearly demonstrate the presence of two conformers, each a boat- (flattened-chair), with the major solution conformer bearing an axial *N*-methyl group and the minor solution conformer bearing an equatorial *N*-methyl, corresponding to the solid-state structure. The phenyl substituent adopts a similar *exo* orientation in both conformers. Energy calculations suggest the two conformers to be of quite similar energy, consistent with the nearly equal amounts (ca. 3 : 2 in CH_2Cl_2 , ca. 1 : 1 in aqueous HCl) of the two conformers present $\langle 89JCS(P2)113 \rangle$. Analogous results were obtained for the *N*-oxide $\langle 90MRC389 \rangle$ and the methiodide $\langle 90CJC1128, 90MRC389 \rangle$; most interestingly, x-ray diffraction analysis of the latter revealed a disordered structure containing both a boat- (flattened-chair) and a twist-boat- (flattened-chair) conformation not represented in solution $\langle 90CJC1128 \rangle$. The implications of the structure of nefopam as a model pharmacophore for serotonin agonists and antagonists has been discussed $\langle 86AP(319)583 \rangle$. A twist-boat-chair conformation for perhydro oxazocine (**77**) was assigned on the basis of its ^{13}C NMR spectral features $\langle 85AJC1591 \rangle$.

Preparation of 4*D*-1,4-oxazocine (**64**; R = D) gave no exchange of deuterium into the ring, suggesting that enamine/imine tautomerization does not occur (Equation (16a)) $\langle 84AG(E)309 \rangle$. Rearrangement of a nitrogen ylide is reported to give as an isolable initial product benzoxazocine tautomer (**84**), which decomposes upon attempted chromatographic purification, but affords the expected product (**67**), the result of tautomerization to regain benzene aromaticity, when treated with diazabicycloundecane (DBU) (Equation (16b)) $\langle 92CBP768 \rangle$.



Benzo derivative (**73**; R = H) is formulated as the enol $\langle 89CPB1694 \rangle$; tautomeric equilibration with the corresponding lactam may account for the somewhat unusual spectral features of this compound in comparison with the enol ether derivatives (Equation (17a)). As for the analogous 1,4-dihydro-1,4-diazocine, formation of (**64**; R = *p*-Me- $\text{C}_6\text{H}_4\text{SO}_2$) via thermal valence tautomerization is irreversible (Equation (17b)) $\langle 83CB2492 \rangle$.



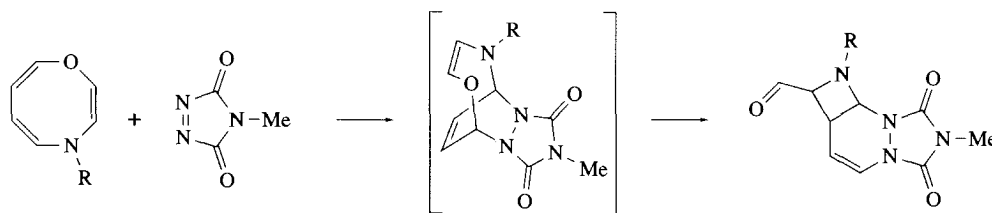
9.23.4.3 Reactivity of Fully Conjugated Rings

Reductive cleavage of the sulfonamide group in (**64**; R = *p*-Me- $\text{C}_6\text{H}_4\text{SO}_2$) with potassium in liquid ammonia affords the potassium salt of 4*H*-1,4-dihydrooxazocine $\langle 84AG(E)309 \rangle$. This salt reacts with

a variety of alkyl and acyl halides, affording *N*-substituted derivatives (**64**; *R* = H, Me, CH₂CH₂CN, PhCH₂, 3,4,5-(MeO)₃C₆H₂CH₂, CONMe₂, CO₂Me) <84AG(E)309>.

Treatment of enol ether (**73**; *R* = Et) with sodium hydroxide in aqueous ethanol affords the hydrolysis product, (**73**; *R* = H), in 74% yield. Attempted hydrolysis under acidic conditions leads only to intractable mixtures of products <89CPB1694>.

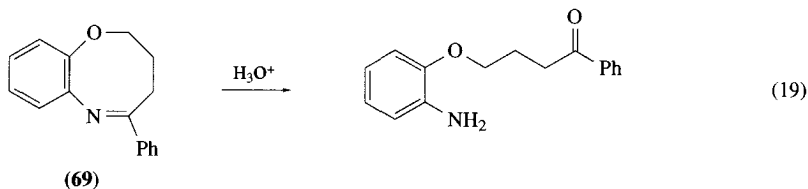
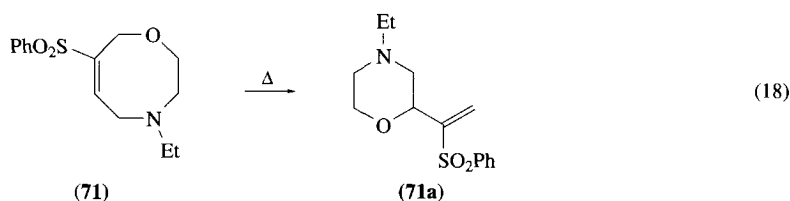
N-sulfonyl-4*H*-1,4-oxazocines do not react with dimethyl acetylenedicarboxylate or with tetracyanoethylene at 80°C. However, they react readily with *N*-methyl- and *N*-phenyltriazolinedione; the putative initial [4 + 2]-cycloadducts undergo facile oxa-Cope rearrangement (Scheme 17) <83CB2492>.



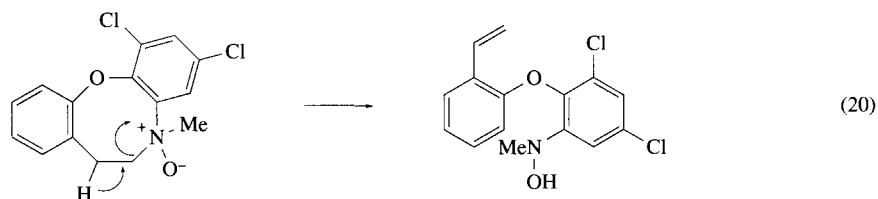
Scheme 17

9.23.4.4 Reactivity of Nonconjugated Rings

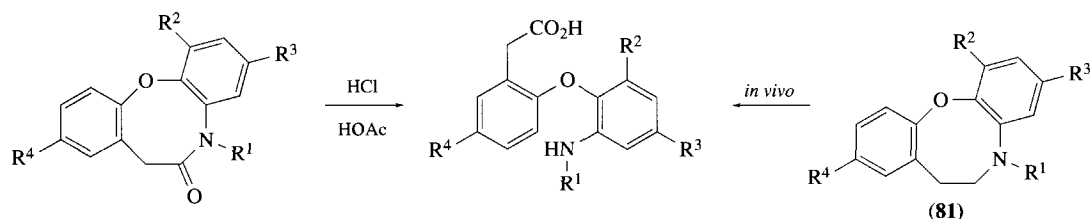
In a reaction analogous to that of the corresponding diazocine (**7**), 2*H*-3,4,5,8-tetrahydro-1,4-oxazocine (**71**) undergoes a 1,3-rearrangement, perhaps via transannular conjugate addition, upon either attempted chromatographic purification or prolonged standing in solution <90JOC4801>. The rearrangement appears effectively irreversible, and energy calculations support this, with the morpholine derivative (**71a**) some 5.9 kcal mol⁻¹ more stable than the oxazocine (Equation (18)). Aqueous acid effects the hydrolysis of the imine functionality in 2*H*-3,4-dihydro-1,6-benzoxazocine (**69**), resulting in ring cleavage (Equation (19)) <84JOC116>.



Numerous reactions of 5*H*-dibenz[*b,g*][1,4]oxazocines (**81**) have been reported in the course of their preparation and evaluation as potential antiinflammatory agents <85JMC225>. Attempted reduction of the lactam functionality in *N*-methylated oxazocinones with lithium aluminum hydride proved unsuccessful for the preparation of (**81**; *R*¹ ≠ H), but reduction of the secondary lactams provides good yields of the corresponding oxazocines (**81**; *R*¹ = H). *N*-Alkylation and acylation of the latter is then easily effected with alkyl and acyl halides. A two-step process of formylation followed by reduction is also effective for *N*-methylation, while reductive amination of propionaldehyde with (**81**; *R*¹ = H) affords (**81**; *R*¹ = Prⁿ). Treatment of *N*-alkyl derivatives with *m*-chloroperbenzoic acid affords the corresponding *N*-oxides, which tend to decompose with ring cleavage, slowly in the solid state and rapidly upon heating in ethyl acetate solution (Equation (20)).

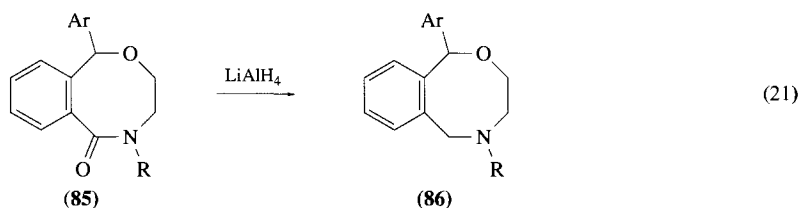


Hydrolytic cleavage of the oxazocine ring is effected with HCl in acetic acid, affording phenoxyphenylacetic acid derivatives (Scheme 18). The same compounds are apparently formed upon metabolic breakdown of the oxazocines, and indeed the ring-cleaved compounds display enhanced pharmacological activity over the oxazocines.

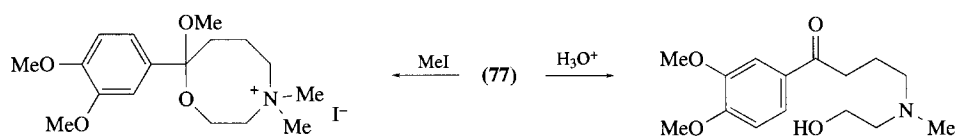


Scheme 18

Methylation of 1*H*-3,4,5,6-tetrahydro-1-phenyl-2,5-benzoxazocine (**76**; R = H) to the corresponding *N*-methyl derivative, nefopam (**1**), has been effected with CH₂O/sodium phosphite <86MIP547661>, CH₂O/NaBH₄ <82AJC2307>, and Me₂SO₄ <86MIP544826>. Further methylation, to the corresponding methiodide, is effected by treatment with methyl iodide <90CJC1128, 90MRC389>, while treatment with hydrogen peroxide affords the *N*-oxide <90MRC389>. The parent 2,5-benzoxazocine (**76**; R = H) is also readily *N*-acylated by acyl chlorides <84JAP(K)5913769>. Nefopam analogues (**86**; R = Me, Ar = *o*-Me-C₆H₄, *p*-Cl-C₆H₄; R = Et, Ar = Ph) (Equation (21)) <82MIP499426>; cyclohexeno analogues have also been reported <86H(24)155>. Biological demethylation of nefopam occurs in the liver, with the product (**76**; R = H) forming an inactive complex with cytochrome P450 <87JPP835>. Prolonged storage of nefopam under conditions of "forcible degradation" (pH 2 or 9, 90°C, 60 days) affords a variety of degradation products, including 1-hydroxy derivative (**66**); initial ring opening via cleavage of the ether linkage is proposed to be the rate-limiting step in both acidic and alkaline media <90MI 923-01>.



Treatment of 2*H*-3,4,5,6,7,8-hexahydro-1,4-oxazocine (**77**) with methyl iodide affords the corresponding methiodide (Scheme 19), while the ketal functionality of this derivative is cleaved by aqueous acid <85AJC1591>. Cyclic peptides (**80**) are prepared from their side-chain *N*-trityl precursors by treatment with HCl <87CC474>; ring cleavage is apparently not observed under these reaction conditions.



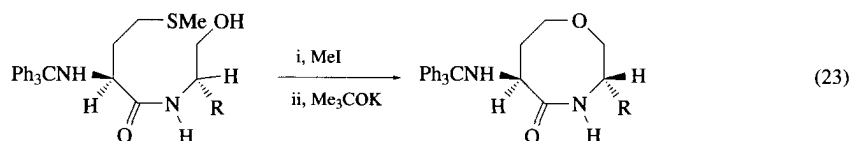
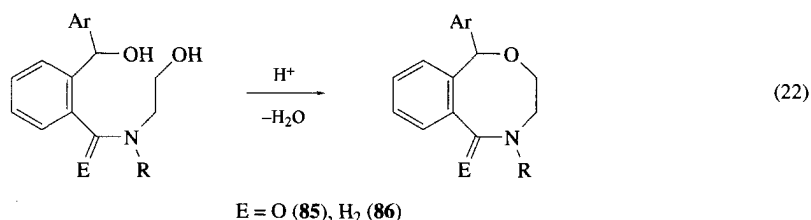
Scheme 19

9.23.4.5 Reactivity of Substituents Attached to Ring Heteroatoms

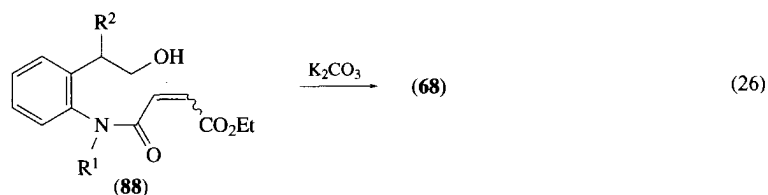
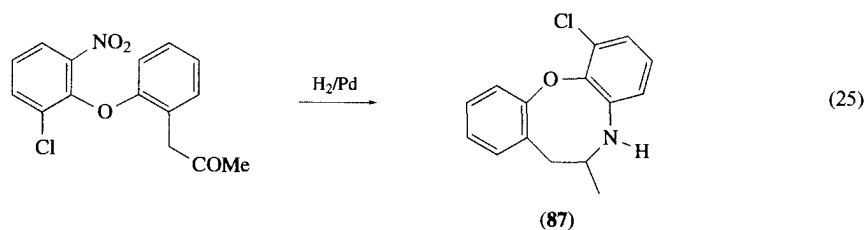
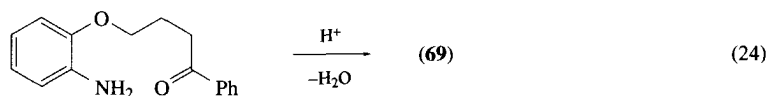
N-Formyl-1*H*-3,4,5,6-tetrahydro-1-phenyl-2,5-benzoxazocine (**76**; R = CHO) is reduced to the *N*-methyl derivative by sodium borohydride [82AJC2307]. Similarly, *N*-acyl derivatives of this benzoxazocine are reduced by lithium aluminum hydride to the corresponding alkyls [84JAP(K)5913769].

9.23.4.6 Ring Syntheses

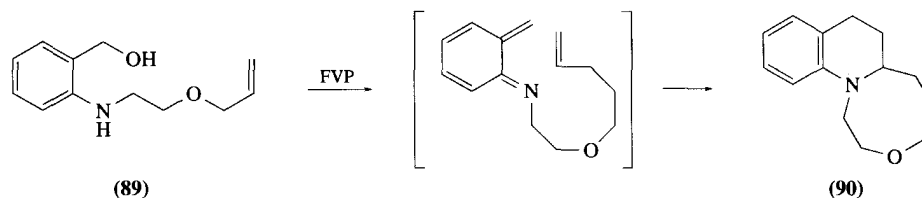
A brief discussion of early synthetic approaches to the oxazocines was provided in Section 5.19.5 of CHEC-I. Formation of 1*H*-3,4,5,6-tetrahydro-1-aryl-2,5-benzoxazocines (**86**) and 6-oxo analogues (**85**) is effected by treatment of acyclic diols with strong acids (e.g. *p*-Me-C₆H₄SO₃H, HBr) (Equation (22)) [72AF132, 82MIP499426, 84MI 923-01, 86MIP544826]. Similar cyclizations, affording *N*-trityl precursors to (**80**), were effected by *S*-methylation of homocysteine thioethers, followed by treatment with base (Equation (23)) [87CC474].



Other unimolecular cyclizations effected by intramolecular nucleophilic addition include the formation of imine (**69**) upon azeotropic removal of water (Equation (24)) [84JOC1116], the related formation of (**87**) upon catalytic reduction (Equation (25)) [85JMC225] and the conjugate addition of hydroxy acrylates (**88**) upon treatment with potassium carbonate in ethanol (R² = H) or CH₂Cl₂/18-crown-6 (R² = Ph) [86CBP140], forming (**68**; R¹ = Me, Prⁱ, PhCH₂, R² = H, Ph) (Equation (26)).

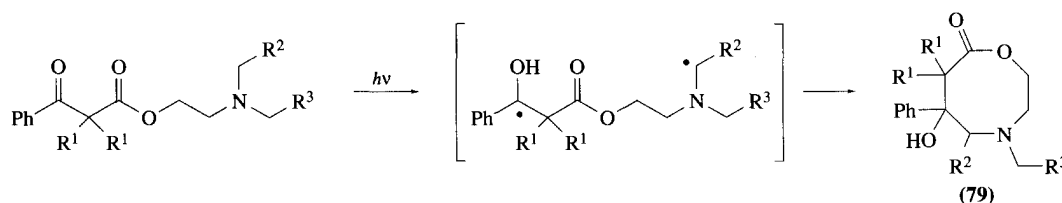


Flash vacuum pyrolysis of (**89**) at 650°C affords a 5% yield of oxazocine (**90**) (Scheme 20), resulting from dehydration to the iminoquinone methide followed by intramolecular Diels–Alder cycloaddition; use of SiO₂ as a catalyst for the pyrolysis affords a higher yield of (**90**) (20%) at lower temperature (425°C) <84TL5435>.



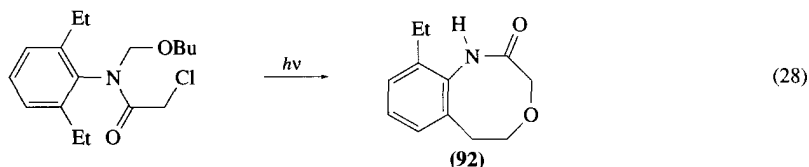
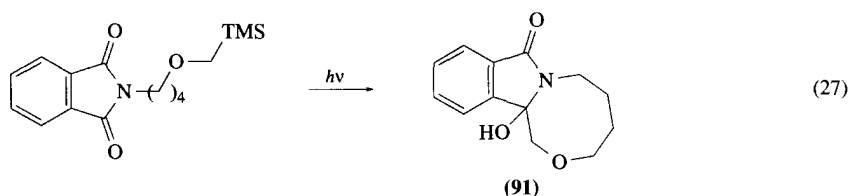
Scheme 20

Photoinduced remote cyclization of amino ketones provides modest yields of mixtures of the *cis* and *trans* isomers of oxazocinones (**79**; R¹ = H, R² = H, Ph, R³ = H, Ph; R¹ = Me, R² = R³ = Ph) (Scheme 21), resulting from intramolecular hydrogen abstraction by the photoexcited ketone in a ten-membered transition state <85CC363, 90JCS(P1)901>.



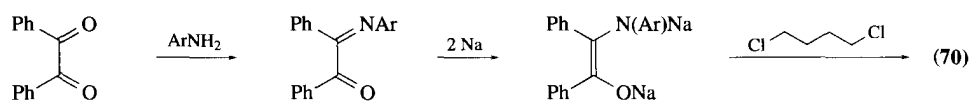
Scheme 21

In a related photocyclization, single electron transfer from ether oxygen to a photoexcited phthalimide moiety, followed by desilylation of the resulting cation radical and cyclization by radical coupling, is proposed as the mechanism for formation of isoindolo-fused oxazocine (**91**) (Equation (27)); similar cyclizations to smaller and larger ring analogues were also demonstrated <92MI 923-01>. Photolysis of butachlor in aqueous solution by either solar or ultraviolet light produces at least 24 products, including 1*H*-4,1-benzoxazocine (**92**) (Equation (28)), also apparently the product of a remote cyclization process <82MI 923-01>.



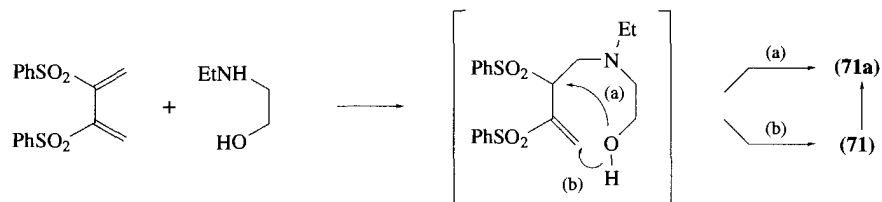
Alkylation of the dianions produced upon reduction of 2-imino-1,2-diphenylethanones with 1,4-dichlorobutane affords modest yields of 4*H*-5,6,7,8-tetrahydro-1,4-oxazocines (Scheme 22) (**70**; Ar = Ph, *p*-Me-C₆H₄) <85BCJ2399>.

Double conjugate addition of *N*-ethyl-2-aminoethanol to 2,3-*bis*(phenylsulfonyl)-1,3-butadiene



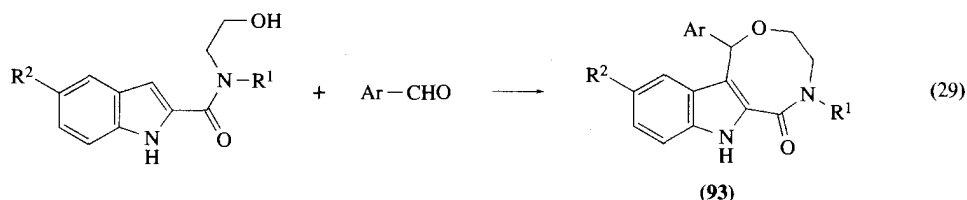
Scheme 22

affords 2,3,5,8-tetrahydro-1,4-oxazocine (**71**), together with small amounts of morpholine (**71a**), formed by an alternative intramolecular attack after the first conjugate addition (Scheme 23); the latter is also formed by thermal rearrangement of the oxazocine <90JOC4801>.



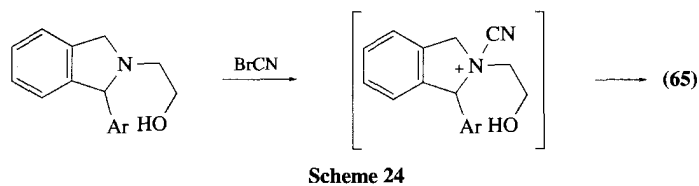
Scheme 23

Treatment of hydroxyalkylindole derivatives with aromatic aldehydes affords indolo-fused oxazocines (Equation (29)) (**93**; Ar = Ph, R¹ = R² = H; Ar = Ph, R¹ = Me, R² = OMe; Ar = Ph, *p*-NO₂-C₆H₄, *p*-Me-OC₆H₄, R¹ = Me, R² = H) <92KFZ23>, perhaps via hemiacetal formation and subsequent electrophilic alkylation of the indole ring.

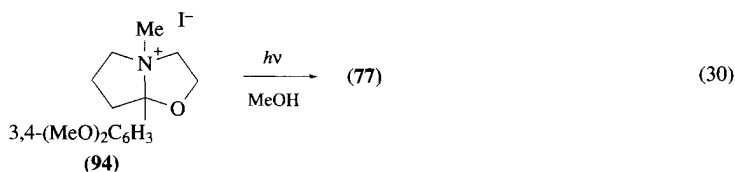


9.23.4.7 Ring Synthesis by Transformation of Another Ring

As noted above, thermal valence tautomerization of benzeneimine oxides affords 1,4-dihydro-1,4-diazocines (**64**) in high yield <83CB2492>. Treatment of hydroxyethyl isoindole derivatives with cyanogen bromide leads to benzoxazocines (**65**; Ar = Ph, *p*-MeO-C₆H₄) (Scheme 24) via *N*-cyanation and regioselective intramolecular nucleophilic attack at the carbon bearing the aryl substituent <82AJC2307>, perhaps indicative of a carbocationic intermediate. Inter-molecular trapping of the carbocation formed upon photolytic cleavage of methiodide (**94**) in methanol affords an 89% yield of (**77**) (Equation (30)) <85AJC1591>.

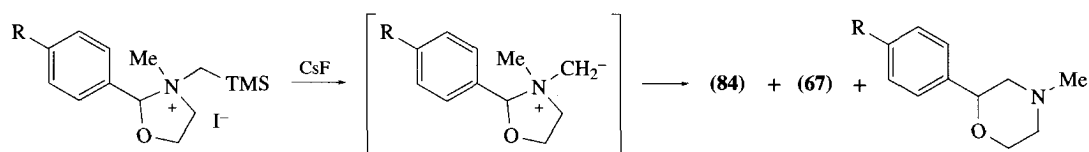


Scheme 24



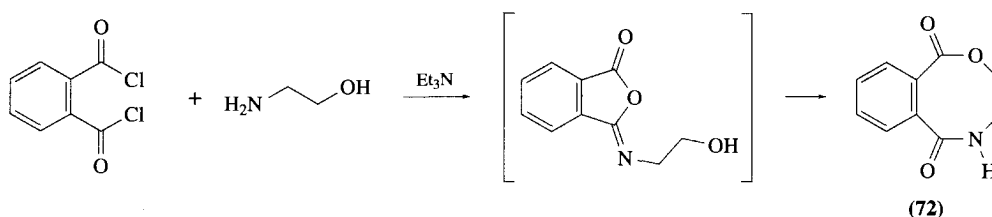
Sommelet-Hauser rearrangement of the nitrogen ylide formed upon desilylation of oxazolinium derivatives affords benzoxazocines (**67**) and/or their putative tautomers (**84**) in low to modest yield

(Scheme 25); Stevens rearrangement accounts for the majority of the product of these reactions <92CBP768>.



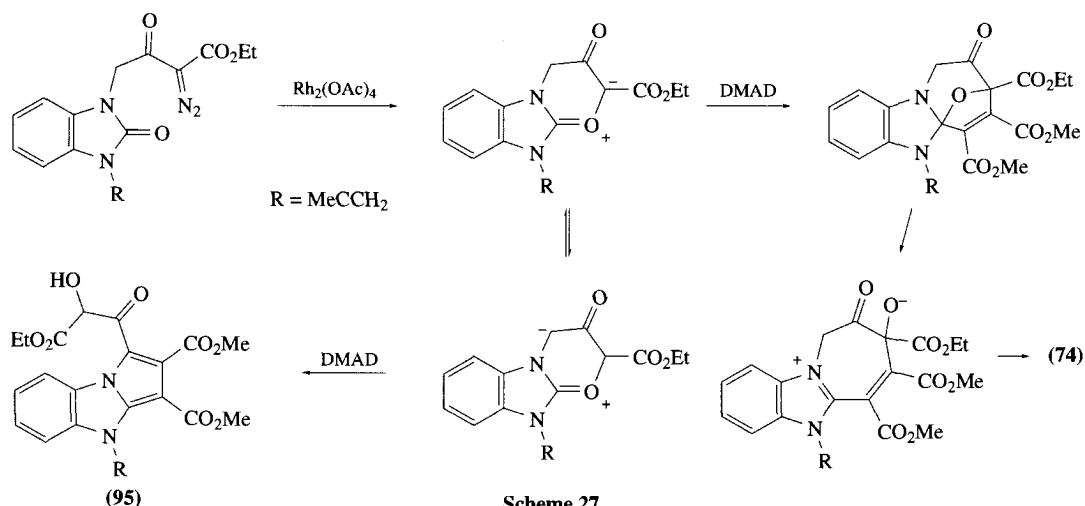
Scheme 25

Treatment of aminoethanol with phthaloyl dichloride affords an unexpected intermediate, which isomerizes to benzoxazocinedione (**72**) (Scheme 26) <85JOU1769>. Despite earlier claims by Gabriel <05CB2389>, alkaline hydrolysis of *N*-bromoethylphthalimide does not afford (**72**).



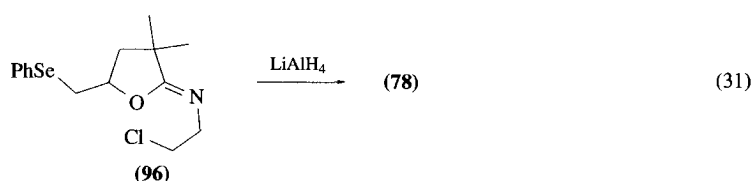
Scheme 26

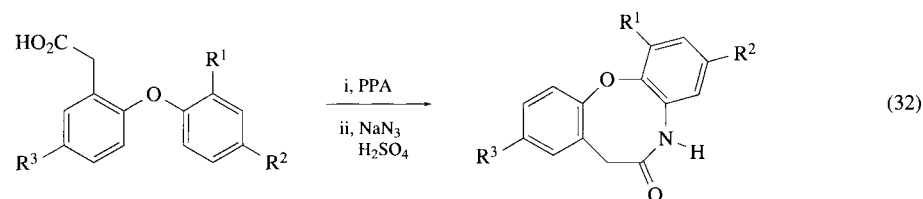
Attempts to trap with dimethyl acetylenedicarboxylate (DMAD) a presumed intermediate ylide formed upon rhodium-catalyzed carbene generation led instead to a 33% yield of oxazocine (**74**), apparently formed by fragmentation of the initial [3 + 2] cycloadduct of DMAD with the ylide, followed by acyl migration (Scheme 27). Ylide tautomerization, followed by an analogous sequence of reactions, accounts for a 24% yield of isomer (**95**) <92TL3273>.



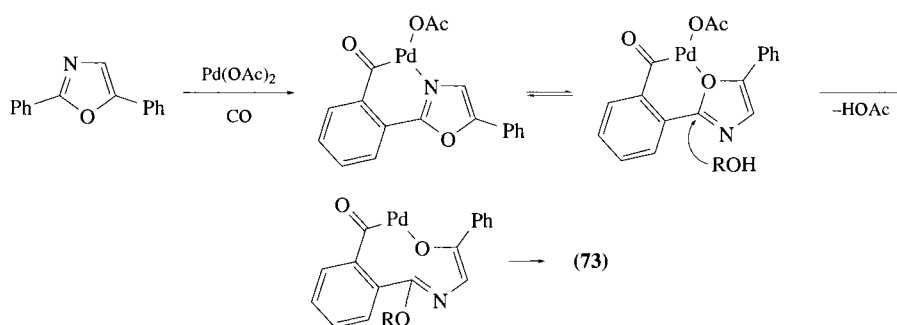
Scheme 27

Treatment of iminolactone (**96**) with lithium aluminum hydride unexpectedly leads to ring expansion, affording oxazocine (**78**) in 89% yield (Equation (31)) <87JOC2018>. Treatment of dibenzoxepinones, prepared by intramolecular acylation of phenoxyphenylacetic acid derivatives, with sodium azide in sulfuric acid affords dibenzoxazocinones in good yield (Equation (32)); Beckman rearrangement of the corresponding oximes, however, did not prove useful <85JMC225>.





Palladium-catalyzed carbonylation of 2,5-diphenyloxazole in alcoholic solvents affords oxazocines (**73**) in modest yield (8–20%) in addition to the products of simple carboalkoxylation (Scheme 28). The former are proposed to form via attack by alcohol at the oxazole ring in the acyl palladium intermediate, followed by reductive elimination; the failure of *t*-butyl alcohol to provide a comparable product is cited in support <89CPBI694>.



Scheme 28

9.23.4.8 Comparison of Synthetic Routes

Although a number of routes to the oxazocine ring system, utilizing both ring-construction and ring-expansion strategies, have been discovered, many of the routes represent rather special cases, with rather limited applicability. Unimolecular cyclizations appear to offer some promise, particularly given the relative ease with which many appropriate cyclization precursors may be prepared, and yields, when reported, are not as disappointing as one might anticipate. The various photochemical routes, while interesting, do not offer promise of high yields and great generality. The Diels–Alder and conjugate addition routes, while virtually unexplored, may open the doors to a number of new syntheses, although both will presumably experience the potential geometric limitations of any such intramolecular cyclizations. Although the valence tautomerization approach affords high yields of fully unsaturated oxazocines (and thus represents the only available route to such materials other than the low-yielding Sommelet–Hauser route to the 1-oxo derivatives), it suffers from the relative inaccessibility of appropriate precursors. The photolytic fragmentation of bicyclic precursors is similarly hampered. The cyanogen bromide route may offer some promise, if it will tolerate more-substituted substrates. In short, the oxazocines, despite the importance of nefopam and the extensive studies of the dibenzo[*b,g*] derivatives, remain rather elusive materials, and synthetic advances offering more general routes for their preparation remain to be made.

9.23.4.9 Important Compounds and Applications

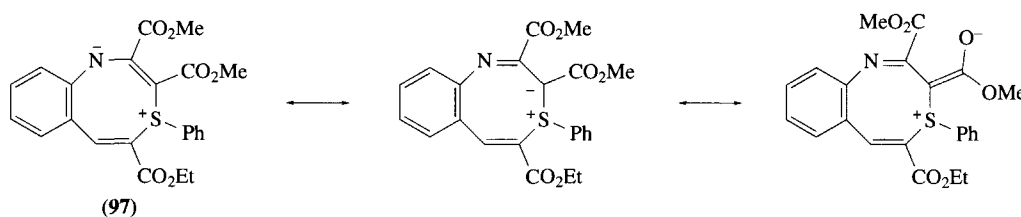
Nefopam is a heavily studied non-opiate analgesic, and the potential analgesic activity of a number of analogues has also been explored <82MIP499426, 84JAP(K)5913769>. Prostaglandin-type compounds bearing cyclic amino substituents, including an oxazocine, have been examined as bronchodilating and platelet aggregation-inhibiting agents <80JAP(K)8218671>. Benzoxazocines (**68**) were prepared in order to assay their anxiolytic activity; in contrast to the seven-membered ring analogues, however, these oxazocines displayed no significant CNS activity <86CBPI40>. The anti-hypoxic and antiarrhythmic activity of indolo-fused oxazocines (**93**) has been assayed <92KFZ23>. Dibenzo[*b,g*] derivatives display good activity as antiinflammatory agents, but poor solubility

characteristics and the instability of the corresponding *N*-oxides prepared to help circumvent this problem have slowed progress in this area <85JMC225>. Porritoxin (**75**) is a non-specific phytotoxin <92P2325, 92MI 923-02>. Cyclic peptides (**80**) are proposed to be cyclically protected precursors of homoserine derivatives bearing resemblance to naturally occurring analogues which display interesting properties such as retardation of fruit ripening and prolongation of the life of cut flowers <87CC474>. Detection of silver at subnanomolar levels has been achieved with *N*-benzyl-2,3,5,6,7,8-hexahydro-4*H*-1,4-oxazocine <84MI 923-02>.

9.23.5 RINGS WITH ONE NITROGEN AND ONE SULFUR (4*H*-1,4-THIAZOCINES)

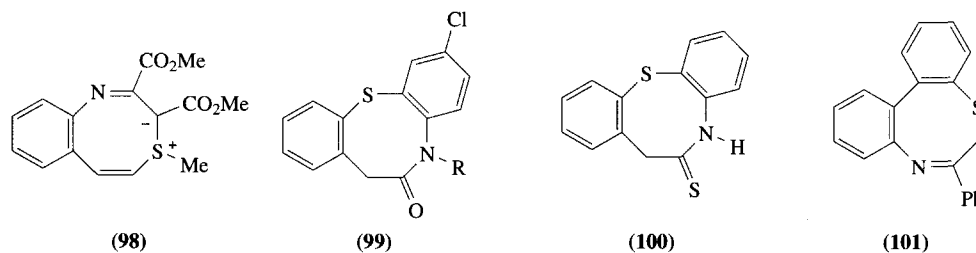
9.23.5.1 Experimental Structural Methods

The results of a single crystal x-ray diffraction analysis of potentially fully conjugated 4,1-benzothiazocine (**97**) have been reported (Scheme 29). Although if planar (**97**) could formally represent an 8π -electron, antiaromatic system, it in fact is tub-shaped. Bond lengths do indicate charge delocalization, but only throughout the N=C=CO portion of the molecule <82CC1060>.



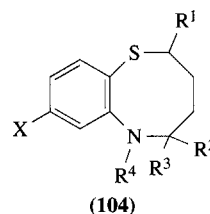
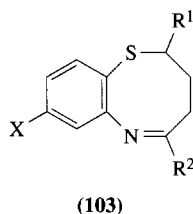
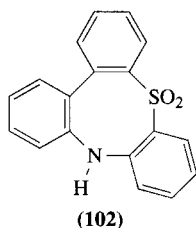
Scheme 29

The alkenic protons in (**98**), an analogue of (**97**), appear at quite low field in the ^1H NMR spectrum (6.25, 7.83 ppm) <84CPB4360>, but this is indicative of the adjacent electron-deficient sulfur center rather than any aromatic stabilization in (**98**), which, by analogy with (**97**), may be presumed to be nonplanar. The ring methylene protons in 5*H*-dibenzo[*b,g*][1,4]thiazocine-6(7*H*)-ones (**99**; R = H, Ac, *p*-Me-C₆H₄SO₂) and the corresponding thione (**100**) appear as a singlet at ca. 3.5–3.75 ppm <74CCC333>, but as an AB quartet (at 3.84 ppm) in 7-phenyl-6*H*-dibenzo[*e,g*][1,4]thiazocine (**101**) <91JCS(PI)1733>, consistent with the expectedly slower conformational equilibria in the latter biphenyl-type derivative.

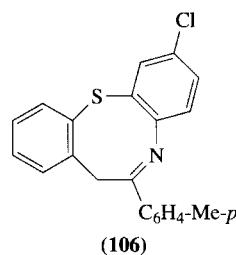
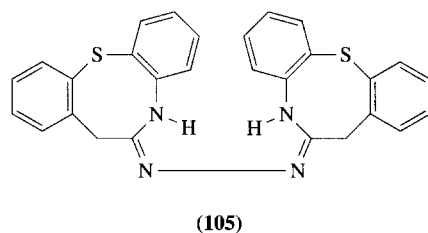


The NH proton in 10*H*-tribenzo[*b,e,g*][1,4]thiazocine 5,5-dioxide (**102**) appears at ca. 5.5 ppm (in CDCl₃) <83T2073>, while the NH proton in *N*-unsubstituted derivative (**100**) appears far downfield, at 12.5 ppm (in DMSO) <83CCC1465>. Partially reduced 1,6-benzothiazocines (**103**; R¹ = Ph, R² = SMe, SEt, NHMe, NHPh, 1-pyrrolidinyl, 1-morpholinyl, 4-Me-1-piperazinyl, X = H; R¹ = X = H, R² = Ph, 2-thienyl; R¹ = H, R² = Ph, *p*-F-C₆H₄, 2-thienyl, X = Cl) and (**104**; R¹ = H, Ph, R² = H, Me, Bu, R³ = Ph, 2-thienyl, *p*-F-C₆H₄, R⁴ = H, Me, Et, Ac, PhCO, X = H, Cl) appear to display normal ^1H chemical shifts <83JHC1593, 84JOC116>; ^{13}C NMR spectroscopy was more useful in structural verification for the 2*H*-3,4-dihydro derivatives (**103**), for which alternative formulation as benzothiazoles was ruled out by observation of an imine carbon (C-5) resonance at ca. 167 ppm <84JOC116>. One quaternary carbon is reported at rather high field (53.9 ppm) in the ^{13}C NMR

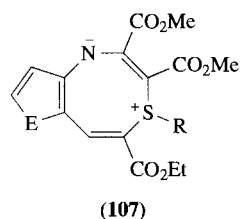
spectrum of 4,1-benzo derivative (**98**) <84CPB4360>; presumably this is the ylide-type carbon attached to sulfur.



The mass spectrum of dibenzo dimer (**105**) displays the parent ion as the base peak; other significant fragments appear to arise from cleavage of bonds in the vicinity of the azine linkage, with the dibenzothiazocine units largely remaining intact <83CCC1465>. Dibenzo[*b,g*]thiazocine (**106**) also appears rather robust, displaying a significant parent ion and fragments resulting from loss of the methyl group of the tolyl substituent as well as loss of the entire tolyl group <74CCC333>. Tribenzo sulfone (**102**), on the other hand, although also displaying a sizable parent ion, yields the M-SO₂ fragment as the base peak <83T2073>. Observation of parent ions upon mass spectral analysis of (**98**) <84CPB4360>, (**101**) <91JCS(P1)1733>, (**103**) <84JOC116>, and (**104**) <83JHC1593> has also been reported; no fragmentation data were provided.



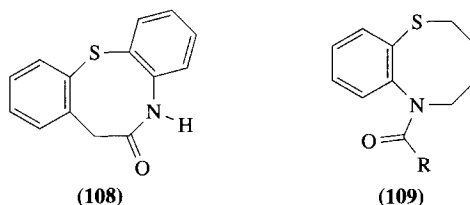
The highly unsaturated thiazocines all absorb in the visible region; ylide (**98**) is reported to be yellow <84CPB4360>, and *S*-phenyl analogue (**97**) and its furano- and thiopheno-fused analogues (**107**; R = Ph, E = O, S; R = Me, E = O) are highly colored, orange to violet materials <82CC1060>.



Dibenzo[*e,g*]thiazocine (**101**) is orange <91JCS(P1)1733>, while monobenzo analogues (**103**; R¹ = Ph, R² = SMe, SEt, pyrrolidinyl, morpholinyl, X = H) are presumably colorless, with no absorption features above ca. 265 nm <83JHC1593>. The 5-aryl analogues (**103**; R² = Ph, 2-thienyl, *p*-F-C₆H₄) display red shifts, with lowest energy absorptions near 300 nm, and may be pale yellow <84JOC116>. Tetrahydrobenzothiazocines, with apparently reduced conjugation, again appear to be colorless; e.g. (**104**; R¹ = R³ = R⁴ = H, R² = Ph, X = Cl) absorbs at 205 and 265 nm <84JOC116>. Thione (**100**) shows spectral features at 250 nm (4.12) and 300 nm (4.24) <83CCC1465>, perhaps leading to a yellow coloration, while tribenzo derivative (**102**) is colorless <83T2073>.

2*H*-3,4-dihydro-1,6-benzothiazocines (**103**; X = H, Cl; R¹ = H; R² = Ph, 2-thienyl) <84JOC116> and (**103**; X = H; R¹ = Ph; R² = SMe, SEt, pyrrolidinyl, morpholinyl) <83JHC1593> all display C=N stretching modes between 1618 and 1640 cm⁻¹. The lactam carbonyl stretching band in (**99**; R = H, *p*-Me-C₆H₄SO₂) and (**108**) appears at ca. 1680 cm⁻¹ <74CCC333>, at higher energy than the exocyclic amide functionality in *N*-acyl derivatives (**109**; R = Me, Ph), which display amide stretches between 1639 and 1667 cm⁻¹ <83JHC1593>. Transannular interactions between the ring sulfur and the lactam carbonyl thus appear unlikely to be significant in (**99**) and (**108**). The thione analogue, (**100**), displays NHC=S modes at 1119 and 1523 cm⁻¹, while the corresponding azine (**105**) shows an apparent C=N mode at 1613 cm⁻¹ <83CCC1465>. Tetrahydro-1,6-benzothiazocines (**109**; R = NH₂, MeNH,

PhNH) <83JHC1593> and tribenzo derivative (**102**) <83T2073> display typical NH and sulfone frequencies. Ylide (**98**) displays one ester carbonyl stretch at normal energy (1720 cm^{-1}), while the α -ester group absorbs at much lower energy (1650 cm^{-1}) <84CPB4360>, consistent with enolate-type charge delocalization.



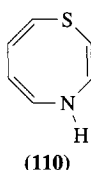
9.23.5.2 Thermodynamic Aspects

The ylide-type benzothiazocines display rather high melting points ((**98**) $171\text{--}173^\circ\text{C}$ <84CPB4360>, (**97**) $175\text{--}176^\circ\text{C}$ <82CC1060>); the corresponding thiopheno derivative (**107**; R = Ph, E = S) is somewhat lower melting ($152\text{--}154^\circ\text{C}$), while the furano analogues (**107**; R = Ph, Me, E = O) show still further decreases in melting point; the very low melting point of (**107**; R = Ph, E = O) ($56\text{--}58^\circ\text{C}$) is noteworthy <82CC1060>. The dibenzo[*b,g*] derivatives ((**99**), (**100**), (**105**), (**106**), (**108**)) all display high melting points, generally in excess of 200°C <74CCC333, 83CCC1465>, as does the tribenzo analogue (**102**) <83T2073>, while dibenzo[*e,g*] derivative (**101**) melts at a considerably lower temperature ($125\text{--}128^\circ\text{C}$) <91JCS(P1)1733>. Comparison of the latter with (**106**) (m.p. $219\text{--}221^\circ\text{C}$) <74CCC333>, which bears great structural similarity, suggests that the enforced nonplanarity of (**101**) due to aryl–aryl torsion may contribute to less-efficient solid-state packing. A number of derivatives of 2*H*-1,6-benzothiazocine has been reported <83JHC1593, 84JOC116>, and solid-state behavior appears largely in accord with that expected for the given structural changes. Within a given series, the 3,4-dihydro derivatives (**103**) appear to be higher melting than the 3,4,5,6-tetrahydro derivatives (**104**) <84JOC116>, with the latter often obtained as oils, which may be distilled <83JHC1593, 84JOC116>. One 3,4-dihydro derivative (**103**; X = R¹ = H, R² = Ph) is reported to sublime at $120^\circ\text{C}/0.05\text{ mm Hg}$ <84JOC116>.

Many of the thiazocines are soluble in CH_2Cl_2 and CHCl_3 , from which they may often be recrystallized by the addition of hydrocarbons <83CCC1465, 83JHC1593, 84CPB4360, 91JCS(P1)1733> or Et_2O <83JHC1593>. The tribenzo derivative (**102**), however, is reported to be soluble in ethereal solvents <83T2073>. Recrystallization from alcohols <74CCC333, 83T2073>, hexane <84JOC116>, and Et_2O <84JOC116> has also been reported. Not surprisingly, the more polar derivatives are insoluble in hydrocarbons, while derivatives bearing hydrophobic groups display higher solubility in such solvents; indeed, (**103**; X = Cl, R¹ = H, R² = Ph) was recrystallized from hexane <84JOC116>, while (**106**) appears to be soluble in cyclohexane <74CCC333>. Chromatographic purification has been effected on both alumina <74CCC333, 83CCC1465> and silica <83JHC1593, 84JOC116, 91JCS(P1)1733>, with often quite nonpolar solvents used for elution. For example (**104**; R¹ = R⁴ = X = H, R² = Ph, R³ = Bu) was eluted with pure hexanes on silica <84JOC116> and (**106**) with benzene/light petroleum ether on alumina <74CCC333>. Ylide (**98**) was purified on silica; however, in accord with its polar nature, it remained at the origin upon elution of impurities with 1:1 ethyl acetate/hexane <84CPB4360>.

By analogy with the 1,4-dihydro-1,4-diazocines and 4*H*-1,4-oxazocines, one might anticipate 4*H*-1,4-thiazocine (**110**) to be a potentially aromatic, 10π -electron system <78AHC(23)55>. Little theoretical attention has been paid to the thiazocines, however, perhaps because no synthetic approaches to the fully-conjugated ring system have been reported.

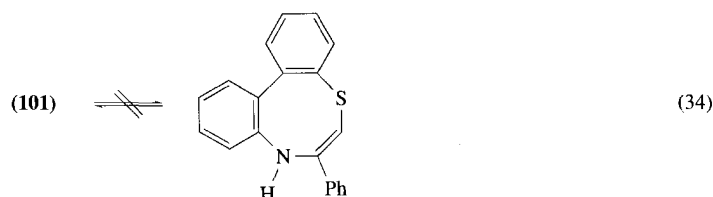
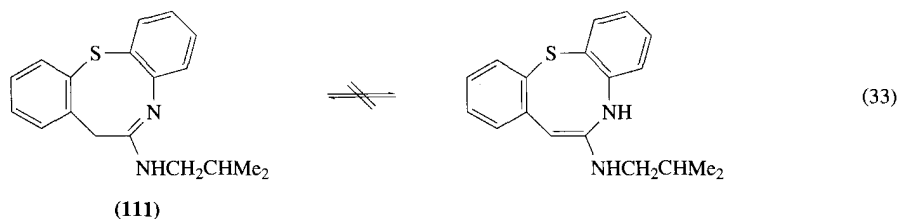
The ylide-type benzo derivatives ((**97**), (**98**), (**107**)) <82CC1060, 84CPB4360> offer the potential for



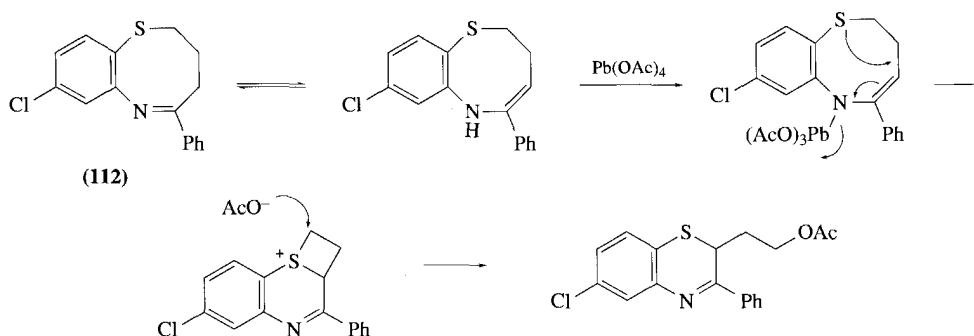
delocalized bonding, although they represent 8π -electron systems which might be expected to be destabilized in a planar conformation. Indeed, structural analysis of (97) noted a distinctly nonplanar thiazocine ring, with bond lengths also supporting the nonaromaticity of this ring system <82CC1060>.

In contrast to the extensive conformational analyses of the diazocines and oxazocines, virtually no attention has been paid to the thiazocines. Ylide derivative (97), as discussed above, adopts a tub shape, perhaps in response to the potential antiaromaticity of the planar conformation <82CC1060>.

Cyclic amidine (111) is reported to have the structure shown rather than the alternative potentially aromatic tautomer (Equation (33)) <74CCC333>. 5*H*-Dibenzo[*b,g*][1,4]thiazocine-6(7*H*)-one (108) and the corresponding thione (100) and azine (105) apparently exist as such <74CCC333, 83CCC1465> rather than the enol tautomers, which might also have been anticipated to display aromatic stabilization. Similarly, although insufficient data are provided to fully assess this issue, imine (101) apparently does not tautomerize to the conjugated enamine (Equation (34)) <91JCS(P1)1733>; biaryl torsion in such a dibenzo[*e,g*] derivative, of course, would preclude planarity and any potential aromatic stabilization.



Imine–enamine tautomerization is proposed to precede the lead tetraacetate-induced ring contraction of benzo derivatives such as (112) (Scheme 30) <84JOC116>.

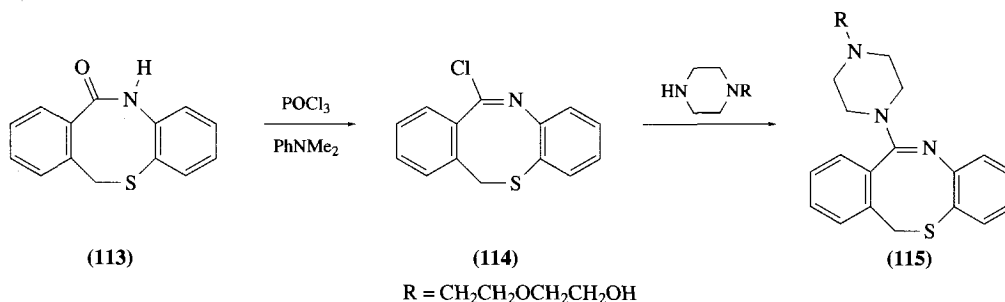


Scheme 30

9.23.5.3 Reactivity of Nonconjugated Rings

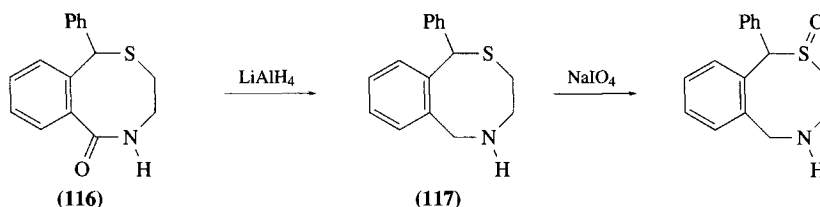
Treatment of lactam (108) with P_2S_5 in refluxing pyridine affords the corresponding thione (100) <83CCC1465>. Hydrazinolysis of (100) gives azine (105) rather than the fused triazole obtained from the seven-membered ring analogue <83CCC1465>. The lactam also reacts with isobutylamine in the presence of $TiCl_4$ to afford cyclic amidine (111) <74CCC333>. Treatment of dibenzo[*b,f*][1,4]thiazocin-

11(6*H*)-one (**113**) with POCl_3 affords 11-chloro derivative (**114**), which undergoes nucleophilic substitution by hydroxyethoxyethylpiperazine to afford (**115**) (Scheme 31) (86EUP240228).



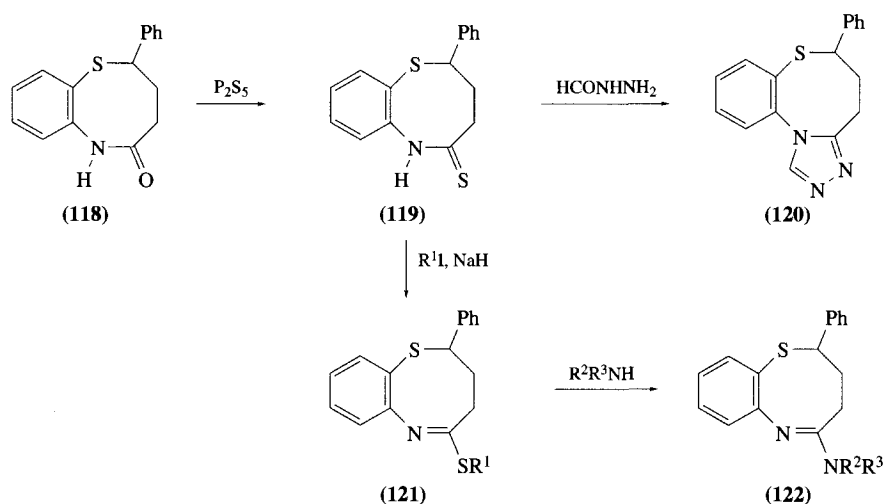
Scheme 31

Lithium aluminum hydride effects the reduction of 1*H*-4,5-dihydro-1-phenyl-2,5-benzothiazocin-6(3*H*)-one (**116**) to the corresponding secondary amine (**117**), which is converted to the *S*-oxide upon treatment with sodium periodate (Scheme 32) (82JAP(K)5913770). The latter reagent also oxidizes benzothiazocine (**103**; $\text{X} = \text{Cl}$, $\text{R}^1 = \text{H}$, $\text{R}^2 = 2\text{-thienyl}$) to the *S*-oxide (84JOC116).



Scheme 32

As for the dibenzo derivative, P_2S_5 in pyridine converts benzothiazocinone (**118**) to the thione (**119**), which condenses with formic acid hydrazide to yield triazole-fused thiazocine (**120**) (Scheme 33) (83JHC1593). The thione may also be deprotonated and alkylated, affording thioethers (**121**; $\text{R}^1 = \text{Me}$, Et), which in turn react with secondary amines to give enamines (**122**; $\text{R}^2\text{R}^3\text{N} = \text{MeNH}$, PhNH , pyrrolidinyl, morpholinyl, *N*-Me-piperazinyl). Addition of butylamine, however, leads to ring cleavage. Lactam (**118**) may also be reduced with lithium aluminum hydride to the tetrahydrothiazocine, which undergoes *N*-acylation and reductive alkylation.

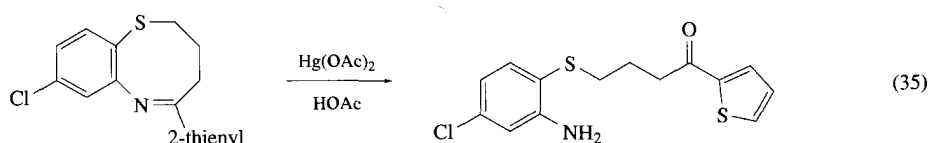
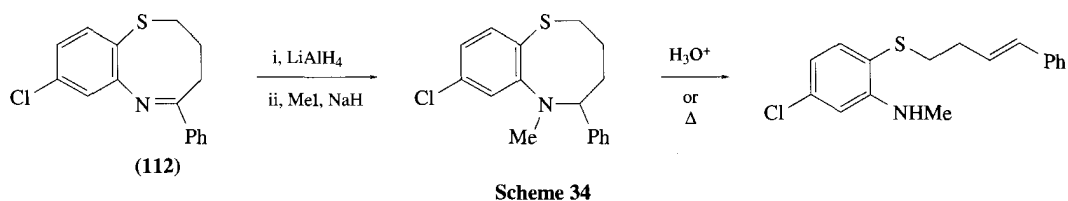


Scheme 33

Hydrolytic cleavage of the imine linkage in (**103**) is effected with aqueous acid (84JOC116). Alkyl lithiates add to (**103**) to afford 5,5-disubstituted derivatives (**104**; $\text{X} = \text{Cl}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = 2\text{-thienyl}$, *p*- $\text{F-C}_6\text{H}_4$; $\text{X} = \text{Cl}$, $\text{R}^2 = \text{Bu}$, $\text{R}^3 = p\text{-F-C}_6\text{H}_4$; $\text{X} = \text{H}$, $\text{R}^2 = \text{Bu}$, $\text{R}^3 = \text{Ph}$), while lithium aluminum

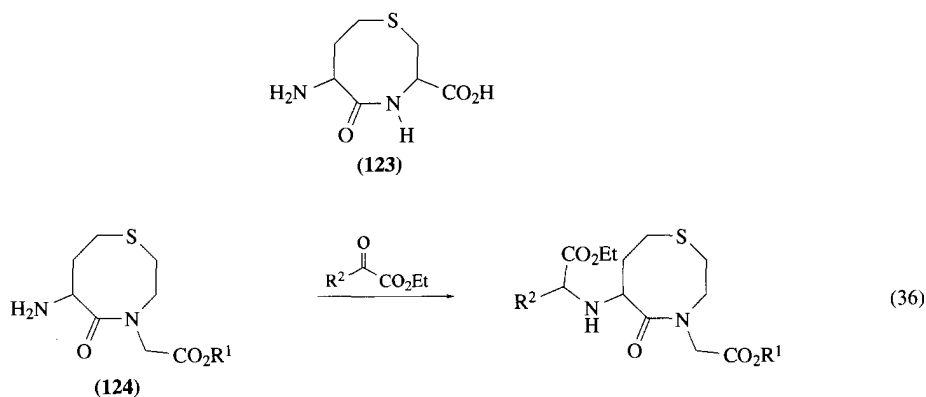
hydride reduction affords 5-monosubstituted analogues, which may be *N*-alkylated or acylated, although rather forcing conditions are required. The latter undergoes rather facile thermal and acid-catalyzed elimination, opening the thiazocine ring (Scheme 34) <84JOC116>.

Lead tetraacetate effects the ring contraction of (103) to the corresponding benzothiazines, apparently via intermediate transannular ring closure, as shown for (112) (Scheme 30), while treatment with mercuric acetate in acetic acid leads only to ring cleavage (Equation (35)) <84JOC116>.



9.23.5.4 Reactivity of Substituents Attached to Ring Carbon Atoms

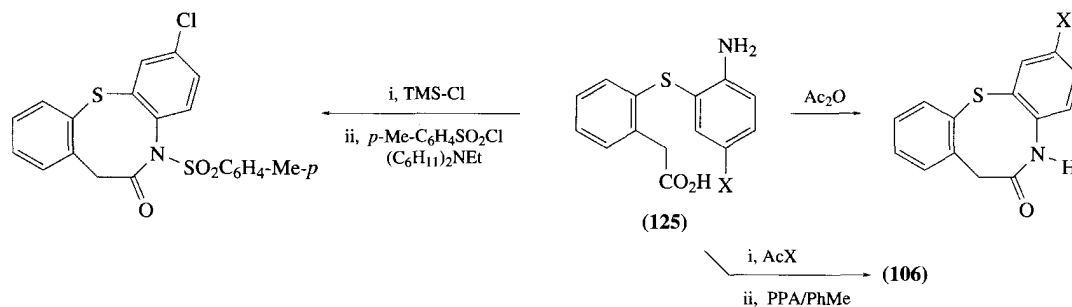
Perhydrothiazocine (123) is reported as a potentially useful synthon for the preparation of cyclic peptides, suggesting it behaves as a typical amino acid <84EUP113029>. The α -amino group in cyclic peptides such as (124) undergoes reductive alkylation with α -ketoesters (Equation (36)) <83EUP68173>.



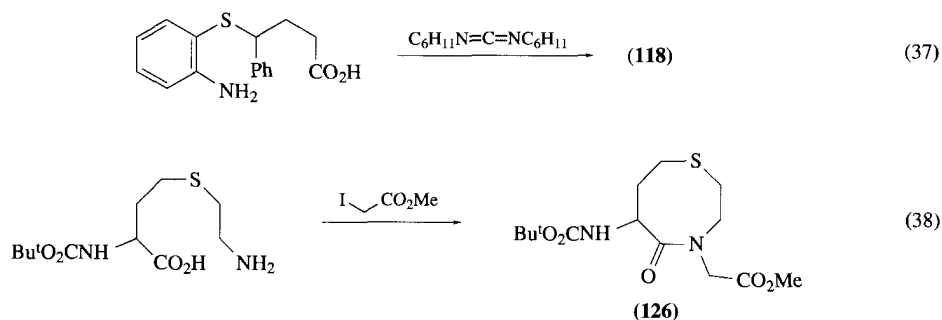
9.23.5.5 Ring Syntheses

Acetic anhydride-mediated cyclization of amino acids (125; X = H, Cl) affords dibenzothiazocinones (99; R = H) and (108) in ca. 80% yield <74CCC333>. Conversion of (125; X = Cl) to the trimethylsilyl ester, followed by treatment with tosyl chloride, affords the corresponding *N*-tosyl thiazocine (99; R = *p*-Me-C₆H₄SO₂), while the *N*-acetyl derivative of (125; X = Cl) cyclizes in the presence of polyphosphoric acid to afford unsaturated analogue (106) (Scheme 35) <74CCC333>.

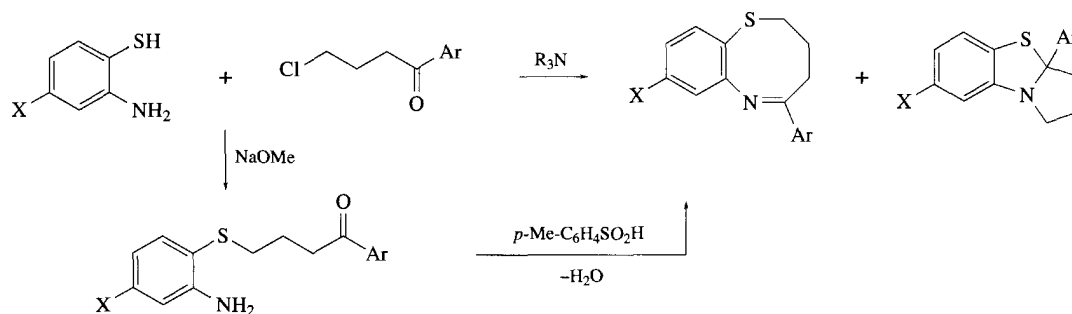
Lactamization affords a 59% yield of benzothiazocinone (118) (Equation (37)) <83JHC1593>, while cyclization of an acyclic homocysteine derivative affords perhydrothiazocine (126) (Equation (38)) <83EUP68173>.



Scheme 35

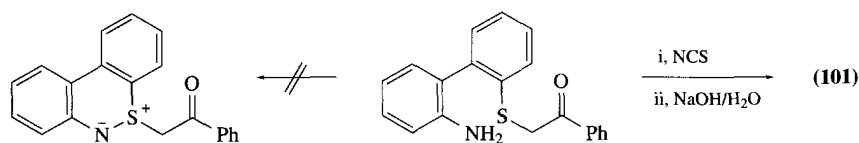


Ortho-amino thiophenols react with γ -chlorobutyrophenone and related aromatic ketones to afford separable mixtures of thiazocines and benzothiazoles. The latter apparently arise from initial *N*-alkylation rather than the desired *S*-alkylation, and the product ratio is quite dependent on the nature of the base used to effect the condensation ^[84JOC116]. Isolation of the intermediate amino ketone derived from *S*-alkylation, followed by acid-catalyzed dehydration with azeotropic removal of water, affords exclusively the thiazocines in good to excellent yield (Scheme 36).



Scheme 36

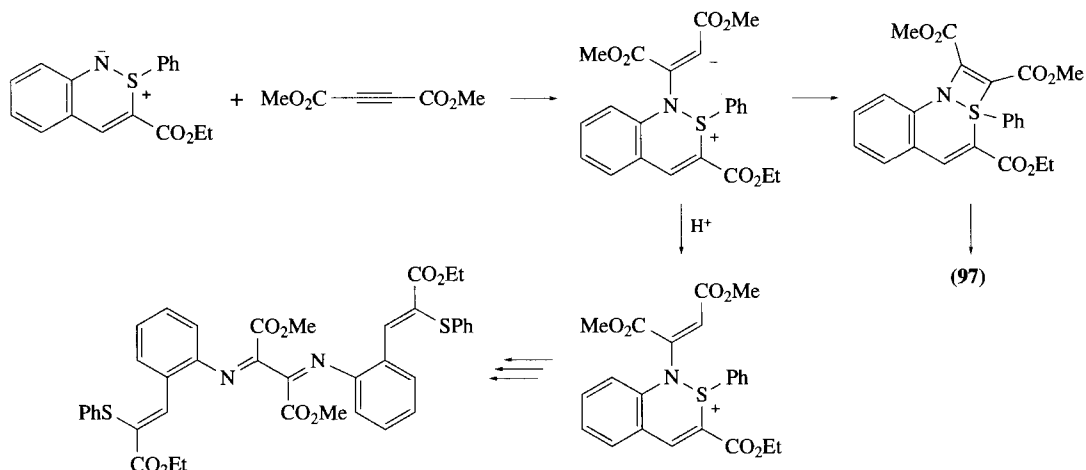
Unexpectedly, treatment of *S*-phenacyl-2-thiol-2'-aminobiphenyl with *N*-chlorosuccinimide affords not the anticipated 9-thia-10-azaphenanthrene, but instead a low yield (12.6%) of (101) (Scheme 37) ^[91JCS(P1)1733].



Scheme 37

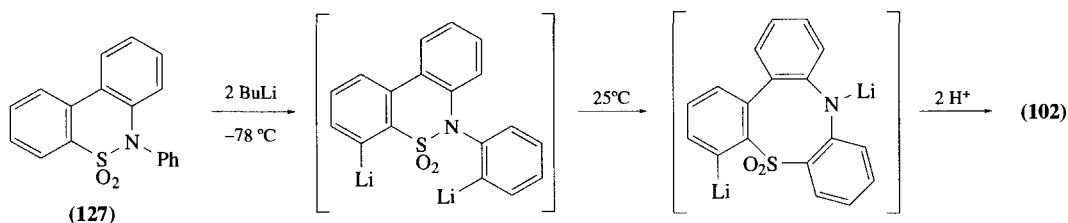
9.23.5.6 Ring Synthesis by Transformation of Another Ring

Azathiabenzenes undergo facile condensations with dimethyl acetylenedicarboxylate in aprotic solvents, affording thiazocine ylides (**97**), (**98**), and (**107**) in 20–98% yield <82CC1060, 84CPB4360>, reportedly through conjugate addition, followed by ring closure and valence tautomerization (Scheme 38). Protic solvents intercept the initial adduct, leading to an acyclic dimer <82CC1060>.



Scheme 38

Warming the dilithiate of dibenzothiazine (**127**) to room temperature results in [1,3]-migration of the sulfonyl group to the neighboring phenyl anion (Scheme 39); protonation of the so-formed anion provides tribenzothiazocine (**102**) in 88% yield <83T2073>.



Scheme 39

9.23.5.7 Comparison of Synthetic Routes

The perhaps surprising success of the cyclization routes to the thiazocines suggests that such strategies could be applicable to the preparation of other members of this still rare class of compounds, while the ring-expansion routes, although novel, appear not to be of general utility. Clearly lacking are routes to the non-benzannellated thiazocines, particularly those in which issues of delocalization and potential aromaticity might be addressed.

9.23.5.8 Important Compounds and Applications

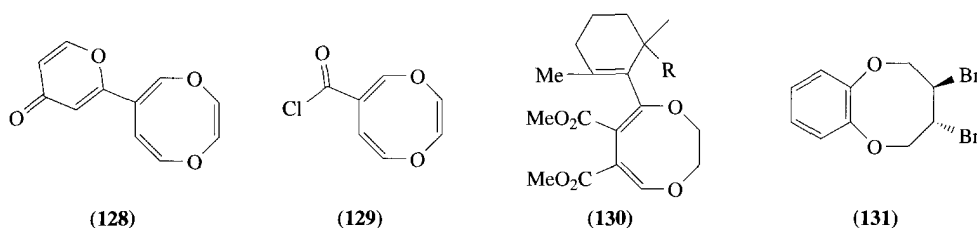
Despite their comparative rarity, the thiazocines have featured in a number of pharmaceutical and other studies. Cyclic amidine (**111**) displays a number of physiological effects in rats and mice, acting as a local anesthetic, an antiarrhythmic, and a spasmolytic agent, lowering blood pressure, and increasing motility of thiopental-treated mice, and also displays broad-spectrum antimicrobial activity *in vitro* <74CCC333>. Examination of a series of 1,6-benzothiazocines for CNS activity revealed no interesting activity, despite the activity of many related heterocycles <83JHC1593>. Dibenzo[*b,g*] derivative (**115**) and its thiazepine analogues were studied as neuroleptic and antipsychotic agents <86EUP240228>. 2*H*-3,4,5,6-Tetrahydro-1,6-benzothiazocine and its *N*-formyl

derivative act as antiulcer agents, inhibiting gastric acid secretion <84JAP(K)60202818>, 1*H*-1-phenyl-3,4,5,6-tetrahydro-2,5-benzothiazocine (**117**) and its *N*-alkylated and *S*-oxide analogues display some analgesic activity (weaker, however, than the oxazocine analogue, nefopam) <82JAP(K)5913770>, and derivatives of cyclic peptides such as (**124**) display antihypertensive activity <83EUP68173>. Cyclic peptide (**123**) was prepared as an intermediate in the synthesis of bicyclic hexapeptide somatostatin analogues <84EUP113029>. Several 1,6-benzothiazocines, including 2*H*-3,4-dihydro-1,6-benzothiazocin-5(6*H*)-thione, the methyl thioether derived from it, *N*-acetyl-2*H*-3,4,5,6-tetrahydro-1,6-benzothiazocine and the trifluoroacetyl analogue, and a series of 2*H*-3,4-dihydro-1,6-benzothiazocin-5(6*H*)-ones, serve as co-catalysts in the chlorination of monoalkylated benzenes, enhancing formation of *para*-chlorination products <88EUP340581, 90GEP(O)3837574>.

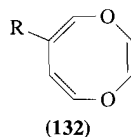
9.23.6 RINGS WITH TWO OXYGENS (1,4-DIOXOCINS)

9.23.6.1 Experimental Structural Methods

Single-crystal x-ray diffraction analyses of 1,4-dioxocin derivative (**128**) <84AG(E)966>, chloroformyl 1,4-dioxocin (**129**) <84AG(E)966>, 2,3-dihydro-1,4-dioxocin (**130**; R = H) <88JOC5672>, and 3,4-dibromo-2,3,4,5-tetrahydro-1,6-benzodioxocin (**131**) <88AX(C)517> have been reported. With the exception of the chloroformyl derivative, which displays a planar 1,4-dioxocin ring, each appears to adopt a decidedly nonplanar, twist-boat conformation, seemingly regardless of the extent of unsaturation. Unfortunately, only the account of (**131**) discusses the metrical parameters of the dioxocin ring, and there is of course no potential for delocalized bonding in this tetrahydro derivative. Conformational features of these dioxocins are discussed further below.

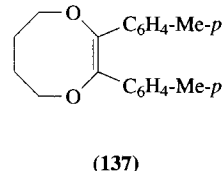
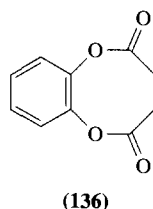
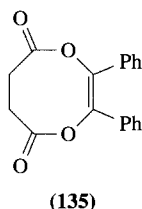
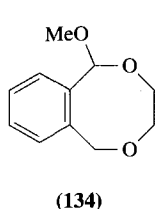
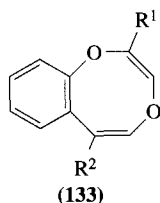


In contrast to the relative ease of classification of the ¹H NMR spectral signatures of the 1,4-diazocines in accord with either planar or nonplanar conformations of the diazocine ring, the ¹H NMR spectra of fully-unsaturated 1,4-dioxocins (**132**; R = H, Br <72AG(E)935>, CHO, CO₂Me, CONH₂, CO₂H, COCl <83AG(E)410, 84AG(E)966>) do not appear to allow any such clear conclusions. However, if one focuses on the two derivatives of known structure, it is apparent that the ring protons of planar, potentially aromatic (**129**) are shifted appreciably downfield from those of nonplanar (**128**).

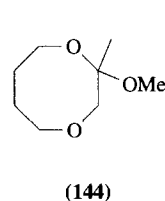
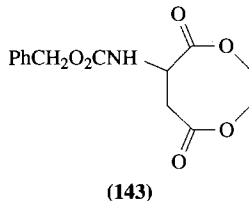
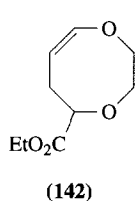
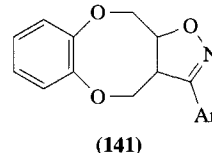
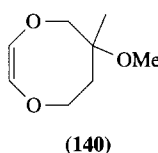
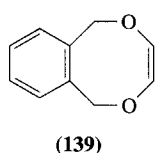
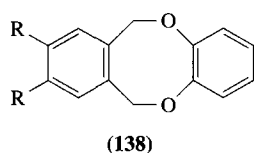


Unique 1,4-benzodioxocin derivatives (**133**; R¹ = R² = H, Me; R¹ = H, R² = Me) display ring proton resonances in the alkene region, and the ¹H and ¹³C NMR spectra of these compounds more closely resemble those of nonplanar monocyclic and 1,6-benzodioxocins than of planar 1,4-diazocines or 1,4-oxazocines, suggesting that they are nonplanar and nonaromatic <85CC1254>. 2,5-Benzo-1,3,4,6-tetrahydrodioxocin (**134**) <89JA1465>, diones (**135**) <83JCS(P1)875> and (**136**) <87IJC(B)30>, and 5,6,7,8-tetrahydro-1,4-dioxocin (**137**) <84IJC(B)1289> all display ¹H NMR resonances in accord with the functionalities present, as do a diverse array of 2,3,4,5-tetrahydro-1,6-benzodioxocins bearing various aromatic ring substituents <83ZN(B)1243, 90JHC177, 91JHC1373, 91JHC1657, 91JHC625>.

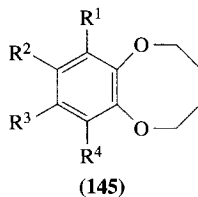
Dihydro-1,4-dioxocins (**138**; R = H, Me) <88SC1283>, (**139**) <88CCC1060>, and (**130**; R = H, Me) <88JOC5672> and tetrahydro-1,4-dioxocins (**140**) <81T3131>, (**141**; Ar = Ph; *m*-Cl-C₆H₄; *p*-X-C₆H₄, X = MeO, Me, F, Cl, Br, NO₂) <88CCC1060>, and (**142**) <84JOC1917>, as well as 1,4-dioxocanes (**143**)



<82JOM(239)301> and (144) <81T3131> have also been examined by ^1H NMR spectroscopy. Although these studies proved of diagnostic value, no unusual chemical shifts or other spectral features were noted. For those few compounds which have been examined by ^{13}C NMR spectroscopy, O-CH₂ resonances invariably fall near 70 ppm <88CCC1060, 88JOC5672, 91JHC1657>.

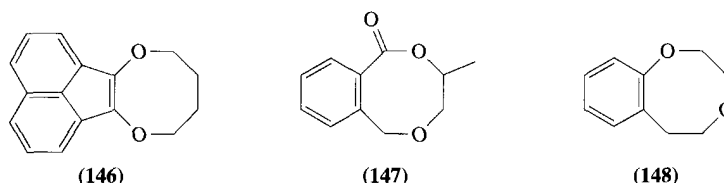


A comparatively large number of 5,6,7,8-tetrahydro-1,4-dioxocins, particularly 1,6-benzo derivatives (145; R¹-R⁴ = H, NO₂, NH₂, N₃, Cl), have been characterized by mass spectroscopy, including a number of compounds in multiple isomeric forms, facilitating an analysis of preferred mass spectral fragmentation patterns for these compounds <90JHC177, 91JHC1373, 91JHC1657>. The parent ion is generally quite prominent, often representing the base peak. The vast majority of these derivatives display M-42 and M-54 peaks, corresponding to loss of either C₃H₆ or CH₂CO (M-42) and C₄H₆ (M-54) fragments, with the latter almost certainly representing loss of the C(2)-C(5) unit of the dioxocin ring. There appears to be some indication that the relative intensity of the M-42 peak is higher for derivatives bearing acetamido groups on the aromatic ring, which might be expected to eliminate CH₂CO (e.g. the M-42 fragment is the base peak for (145; R¹ = R³ = NO₂, R³ = NHAc, R⁴ = H) <91JHC1373>, but there are exceptions. A great many of these derivatives also display a large fragment at m/z 55 (C₄H₇), corresponding to the C(2)-C(5) unit.

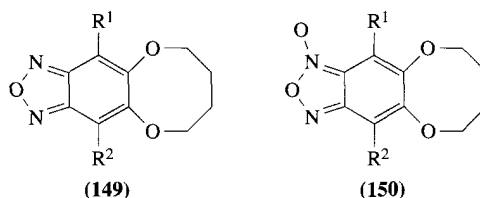


Acenaphthene derivative (146) behaves somewhat differently, with the M-42 fragment prominent, but no M-54 fragment reported; loss of CHO represents the base peak for this compound <84IJC(B)1289>. Monocyclic 5,6,7,8-tetrahydrodioxocins also appear to fragment with cleavage of

the C(5)—O and C(8)—O bonds; the base peaks for **(135)** and **(137)** correspond either to ArCO or doubly charged (ArCO)₂ fragments <83JCS(P1)875, 84IJC(B)1289>. Tetrahydro-2,5-benzodioxocin (**147**), characterized only by mass spectral analysis, gives a weak parent ion <89JMOC145>; cleavage of the C(1)—O and C(6)—O bonds appears to be responsible for the major fragments observed. Chemical ionization (using ammonia) provides a much higher intensity parent ion. The fully unsaturated 1,4-dioxocins (**132**; R = CO₂H, COCl, CONH₂) share the common fragmentation path of loss of CHO <83AG(E)410>; fragmentation data for (**132**; R = CHO, CO₂Me) were not reported, although the latter do yield significant parent ions. Parent ions were also noted, without indication of fragmentation patterns, for tetrahydro-1,6-benzodioxocin (**136**) <87IJC(B)30>, tetrahydro-1,4-benzodioxocin (**148**) <85CC1254>, dibenzo[*b,f*][1,4]dioxocins (**138**; R = H, Me) <88SC1283>, and perhydrodioxocindione (**143**) <82JOM(239)301>.



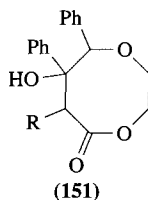
The parent 1,4-dioxocin (**132**; R = H) is colorless, with its major absorption band well into the ultraviolet [238 nm (3.86)] and a weak shoulder at 285 nm (2.50), a spectrum similar to that of 1,3,6-cyclooctatriene <72AG(E)935>. The formyl, carboxy, and carbomethoxy derivatives display absorption bands near 250 nm (ca. 3.5) <83AG(E)410>. Many of the 5,6,7,8-tetrahydro-1,6-benzodioxocins (**145**) absorb in the visible region, but these colors correspond to those of typical non-dioxocin-fused aromatic compounds, with nitroaniline derivatives displaying the most intense colors <91JHC1373>. Spectral data were reported only for the benzofurazans (**149**) and their *N*-oxides, the benzofuroxans (**150**); observed ultraviolet spectral features are in accord with the reported colors of these derivatives, with those compounds displaying no significant absorption bands above ca. 370 nm being colorless (e.g. (**149**; R¹ = H, R² = NHAc)) and those displaying such bands appearing yellow due to tailing of their absorptions into the visible region (e.g. (**150**; R¹ = H, R² = NO₂)) <91JHC1373>.



Isoxazoline-fused derivatives (**141**) absorb at ca. 285 nm; this absorption appears to be localized in the isoxazoline moiety <88CCC1060>. Acenaphthene derivative (**146**) absorbs at 340 (3.66), 315 (3.68), and 250 (4.08) nm, while monocyclic tetrahydrodioxocin (**137**) displays bands shifted further into the ultraviolet, at 260 (5.51) and 222 (5.33) nm <84IJC(B)1289>. The intensities of the latter absorptions, an order of magnitude higher than those of the corresponding benzo derivatives, appear curious.

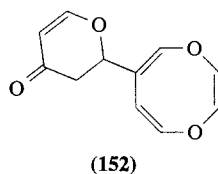
Infrared spectral data reported for the fully unsaturated 1,4-dioxocins focus only on the obvious functional groups; carbonyl stretching bands in (**132**; R = CHO, CO₂H, COCl, CO₂Me, CONH₂) <83AG(E)410> fall into the ranges typically seen for simple α,β -unsaturated and aryl analogues. Dihydrodioxocins (**130**; R = H, Me) display, in addition to an ester stretch at 1720 cm⁻¹, an apparent C=C stretching band at 1620 cm⁻¹ and a C—O mode at ca. 1100 cm⁻¹ <88JOC5672>. An analogous C—O stretching band is also seen in dibenzo[*b,f*][1,4]dioxocin (**138**; R = H) <88SC1283>. The 1100 cm⁻¹ stretch is not reported for (**138**; R = Me) <88SC1283>, but a band at 1230 cm⁻¹ is suggestive of the reported C—O—C mode in (**137**) (1270 cm⁻¹) and (**146**) (1250 cm⁻¹) <84IJC(B)1289>. The C=C modes in the latter occur at 1610 and 1658 cm⁻¹, respectively. Full infrared data were reported for a large number of 2,3,4,5-tetrahydro-1,6-benzodioxocins (**145**) <90JHC177, 91JHC1373, 91JHC1657>, nearly all display modes in the 1220–1290 cm⁻¹ and 1000–1100 cm⁻¹ regions which presumably arise from C—O and C—O—C vibrational modes. Only C=O and O—H modes were reported for (**145**; R¹ = R⁴ = Me, R² = CHO, R³ = H) and (**145**; R¹ = R⁴ = Me, R² = OH, R³ = H),

respectively $\langle 83ZN(B)1243 \rangle$. Saturated lactones (**143**) and (**151**; $R = H$) display typical $C=O$ stretches, at 1740 cm^{-1} $\langle 82JOM(239)301 \rangle$ and 1705 cm^{-1} $\langle 91CC1617 \rangle$, respectively, which stand in contrast to the rather high energy stretch reported for benzo analogue (**136**) (1770 cm^{-1}) $\langle 87IJC(B)30 \rangle$.



9.23.6.2 Thermodynamic Aspects

The fully unsaturated 1,4-dioxocins are all either liquids (**132**; $R = H$, Br $\langle 72AG(E)935 \rangle$, CHO , CO_2Me $\langle 83AG(E)410 \rangle$) or rather low-melting solids ((**132**; $R = CO_2H$, $COCl$, $CONH_2$) $\langle 83AG(E)410 \rangle$, (**128**), (**152**) $\langle 84AG(E)966 \rangle$), consistent with the limited intermolecular interactions in the solid state expected for such structures.



Similarly, 1,4-benzodioxocins (**133**; $R^1 = R^2 = H$, Me ; $R^1 = H$, $R^2 = Me$) are liquids, as is the 2,3,5,6-tetrahydro analogue (**148**) $\langle 85CC1254 \rangle$. Dibenzobenzodioxocin (**138**; $R = H$) is also rather low melting (m.p. $74\text{--}80^\circ\text{C}$), while (**138**; $R = Me$), with reduced symmetry, melts at 28°C $\langle 88SC1283 \rangle$. 2,3-Dihydro-1,4-dioxocins (**130**) melt at $106\text{--}108^\circ\text{C}$ ($R = Me$) and $74\text{--}76^\circ\text{C}$ ($R = H$) $\langle 88JOC5672 \rangle$; reduced symmetry again leads to a lower melting point. Again, lacking the potential for significant intermolecular interactions, tetrahydro acetal (**140**) is a liquid $\langle 81T3131 \rangle$, while 5,6,7,8-tetrahydrodioxocins (**135**) $\langle 83JCS(P1)875 \rangle$, (**137**), and (**146**) $\langle 84IJC(B)1289 \rangle$, which offer potential dipole-dipole or π -stacking interactions, melt near 100°C . The lack of any significant elevation of melting point for (**146**), with its extended planar aromatic group, however, may argue against the significance of the latter effect. The ca. 200°C melting point reported for (**136**) $\langle 87IJC(B)30 \rangle$, representing one of the highest melting points reported for any benzodioxocin derivative, including those with multiple polar and/or H -bonding substituents on the aromatic ring $\langle 83ZN(B)1243$, $88CCC1060$, $90JHC177$, $91JHC1373$, $91JHC1657 \rangle$, may cast some doubt upon the structural assignment of this compound. With regard to the issue of intermolecular H -bonding, phenol (**145**; $R^1 = R^4 = Me$, $R^2 = OH$, $R^3 = H$) is a crystalline solid (m.p. $113.5\text{--}114.5^\circ\text{C}$), sublimable at $100^\circ\text{C}/0.02\text{ mm Hg}$, while the precursors to this compound (**145**; $R^1 = R^4 = Me$; $R^2 = H$, CHO ; $R^3 = H$) are both liquids $\langle 83ZN(B)1243 \rangle$. Perhaps due to both dipole-dipole and intermolecular H -bonding interactions, perhydrodioxocin (**143**) is crystalline (m.p. 112°C) $\langle 82JOM(239)301 \rangle$, while unsubstituted 1,4-dioxocane, lacking any such potential, is a liquid $\langle 72AG(E)935 \rangle$.

Dioxocins (**132**) are soluble in a variety of common organic solvents, including acetone, $CHCl_3$, CCl_4 and Et_2O , from which the carboxylic acid and acyl chloride derivatives may be recrystallized upon addition of pentane $\langle 83AG(E)410$, $84AG(E)966 \rangle$. Virtually all the other reported dioxocin derivatives, regardless of oxidation state or extent of benzannelation, appear to display good solubility in chlorinated methanes, with $CDCl_3$ the solvent of choice for NMR spectral studies. Recrystallization has been effected from alcohols $\langle 84IJC(B)1289$, $88JOC5672$, $90JHC177$, $91JHC1373$, $91JHC1657$, $91JHC625 \rangle$, pentane $\langle 83JCS(P1)875 \rangle$, CH_2Cl_2 $\langle 87IJC(B)30 \rangle$, aqueous acetic acid $\langle 91JHC1373 \rangle$, Et_2O $\langle 90JHC177 \rangle$, and water $\langle 90JHC177 \rangle$; ethanol appears to be the preferred solvent for recrystallization of many of the 1,6-benzodioxocins. Chromatographic purification of a variety of dioxocins has been reported, invariably using silica and relatively nonpolar elution solvents (often alkanes admixed with 10–20% ethyl acetate) $\langle 82JOM(239)301$, $84AG(E)966$, $86JA6062$, $88JOC5672$, $88CCC1060$, $89JA1465$, $90JHC177$, $91JHC1373$, $91JHC1657 \rangle$. Mononitro-1,6-benzodioxocins (**145**; $R^1 = NO_2$, $R^2 = R^3 = R^4 = H$) and (**145**; $R^2 = NO_2$, $R^1 = R^3 = R^4 = H$), inseparable by conventional column chromatography, were separated

preparatively by gas chromatography using a silicone (SE-30) column <90JHC177>, and acetals (**140**) and (**144**) were similarly purified <81T3131>. The yield of lactone (**147**) was determined by capillary gas chromatography <89JMOC145>.

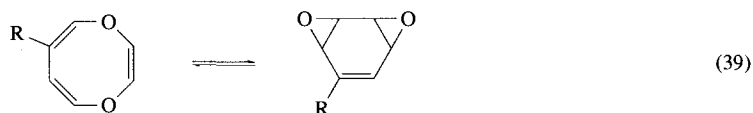
In contrast to the sometimes confusing state of affairs regarding theoretical studies of several classes of diheterocins, an apparently consistent picture has arisen from several semiempirical molecular orbital analyses of 1,4-dioxocin (**132**; R = H). Unlike the cyclooctatetraene dianion, 1,4-dioxocin has no strain-free conformations; a strain of ca. 43 kcal mol⁻¹ was calculated for the planar form, leading to the conclusion that the dioxocin ring should be nonplanar <65RRC1059>. SINDO1 calculations, which successfully reproduced both the geometry and the aromaticity of the cyclooctatetraene dianion, predict a high degree of bond localization and nonplanarity for 1,4-dioxocin and its derivatives <84JOC4475>. AM1 calculations also point to bond localization and a nonplanar conformation for the dioxocin ring, which is, in contrast to several other diheterocins, calculated to represent a minimum on the singlet potential energy surface <91RRC333>. Experimental results, with x-ray crystallographic and NMR spectral analyses being particularly informative, appear largely in accord with these theoretical predictions <78AHC(23)55>, although there does appear to be some uncertainty about whether conversion to planar, potentially delocalized structures is favored by strongly electron-donating <84JOC4475> or -withdrawing <84AG(E)966> substituents. Chemically as well, 1,4-dioxocin appears to behave as an alkene rather than as an aromatic compound. Thus, it is readily hydrogenated to 1,4-dioxocane and polymerizes readily upon standing <72AG(E)935>. In addition, in contrast to the irreversible formation of the at least partially delocalized diaza and oxaza analogues by thermal valence tautomerization, the analogous formation of 1,4-dioxocin (see below) is reversible <72AG(E)937, 84AG(E)966>. Although it is tempting to suggest that the lack of delocalization is due to the relative reluctance of oxygen to participate in delocalized bonding, the nonaromaticity of 1,4-dithiocin (see below) suggests that this certainly cannot be the only explanation. 1,4-Benzodioxocins (**133**), also representing potentially fully conjugated, 10 π -electron systems, are similarly nonaromatic, displaying NMR parameters more consistent with localized bonding and readily reduced to the corresponding tetrahydro derivatives upon catalytic hydrogenation <85CC1254>. The simple dilactone (**135**) is reported to be unstable in air; the nature of the decomposition products, however, was not revealed <83JCS(P1)875>.

In addition to theoretical analyses of the 1,4-dioxocin ring, all directed toward elucidation of its potential for planarity and aromaticity <65RRC1059, 78AHC(23)55, 84JOC4475, 91RRC333>, a number of experimental studies of the conformation of dioxocins and their reduced analogues have appeared. The twist-boat conformation revealed by solid-state structural analysis of pyrone (**128**) appears to be maintained in solution for many of the 1,4-dioxocins (**132**), although the carbaldehyde and acyl chloride derivatives display distinctive NMR spectral features consistent with the presence of a planar ring <84AG(E)966>. The twist-boat-like form of tetrahydro derivative (**131**), demonstrated by solid-state structural analysis, is highlighted by the approximate C₂ axis passing through the C(3)—C(4) bond and the benzo group <88AX(C)517>. Also noteworthy in this structure is the orientation of the C(3)—C(4) bond, which makes an angle of ca. 74° relative to the normal to the benzene ring. In contrast, the corresponding angle in a related dithiocin <78AX3833> (see below) is only 34°; eclipsing interactions between the C-2 and C-3 hydrogens would become severe if this angle were maintained in the dioxocin. Benzodioxocins (**133**) are also nonplanar, although no detailed analysis of their conformations have been made <85CC1254>. Dihydro derivatives also appear to favor a twist-boat-like conformation, as revealed by the crystallographic analysis of (**130**) <88JOC5672>.

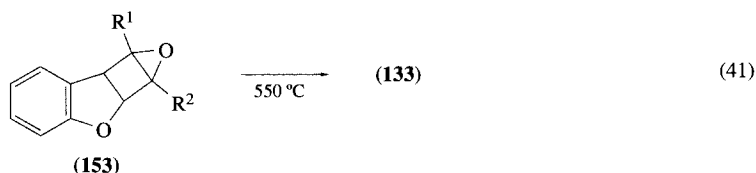
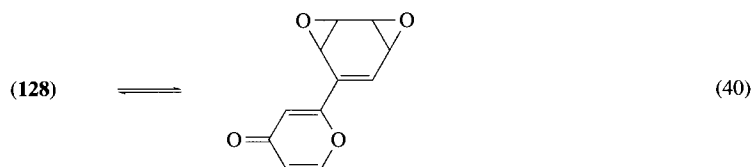
Extensive NMR conformational studies of 2,5-dihydro-1,6-benzodioxocin (**139**) and the dibenzo analogue (**138**; R = H), in parallel with analogous studies of diazocines, oxazocines, and oxathiocins, have revealed multiple conformational equilibria <88M233>. As for the diheterocins discussed above, the energetics of the twist-boat inversional mode were not accessible by NMR studies given the low barrier to this interconversion. In addition, the alternative boat inversional mode discussed for the other diheterocins, of unknown transition state, was sufficiently rapid even at the lowest temperatures studied to preclude determination of its energetics. Apparently oxygen is both less effective at stabilizing the ground state and less destabilizing of the transition state than is nitrogen or sulfur. On a somewhat different note, conformational and other effects on the nitration of 1,6-benzodioxocins have been critically assessed through a systematic study of a wide array of analogues <91JHC625>.

Studies related to the tautomerization of 1,4-dioxocins have focused exclusively on the valence tautomerization of fully unsaturated derivatives. The energetics of the thermal cycloreversion of 6-bromo-1,4-dioxocin (**132**; R = Br) to its benzene dioxide valence tautomer have been examined. The ring contraction displays an activation energy of 28.5 kcal mol⁻¹, with an *A* factor of 3.8 × 10¹³ in

CCl_4 , while the cycloreversion to the dioxocin has a barrier of $25.6 \text{ kcal mol}^{-1}$, with an A factor of 3.2×10^{12} , giving a 65:35 mixture of dioxocin and benzene dioxide at 77°C (Equation (39)) $\langle 72\text{AG(E)935} \rangle$.



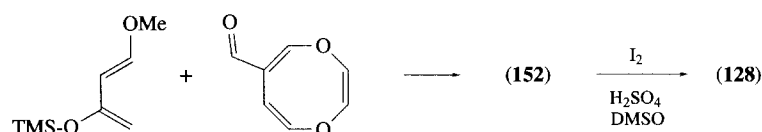
The parent 1,4-dioxocin shows no evidence of tautomerization in CCl_4 at 100°C , but gives a 95:5 ratio of dioxocin and benzene dioxide at 60°C in benzene; the energetics for this interconversion are similar to those of the bromo derivative $\langle 72\text{AG(E)937} \rangle$. Dioxocins bearing electron-withdrawing substituents (**132**; $\text{R} = \text{CO}_2\text{H}$, CHO) are formed quantitatively from their benzene dioxide precursors upon refluxing in CCl_4 ($\text{R} = \text{CO}_2\text{H}$) or acetone ($\text{R} = \text{CHO}$), while heating either of these in methanol affords an equilibrium mixture comprised of 68% dioxocin and 32% benzene dioxide $\langle 83\text{AG(E)410} \rangle$. Similarly, dioxocin (**128**) is thermally equilibrated to the benzene dioxide upon refluxing in acetone; the latter compound, identical to the fungal antibiotic LL-21220, is formed in ca. 30% yield under these equilibrating conditions and may be chromatographically separated from (**128**) (Equation (40)) $\langle 84\text{AG(E)966} \rangle$. An alternative valence tautomerization occurs upon flash vacuum pyrolysis of polycyclic epoxides (**153**), affording 1,4-benzodioxocins (**133**) in 15–25% yield (Equation (41)). No such isomerization is observed in solution at 250°C , and the isomerization is presumably irreversible $\langle 85\text{CC1254} \rangle$.



9.23.6.3 Reactivity of Fully Conjugated Rings

Fully conjugated 1,4-dioxocins undergo thermal equilibration with their benzene dioxide valence tautomers $\langle 72\text{AG(E)937}$, 72AG(E)935 , 83AG(E)410 , 84AG(E)966 , $85\text{CC1254} \rangle$, as discussed above. Treatment of 6-bromo-1,4-dioxocin (**132**; $\text{R} = \text{Br}$) with tributyltin hydride affords the parent 1,4-dioxocin (**132**; $\text{R} = \text{H}$) in 32% yield $\langle 72\text{AG(E)935} \rangle$. Both 1,4-dioxocin (**132**; $\text{R} = \text{H}$) and 1,4-benzodioxocin (**133**; $\text{R}^1 = \text{R}^2 = \text{H}$) are readily hydrogenated over palladium to afford, in high yield, 1,4-dioxocane $\langle 72\text{AG(E)935} \rangle$ and 2,3,5,6-tetrahydro-1,4-benzodioxocin (**148**) $\langle 85\text{CC1254} \rangle$, respectively.

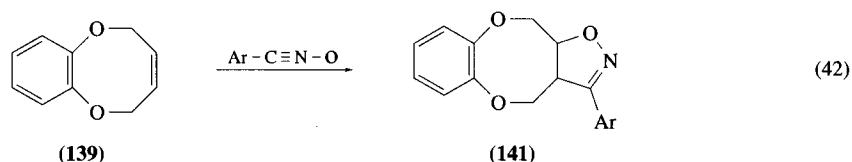
The reactivity of the 1,4-dioxocin ring toward potential dienophiles (e.g. triazolinediones) has apparently not been explored. The carbalddehyde side chain of 1,4-dioxocin (**132**; $\text{R} = \text{CHO}$) behaves as a dienophile toward 1-methoxy-3-trimethylsiloxy-1,3-butadiene, affording dihydropyrone (**152**) in 25% yield (Scheme 40); oxidation of (**152**) affords a low yield (5%) of the corresponding pyrone (**128**) $\langle 84\text{AG(E)966} \rangle$.



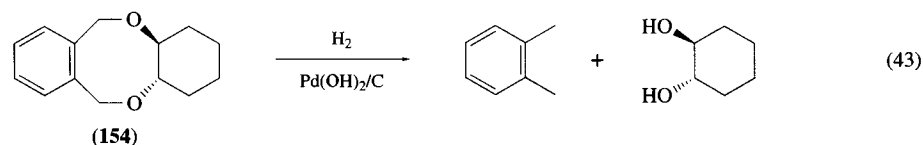
Scheme 40

9.23.6.4 Reactivity of Nonconjugated Rings

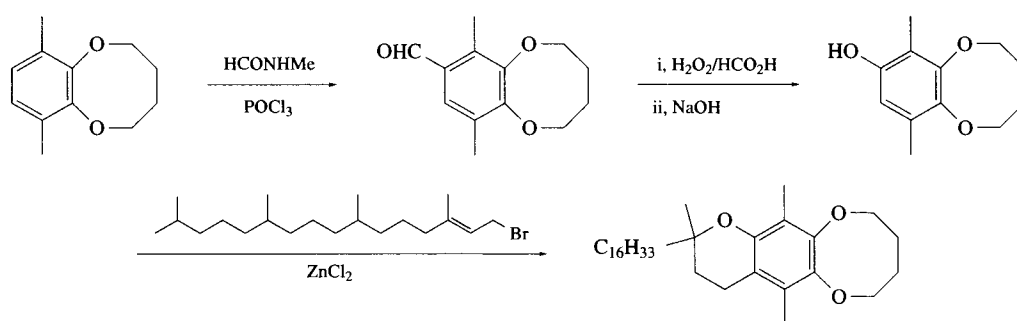
2,5-Dihydro-1,6-benzodioxocin (**139**) undergoes 1,3-dipolar cycloaddition with nitrile oxides to afford moderate yields of isoxazolino-fused dioxocins (**141**) (Equation (42)); the corresponding diazocines did not yield cycloadducts under identical reaction conditions. Attempted photoisomerization of these isoxazolines, while successful with simpler systems, afforded only tarry products <88CCC1060>.



Catalytic hydrogenolysis of 6,11-dihydrodibenzo[*b,f*][1,4]dioxocin (**138**; R = H) over Pearlman's catalyst affords catechol in 99% yield, suggesting the possible utility of such derivatives as protecting groups for 1,2-diols; 1,2,3,4,4a,6,11,12a-octahydrodibenzo[*b,f*][1,4]dioxocin (**154**) is similarly converted to cyclohexanediol <89SC3363>.



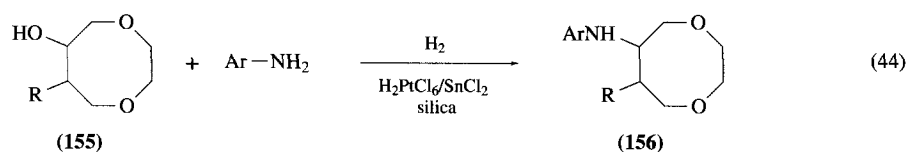
With one exception, the reported hydrolytic cleavage of tetrahydrodioxocin acetal (**134**) <89JA1465>, all reported reaction chemistry of tetrahydrodioxocins has involved electrophilic aromatic substitution and subsequent transformations of the so-introduced aromatic substituents in 2,3,4,5-tetrahydro-1,6-benzodioxocins (**145**). Thus, for example, the aromatic ring undergoes AlCl_3 -catalyzed Friedel–Crafts acylation <89KFZ413, 89KFZ435, 90KFZ50, 91KFZ14, 91MI 923-02>, and the resulting ketones undergo Mannich condensation <90KFZ50>, reduction <91KFZ14>, and amination <89KFZ413>. Aromatic formylation, followed by Baeyer–Villiger oxidation, saponification, and ZnCl_2 -catalyzed condensation to chroman derivatives, has also been reported (Scheme 41) <83ZN(B)1243>.



Scheme 41

Nitration of the aromatic ring has been studied in great detail, as has been the reduction, acetylation, and nucleophilic displacement by azide of the resulting functionalized products <90JHC177, 91JHC1373, 91JHC1657, 91JHC625>. In all of these reactions, the dioxocin ring largely acts as an innocent, unreactive bystander, although it appears to exert rather important effects in the aromatic nitration reactions <91JHC625>.

Aryl amines react with 1,4-dioxocan-6-ols (**155**; R = H, Me) upon hydrogenation over a platinized silica catalyst at 150–300°C to afford 6-amino analogues (**156**; R = H, Ar = 2,6-Me₂C₆H₃; R = Me, Ar = 2-Me-C₆H₄) (Equation (44)) <90USP4921980>.

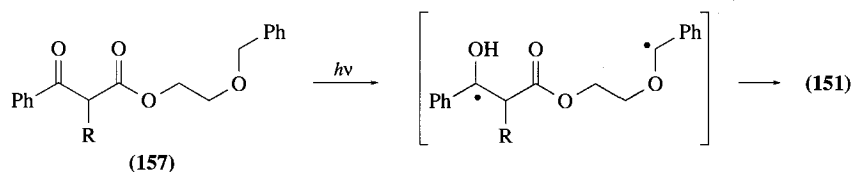


9.23.6.5 Reactivity of Substituents Attached to Ring Carbon Atoms

6-Carboxy-1,4-dioxocin (**132**; R = CO₂H) behaves as a typical carboxylic acid, undergoing conversion to the corresponding acyl chloride upon treatment with thionyl chloride; the latter in turn may be converted to the corresponding methyl ester or amide <83AG(E)410>. Diels–Alder cycloaddition to the aldehyde group in 1,4-dioxocin-6-carbaldehyde <84AG(E)966> is discussed above.

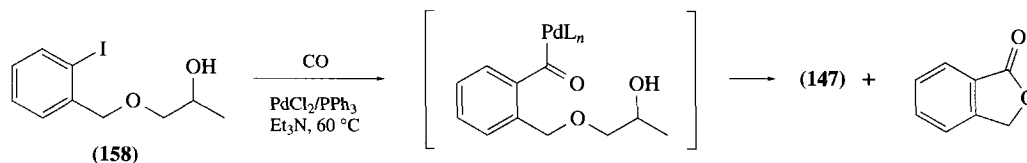
9.23.6.6 Ring Syntheses

Both unimolecular cyclizations and condensation reactions have been used to effect closure of the 1,4-dioxocin ring. Although these are discussed separately below, the condensation reactions presumably occur in a stepwise manner, and thus formally are perhaps better considered to be cyclization reactions also. Photoinduced remote cyclization of ketoethers (**157**; R = H, Me) affords the corresponding dioxocanones (**151**) in 48% (R = H) and 76% (R = Me) yield, apparently via an intermediate *H*-atom abstraction via a ten-membered ring-transition state (Scheme 42). Compound (**151**; R = H) is obtained as a single stereoisomer, presumably with *trans* phenyl groups, while (**151**; R = Me) is obtained as a ca. 1 : 1 mixture of *cis* and *trans* isomers <91CC1617>.



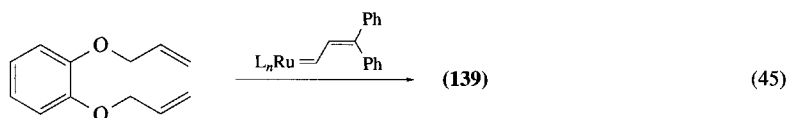
Scheme 42

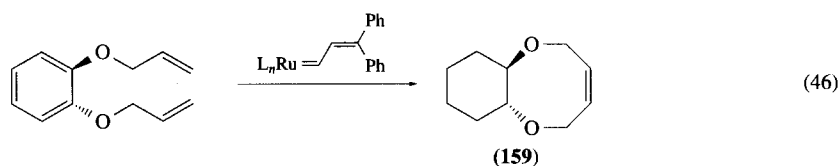
Palladium-catalyzed carbonylation of iodo alcohol (**158**) affords a 22% yield of dioxocinone (**147**), together with a 12% yield of phthalide (Scheme 43); the latter is the sole product obtained upon attempted formation of the ten-membered ring analogue <89JMOC145>.



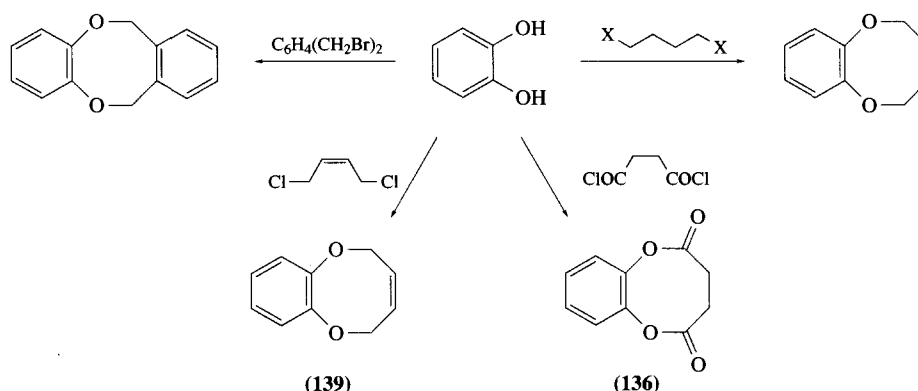
Scheme 43

Despite unsuccessful earlier attempts to effect the closure of eight-membered rings via ring-closing metathesis reactions, conformationally less flexible bis(allyl ethers) readily undergo such ring closure, affording dioxocins (**139**) (Equation (45)) and *trans*-(**159**) (Equation (46)) in good yield; *cis*-(**159**) is formed in lower (20%) yield <95JA2108>.



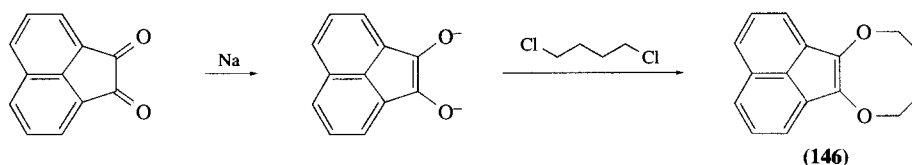


Treatment of catechol with *cis*-1,4-dichloro-2-butene affords 2,5-dihydro-1,6-benzodioxocin (**139**) <67AG(E)697>. Similarly, catechol and its derivatives react with α,α' -xylylene dibromide to afford 6,11-dihydrodibenzo[*b,f*][1,4]dioxocins (**138**; R = H, Me) <88SC1283, 89SC3363>, with 1,4-dihalobutanes to afford tetrahydro-1,6-benzodioxocins (**145**) <83ZN(B)1243, 91MI 923-02> and with succinoyl dichloride to afford 2,5-dione (**136**) (Scheme 44) <87IJC(B)30>.

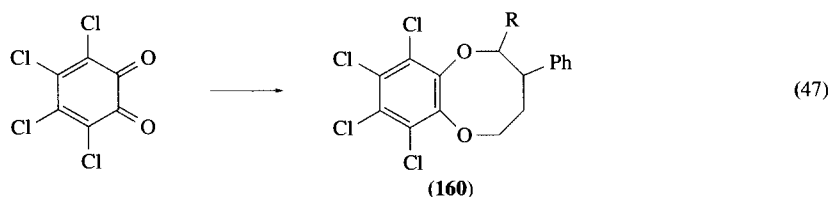


Scheme 44

Sodium metal reduction of α -diketones affords enediolates, alkylation of which by 1,4-dichlorobutane affords the tetrahydrodioxocins (**137**) and (**146**) in ca. 70% yield (Scheme 45) <84IJC(B)1289>. Tetrachloroquinone is reported to react, with unspecified reagents, to form tetrahydro-1,6-benzodioxocins (**160**; R = Me, Ph) (Equation (47)) <83URP938557>.

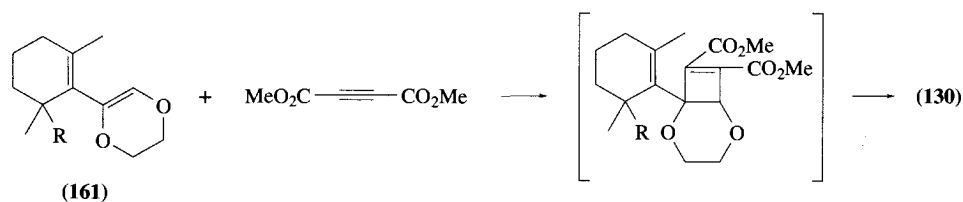


Scheme 45



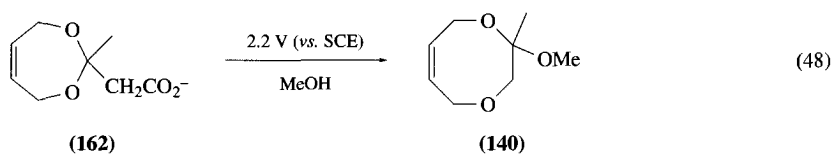
9.23.6.7 Ring Synthesis by Transformation of Another Ring

Unimolecular rearrangements of benzene dioxides to 1,4-dioxocins <72AG(E)935, 72AG(E)937, 83AG(E)410>, and of polycyclic epoxide (**153**) to the corresponding 1,4-benzodioxocin <85CC1254> are discussed above. Yields of the former are in general high, while the flash vacuum pyrolysis approach to the latter affords the dioxocin in 15–25% yield. Treatment of 1,4-dioxene derivative (**161**) with dimethyl acetylenedicarboxylate, under EtAlCl₂ catalysis, is proposed to yield an intermediate dioxabicyclo[4.2.0]octane (Scheme 46), which undergoes irreversible ring opening to the 2,3-dihydro-1,4-dioxocins (**130**; R = H, Me) in ca. 90% yield <88JOC5672>.

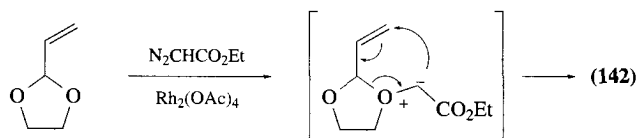


Scheme 46

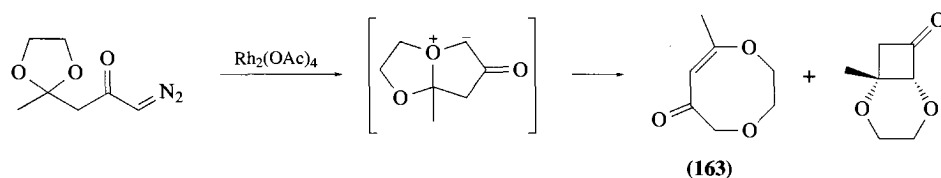
Anodic oxidation of dioxepin **(162)** in methanol affords a 23% yield of dioxocin acetal **(140)** (Equation (48)); saturated analogue **(144)** is prepared analogously $\langle 81\text{T}3131 \rangle$.



Inter- and intramolecular addition of carbenes to 1,3-dioxolanes, followed by [2,3]-sigmatropic rearrangement of the resulting *O*-ylides, provides low $\langle 86\text{JA}6062, 87\text{PAC}969 \rangle$ to modest $\langle 84\text{JOC}1917 \rangle$ yields of 1,4-dioxocins **(142)** (Scheme 47) and **(163)** (Scheme 48). The major product in the reaction affording **(163)** is a bicyclo[4.2.0]octanone, and use of a cyclization precursor bearing an α -methyl substituent affords only the bicyclooctane.

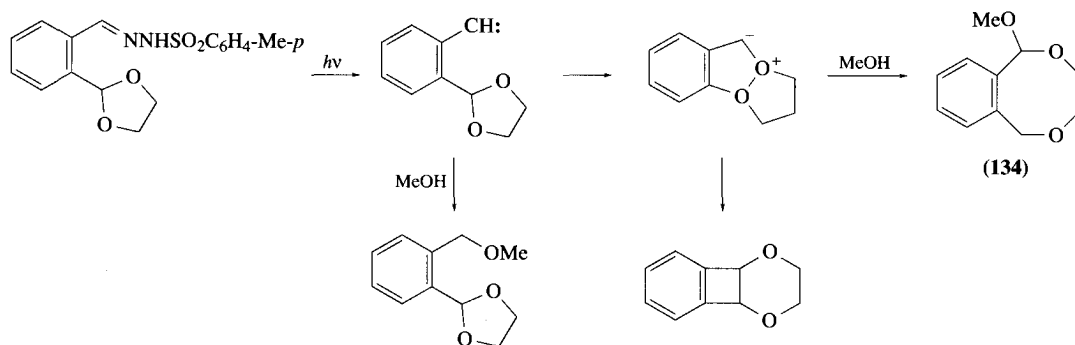


Scheme 47



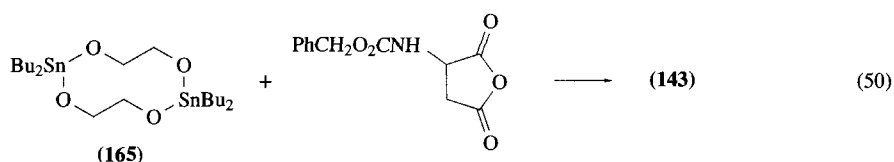
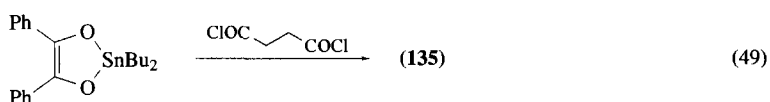
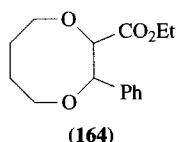
Scheme 48

In one reported case, photochemical (instead of metal-catalyzed) carbene generation affords a higher yield (up to 43%) of benzodioxocin **(134)** (Scheme 49); careful selection of an appropriate base was required to avoid diversion of the reaction to other products $\langle 89\text{JA}1465 \rangle$.



Scheme 49

Ring expansion via carboethoxycarbene insertion is reported to yield dioxocane (**164**) <80MI 923-01>. The cyclic tin enediolate derived from benzoin reacts with succinoyl dichloride to afford dioxocindione (**135**) in 49% yield (Equation (49)) <83JCS(P1)875>; similarly, cyclic tin oxide (**165**) reacts with aminosuccinic anhydride to give dione (**143**) in 35% yield (Equation (50)) <82JOM(239)301>.



9.23.6.8 Comparison of Synthetic Routes

Unimolecular cyclization routes to the dioxocin ring system appear rather limited in scope, although the ring-closing metathesis approach, given its tolerance of a variety of functional groups, may prove of fairly general utility for the generation of fused ring analogues. Dialkylation of 1,2-diols appears fairly versatile, although it appears to allow access only to 1,6-benzo-type fused-ring derivatives. The unimolecular rearrangement routes appear to suffer from the inaccessibility of appropriate precursors, and the dimethyl acetylenedicarboxylate addition to 1,4-dioxene, while appealing, will presumably be effective in only limited cases. Ylide rearrangement routes provide an interesting entry to the dioxocin ring system, but yields thus far have been modest. The tin-mediated cyclizations appear to offer some promise, at least for the preparation of lactone derivatives. The few additional syntheses of 1,4-dioxocins reported in CHEC-I (Sections 5.19.7.3, 5.19.7.5, and 5.19.4.4.2) provide no additional versatility, and new synthetic routes for their preparation would certainly be welcome; the near absence of 1,4-benzo derivatives is particularly conspicuous.

9.23.6.9 Important Compounds and Applications

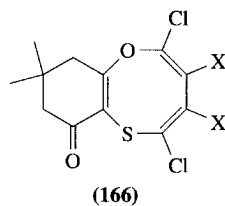
Dioxocin derivatives have been explored as anti-anxiety <89MIP8906961>, local anesthetic <89KFZ413>, nerve cell repair <90EUP382213>, and antiinflammatory agents <89KFZ435, 89KFZ1466, 90KFZ50, 91KFZ14, 91MI 923-02>. Derivatives bearing *N*-carboxymethyl groups have been explored as possible metal chelators for treatment of manganese <82MI 923-02>, nickel <83MI 923-03>, and other heavy metal <81MI 923-01> poisoning. More general applications to the field of organic synthesis include their use as protecting groups for 1,2-diols <89SC3363> and as intermediates in the synthesis of pesticides <90USP4921980>. Dioxocin derivatives have also been noted as agents for effecting clear images in water-based ink-jet recording sheets <87JAP(K)62156983>, cross-linking additives in epoxy resins <89MI 923-01>, and stabilizers for petrochemical extraction solvents, protecting hydrocarbons and oxygenates such as sulfolane and tetraethylene glycol from oxidation <92EUP467843>.

9.23.7 RINGS WITH ONE OXYGEN AND ONE SULFUR (1,4-OXATHIOCINS)

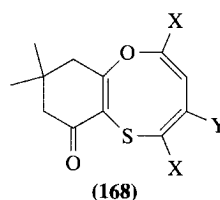
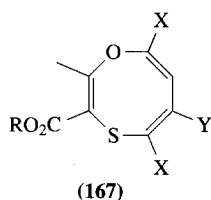
9.23.7.1 Experimental Structural Methods

A single 1,4-oxathiocin, cyclohexeno-fused fully unsaturated derivative (**166**; X = Cl), has been structurally characterized by single crystal x-ray diffraction analysis <88CC138>. Unfortunately, no

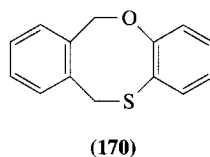
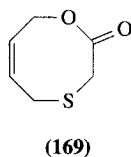
discussion of molecular dimensions was provided; however, the nonplanar conformation displayed by (166) obviates any discussion of potential bond delocalization.



The oxathiocine ring protons in fully unsaturated derivatives (166; X = H), (167; X = Cl, Y = H, Me, R = Et, Bu^t; X = Cl, Br, Y = Br, R = Et), and (168; X = Cl, Y = Br, Me; X = Y = Br) fall in the range 5.8–6.7 ppm <89JOC4822, 91PS(63)61>. The upfield shifts of these resonances relative to those in the thiophene precursors to the oxathiocines was suggested to be consistent with loss of aromaticity <91PS(63)161>; the fact that they are downfield from those of the 1,4-dioxocins is in accord with the deshielding effects of the vicinal halides in these oxathiocines <89JOC4822>.



The vicinal coupling constant in 6,7-unsubstituted derivative (168; X = Cl, Y = H) is quite small (1.5 Hz) <89JOC4822>. Ring carbons fall into fairly narrow and diagnostic ranges in the ¹³C NMR spectra of the oxathiocines, with C-2 found from 156 to 162 ppm, C-3 from 106 to 118 ppm, C-5 and C-8 (halogenated in all cases examined) from 131 to 139 ppm, and C-6 and C-7 from 114 to 116 ppm if unsubstituted and from 122 to 125 ppm if halogenated <89JOC4822, 91PS(63)61>. In all cases, the resonances are in accord with simple alkene-type structures. The alkene protons in 5,8-dihydro-1,4-oxathiocine-2(3*H*)-one (169) appear at 5.57 and 5.67 ppm, with a vicinal coupling constant of 11 Hz. The alkene carbons appear at 127 and 128 ppm, while the lactone is at 170 ppm <90CC138, 92JCS(P1)191>. 6,11-Dihydrodibenz[*b,f*][1,4]oxathiocine (170) displays typical ¹H and ¹³C chemical shifts, with the CH₂O group at 5.35 (76.7) ppm and the CH₂S somewhat upfield from this, at 4.40 (36.5) ppm <88M233>. The latter oxathiocine displays dynamic NMR behavior consistent with conformational equilibration, as discussed below.

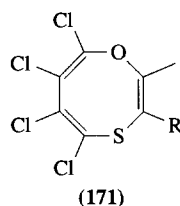


Although mass spectral data have been reported for several of the oxathiocines (166)–(168) <89JOC4822, 91PS(63)61>, no clearly consistent picture of preferred fragmentation modes is discernible, with structurally very similar compounds sharing few mass spectral features. Although the oxathiocines undergo thermal extrusion of sulfur (see below), only (167; X = Cl, Y = Me, R = Et) displays a simple fragment consistent with loss of sulfur upon mass spectral analysis <91PS(63)61>. Parent ions in general appear weak to absent for these derivatives, with rather low mass peaks (e.g. *m/z* 43) often the base peaks in the spectra. Both (169) <92JCS(P1)191> and (170) <87ZC67> display parent ions; no fragmentation data were reported.

Oxathiocines (167) display ester carbonyl stretching modes in the range 1713–1721 cm⁻¹, as expected for simple, unsaturated esters, while the 3-acyl analogues (166) and (168) display ketone stretches near 1680 cm⁻¹ <89JOC4822, 91PS(63)61>. An additional band reported at ca. 1600–1620 cm⁻¹ apparently correspond to an intra-ring C=C vibrational mode. The carbonyl stretching frequency in lactone (169), at 1760 cm⁻¹ <92JCS(P1)191>, appears rather high.

9.23.7.2 Thermodynamic Aspects

The majority of the fully unsaturated oxathiocins are reported to be oils (<89JOC4822, 91PS(63)61>), consistent with their anticipated, rather limited capability for significant intermolecular interactions in the solid state, although derivatives bearing C(3)-keto groups rather than ester substituents are crystalline, with melting points ranging from 83 °C for 3-acetyl derivative (**171**; R = Ac) (<89JOC4822> to ca. 140 °C for several of the cyclohexeno-fused compounds (<91PS(63)61>). The 3-tosyl compound (**171**; R = *p*-Me-C₆H₄SO₂) is comparatively high melting (181–182 °C) (<89JOC4822>). Dibenzo[*b,f*] derivative (**170**), in common with its diheterocin analogues, is fairly low melting (94 °C) (<87ZC67>), while lactone (**169**) is an oil (<92JCS(P1)191>).



Although data are rather limited, the oxathiocins appear to display the solubility anticipated for simpler compounds bearing analogous functionality, dissolving readily in CHCl₃ (<89JOC4822, 91PS(63)61, 92JCS(P1)191>) and other chlorinated methanes (<87ZC67, 92JCS(P1)191>), as well as in THF (<87ZC67>). Chromatographic purification has been effected on silica, eluting with CHCl₃ or Et₂O/petroleum ether mixtures for the oxathiocins (<89JOC4822, 91PS(63)61>) and hexane/EtOAc for oxathiocinone (**169**) (<92JCS(P1)191>). Dibenzo[*b,f*] derivative (**170**) was purified by high-performance liquid chromatography on reversed-phase silica, eluting with aqueous methanol (<87ZC67>).

General theoretical issues regarding the potential aromaticity of the 1,4-diheterocins have been reviewed (<78AHC(23)55>), although at the time of writing, no fully unsaturated oxathiocins had been prepared. When such derivatives were finally isolated, as noted above, they displayed NMR spectral properties in accord with formulation as nonplanar and nonaromatic (<89JOC4822>), and x-ray crystallographic analysis confirmed such a nonplanar conformation in the solid state (<88CC138>). Despite the apparent lack of aromatic stabilization, the 1,4-oxathiocins nonetheless appear to be rather stable, with no unusual sensitivity to air or heat noted, although several derivatives undergo thermal extrusion of sulfur when heated at 110–130 °C for 6–15 h (<91PS(63)61>).

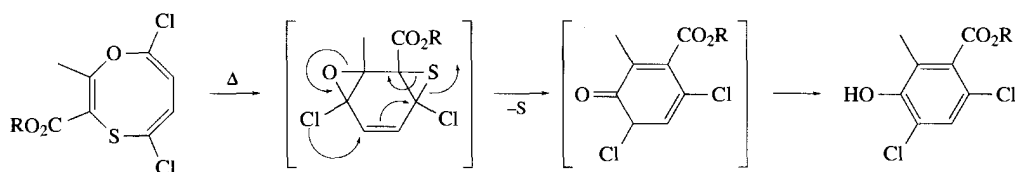
Crystallographic analysis revealed a distinctly nonplanar conformation for oxathiocin (**166**; X = Cl) (<88CC138>); as appears almost invariably to be the case for the 1,4-diheterocins, the conformation, described as “highly puckered,” appears to be of the twist-boat type. NMR spectral data are in accord with maintenance of the nonplanar structure in solution (<89JOC4822>). Dynamic NMR studies of 6,11-dihydrodibenzo[*b,f*][1,4]oxathiocin (**170**) were carried out in order to assess its conformational preferences (<88M233>). This oxathiocin displays an activation barrier for the boat inversional mode lower than that of the *N*-containing diheterocins, but somewhat higher than that of the corresponding dioxocin. This process was studied in four solvents in order to assess the effects of solvent polarity; the barrier was lowest in CD₂Cl₂ and in toluene (ΔG_{act} 8.3 kcal mol⁻¹), higher in CD₃OD (8.5 kcal mol⁻¹), and highest in acetone (8.6 kcal mol⁻¹), suggesting the ground-state, twist-boat conformation to be more polar than the transition state for the boat-inversional mode and thus better stabilized by polar solvents. As for the other diheterocins, the low activation energy process resulting in twist-boat interchange through a boat-like transition state could not be assayed by NMR spectral means.

Simple proton tautomerizations of oxathiocins are unreported. The thermal extrusion of sulfur from the 1,4-oxathiocins is proposed, by analogy with the known reactivity of the 1,4-dioxocins, to proceed via initial valence tautomerization to the benzene oxide sulfide, as discussed below (<88CC138>).

9.23.7.3 Reactivity of Fully Conjugated Rings

Heating oxathiocins (**167**; X = Cl, Y = H, R = Et, Bu^t) at reflux in toluene (R = Bu^t, 15 h) or chlorobenzene (R = Et, 6 h) affords the corresponding phenols in 63% (R = Et) and 79% (R = Bu^t) yield (<88CC138, 91PS(63)61>), reportedly via initial valence tautomerization followed by chelotropic extrusion of sulfur, with the latter promoted by the adjacent vinyl group (Scheme 50). Migration of

chloride accompanies this extrusion reaction, affording the keto tautomer of the phenol, which rapidly aromatizes.

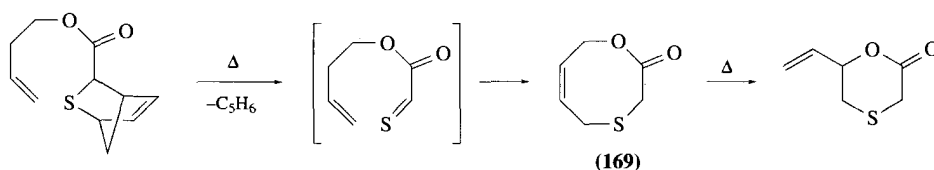


Scheme 50

Interestingly, phenolic products were not obtained upon attempted sulfur extrusion from those oxathiocins bearing substituents on C-6 and C-7, consistent with the inability of these derivatives to rearomatize following loss of sulfur. This observation assisted in the elucidation of the structures of these oxathiocins, as discussed below.

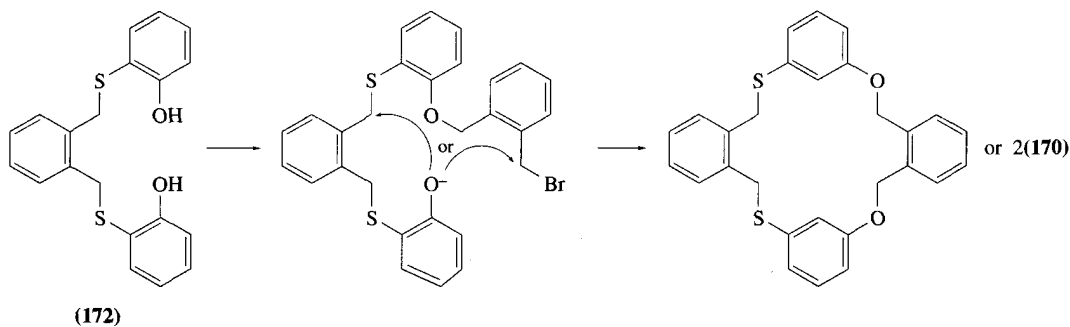
9.23.7.4 Ring Syntheses

Oxathiocinone (**169**) is formed in low yield (13%), together with larger amounts (29%) of the product of its [3,3]-sigmatropic rearrangement, via the intramolecular ene reaction of a transiently generated thioaldehyde upon flash vacuum pyrolysis at ca. 500°C (Scheme 51) <90CC138, 92JCS(P1)191>. The reaction is rather sensitive to pyrolysis conditions, with somewhat lower temperatures (400°C) eliminating the [3,3]-rearrangement product, but giving a diminished yield of the oxathiocin (14%), while higher temperatures afford only the rearrangement product (34%), together with polymeric materials. Smaller and larger ring analogues are also preparable by this method, all in higher yield than that for the oxathiocin.

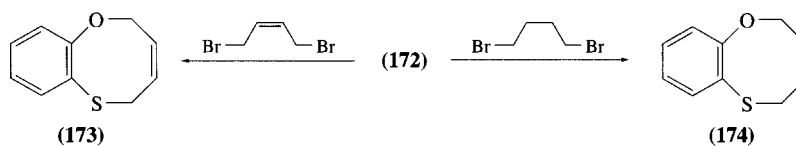


Scheme 51

Curiously, the attempted direct preparation of 6,11-dibenzo[*b,f*][1,4]oxathiocin (**170**) through the reaction of *o*-xylene dibromide with *o*-thiophenol fails, although this route works quite well for a variety of 1,4-dioxocin derivatives. However, treatment of the dibromide with two equivalents of *o*-thiophenol affords acyclic diol intermediate (**172**), and attempted macrocyclization of this diol with a second equivalent of *o*-xylene dibromide affords, in addition to the expected macrocyclic product, a 20% yield of (**170**) (Scheme 52) <87ZC67>. Apparently, following the first alkylation of the diol, the remaining phenolic group carries out an "intra-chain cyclization" by displacement of thiolate in competition with the anticipated displacement of bromide. Analogous reactions of (**172**) with *cis*-1,4-dibromo-2-butene and with 1,4-dibromobutane afford the corresponding oxathiocins (**173**) and (**174**) in unspecified yield (Scheme 53) <87ZC67>.



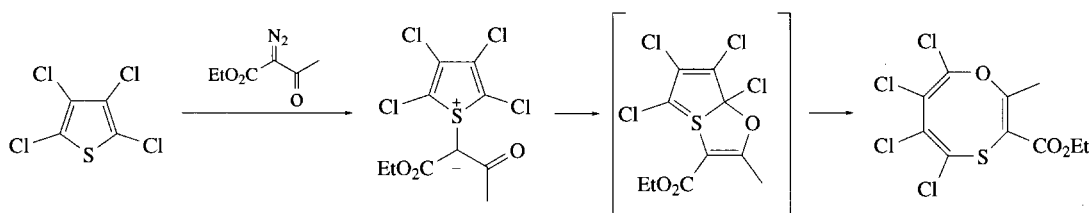
Scheme 52



Scheme 53

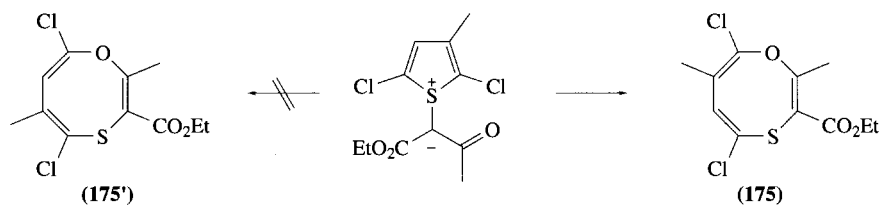
9.23.7.5 Ring Synthesis by Transformation of Another Ring

2,5-Dichlorothiophenes react with acyl carbenes to form intermediate sulfur ylides, which in most cases are isolable (Scheme 54). These ylides undergo thermal rearrangement to the corresponding oxathiocins in moderate to excellent yield, apparently via the electrocyclic ring opening of bicyclic intermediates formed by addition of the enolate-type oxygen of the ylide to the thiophene α -carbon <88CC138, 89JOC4822, 91PS(63)61>.



Scheme 54

These reactions had been reported earlier, but the oxathiocin products were incorrectly identified as a 2-thiabicyclo[3.1.0]hex-3-ene ($X = H$) and as the sulfur ylide ($X = Cl$) <81T743>. This rearrangement route was ambiguous with regards to the orientation of addition of unsymmetrically substituted thiophene derivatives. Consideration of the mechanism of thermal sulfur extrusion, discussed above, sheds light on this regiochemical issue, supporting formulation as (175) rather than as the regioisomeric oxathiocins (175') (Scheme 55) <91PS(63)61>.



Scheme 55

9.23.7.6 Comparison of Synthetic Routes

The oxathiocins remain extremely rare members of the class of 1,4-diheterocins. Ring-formation reactions, through either unimolecular cyclization or condensation, have been scarcely examined, and those cases reported suffer from low yields. The thiophene ylide rearrangement route provides ready access to the fully unsaturated oxathiocin ring system, but demands the use of 2,5-dihalo-thiophenes. This may not represent an insurmountable problem, and in fact the halides may permit functionalization of the oxathiocins through, for example, nucleophilic displacement, but apparently no such studies have yet been carried out.

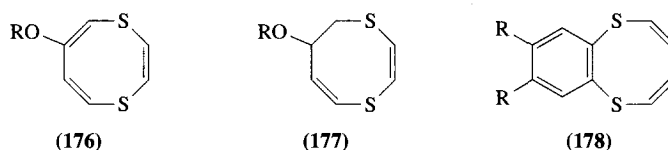
9.23.7.7 Important Compounds and Applications

Given their rarity, it is not surprising that no commercial applications of the oxathiocins have been reported. However, given the range of interesting properties displayed by the dioxocin and nitrogen-containing analogues, and given the apparent comparative stability of the oxathiocins, they appear to represent promising targets for further synthetic pursuit.

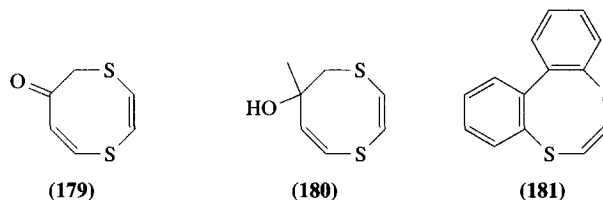
9.23.8 RINGS WITH TWO SULFURS (1,4-DITHIOCINS)

9.23.8.1 Experimental Structural Methods

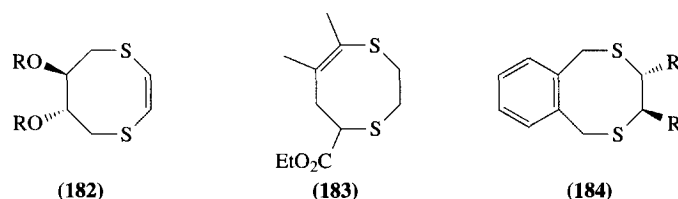
Crystallographic analysis of 6-acetoxy-1,4-dithiocin (**176**; R = Ac), which displays a distinctly nonplanar conformation in the solid state, provided metrical parameters consistent with the bond localization anticipated on the basis of such a nonplanar conformation $\langle 78T3631 \rangle$. Bond lengths and angles are largely unremarkable, although the torsion of the C(7)=C(8) double bond by 11° and the rather expanded bond angle at S-1, larger than that in dihydrodithiocin (**177**; R = Ac) $\langle 75CSC627 \rangle$ by ca. 14°C , are noteworthy. These distortions were taken to indicate higher strain in the fully unsaturated 1,4-dithiocin derivative. 8,9-Dimethyl-1,6-benzodithiocin (**178**; R = Me) also displays a nonplanar dithiocin ring; the C(3)—C(4) bond makes an angle of 34° relative to the normal to the benzene ring, representing a smaller distortion of the ring than that found in the corresponding dioxocin (see above) $\langle 78AX(B)3833 \rangle$. As for (**176**), bond lengths and angles support localized bonding in (**178**).



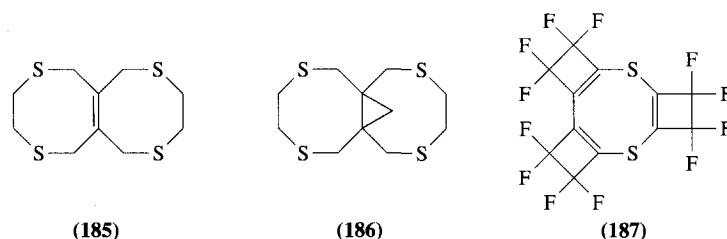
Fully unsaturated 1,4-dithiocins (**176**; R = Ac, TMS) display alkenic proton resonances in the region 5.1–6.9 ppm; the C-7 and C-8 protons in each display a vicinal coupling constant of 9 Hz $\langle 78T3631 \rangle$. Both these chemical shift values and the coupling constant are analogous to those in the dihydro derivatives (**179**) and (**180**) $\langle 77T2151 \rangle$, suggesting the absence of planarity (expected to influence the coupling constant) and of any ring current effects. The dithiocin ring protons in dibenzo[*e,g*][1,4]dithiocin (**181**) appear at 6.26 ppm; again, formulation as a simple alkene, with no delocalization, best accounts for this chemical shift $\langle 69ZC184 \rangle$.



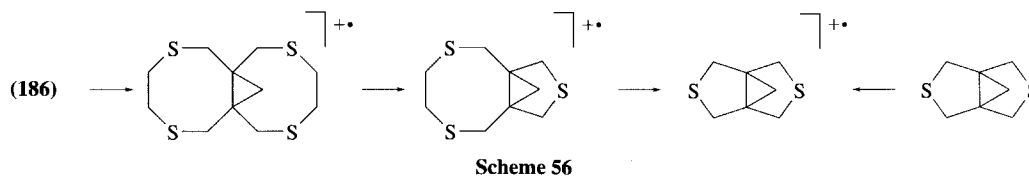
In a series of 5,6-dihydro-1,4-dithiocins (**177**; R = H, Me, Ac, CO₂Me), largely consistent proton chemical shifts are observed; H-7 and H-8 typically fall near 6 ppm, while H-2 and H-3 tend to be slightly further downfield, at ca. 6.2–6.3 ppm; the chemically inequivalent H-5 protons appear near 2.5 and 4 ppm, while H-6 typically is found from 4.5 to 6 ppm $\langle 77T2151 \rangle$. Dithioester derivative (**177**; R = CS₂Me) displays a rather downfield shift of H-6, at ca. 6.8 ppm; H-7 is also shifted downfield, to ca. 6.7 ppm, in this derivative. Tetrahydrodithiocins (**182**; R₂ = H₂, CMe₂, (MeSO₂)₂, (*p*-MeC₆H₄SO₂)₂) $\langle 77T2151 \rangle$, (**183**) $\langle 84JOC1917 \rangle$ and (**184**; R₂ = Me₂, Et₂, (CH₂)₃) $\langle 92TL947 \rangle$ appear to display no unusual chemical shifts in their ¹H NMR spectra. Analysis of coupling constants assisted in the determination of stereochemistry in both (**183**) and (**184**). Thus, H-5 couples equally to each of the chemically inequivalent H-6 protons in (**183**), whereas molecular models suggest that (*E*)-(**183**) would eclipse H-5 and one of the H-6 protons, resulting in unequal vicinal coupling constants $\langle 84JOC1917 \rangle$. Similar analyses confirmed the *trans* disposition of the cyclopentano-fused ring in (**184**; R₂ = (CH₂)₃), and assisted in the determination of stereochemistry of analogues (**184**; R₂ = Me₂, Et₂) as well $\langle 92TL947 \rangle$.



1*H*,6*H*-[1,4]Dithiocino[6,7-*f*][1,4]dithiocin (**185**) and the cyclopropane derived therefrom (**186**) display typical ^1H NMR spectral features <85M229>. In contrast to the conclusions regarding potential planarity and aromaticity of the 1,4-dithiocins based on ^1H NMR spectral analysis, ^{19}F NMR spectroscopy of tricyclobuteno compound (**187**) was cited in support of the presence of an aromatic ring current <71TL2871>. No ^{13}C NMR spectra of 1,4-dithiocins appear to have been reported.



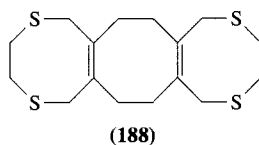
Mass spectral analysis of (**187**) <71TL2871> and dibenzo[*e,g*][1,4]dithiocin (**181**) <69ZC184> revealed the anticipated parent ion for each. Benzodithiocin (**184**; $\text{R}_2 = (\text{CH}_2)_3$) appears to fragment through cleavage of C—S bonds, giving, in addition to the parent ion, a base peak at m/z 135 (corresponding to unsymmetrical cleavage of two C—S bonds) and a prominent peak at m/z 104 ($\text{C}_6\text{H}_4(\text{CH}_2)_2$) <92TL947>. 6-Acetoxy-1,4-dithiocin (**176**; $\text{R} = \text{Ac}$) gives a weak parent ion <78T3631>; the base peak (m/z 43) and one of the prominent fragments (m/z 158) appear to result from cleavage of the acetoxy side chain, while other fragments at 113, 94 ($(\text{CH})_4\text{S}$) and 45 (CHS) presumably arise from cleavage of the dithiocin ring. Tetrathia[6.6.1]propellane (**186**) fragments by successive loss of $\text{CH}_2=\text{CHSH}$ units, affording ultimately a fragment (m/z 158) which appears identical, based upon subsequent fragmentation, to the parent ion seen upon mass spectral analysis of dithia[3.3.1]propellane (Scheme 56); this analysis featured prominently in the elucidation of the structure of (**186**) <85M229>.



The ultraviolet absorption spectrum of 6-acetoxy-1,4-dithiocin (**176**; $\text{R} = \text{Ac}$) displays features at 225 (3.73), 249 (sh, 3.48), 255 (sh, 3.41) and 285 (3.49) nm <78T3631>. Although the 285 nm band differentiates this diheterocin from 1,4-dioxocin and 1,3,6-cyclooctatriene, an analogous absorption is seen in nonconjugated dihydro derivative (**177**; $\text{R} = \text{Ac}$); it is clearly not indicative of delocalization or aromaticity.

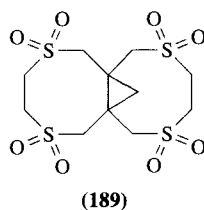
Dibenzo[*e,g*][1,4]dithiocin (**181**) displays an analogous absorption, at 273 nm (3.69) <69ZC184>. Both (**184**; $\text{R}_2 = (\text{CH}_2)_3$) <92TL947> and propellane (**186**) <85M229> are colorless; the latter displays an absorption band well into the ultraviolet, at 217 nm (3.01). Again in contrast to the results from simpler systems, the absorption spectrum of tricyclobutenodithiocin (**187**) was suggested to indicate a highly conjugated system, with absorptions at 230 (4.62), 237 (4.36), 295 (3.87), and 317 (3.81) nm <71TL2871>.

Fully unsaturated dithiocins (**176**; $\text{R} = \text{TMS}$, Ac) display a band at 1570 cm^{-1} ($\text{R} = \text{TMS}$) and 1585 cm^{-1} ($\text{R} = \text{Ac}$) <78T3631> which does not appear in the infrared spectra of their dihydro- and tetrahydrodithiocin precursors <77T2151>; this band may correspond to an intra-ring stretching mode. The carbonyl stretching band noted for dithiocinone (**179**) (1665 cm^{-1}) falls in the range typically seen for large-ring unsaturated ketones <77T2151>. Other spectral data provided for these derivatives correspond to the anticipated vibrational modes for the pendant functional groups, with no particularly noteworthy features apparent. Tricyclobuteno compound (**187**) displays absorption bands at 1634 and 1538 cm^{-1} , as well as a number of lower energy bands <71TL2871>; these may also correspond to ring $\text{C}=\text{C}$ vibrational modes. The C—S stretching mode, at $675\text{--}710\text{ cm}^{-1}$, was identified in polycyclic derivatives (**185**), (**186**), and (**188**) <85M229>; no analogous band was reported for benzo derivative (**184**) ($\text{R}_2 = (\text{CH}_2)_3$) <92TL947>.

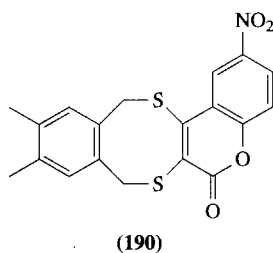


9.23.8.2 Thermodynamic Aspects

Most of the partially to completely unsaturated dithiocins are rather low-melting solids, with only the bis(sulfonates) of 6,7-dihydroxy-1,4-dithiocins (**182**; $R_2 = (\text{MeSO}_2)_2$, $(p\text{-Me-C}_6\text{H}_4\text{SO}_2)_2$) melting above 100°C $\langle 77\text{T}2151, 78\text{T}3631 \rangle$. Insufficient data are available to permit firm conclusions about solid-state effects responsible for the observed melting behaviors; however, one potentially revealing comparison is provided by dihydroacetate (**177**; $R = \text{Ac}$) (m.p. 84°C) and its fully-unsaturated analogue (**176**; $R = \text{Ac}$) (m.p. 45°C) $\langle 77\text{T}2151, 78\text{T}3631 \rangle$. Simpler derivatives lacking appreciably polar functionalities are lower melting; (**177**; $R = \text{Me}$) $\langle 77\text{T}2151 \rangle$ and (**176**; $R = \text{TMS}$) $\langle 78\text{T}3631 \rangle$ are liquids. Dithiocins (**177**; $R = \text{Ac}$) and (**180**) are sublimable $\langle 77\text{T}2151 \rangle$. Dibenzo[*e,g*]dithiocin (**181**) melts at 121°C $\langle 69\text{ZC}184 \rangle$, quite close to the melting point of the corresponding *N,N'*-dimethyl-dibenzodiazocine $\langle 84\text{JCS(P}1\text{)2013} \rangle$. Tricyclobutenodithiocin (**187**) melts at ca. 144°C $\langle 71\text{TL}2871 \rangle$; perhaps stacking interactions play a role in stabilization of the solid state for this unusual compound. Tricyclic benzodithiocin (**184**; $R_2 = (\text{CH}_2)_3$) melts at 99°C $\langle 92\text{TL}947 \rangle$, while propellane (**186**) and its bicyclic precursor (**185**) are both quite high melting ($203\text{--}204^\circ\text{C}$ and $165\text{--}166^\circ\text{C}$, respectively) $\langle 85\text{M}229 \rangle$. The tetraoxide of the propellane (**189**) (m.p. $> 360^\circ\text{C}$) and tricyclic bis(dithiocin) (**188**) (m.p. $196\text{--}198^\circ\text{C}$) are also noteworthy $\langle 85\text{M}229 \rangle$.

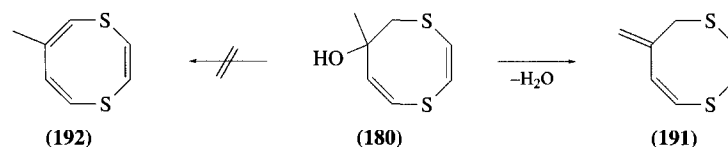


Solubilities of the reported dithiocins are largely as anticipated, with generally good solubility in CHCl_3 $\langle 69\text{ZC}184, 77\text{T}2151, 84\text{JOC}1917, 92\text{TL}947 \rangle$ and CH_2Cl_2 $\langle 92\text{TL}947 \rangle$ and poor solubility in hydrocarbons $\langle 77\text{T}2151, 92\text{TL}947 \rangle$. Recrystallization has been effected from methanol $\langle 77\text{T}2151 \rangle$, CHCl_3 $\langle 85\text{M}229 \rangle$, and benzene $\langle 85\text{M}229 \rangle$, as well as from solvent mixtures of comparable polarities (e.g. $\text{CHCl}_3/\text{Et}_2\text{O}$, $\text{CH}_2\text{Cl}_2/\text{hexane}$) $\langle 77\text{T}2151, 92\text{TL}947 \rangle$. Acetoxydithiocin (**176**; $R = \text{Ac}$) displays higher solubility in low-polarity solvents, dissolving in cyclohexane and crystallizing from hexane $\langle 78\text{T}3631 \rangle$, while high-melting polycyclic derivatives (**188**) and (**189**) are quite insoluble in organic solvents $\langle 85\text{M}229 \rangle$. Similarly, polycyclic (**190**) is insoluble in both benzene and acetonitrile $\langle 91\text{JOU}163 \rangle$. Several of the dihydrodithiocins were purified by preparative thin-layer chromatography on silica, eluting with CHCl_3 $\langle 77\text{T}2151 \rangle$. Tetrahydrodithiocin (**183**) was chromatographed on alumina, eluting with Et_2O $\langle 84\text{JOC}1917 \rangle$, while propellane (**186**) and its bicyclic precursor (**185**) were eluted on acidic alumina with benzene $\langle 85\text{M}229 \rangle$.



Although simple electronegativity issues suggested that 1,4-dithiocin might be expected to be the “most aromatic” of the 1,4-diheterocins $\langle 77\text{T}2151 \rangle$, theoretical studies show that, as for 1,4-dioxocin, strain energy dominates its energetics. Thus, Hückel molecular orbital calculations do display the expected enhanced delocalization energy for 1,4-dithiocin relative to 1,4-dioxocin; however,

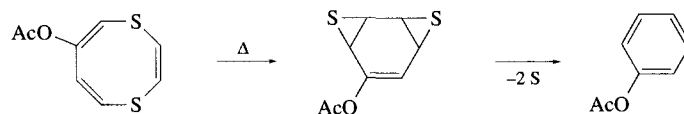
1,4-dithiocin bears a correspondingly higher ring strain energy, balancing the delocalization effect and, as for 1,4-dioxocin, precluding a planar, delocalized dithiocin ring <65RRC1059, 78AHC(23)55>. The successful synthesis of the 6-acetoxy compound, which displays solution spectral parameters and reactivity consistent with its demonstrated solid-state nonplanarity and nonaromaticity <78T3631>, supports these theoretical studies. Particularly revealing is the dehydration of alcohol (180), which gives exclusively exocyclic alkene (191) (Scheme 57) rather than 6-methyl-1,4-dithiocin (192) <77T2151>. In rather stark contrast to these results stands heavily substituted dithiocin (187), which displays ^{19}F NMR spectral parameters claimed to be consistent with the presence of a diamagnetic ring current <71TL2871>.



Scheme 57

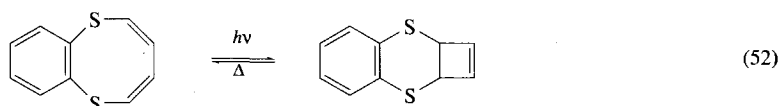
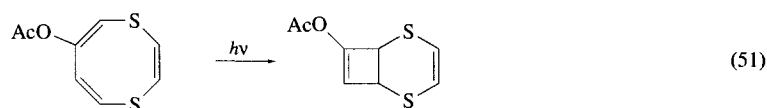
Little additional information is available regarding the details of the conformation of the 1,4-dithiocin ring. Perhaps noteworthy, however, is the solid-state conformation of 6-acetoxy-1,4-dithiocin (176; R = Ac) <78T3631>, which appears somewhat unusual. In contrast to the almost invariant twist-boat conformations seen for so many of the diheterocins, and reported for propellane (186) (which displays two conformations, of C_2 and C_s symmetry, each with a "twist-tub" conformation of the dithiocin rings <85M229>), the dithiocin ring in (176; R = Ac) appears rather flattened, although still decidedly nonplanar. Atoms C-8, S-1, C-2, C-3, and S-4 all are nearly coplanar, with the rest of the molecule making a rather steep angle with respect to this plane, while the diene portion (C(5)—C(6)—C(7)—C(8)) is nonplanar, with the C(7)=C(8) double bond displaying a twist of 11° . The dihydrodithiocin analogue (177; R = Ac) displays some common conformational features in the solid state, although the ring flattening appears less pronounced in this derivative, in which C-8 is not co-planar with the S(1)—C(2)—C(3)—S(4) substructure <75CSC627>. Detailed solution conformational analyses, beyond the simple demonstration of nonplanarity, have not been carried out for the monocyclic dithiocins. Given the unusual spectral and solid-state properties of (187), which has been suggested to bear a planar, aromatic dithiocin ring <71TL2871>, crystallographic analysis of this derivative would be revealing.

Although the enolate of ketone (179) may be prepared and *O*-alkylated, the ketone itself is not reported to enolize in solution <77T2151>. Acetoxy-1,4-dithiocin (176; R = Ac) is thermally unstable, decomposing when heated above 50°C with extrusion of sulfur. By analogy with related studies of other 1,4-diheterocins and with the failure of attempts to prepare the parent 1,4-dithiocin via the valence tautomerization of benzene disulfides <74AG818>, it is proposed that this thermal decomposition occurs via thermal valence tautomerization in the reverse direction, followed by sulfur extrusion from the so-formed arene disulfide (Scheme 58) <78T3631>.



Scheme 58

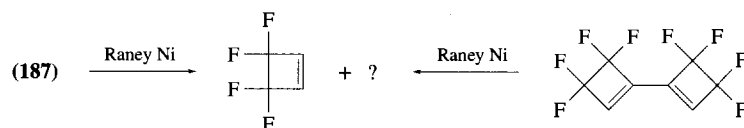
Acetoxydithiocin (176; R = Ac) is photochemically converted to its dithiabicyclooctadiene valence tautomer (Equation (51)) <78T3631>. Similarly, 1,6-benzodithiocin (178; R = H) undergoes photochemically induced valence tautomerization to the dithiabicyclooctadiene, which thermally reverts to the dithiocin (Equation (52)) <71JA4627>.



9.23.8.3 Reactivity of Fully Conjugated Rings

Mild thermolysis of acetoxydithiocin (**176**; R = Ac) affords phenyl acetate in unreported yield <78T3631>. As discussed above, this reaction is proposed to proceed via thermally induced valence tautomerization, followed by sulfur extrusion <78T3631>. The photochemical valence tautomerization of this 1,4-dithiocin and of its benzo analogue is discussed above.

Perfluorodithiocin (**187**), in apparent accord with its formulation as a delocalized system, is unreactive toward electrophilic addition of bromine (Br₂/CCl₄) and toward oxidation (NaIO₄/MeOH) <71TL2871>. This compound may be desulfurized with Raney nickel, affording tetrafluorocyclobutene and a second product, of unidentified structure, which appears to arise from further reduction of the anticipated bicyclobutenyl derivative. The latter is identical to the product formed by the treatment of authentic bicyclobutenyl with Raney nickel (Scheme 59) <71TL2871>.

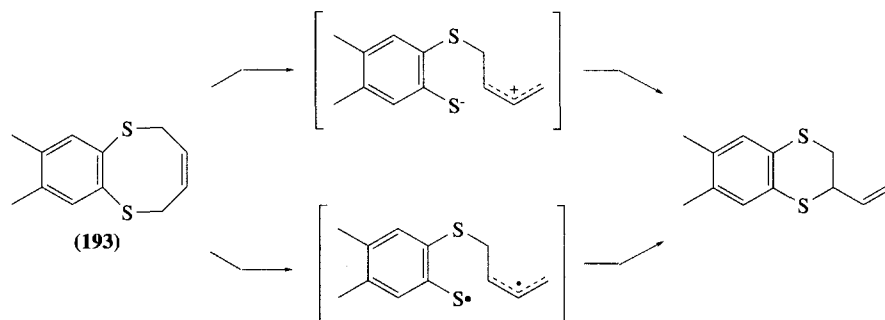


Scheme 59

The twisted alkene present in acetoxydithiocin (**176**; R = Ac) was suggested to be a possible cause of its relative unreactivity as a diene in Diels–Alder cycloaddition reactions. No reaction is seen with maleic anhydride, tetracyanoethylene, or hexafluoro-2-butyne at 45°C; higher temperatures were precluded by the thermal instability of (**176**; R = Ac) <78T3631>. *N*-Phenyltriazolinedione reacted with (**176**; R = Ac), but afforded no identifiable products.

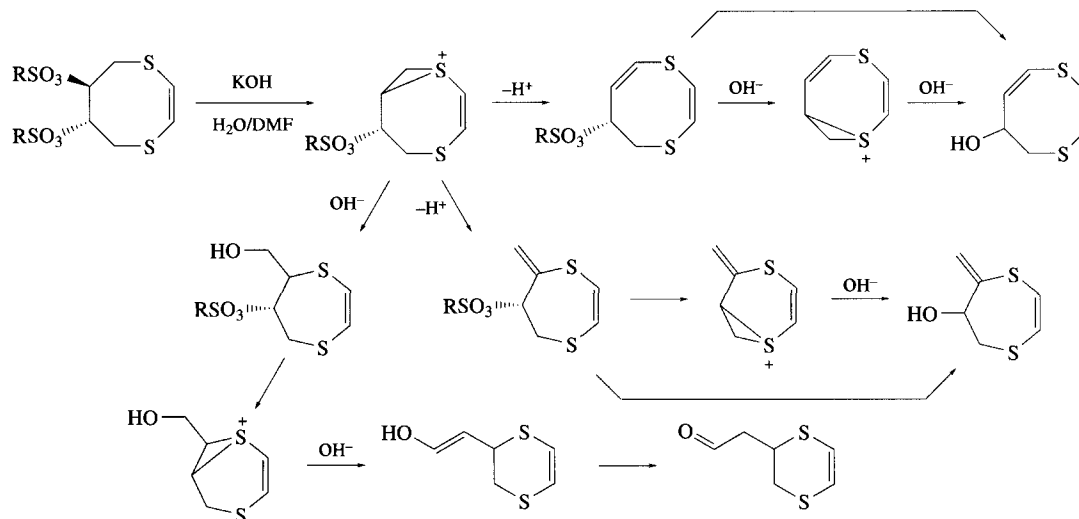
9.23.8.4 Reactivity of Nonconjugated Rings

5,6-Dihydro-1,4-dithiocin-6-ol (**177**; R = H) affords only intractable products upon attempted dehydration or chlorination, attributed to a neighboring group effect of the proximal sulfur <77T2151>. The alcohol does react with several electrophilic reagents, allowing the preparation of acetoxy compound (**177**; R = Ac) as well as the carbonate (R = CO₂Me) and dithiocarbonate (R = CS₂Me). Oxidation of the alcohol to ketone (**179**) was effected in low yield by CrO₃, and the tertiary alcohol formed by addition of methylmagnesium bromide to this ketone undergoes elimination to exocyclic alkene (**191**) <77T2151>. Ketone (**179**) may be deprotonated with lithium diisopropylamide to afford the unstable enolate, which can be intercepted at low temperature by acetylation and trimethylsilylation; attempted methylation with methyl iodide or methyl trifluoromethanesulfonate was unsuccessful <78T3631>. 1,6-Benzodithiocin (**193**) undergoes Lewis acid-catalyzed allylic rearrangement, affording the ring-contraction product in quantitative yield (Scheme 60) <84ZC436>. The benzodithiocin also undergoes thermal and photochemical rearrangement, affording a 20% yield of the same product after 4 h at 170–190°C and a lower yield upon high-pressure mercury lamp photolysis. In contrast to the presumably ionic nature of the acid-catalyzed rearrangement, the thermal reaction appears to proceed via bond homolysis, as indicated by its inhibition by benzoquinone (Scheme 60).



Scheme 60

Tetrahydrodithiocin-6,7-diol derivatives (**182**) undergo reactions typical of vicinal diols, although the reactions are largely unforgiving, with yields critically dependent on choice of reagents and reaction conditions <77T2151>. Elimination reactions afford the dihydrodithiocin under some conditions, but never the fully unsaturated 1,4-dithiocin itself. Under some conditions, ring-contraction products are formed. Both elimination and ring contraction are apparently initiated by a neighboring group interaction of the proximal sulfur, affording intermediate thiiranium ions which then partition between several base- or nucleophile-mediated paths (Scheme 61) <77T2151>.

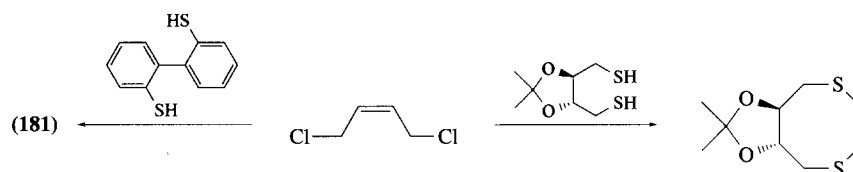


Scheme 61

Perhydrodithiocin propellane (**186**) is oxidized by H_2O_2 to the corresponding tetrasulfone (**189**) <85M229>. Other reactions of dithiocanes were briefly discussed in CHEC-I (Section 5.19.8.3).

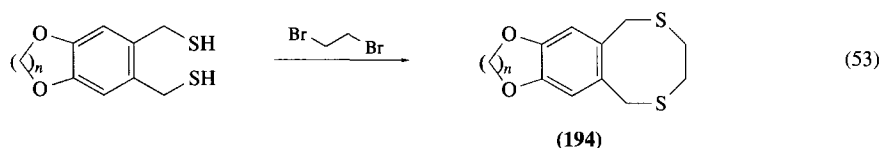
9.23.8.5 Ring Syntheses

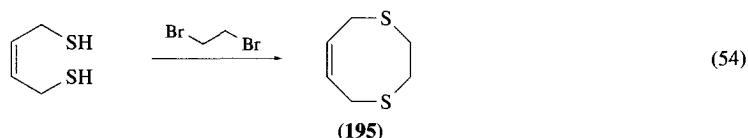
No unimolecular cyclization routes to the 1,4-dithiocins have been reported. Addition of 1,4-dihalides to vicinal dithiols and of 1,4-dithiols to vicinal dihalides both represent common approaches to the ring system. Thus, 2,2'-dithiolbiphenyl reacts with *cis*-1,2-dichloroethene to afford a low yield of dibenzo[*e,g*][1,4]dithiocin (**181**) (Scheme 62) <69ZC184>. Similarly, *cis*-1,2-dichloroethene reacts with the acetone ketal of dithiothreitol to afford tetrahydrodithiocin (**182**; $\text{R}_2 = \text{CMe}_2$) in 40% yield, with the low yield in part due to losses upon purification <77T2151>.



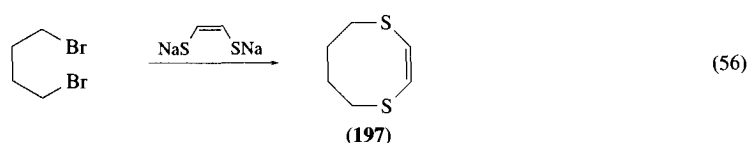
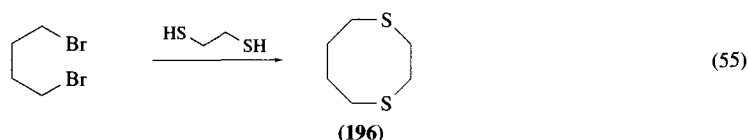
Scheme 62

Dibromoethane reacts with *o*-xylylene dithiols, giving around 65–70% yields of 2,5-benzodithiocins (**194**; $n = 1, 2$) (Equation (53)) <89MI 923-02>, and with *cis*-1,4-dimercapto-2-butene, giving 2,3,5,8-tetrahydro-1,4-dithiocin (**195**) in 35% yield (Equation (54)) <64ZC302>.

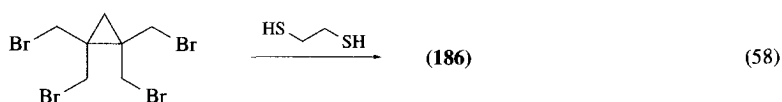
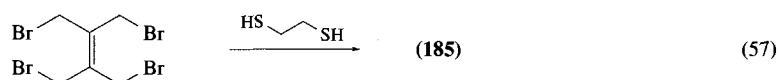




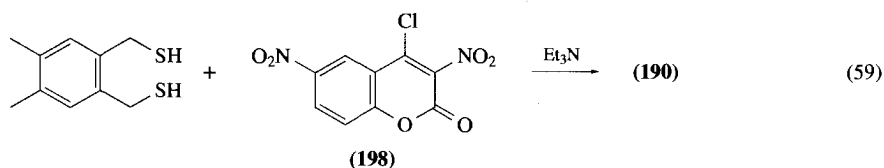
Similarly, 1,4-dibromobutane reacts with ethanedithiol to afford a 7% yield of the parent 1,4-dithiocane (**196**) (Equation (55)) <78JA6416> and with dithiolethene to give 5,6,7,8-tetrahydro-1,4-dithiocin (**197**) (Equation (56)) <64ZC302>.



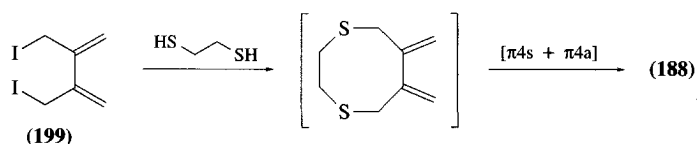
o-Xylylene dibromide and *cis*-1,4-dichloro-2-butene react similarly with ethanedithiol <64ZC302>, while alkylation of ethanedithiol with tetrabromides under high dilution conditions affords bis(dithiocin) (**185**) (Equation (57)) and propellane (**186**) (Equation (58)) (also preparable by carbene addition to (**185**)) in 57% and 15% yields, respectively <85M229>.



Highly reactive coumarin (**198**) reacts with *o*-xylylene dithiol to afford benzodithiocin (**190**) (Equation (59)) <91JOU163>.

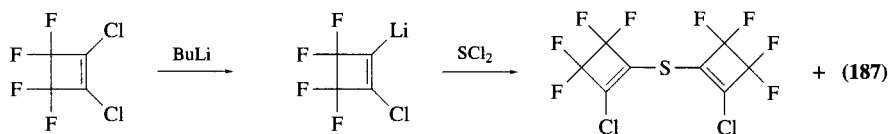


Treatment of ethanedithiol with diiodide (**199**) affords dithiocin dimer (**188**) (Scheme 63), reportedly through [4 + 4] cyclodimerization of the *bis*(methylene)dithiocin anticipated to be the initial product of the reaction <85M229>.



Scheme 63

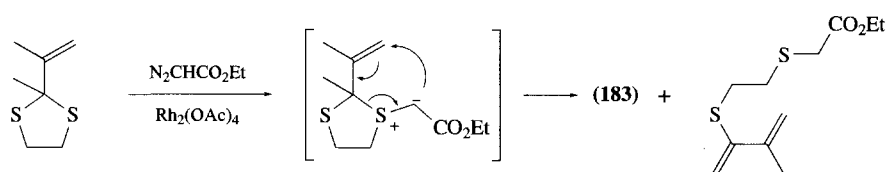
Lithiation of tetrafluorodichlorocyclobutene, followed by treatment with SCl_2 or S_2Cl_2 , affords the anticipated sulfide together with a low yield of the tricyclobuteno dithiocin (**187**) (Scheme 64) <71TL2871>; it is unclear by what mechanism (**187**) is formed.



Scheme 64

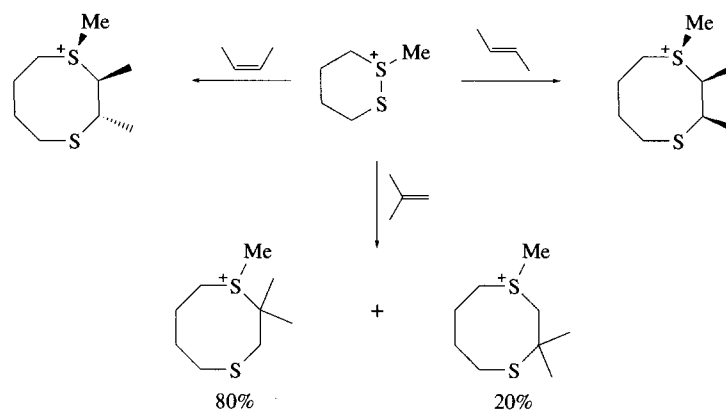
9.23.8.6 Ring Synthesis by Transformation of Another Ring

Carbene addition to a dithioketal affords an intermediate sulfur ylide which undergoes [2,3]-sigmatropic rearrangement, affording dithiocin (**183**) in 53% yield, together with a 39% yield of an elimination product (Scheme 65) [84JOC1917]. The rearrangement/elimination ratio is enhanced in this case over that of the corresponding oxygen ylide reactions.



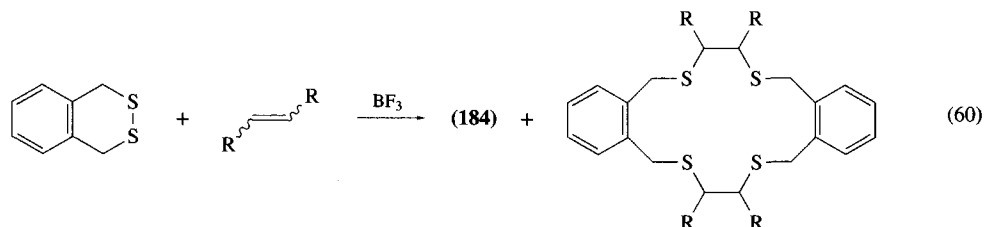
Scheme 65

S-Methyl-1,2-dithiane reacts with alkenes to afford 1,4-dithiocanes in high yield (90–98%), with good regiochemical and stereochemical control (Scheme 66) [82JA3231].



Scheme 66

Similarly, benzodithiane undergoes BF_3 -catalyzed addition of alkenes to afford analogous products (**184**; $\text{R}_2 = \text{Me}_2, \text{Et}_2, (\text{CH}_2)_3$) in modest-to-excellent yield (Equation (60)); macrocyclic dimers represent the major products under some reaction conditions [92TL947].



9.23.8.7 Comparison of Synthetic Routes

The cyclization of dihalides with dithiols appears to represent a reasonably versatile approach to a number of dithiocins and their benzannelated analogues, in low-to-moderate yields. The sulfur

ylide approach provides moderate yields of functionalized dithiocins and may prove useful in certain cases, while the dithiane ring expansion appears to offer alternative access to the 1,4-dithiocane and 2,5-benzodithiocin ring systems.

9.23.8.8 Important Compounds and Applications

Beyond a reported photophysical study of the nickel complex of 5,6,7,8-tetrahydro-1,4-dithiocin-2,3-dithiol carried out in the course of studies of nonlinear optical materials $\langle 89ZC149 \rangle$, no practical applications of the dithiocins have been reported. Given the range of interesting properties displayed by the nitrogen- and oxygen-containing diheterocins, further study of the dithiocins appears in order.

9.24

Eight-membered Rings with Two Heteroatoms 1,5

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9.24.1 INTRODUCTION

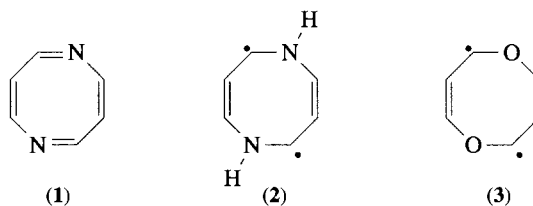
Of all the diheterocins, those with the two heteroatoms in a 1,5-relationship have received perhaps the greatest attention, although this attention has been focused primarily on the diaza and dithia compounds. Interest in the 1,5-diheterocins appears more broadly based than that in the other positional isomers, with both demonstrated and potential pharmacological activity, versatile metal ion coordination chemistry, and unusual chemical properties, including a number of transannularly bonded systems, representing a few of the diverse array of reported studies.

Only those compounds with nitrogen, oxygen, and/or sulfur as heteroatoms are covered in this chapter. (Compounds with "unusual" heteroatoms are covered in later chapters in this volume.) Nomenclature for the 1,5-diheterocins follows the standard system, with some permissible variability introduced for the completely reduced compounds. The parent unsaturated systems, of which comparatively few have been prepared, are 1,5-diazocine (the only 1,5-diheterocin for which complete conjugation is theoretically possible), 2*H*-1,5-oxazocine, 2*H*-1,5-thiazocine, 2*H*,6*H*-1,5-dioxocin, 2*H*,6*H*-1,5-oxathiocin, and 2*H*,6*H*-1,5-dithiocin. Reduced analogues may be named as di-, tetra-, hexa-, or, for the diaza compounds, octahydro derivatives of these parent compounds. In some cases, particularly the diaza, dioxa, and dithia derivatives, the fully-saturated rings are more often referred to as the corresponding -anes, 1,5-diazocane, 1,5-dioxocane, and 1,5-dithiocane. Benzo and dibenzo derivatives also follow standard nomenclature. Specific nomenclature is introduced, as appropriate, within the following individual sections. Compounds in which ring heteroatoms are members of another fused ring and bridged polycyclic compounds are, with few exceptions, not covered in this chapter.

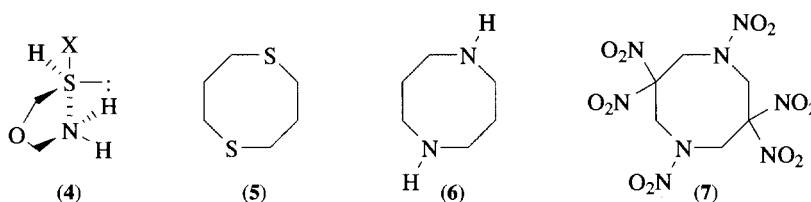
Following a general discussion of theoretical studies of the title heterocycles, each class is discussed separately, with each discussion following the same general format. Within discussions of physical, chemical, and spectral properties, reported compounds have in general been grouped according to the extent of unsaturation of the diheterocin ring, with fully-unsaturated ring systems discussed first and fully-saturated derivatives last. "Missing" section headings (e.g. "Reactivity of substituents attached to ring heteroatoms") correspond to cases in which no relevant chemistry has been reported. Coverage in the first edition of *Comprehensive Heterocyclic Chemistry*, (CHEC-I), in which all eight-membered ring heterocycles with one or more heteroatoms were treated in a single chapter, focused primarily on the nitrogen-containing compounds, the best-known members of this family of heterocycles, with relatively brief coverage of oxygen- and/or sulfur-containing analogues. Comprehensive reviews of the preparation, structure, and reaction chemistry of the 1,5-diazocines <89AHC(46)1> and their benzo analogues <87H(26)2477> and of the 1,5-oxazocines <82H(19)709> have appeared, and the diazocine and oxazocine sections thus focus primarily on developments since the mid 1980s in the chemistry of these derivatives. Coverage of the remaining classes of 1,5-diheterocins, which received little attention in CHEC-I, is more complete, with appropriate discussion of earlier work as well as more recent developments, although, given space restrictions, the coverage of earlier studies of these compounds is not comprehensive.

9.24.2 THEORETICAL METHODS

Hückel molecular orbital calculations for 1,5-diazocine (1), the only closed-shell 1,5-diheterocin with the potential for complete conjugation, revealed a resonance energy comparable to that found for the 1,3-positional isomer <75T295>, and decreased antiaromaticity relative to cyclooctatetraene was suggested by PPP-type molecular orbital calculations <83MI 924-01>. Semiempirical AM1 molecular orbital calculations for open-shell diazocine (2) also revealed a similarity to the 1,3-analogue; both display a rather large degree of bond length equalization, nearly comparable to that calculated for the aromatic cyclooctatetraene dianion and significantly greater than that seen for clearly nondelocalized 1,4-diazocine <91RRC333>. In the dioxocin series, open-shell 1,5-dioxocin (3), although the only 1,*n*-dioxocin found to correspond to a minimum on the singlet potential energy surface rather than a saddle point, was found to be considerably less stable than closed-shell 1,2-dioxocin <91RRC333>.



In order to assay the nature of transannular bonding in the thiazocine series, Hartree–Fock calculations were conducted for simple model compound (4; X = H, Cl). Use of a 4-31G basis set augmented with sulfur *d*-orbitals reproduced the experimentally-observed N—S interaction, while omission of *d*-orbitals on sulfur led to no predicted bonding interaction between sulfur and nitrogen, even with an extended *sp* basis set for sulfur <84CL1557, 86JA6320>. *Ab initio* (STO-3G) calculations predict similar transannular bonding in 1,5-dithiocane (5) and its dication <89JPC6052>; the transannular interaction in (5) was also indicated by a semiempirical (MINDO/3) study <81T2743>. Hartree–Fock and complete active space self-consistent field calculations for a series of cyclic diamines, including octahydro-1,5-diazocine (1,5-diazocane) (6), at the STO-3G level for (6) and the 6-311G* level for smaller diamines, were carried out to assay the extent of interaction between the *N*-lone pairs. A significant contribution from both through-bond and through-space interaction to the ionization potential of (6) was found <92JPC9218>. CNDO/2 Calculations for hexanitrodiazocine (7) revealed a relatively weak carbon—nitrogen bond for the *gem*-dinitro group, suggesting this to be the initiating bond for the (explosive) thermal decomposition of (7) <87MI 924-03, 88MI 924-02>.



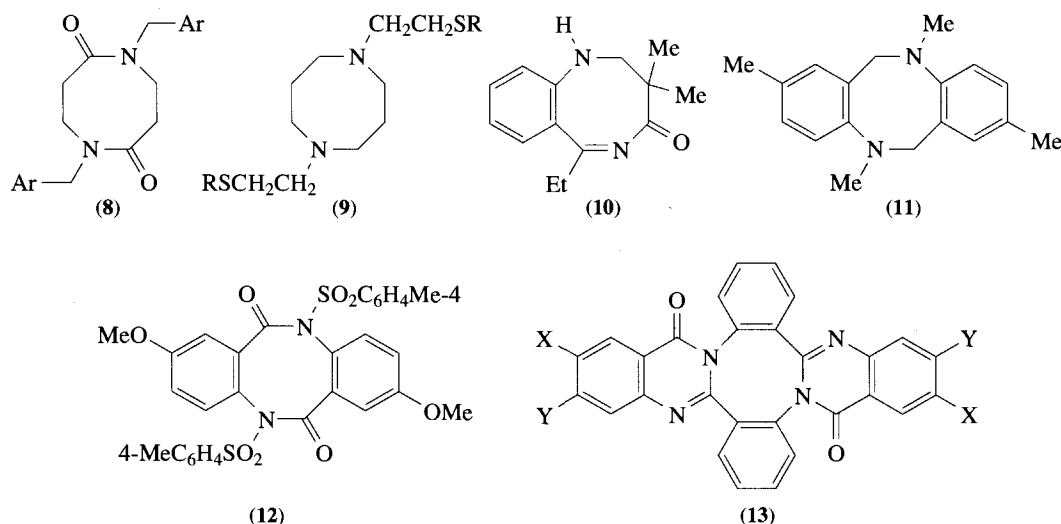
Molecular mechanics calculations suggested the boat–chair conformation of 1,5-dithiocane (5) to be favored, but this conclusion was tentative, since it led to the prediction of a larger degree of sulfur–sulfur interaction than was experimentally observed <81T2743>. Later molecular mechanics studies suggested the boat–chair form to be somewhat higher in energy (18.7 kcal mol^{−1}) than both the chair–chair (15.7 kcal mol^{−1}) and the twist–boat–boat (16.3 kcal mol^{−1}) conformations <88JPC1747>. Molecular mechanics-assisted conformational analyses have been reported for several other diheterocins, including the lactone derived from bourgeanic acid <90JOC5938>, 1,3,3,5,7,7-hexamethyl-1,5-diazocane and its dimethiodide <90TH924-01>, and 1,5-diazocane-1,5-diacetic acid, which when singly ionized was found to adopt a boat form in order to allow formation of a transannular *H*-bond <90JCS(P2)2211>. Conformational aspects of metal ion chelation by 1,5-diazocine derivatives have been assayed by molecular mechanics methods <90IC264, 92IC4965>, and a calculational method for estimation of crystal field parameters for such metal complexes has also been reported <88MI 924-01>.

9.24.3 RINGS WITH TWO NITROGENS (1,5-DIAZOCINES)

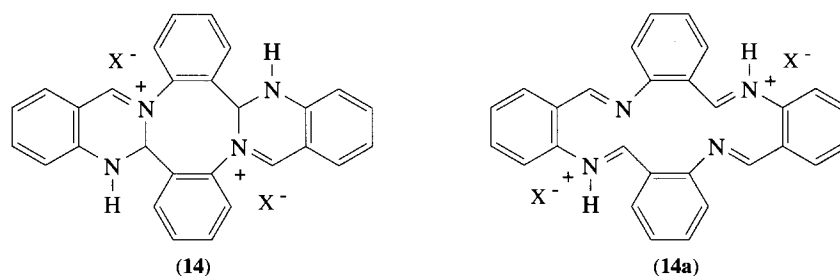
Given the comparatively large amount of attention paid to the 1,5-diazocines, exhaustive coverage of their structural and chemical features is beyond the scope of this chapter. CHEC-I reviewed the earlier literature, and more recent comprehensive reviews of the 1,5-diazocines (Section 5.19.7.5) <89AHC(16)1> and the benzodiazocines <87H(26)2477>, as well as the metal ion coordination chemistry of the diazocines <92CCR133>, have appeared. This section, then, provides comprehensive coverage of the literature from 1987 to 1995, with occasional reference to earlier work as appropriate.

9.24.3.1 Experimental Structural Methods

The abundance of crystallographic studies of the 1,5-diazocines stands in contrast to the dearth of such studies for the other 1,5-diheterocins. Single crystal x-ray diffraction analyses have been reported for octahydro-1,5-diazocines (1,5-diazocanes) (7) <87IZV576>, (8; Ar = 2-OH-3,5-Me₂C₆H₂) <92JHC317> and (9; R = H, Me) <90IC4364>, with the last in the form of their nickel complexes, and for less-reduced mono- and dibenzodiazocines (10) <87AX(C)2447>, (11) <93AX(C)531>, (12) <88MI 924-08>, (13; X = Y = H) <90IZV2630>, and (14; X = BF₄, HSO₄, picrate) <88AX(B)39>, with the aim of elucidation of structural, conformational, and/or reactivity issues.

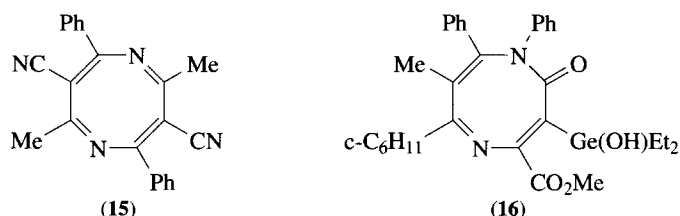


Bond lengths and angles observed in each of these diazocines fall within the standard range seen for molecules displaying related functionalities, and the primary interest in these structures appears to be in their revelation of conformational and solid-state packing details, as discussed below. An earlier suggestion that the reactions leading to dicationic species (14) instead afforded a macrocyclic valence tautomer (14a) was put to rest by the structural analyses of three salts of (14), each of which is clearly best formulated as a diazocine derivative <88AX(B)39>. Most revealing is the C(sp³)—N(sp²) bond length, which is absolutely normal at 1.45–1.48 Å; the large-ring valence tautomer would be expected to display a significantly larger distance between these atoms.

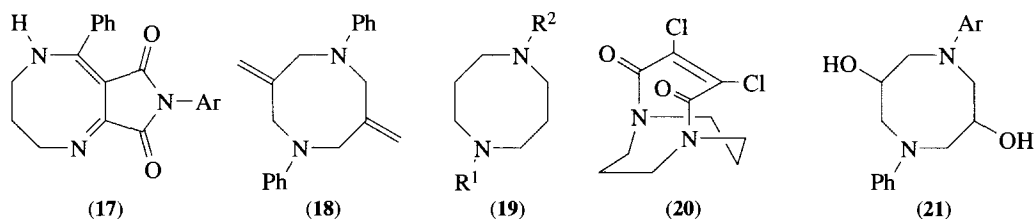


Fully-unsaturated 1,5-diazocine (15) displays ¹H and ¹³C NMR resonances consistent with its proposed structure <92TL8047>. The rather downfield methyl proton resonance (2.5 ppm) in (15) is

in accord with its proximity to the electron-withdrawing cyano substituents; the ring methyl group in less electron-deficient 1*H*-diazocin-2-one (**16**) is appropriately found at 2.1 ppm <92OM2348>. Although these data do not unequivocally address the issue of delocalization in fully-unsaturated diazocines, the ^{13}C spectra of (**15**) and (**16**) are in accordance with localized structures, and the tub-like conformations expected for these derivatives (see below) would, of course, preclude any significant delocalization.

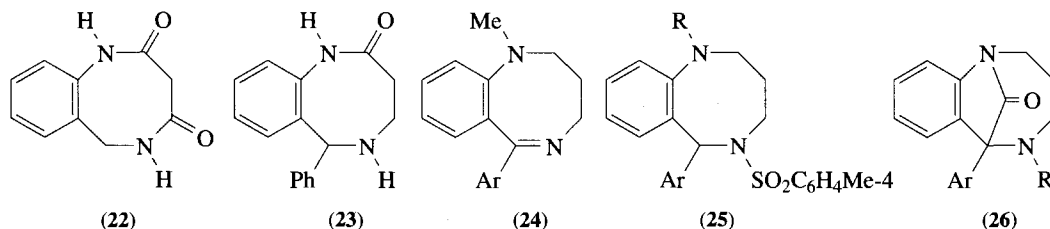


Proton and carbon-13 NMR allowed assignment of the indicated tautomeric structure for tetrahydrodiazocines (**17**; Ar = 4-RC₆H₄, R = H, Me, Cl) <89JPR(331)700>. The ring N-CH₂ protons in (**17**) appear at fairly low field (ca. 3.4 and 4.1 ppm), while those in other reported diazocines, whether partially-unsaturated (e.g., tetrahydrodiazocin-2,6(1*H*,3*H*)-dione (**8**; Ar = 2-OH-3,5-Me₂C₆H₂) <92JHC317>, 3,7-bis(methylene) derivative (**18**) <89JOU2210>), or fully-saturated (e.g. (**19**; R¹ = R² = 4-MeC₆H₄SO₂) <8IJC(B)790, 91ACS621>, (**19**; R¹ = R² = CH₂CH₂NH₂) <90IC264>, (**19**; R¹ = R² = CH₂CO₂H) <90JCS(P2)2211>, (**19**; R¹ = R² = 4-MeC₆H₄) <89T629>, (**20**) <92JHC1735>), all appear at ca. 3.1–3.8 ppm, although 3,7-dihydroxy-1,5-diazocanes (**21**; Ar = Ph, 4-MeC₆H₄) do display a downfield resonance (ca. 4.1 ppm) for the equatorial N-CH₂ protons <87MI 924-08>.



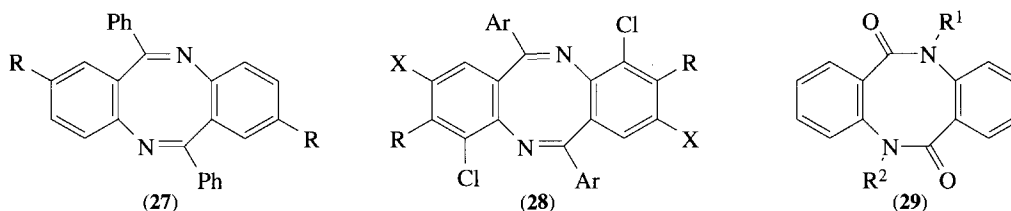
Carbon-13 NMR spectroscopy, invaluable in revealing the *cis/trans* isomerism of dihydroxy derivatives (**21**) <87MI 924-06, 87MI 924-07, 87MI 924-08, 91MI 924-05>, reveals no unusual features in (**8**) <92JHC317>, (**19**; R¹ = R² = 4-MeC₆H₄) <89T629>, or (**20**) <92JHC1735>. Protonation of 1,5-diazocane (**19**; R¹ = R² = H) gives the expected downfield shift of the N-CH₂ resonance to ca. 4.8 ppm <91ACS621>. Proton NMR spectroscopy has also been used to assay the protonation equilibria of diacetic acid derivative (**19**; R¹ = R² = CH₂CO₂H) <90JCS(P2)2211> and the structure of the nickel complex of (**19**; R¹ = R² = H) <88ICA119, 92IC4965>.

Proton ^1H NMR spectra of benzodiazocines (**22**) <92G485>, (**23**) <91T9599>, (**24**; Ar = 3-ClC₆H₄) <91JCS(P1)1975>, and (**25**; Ar = 3-ClC₆H₄, R = Me, AcO) <91JCS(P1)1975>, as well as bridged derivatives (**26**; R = H, Ar = Ph, 3-ClC₆H₄; R = Me, PhSO₂, Ar = 3-ClC₆H₄; R = 4-MeC₆H₄SO₂, Ar = Ph, 3-ClC₆H₄) <91JCS(P1)1975> have been reported; observed chemical shifts are in accordance with the functionalities present, as are the ^{13}C chemical shifts of (**25**; R = AcO) and (**26**) <91JCS(P1)1975>.

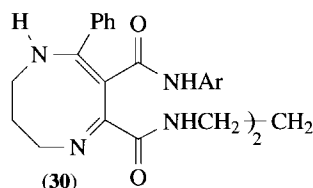


Proton NMR data for dibenzo[*b,f*][1,5]diazocines (**27**; R = NO₂, NH₂, etc.) <90JIC48> and (**28**; Ar = Ph, R = H, X = Br, Cl, NO₂; Ar = 4-MeOC₆H₄, 4-AcOC₆H₄, R = H, X = Cl; Ar = Ph, R = Me, X = Cl) <88JHC459> support the symmetrical structures of these derivatives. Dibenzo[*b,f*][1,5]diazocin-6,12-diones ("dianthranilides") (**29**; R¹ = Me, R² = H, Me), the targets of earlier intense NMR conformational study <82JCS(P1)1649>, display the expected ^1H NMR features

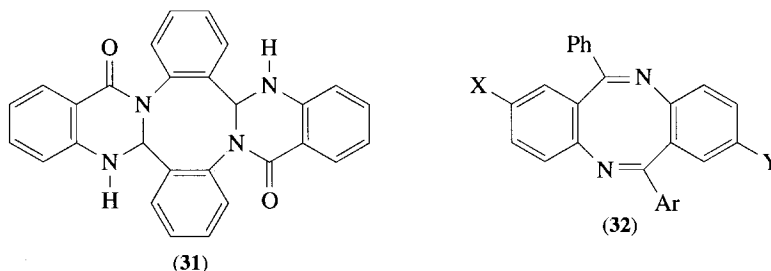
<88IJC(B)225>. Proton and carbon-13 NMR spectral data have been reported as part of the routine characterization of dianthranilides (**29**; $R^1 = R^2 = \text{ArCO}$, $\text{Ar} = 2\text{-N}_3\text{C}_6\text{H}_4$, $2\text{-N}_3\text{-5-ClC}_6\text{H}_3$, $2\text{-N}_3\text{-4,5-(MeO)}_2\text{C}_6\text{H}_2$) and the polycyclic diazocines (**13**; $\text{X} = \text{Y} = \text{H}$, MeO ; $\text{X} = \text{Cl}$, $\text{Y} = \text{H}$) derived therefrom as well <92JOC6975>.



Electron impact mass spectral analysis of (**21**; $\text{Ar} = \text{Ph}$) affords fragments assigned as $\text{PhN}(\text{CH}_2\text{CHO})(\text{CH}=\text{CHCH}_2)$, $\text{PhN}(\text{CH}_2)(\text{CH}_2\text{CH}=\text{CH}_2)$ and $\text{PhN}(\text{CH}_2)\text{H}$; substituted aromatic analogues fragment analogously <91MI 924-05>. 1,5-Diazocane (**19**; $R^1 = R^2 = 4\text{-MeC}_6\text{H}_4$) reveals the expected parent ion as well as fragments apparently resulting from cleavage of ring C—C and C—N bonds; recognizable fragments include the *p*-tolyl analogues of several of the fragments derived from (**21**; $\text{Ar} = \text{Ph}$), including $\text{MeC}_6\text{H}_4\text{N}(\text{CH}_2)(\text{CH}_2\text{CH}=\text{CH}_2)$ and $\text{MeC}_6\text{H}_4\text{N}(\text{CH}_2)\text{H}$, as well as MeC_6H_4 , $\text{MeC}_6\text{H}_4\text{N}$, and $\text{MeC}_6\text{H}_4\text{NCH}_2$ <89T629>. Diazocine-2,6-dione (**8**), displaying a parent ion and a base peak corresponding to loss of ArCH_2NH , appears to fragment similarly <92JHC317>. Fused-ring diazocines (**17**) all display parent ions and fragments derived from cleavages within the phthalimide ring, as well as the $\text{C}_6\text{H}_6\text{N}_2$ diazocine “core” fragment <89JPR(331)700>; side-chain cleavage appears to dominate the mass spectra of the related bis(diazocines) (**30**; $\text{Ar} = 4\text{-RC}_6\text{H}_4$, $\text{R} = \text{H}$, Me , Cl) <89JPR(331)700>.



Bridged benzodiazocines (**26**; $\text{R} = \text{H}$, Me , $\text{Ar} = 3\text{-ClC}_6\text{H}_4$) fragment with loss of CO , while the mass spectra of sulfonyl analogues (**26**; $\text{R} = \text{PhSO}_2$, $4\text{-MeC}_6\text{H}_4\text{SO}_2$, $\text{Ar} = 3\text{-ClC}_6\text{H}_4$) are dominated by loss of the *N*-sulfonyl group <91JCS(P1)1975>. Similar cleavage accounts for the base peak in (**25**; $\text{R} = \text{AcO}$, $\text{Ar} = 3\text{-ClC}_6\text{H}_4$), while (**24**; $\text{Ar} = 3\text{-ClC}_6\text{H}_4$) displays a prominent parent ion as well as ring- and side-chain cleavage fragments <91JCS(P1)1975>. Dianthranilide (**29**; $R^1 = \text{Me}$, $R^2 = \text{H}$), in addition to a parent ion, displays fragments resulting from both pseudo-symmetrical ring cleavage to $\text{C}_6\text{H}_4\text{CONH}$ and $\text{C}_6\text{H}_4\text{CONMe}$ and unsymmetrical cleavage, giving $\text{M-C}_6\text{H}_4\text{NH}$ and $\text{M-C}_6\text{H}_4\text{NMe}$ fragments <88IJC(B)225>. Mass spectral data have also been reported for polycyclic derivatives (**13**; $\text{X} = \text{Y} = \text{OMe}$; $\text{X} = \text{Cl}$, $\text{Y} = \text{H}$) for which parent ions and symmetrical cleavage ($\text{M}/2$) are observed, and for reduced analogue (**31**), which appears to fragment via loss of $\text{C}_6\text{H}_4\text{CONH}$ <92JOC6975>. Mass spectral parent ions, with no indication of fragmentation patterns, have also been reported for fully-unsaturated diazocines (**15**) <92TL8047> and (**16**) <92OM2348> and dibenzo[*b,f*][1,5]diazocines (**28**; $\text{Ar} = \text{Ph}$, $\text{R} = \text{H}$, $\text{X} = \text{Br}$, Cl , NO_2 ; $\text{Ar} = 4\text{-MeOC}_6\text{H}_4$, $4\text{-AcOC}_6\text{H}_4$, $\text{R} = \text{H}$, $\text{X} = \text{Cl}$; $\text{Ar} = \text{Ph}$, $\text{R} = \text{Me}$, $\text{X} = \text{Cl}$) <88JHC459> and (**32**; $\text{Ar} = \text{Ph}$, $\text{X} = \text{H}$, $\text{Y} = \text{Cl}$) <86S324>.

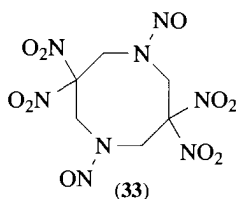


Only scattered electronic absorption data has been reported for the 1,5-diazocines. Bridged amines (**26**; $\text{R} = \text{H}$, Me , $\text{Ar} = 3\text{-ClC}_6\text{H}_4$) are yellow, apparently due to a low-energy absorption in the visible

region (425 nm ($\log \epsilon$ 3.50) for $R = H$, 443 (3.53) for $R = Me$); each also displays more intense absorption bands in the ultraviolet region (91JCS(P1)1975). Tetrahydrobenzodiazocine (**24**; $Ar = 3-ClC_6H_4$) is colorless, with a weak absorption band at 365 nm (3.43) and no other absorptions above 260 nm, while hexahydro derivatives (**25**; $R = AcO$, Me , $Ar = 3-ClC_6H_4$) absorb at around 230 nm (4.22) (91JCS(P1)1975). Given this data, the reported yellow color of bis(methylene) derivative (**18**) (89JOU2210) is probably an artifact. Dianthranilide (**29**; $R^1 = Me$, $R^2 = H$) absorbs at 212 nm (88IJC(B)225). Diazocine (**15**) (92TL8047) and benzo derivative (**10**) (87AX(C)2447) are reported to be yellow, while polycyclic derivatives (**13**) and (**31**) are colorless, as are their *N*-acyldianthranilide precursors (92JOC6975).

The IR spectrum of diazocine (**16**) is reported to display lactam and ester carbonyl absorptions at 1710 and 1730 cm^{-1} (92OM2348), while the lactam absorption in dione (**8**) appears at considerably lower (and more typical) energy (ca. 1620 cm^{-1}) (92JHC317). Tetrahydrodiazocines (**17**) and (**30**), in addition to modes associated with the peripheral functionalities, display intra-ring C=N stretching bands at around 1605–1645 cm^{-1} (89JPR(331)700). The *trans* isomers of diols (**21**) display IR behavior consistent with the presence of a transannular *H*-bond, while the *cis* isomers, for which the conformation for such an interaction is sterically prohibited, do not (91MI 924-05). Chloroaromatic derivatives (**21**; $Ar = 2,6-Cl_2C_6H_3$, $2,4,6-Cl_3C_6H_2$) show both free and *H*-bonded OH stretches, with the latter attributed to (weak) interaction between equatorially-situated hydroxyl groups and adjacent chlorines (91MI 924-05). Only CH (2800 cm^{-1}), C=C (1590 cm^{-1}), and S=O (1340 cm^{-1}) modes, of characteristic energies, were reported for ditosylate (**19**; $R^1 = R^2 = 4-MeC_6H_4SO_2$) (88IJC(B)790). Lactams (**22**) (92G485) and (**23**) (91T9599) absorb at around 1650 cm^{-1} . Somewhat curiously, bridged diazocines (**26**; $R = H$, $Ar = Ph$, $3-ClC_6H_4$; $R = Me$, $Ar = 3-ClC_6H_4$) display carbonyl stretching bands at around 1690–1710 cm^{-1} , while *N*-sulfonyl analogues (**26**; $R = PhSO_2$, $Ar = 3-ClC_6H_4$; $R = 4-MeC_6H_4SO_2$, $Ar = Ph$, $3-ClC_6H_4$) all absorb at much higher energy (ca. 1760 cm^{-1}) (91JCS(P1)1975). Unbridged derivative (**24**; $Ar = 3-ClC_6H_4$) displays a C=N mode at 1610 cm^{-1} , while *N*-sulfonyl derivatives (**25**; $R = AcO$, Me , $Ar = 3-ClC_6H_4$) display absorptions consistent with the functionalities present (91JCS(P1)1975). The C=N modes in dibenzo[*b,f*][1,5]diazocines (**27**) (90JIC48), (**28**) (88JHC459), and (**32**) (86S324) all appear at around 1610–1630 cm^{-1} , regardless of substitution pattern, while the dianthranilides (**29**; $R^1 = Me$, $R^2 = H$, Me) display lactam bands at 1640–1680 cm^{-1} (88IJC(B)225). Polycyclic lactams (**13**) also absorb at around 1680 cm^{-1} , while reduced derivative (**31**) displays a lactam carbonyl absorption band at 1634 cm^{-1} (92JOC6975).

X-ray photoelectron spectroscopic analysis of a series of polynitro compounds, including 1,5-dinitroso-3,3,7,7-tetranitro-1,5-diazocane (**33**), was carried out to assay the extent of intramolecular charge transfer. No such charge transfer is found in (**33**), which displays a rather high N(1s) binding energy for the ring nitrogens, consistent with the inductive effect of the nitro and nitroso groups (88MI 924-07).



9.24.3.2 Thermodynamic Aspects

Despite the presence of rather different arrays of functionalities, fully-unsaturated diazocines (**15**) (92TL8047) and (**16**) (92OM2348), both melt at around 150°C. Tetrahydrodiazocines (**17**) melt above 250°C, while the phthalimide-cleaved dimers (**30**) display somewhat reduced melting points (still, however, in excess of 200°C) consistent with their increased flexibility (89JPR(331)700). Even simple bis(methylene) derivative (**18**) is reported to melt at 210°C (89JOU2210), suggesting rather remarkable solid-state stability. The x-ray crystal structure of dione (**8**), bearing vague structural similarity to (**18**), reveals multiple close and favorable intermolecular van der Waals interactions, together apparently leading to high solid-state stability (m.p. 242°C) (92JHC317). *Cis* diol (**21**; $Ar = Ph$) melts at around 200°C, while the *trans* isomer is lower melting (91MI 924-05); the capability of the *trans* isomer to engage in intramolecular *H*-bonding presumably leads to diminished intermolecular interactions relative to the *cis* isomer, for which intramolecular *H*-bonding is sterically prohibited.

Unfortunately, substituted analogues (**21**; Ar = 3-(CF₃)C₆H₄, 3,5-(CF₃)₂C₆H₃, 2,6-Cl₂C₆H₃, 2,6-Me₂C₆H₃, 2,4,6-Cl₃C₆H₂) were not obtained in crystalline form, precluding further assessment of this issue. Ditosylate (**19**; R¹ = R² = 4-MeC₆H₄SO₂) <88IJC(B)790, 91ACS621> and bicyclic derivative (**20**) <92JHC1735> are high-melting solids, consistent with strong intermolecular dipole-dipole interactions, while diaryl derivative (**19**; R¹ = R² = 4-MeC₆H₄) is comparatively low-melting (m.p. 114°C) <89T629> and bis(aminoethyl) compound (**19**; R¹ = R² = CH₂CH₂NH₂) is a liquid <90IC264>.

Given the quite high melting points of many of the monocyclic diazocines, the lower melting points of benzo lactams (**22**) (145°C) <92G485> and (**23**) (189°C) <91T9599> are somewhat surprising, particularly in light of their potential for intermolecular *H*-bonding, as displayed in the solid-state structure of (**10**) <87AX(C)2447>. Bridged diazocine sulfonamides (**26**; R = PhSO₂, Ar = 3-ClC₆H₄; R = 4-MeC₆H₄SO₂, Ar = Ph, 3-ClC₆H₄) melt near 180°C, while the related amines (**26**; R = H, Me, Ar = 3-ClC₆H₄) melt at 128°C and 146°C, respectively. Benzo derivatives (**25**; R = Me, AcO, Ar = 3-ClC₆H₄) are also lower melting and (**24**; Ar = 3-ClC₆H₄) is a liquid <91JCS(P1)1975>.

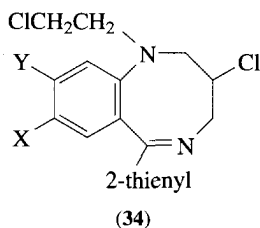
6,12-Diphenyldibenzo[*b,f*][1,5]diazocine (**27**; R = H) melts at 188°C <86S324, 87BCJ4417>, while its more heavily substituted derivatives (**27**; R ≠ H) <90JIC48>, (**28**) <88JHC459>, and (**32**) <86S324> are, in general, higher-melting when symmetrically-substituted and lower-melting when not. Tetrahydrodibenzo[*b,f*][1,5]diazocine (**11**) also displays a lower melting point (ca. 150°C) <86PS(26)185, 87JCS(P1)1547>, while dianthranilides (**29**; R¹ = Me, R² = H, Me) <88IJC(B)225> and (**12**) <88MI 924-08> display rather high solid-state stability. Here again *H*-bonding appears to play a key role. Thus, despite the lower symmetry of (**29**; R¹ = Me, R² = H) relative to (**29**; R¹ = R² = Me), the former melts around 50°C higher than the latter <88IJC(B)225>. Ditosylate (**12**) appears to be stabilized in the solid state by rather unusual *H*-bonding, with each benzene ring participating in two intermolecular *H*-bonds to sulfonyl groups. Acylation of ring nitrogens in the dianthranilide series (**29**; R¹ = R² = ArCO) in general lowers the melting point, while the highly symmetrical polycyclic diazocines (**13**) derived from these intermediates all melt in excess of 300°C <92JOC6975>. In a rather different vein, but of relevance to a discussion of solid-state phenomena, a copper complex of 1,5-diazocane ("daco"), (Cu(daco)₂)(NO₃)₂, undergoes a reversible thermochromic phase transition at ca. 90°C, with the transition apparently involving an alteration in the pattern of *H*-bonding in the solid state <89BCJ1822>.

In contrast to the rather high solubility of many of the 1,5-diheterocins, numerous 1,5-diazocines appear to display more limited solubility, providing additional support for the relatively high extent of intermolecular interaction in the solid state of many of these materials. Chloroform and/or methylene chloride dissolve most of the monocyclic derivatives, including fully-unsaturated diazocines (**15**) <92TL8047> and (**16**) <92OM2348> as well as perhydro derivatives (**19**; R¹ = R² = 4-MeC₆H₄ <89T629>, R¹ = R² = 4-MeC₆H₄SO₂ <91ACS621>, R¹ = R² = CH₂CH₂NH₂ <90IC264>), (**8**) <92JHC317>, bicyclic derivative (**20**) <92JHC1735>, and unsymmetrically-substituted diols (**21**; Ar = 3-(CF₃)C₆H₄, 3,5-(CF₃)₂C₆H₃, 2,6-Cl₂C₆H₃, 2,6-Me₂C₆H₃, 2,4,6-Cl₃C₆H₂) <91MI 924-05>. Tetrahydrodiazocines (**17**) are sparingly soluble in benzene, from which they may be recrystallized, but dissolve in *N,N*-dimethylformamide and, to some extent, in hexachlorobutadiene, while the bicyclic products derived therefrom (**30**) are insoluble in common organic solvents <89JPR(331)700>. Bis(methylene) derivative (**18**) is soluble in nonpolar media, including CCl₄ and benzene <89JOU2210>, while symmetrically-substituted (**21**; Ar = Ph) is appreciably less soluble, requiring acetone for acquisition of NMR spectral data <87MI 924-08, 91MI 924-04, 91MI 924-05>. Diazocine (**16**) is also soluble in diethyl ether <92OM2348>. The *meso* form of diol (**21**; Ar = Ph) crystallizes from toluene as it is formed <91MI 924-04>, and the diols in general may be recrystallized from ethanol <87MI 924-08>. Other recrystallization solvents for monocyclic diazocines include methanol ((**8**) <92JHC317>), CH₂Cl₂/EtOH ((**19**; R¹ = R² = 4-MeC₆H₄SO₂) <91ACS621>), CH₂Cl₂/cyclohexane ((**20**) <92JHC1735>), and Et₂O/hexane ((**16**) <92OM2348>). The barium salt of 1,5-diazocane-1,5-diacetic acid is insoluble in water, ethanol, and Et₂O <91IC3875>.

Chromatographic separation of diazocines has been effected on both normal phase silica, eluting with solvents of low <89JOU2210, 92TL8047> to moderate polarity <88MI 924-07, 91ACS621, 91MI 924-05> and reversed phase silica, eluting with aqueous THF <91MI 924-06> or methanol <91MI 924-04>. *Meso* diol (**21**; Ar = Ph) elutes before the racemate under reversed phase conditions <91MI 924-04>. Bis(methylene) compound (**18**) has been successfully analyzed by gas chromatography (5% Luco-pren G-1000, 190°C) <89JOU2210>. Pyrolysis gas chromatography of thermally labile 1,3,3,5,7,7-hexanitro-1,5-diazocane (**7**) and other explosive materials affords "fingerprint pyrograms" of their thermal decomposition products <88MI 924-03>.

A more varied selection of solvents is reported for the benzodiazocines; for example, benzo compounds (**10**) <87AX(C)2447> and (**25**; R = AcO, Ar = 3-ClC₆H₄) <91JCS(P1)1975> may be recrystallized from acetonitrile <87AX(C)2447>, *N*-methyl analogue (**25**; R = Me, Ar = 3-ClC₆H₄) from

toluene/light petroleum <91JCS(P1)1975>, and bridged derivatives (**26**) from ethanol, ethyl acetate, or H₂O/DMF/MeOH <91JCS(P1)1975>. The latter are soluble in aromatic hydrocarbons and in chloroform <91JCS(P1)1975>; chloroform also dissolves lactam (**23**) <91T9599>, while dione (**22**) requires DMSO as a solvent for NMR spectroscopy <92G485>. Chromatographic separation, including that of isomeric compounds (**34**; X = F, Y = H; X = H, Y = F) <86MI 924-02>, has been effected on both silica <91JCS(P1)1975, 91T9599, 92G485> and alumina <91JCS(P1)1975>.



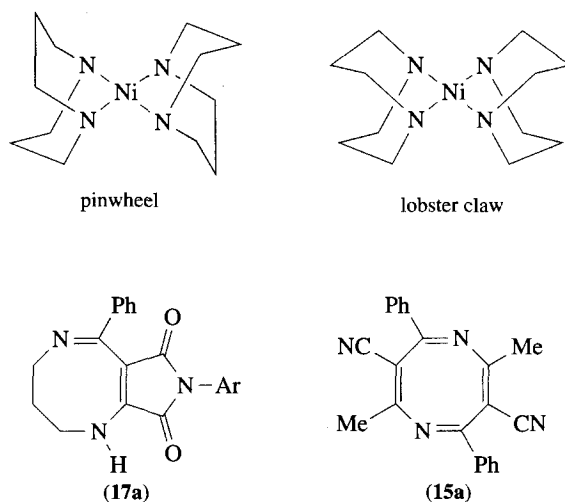
The various dibenzo[*b,f*][1,5]diazocines discussed above display typical solubility behavior in common organic solvents, and may be recrystallized from alcohols <86S324, 87BCJ4417, 90JIC48, 93AX(C)531>, acetonitrile <88JHC459>, or acetone <88JHC459>. Polycyclic cations (**14**) crystallize from acetonitrile as they are formed <88AX(B)39>. Chromatography has been successfully carried out over both silica, eluting with solvents of moderate polarity <88IJC(B)225, 89JHC1611, 89JOC4700, 92JOC6975>, and alumina, eluting with rather nonpolar benzene/hexane mixtures <86S324>.

Several 1,5-diazocanes have received considerable attention with regard to the stability of their metal complexes and of their protonated forms. 1,5-Dimethyl-1,5-diazocane (**19**; R¹ = R² = Me) undergoes successive protonations (pK_{a1} 11.9 and pK_{a2} 5.54 in H₂O), while its ten-membered ring analogue displays pK_{a1} > 12 and pK_{a2} = 0.4 <88CC1528>. The latter values are indicative of formation of an intramolecular *H*-bond in the monoprotinated species, as also revealed by x-ray diffraction analysis, while the diazocine, given its smaller ring, apparently does not have sufficient flexibility to allow optimal *H*-bonding. However, whether optimal or not, an intramolecular *H*-bond apparently is possible in the diazocine system, as evidenced by calorimetric studies and molecular mechanics calculations of 1,5-diazocane-1,5-diacetic acid (**19**; R¹ = R² = CH₂CO₂H); smaller-ring compounds, however, are precluded from forming such an intramolecular *H*-bond <90JCS(P2)2211>.

In order to attain the proper alignment for intramolecular *H*-bonding, the diazocine ring in (**19**; R¹ = R² = CH₂CO₂H) adopts a boat conformation <90JCS(P2)2211>. In the absence of such intramolecular interactions, alternative conformations appear to be favored; thus, diols (**21**; Ar = Ph, 4-MeC₆H₄, 3-(CF₃)C₆H₄, 3,5-(CF₃)₂C₆H₃, 2,6-Cl₂C₆H₃, 2,6-Me₂C₆H₃, 2,4,6-Cl₃C₆H₂) adopt a chair-chair ("crown") conformation, as indicated by NMR spectral analysis <87MI 924-08, 91MI 924-05>, as does dione (**8**) <92JHC317>. However, energy differences appear to be small, and in fact x-ray structural analysis of (**8**) revealed both the chair-type and twist-boat conformations in the solid state <88MI 924-07>. Benzodiazocine (**10**) <87AX(C)2447>, dibenzodiazocines (**11**) <93AX(C)531> and (**12**) <88MI 924-08>, and polycyclic analogues (**13**; X = Y = H) <90IZV2630> and (**14**) <88AX(B)39> all display boat or twist-boat conformations; the nonplanar structures of even the fully-unsaturated derivatives confirm the absence of delocalized bonding. Not surprisingly, bicyclic diazocine (**20**) adopts a conformation maintaining amide-type delocalization rather than one placing the carbonyl groups into conjugation with the bridging C=C double bond <92JHC1735>. Conformational studies of 1,3,3,5,7,7-hexamethyl-1,5-diazocane <90TH924-01> and diol (**21**; Ar = Ph) <88MI 924-06> have also appeared.

Numerous metal complexes bearing diazocine or diazocine-derived ligands have been structurally characterized <92CCR133>. The diazocine ring in these complexes most often is found in a boat-chair conformation, but twist-boat and chair-chair conformations have also been found <90IC4364, 92IC4965, 93AG(E)116>. The bis(1,5-diazocane) complex of Ni^{II} displays both chair and boat conformations, with conformational interconversion rapid even at -80°C; molecular mechanics calculations revealed two low-energy forms, one with two chair and two boat chelate rings ("pinwheel"), the other with four chair chelate rings ("lobster claw") <92IC4965>.

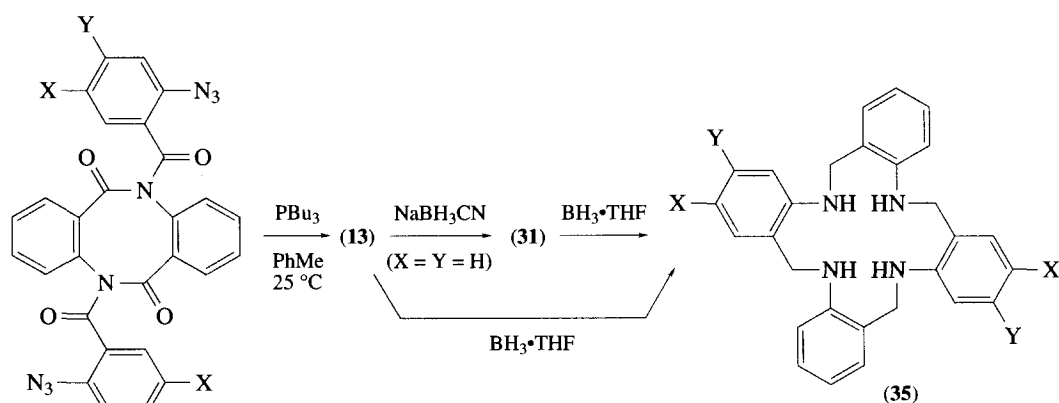
Dicationic diazocine (**14**), earlier suggested to exist as the macrocyclic tautomer (**14a**), was shown by x-ray diffraction analysis to exist in the solid state in the diazocine form <88AX(B)39>. Carbon-13 NMR spectral analysis of fused-ring tetrahydrodiazocines (**17**), which exist as single tautomers, led to assignment of structure (**17**) rather than (**17a**) <89JPR(331)700>. Spectral analysis of the fully-unsaturated diazocine derived from the apparently irreversible valence isomerization of a putative diazasemibullvalene intermediate (see below) led to the assignment of structure (**15**) rather than double bond-shifted tautomeric structure (**15a**) <92TL8047>.



9.24.3.3 Reactivity of Nonconjugated Rings

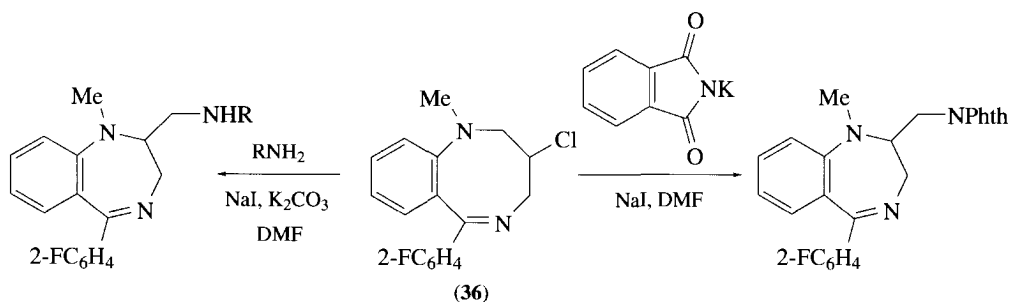
Little reaction chemistry has been reported for the comparatively rare fully-unsaturated 1,5-diazocines, although valence isomerization and a handful of other reactions, particularly of the dibenzo[*b,f*][1,5]diazocines, have been reported, as summarized in CHEC-I (Section 5.19.4.5) and in reviews (87H(26)2477, 89AHC(46)1). These derivatives are discussed here rather than in a separate section devoted to fully-conjugated compounds, as their decidedly nonplanar conformations clearly obviate any possibility of delocalized bonding.

Dibenzo[*b,f*][1,5]diazocin-6,12-dione (**29**; $R^1 = \text{Me}$, $R^2 = \text{H}$) may be *N*-methylated under phase-transfer catalysis conditions, affording (**29**; $R^1 = R^2 = \text{Me}$) (88IJC(B)225). The parent dione (**29**; $R^1 = R^2 = \text{H}$) is *N*-acylated by aroyl chlorides giving (**29**; $R^1 = R^2 = \text{ArCO}$, $\text{Ar} = 2\text{-N}_3\text{C}_6\text{H}_4$, $2\text{-N}_3\text{-4,5-(MeO)}_2\text{C}_6\text{H}_2$, $2\text{-N}_3\text{-5-ClC}_6\text{H}_3$) in moderate yield. These azides undergo tandem Staudinger and aza-Wittig reactions when treated with PBu_3 , affording (**13**; $\text{X} = \text{Y} = \text{H}$, OMe ; $\text{X} = \text{Cl}$, $\text{Y} = \text{H}$), which in turn afford dihydro derivatives (**31**) upon treatment with NaBH_3CN . Further reduction of (**31**) with BH_3 affords macrocyclic polyamines (**35**), also obtainable directly from (**13**) (Scheme 1) (92JOC6975).

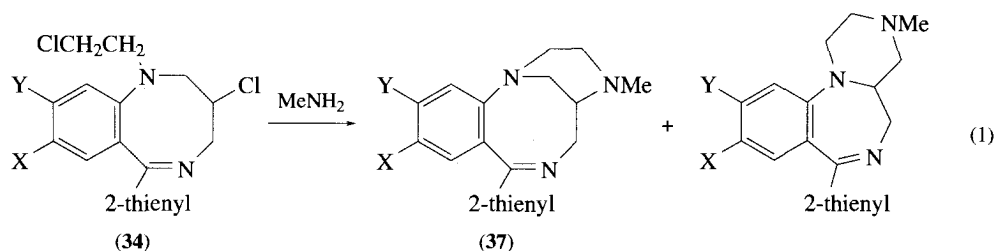


Scheme 1

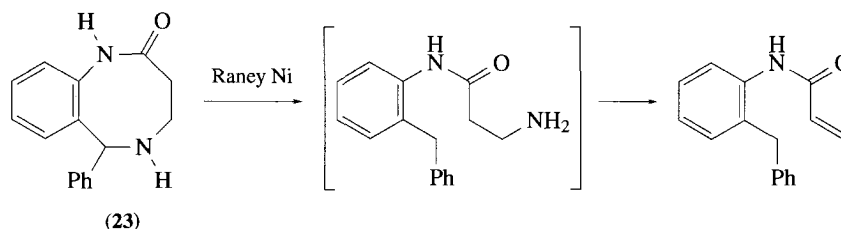
Treatment of tetrahydro-1,5-benzodiazocine (**36**) with potassium phthalimide or primary amines affords substituted benzodiazepine derivatives (Scheme 2) (90JMC450), with the observed ring contraction suggesting neighboring group participation, as seen, for example, for the dithiocins (see below). Treatment of *N*-chloroethyl derivatives (**34**; $\text{X} = \text{H}$, $\text{Y} = \text{F}$; $\text{X} = \text{F}$, $\text{Y} = \text{H}$) with methylamine affords both ring-contracted and *unrearranged* cyclization products (**37**; $\text{X} = \text{H}$, $\text{Y} = \text{F}$; $\text{X} = \text{F}$, $\text{Y} = \text{H}$), with ring contraction the favored reaction path (Equation (1)) (88EJM249).



Scheme 2



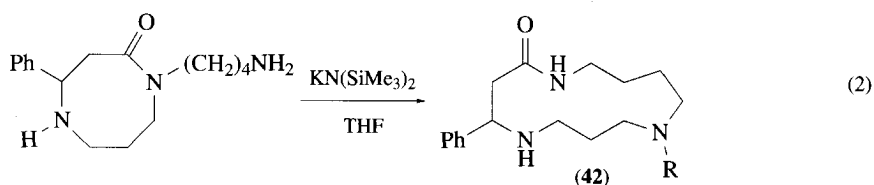
Bicyclic lactam (**26**; $R = 4\text{-MeC}_6\text{H}_4\text{SO}_2$, $\text{Ar} = 3\text{-ClC}_6\text{H}_4$) is cleaved by lithium aluminum hydride to afford (**24**; $\text{Ar} = 3\text{-ClC}_6\text{H}_4$); further reduction of the imine functionality in (**24**) is apparently sterically prevented (91JCS(P1)1975). Raney nickel effects the reductive ring cleavage of benzo-diazocinone (**23**) (Scheme 3) (91T9599).

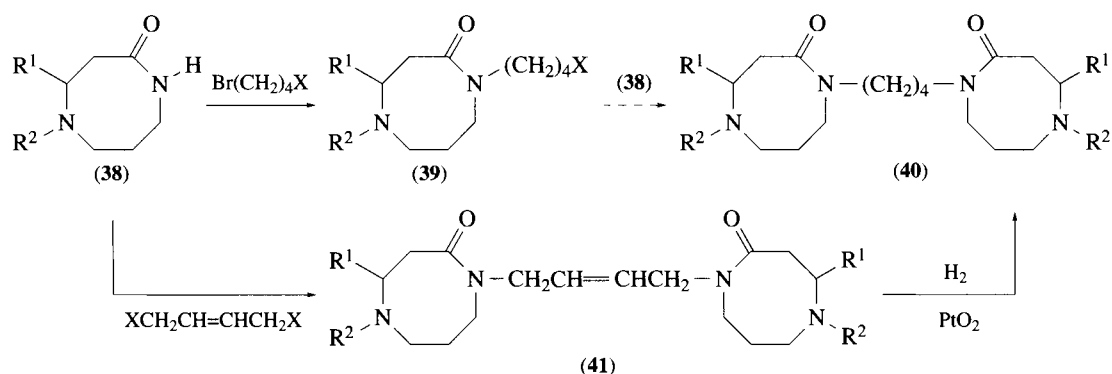


Scheme 3

A variety of *N*-alkylation and *N*-acylation reactions of 1,5-diazocanes has been reported. The parent derivative (**19**; $R^1 = R^2 = \text{H}$) has been methylated (88CC1528) and alkylated with chloroacetic acid (90JCS(P2)2211, 91IC3875), bromoethylphthalimide (90IC264), and ethylene sulfide (90IC4364, 92IC3497), and acylated with dichloroacetyl chloride (92JHC1735), affording in each case the *N,N'*-disubstituted diazocane. Lactams (**38**; $R^1 = \text{Ph}$, C_5H_{11} , C_7H_{15} , $\text{CH}_2\text{CH}(\text{C}_5\text{H}_{11})\text{OSiMe}_2\text{Bu}^t$, $R^2 = \text{H}$) are reductively methylated ($\text{CH}_2\text{O}/\text{NaBH}_3\text{CN}$) or benzyloxycarbonylated to afford (**38**; $R^1 = \text{Ph}$, C_5H_{11} , C_7H_{15} , $\text{CH}_2\text{CH}(\text{C}_5\text{H}_{11})\text{OSiMe}_2\text{Bu}^t$, $R^2 = \text{Me}$, PhCH_2OCO) (86TL5147). These derivatives may in turn be *N*-alkylated with 1,4-dibromobutane (86TL5147) or 1-bromo-4-chlorobutane (86TL5151), affording (**39**; $\text{X} = \text{Br}$, Cl) (Scheme 4). Attempts to effect a second diazocinone alkylation with (**39**; $\text{X} = \text{Br}$), affording homaline (**40**; $R^1 = \text{Ph}$, $R^2 = \text{Me}$) and related *Homalium* alkaloids, however, were unsuccessful. Alkylation with 1,4-dihalo-2-butenes, affording intermediates (**41**), permitted the successful coupling of diazocinones, affording access, following catalytic reduction, to both homaline and, through step-wise couplings, its unsymmetrical relatives (86TL5147).

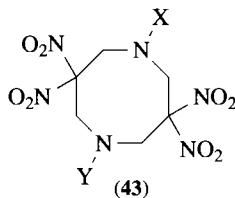
Aminobutyl derivative (**39**; $R^1 = \text{Ph}$, $R^2 = \text{H}$, $\text{X} = \text{NH}_2$), derived from aminolysis of the corresponding chloride in liquid ammonia, undergoes base-mediated intramolecular transamidation, affording macrocyclic lactam (**42**; $R = \text{H}$) in 21% yield (Equation (2)); acylation of this product with cinnamoyl chloride affords ($\pm$)-dihydroperiphylline (**42**; $R = \text{PhCHCHCO}$) (86TL5151).





Scheme 4

N-Nitration and *N*-nitrosation reactions afford 1,5-diazocanes (**43**; X = H, Y = NO, NO₂; X = NO, Y = NO₂; X = Y = NO, NO₂) <87MI 924-03, 88MI 924-02>, and the explosive thermal decomposition of these derivatives has been extensively examined both experimentally <87MI 924-05, 91MI 924-03> and theoretically <91MI 924-01, 92JEM287>.



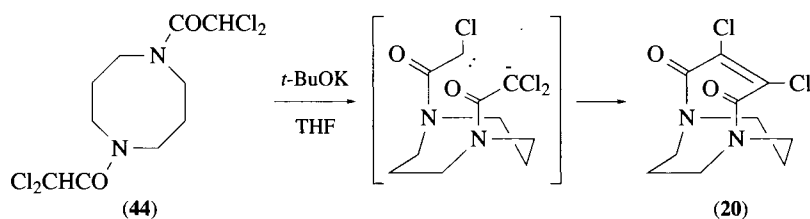
9.24.3.4 Reactivity of Substituents Attached to Ring Carbon Atoms

In those few cases in which relevant reactivity studies have been reported, diazocine ring side-chain substituents appear to display normal reactivity. The phthalimide ring in tetrahydrodiazocines (**17**) undergoes aminolysis with 1,3-diaminopropane, affording diazocine dimers (**30**) <89JPR(331)700>. Catalytic reduction of 2,8-dinitro-6,12-diphenyldibenzo[*b,f*][1,5]diazocine (**27**; R = NO₂) affords the corresponding diamine (**27**; R = NH₂), which undergoes typical reactions of aromatic amines (e.g. acylation, Schiff base formation, condensation with isothiocyanates) without interference by the diazocine ring <90JIC48>.

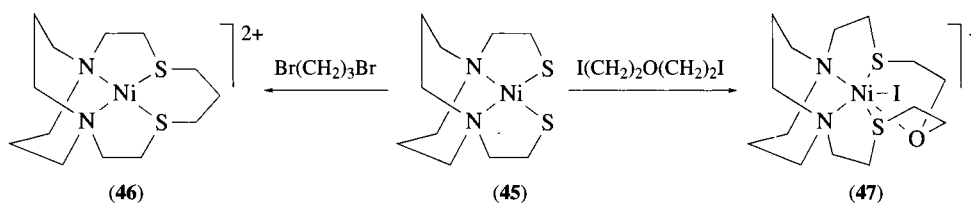
9.24.3.5 Reactivity of Substituents Attached to Ring Heteroatoms

Side-chain functionalities in *N*-substituted diazocines display normal reactivity. Nucleophilic displacement reactions of (**39**; R¹ = Ph, R² = H, X = Cl) with ammonia <86TL5151> and (**34**) with methylamine <88EJM249>, catalytic reduction of butenyl derivative (**41**) <86TL5147>, and reductive cleavage of bridged lactams (**26**) <91JCS(P1)1975> were noted above. The sulfonamide groups in (**19**; R¹ = R² = 4-MeC₆H₄SO₂) are removed by HBr and phenol in acetic acid, affording 1,5-diazocane <90IC264, 91ACS62>, and aqueous sodium hydroxide effects the cleavage of the phthalimide groups in (**19**; R¹ = R² = CH₂CH₂NPhth), affording (**19**; R¹ = R² = CH₂CH₂NH₂) <90IC264>. Treatment of bis(dichloroacetyl) derivative (**44**) with potassium *t*-butoxide affords bicyclic diazocine (**20**), apparently via intramolecular carbene-carbanion coupling (Scheme 5) <92JHC1735>.

Numerous alkylation reactions of metal complexes of 1,5-bis(thiolethyl)-1,5-diazocane (**9**; R = H) have been reported. For example, alkylation of nickel complex (**45**) affords (**9**; R = Me <90IC4364>, R = Et, PhCH₂, Prⁱ <91JA1421> and R = CH₂CO₂⁻), all in the form of their metal complexes, as well as macrocyclic complexes (**46**) and (**47**) (Scheme 6) <92IC4965>. The latter macrocycles are formed in good yield (ca. 80%), consistent with the template-type synthesis, and may be obtained in uncomplexed form by demetalation with excess cyanide. Oxidation of (**45**) by either molecular oxygen or hydrogen peroxide affords mixtures of mono- and bis(sulfinic acid) complexes <92JA4601>.



Scheme 5

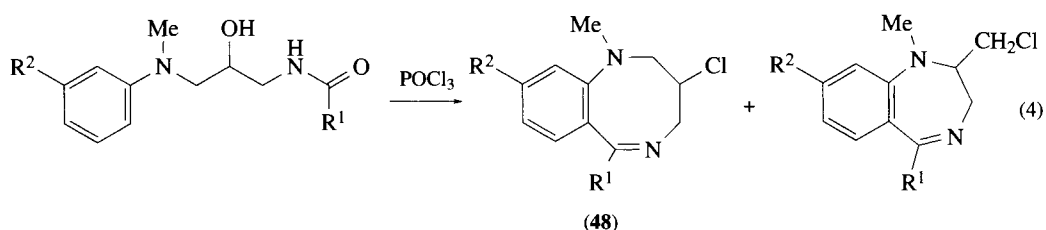
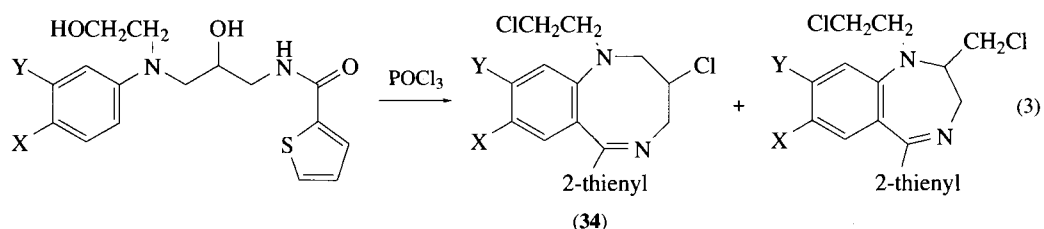


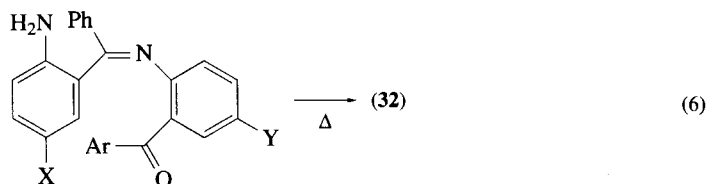
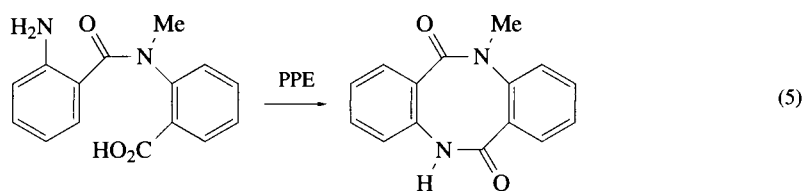
Scheme 6

Inasmuch as complexed metal ions formally represent *N*-substituents, reported kinetic analyses of the hydrolytic decomplexation of the 1,5-diazocane ligand from its Ni(II) and more labile Cu(II) complexes <89AJC1611, 90ICA179> merit mention here.

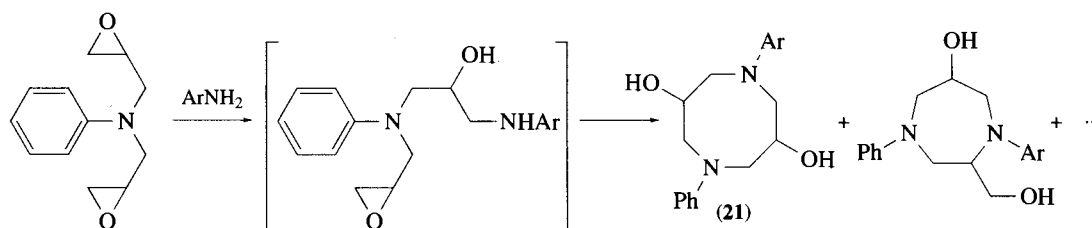
9.24.3.6 Ring Syntheses

Comparatively few unimolecular cyclization routes to the 1,5-diazocines have been reported, although, in general, each of the condensation routes discussed below has either been demonstrated or may reasonably be inferred to proceed via such cyclization of intermediates formed *in situ*. Bischler–Napieralski cyclization yields benzodiazocines (**34**; X = F, Y = H; X = H, Y = F) (Equation (3)) <88EJM249> and (**48**; R¹ = cyclo-C₆H₁₁, R² = H; R¹ = Ph, R² = OMe) (Equation (4)) <90GEP(O)3907390>, together with ring-contracted analogues, while lactamization and intramolecular Schiff base formation afford access to dibenzo[*b,f*][1,5]diazocine derivatives (**29**; R¹ = Me, R² = H) (Equation (5)) <88IJC(B)225> and (**32**; X = Y = H, Ar = Ph, 4-MeC₆H₄; X = Cl, Y = H, Cl, Ar = Ph) <86S324, 87JCR(S)96>, respectively.



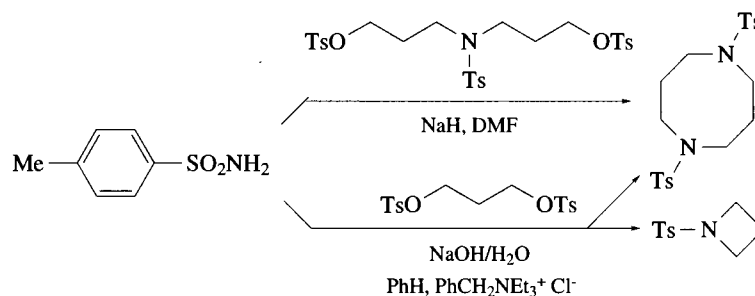


Condensation of diglycidylaniline with aromatic amines, studied as a model for the curing reactions of related epoxy resin systems, affords diols (**21**; Ar = Ph, 4-MeC₆H₄, 3-(CF₃)C₆H₄, 3,5-(CF₃)₂C₆H₃, 2,6-Cl₂C₆H₃, 2,6-Me₂C₆H₃, 2,4,6-Cl₃C₆H₂) in modest yield (Scheme 7), together with other products arising from a common acyclic intermediate <87MI 924-08, 88MI 924-06, 91MI 924-05, 91MI 924-06>; the symmetrically-substituted 1,5-bis(4-MeC₆H₄) derivative is prepared analogously from diglycidyltoluidine <87MI 924-06>. The diols are obtained as roughly equimolar mixtures of *cis* and *trans* isomers; earlier claims that the components of the product mixtures were simply conformational isomers were shown to be incorrect <91MI 924-06>.



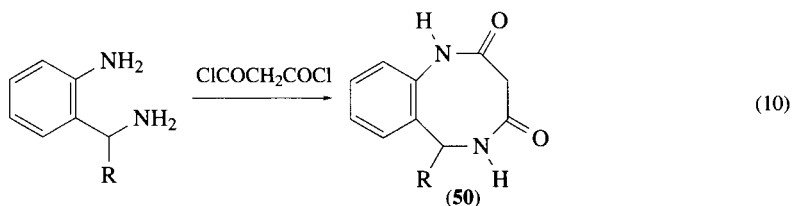
Scheme 7

Dialkylation of *p*-toluenesulfonamide affords (**19**; R¹ = R² = 4-MeC₆H₄SO₂) in 55% yield (Scheme 8) <91ACS621>; the same diazocine is formed in lower yield (20%), together with the expected azetane (23%), upon alkylation of *p*-toluenesulfonamide with 1,3-propanediol ditosylate <85MI 924-05, 88IJC(B)790>.

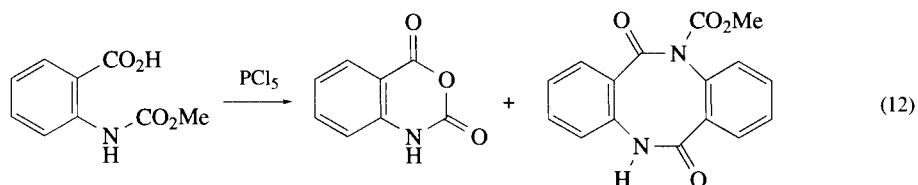
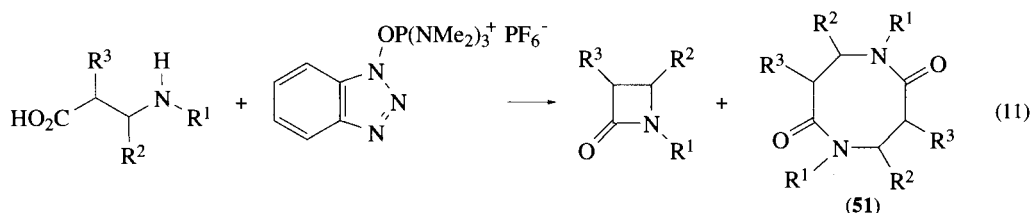


Scheme 8

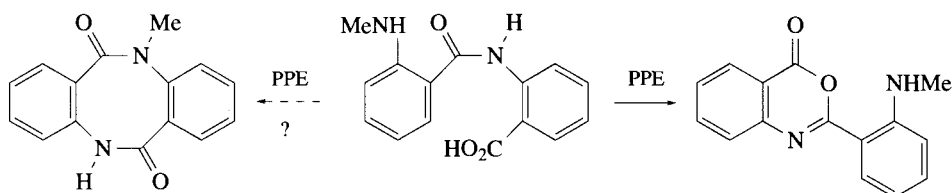
p-Toluidine reacts analogously with 1,3-dibromopropane, affording diazocine (**19**; R¹ = R² = 4-MeC₆H₄, 22%) and the azetane (14%), as well as a small amount (2%) of a macrocyclic tetramer (Equation (7)) <89T629>.



Various dimerization reactions lead to a number of 1,5-diazocines. Thus, for example, treatment of $\text{ArCH}_2\text{NHCH}_2\text{CH}_2\text{CO}_2\text{H}$ with POCl_3 and ZnCl_2 affords diazocin-2,6-dione (**8**; $\text{Ar} = 2\text{-OH-3,5-Me}_2\text{C}_6\text{H}_2$) in 60% yield [92JHC317]. Indeed, the diazocines not infrequently arise as undesired by-products in the synthesis of smaller-ring compounds; for example, (**51**; $\text{R}^1 = \text{PhCH}_2$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$; $\text{R}^1 = \text{PhCH}_2$, cyclohexyl, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Me}$) (Equation (11)) are formed together with the desired β -lactams in the lactamization of β -amino acids [88MI 924-05], and dianthranilide (**29**; $\text{R}^1 = \text{CO}_2\text{Me}$, $\text{R}^2 = \text{H}$) forms together with a 3,1-benzoxazin-2,4-dione upon dehydration of an *o*-carboxyphenyl urethane (Equation (12)) [89DOK(7)41].

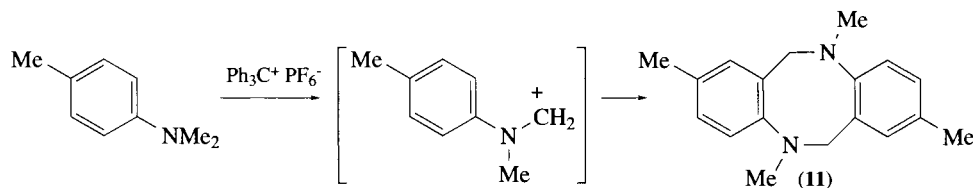


Intentional dimerization of *o*-aminobenzoic acid derivatives affords access to the dianthranilides in generally poor yield [82JCS(P1)1649, 88IJC(B)225]; some uncertainty exists in the literature regarding the course of these reactions, and apparently some structural misassignments have been made for example, it has been suggested that earlier reports of the synthesis of (**29**; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$) actually afforded an isomeric benzoxazinone (Scheme 10) [88IJC(B)225].



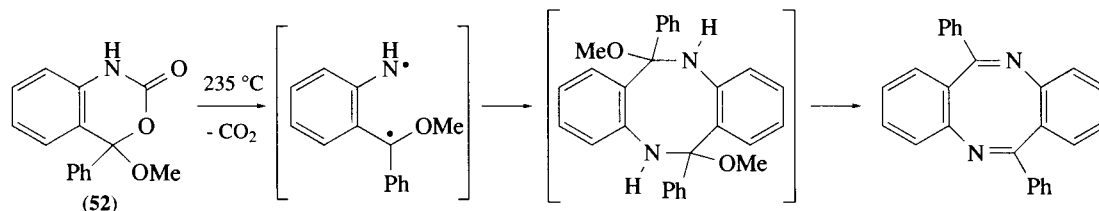
Scheme 10

Tetrahydrodibenzo[*b,f*][1,5]diazocine (**11**) is formed in 41% yield (Scheme 11), apparently via Friedel-Crafts-type condensation, upon treatment of *p*-toluidine with triphenylcarbenium hexafluorophosphate [86PS(26)185, 87JCS(P1)1547]. The same diazocine is formed in low yield (ca. 5%) upon one-electron oxidation of *p*-toluidine [89JOC4700, 93AX(C)531].



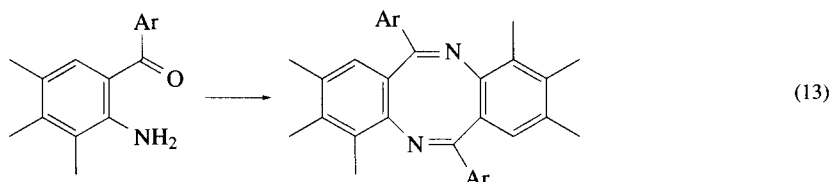
Scheme 11

Pyrolysis of benzoxazin-2-one (**52**) affords diazocine (**27**; R = H) in ca. 8% yield, reportedly as a result of dimerization of the first-formed biradical (Scheme 12) <87BCJ4417>. However, *o*-amino-benzophenone is the major product of this pyrolysis (49%) and, given the known self-condensation of such compounds to dibenzodiazocines (**27**; R = H), may represent a secondary product of this pyrolysis.



Scheme 12

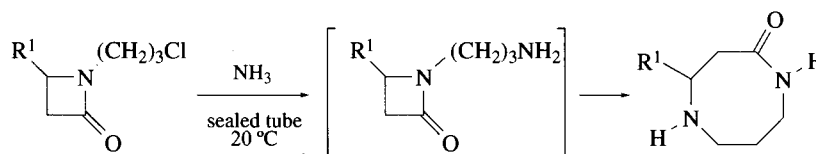
Regarding the latter self-condensation, various substituted *o*-aminobenzophenones condense to afford 6,12-diaryldibenzo[*b,f*][1,5]diazocines in often excellent yield (Equation (13)) <86S324, 88JHC459, 89JHC1611, 90JIC48>.



o-Aminobenzaldehyde has long been known to undergo self-condensation as well, affording a dicationic tetramer proven by x-ray crystallographic analysis to be the diazocine (**14**) rather than valence tautomeric macrocycle (**14a**) <88AX(B)39>.

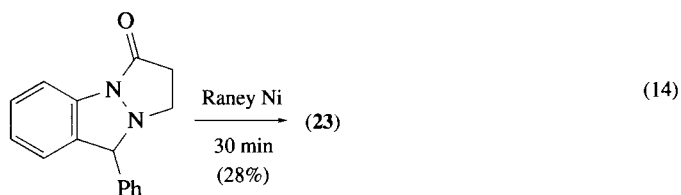
9.24.3.7 Ring Synthesis by Transformation of Another Ring

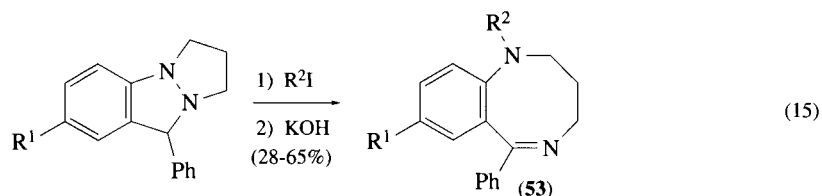
Treatment of *N*-(4-chlorobutyl) β -lactams with ammonia results in spontaneous intramolecular transamidation of the initially formed amine, affording diazocinones (**38**; R¹ = Ph, C₅H₁₁, C₇H₁₅, CH₂CH(C₅H₁₁)OSiMe₂Bu^t, R² = H) in excellent yield (Scheme 13) <86TL5147>.



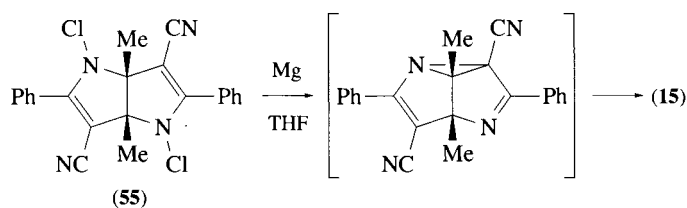
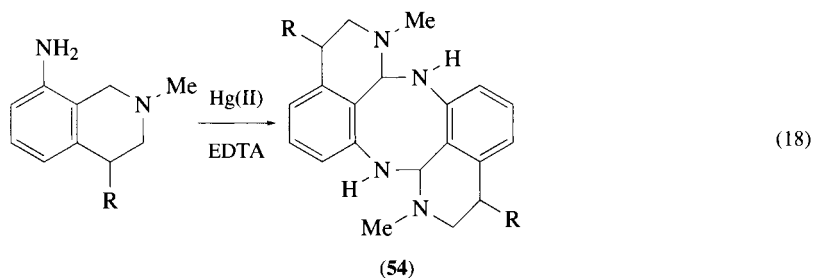
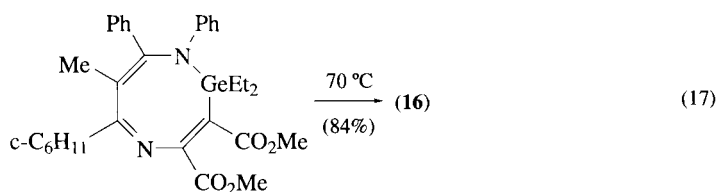
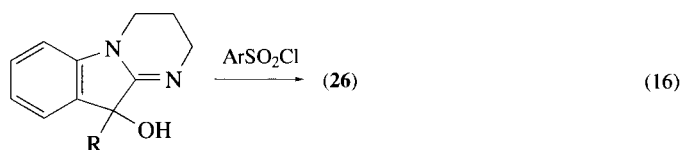
Scheme 13

Cleavage of the N—N bond of bicyclo[3.3.0] compounds affords access to a number of diazocines, including (**23**) (Equation (14)) <91T9599> and (**53**; R¹ = H, Me, R² = Me, Et; R¹ = Cl, R² = Me, Pr) (Equation (15)) <86H(24)3187>, as well as 1,5-diazocane itself <91IC3875>. The reduction affording (**23**) is quite sensitive to steric effects, and *gem*-disubstituted precursors are not cleaved <91T9599>.





More unusual ring transformation routes include the conversion of bicyclo[4.3.0] compounds to carbonyl-bridged diazocines (**26**) (Equation (16)) <91JCS(P1)1975>, the thermal rearrangement of a diazagermocine to diazocine (**16**) (Equation (17)) <92OM2348>, the oxidative dehydrogenation of 8-aminotetrahydroisoquinolines, affording (**54**; R = H, Ph) (Equation (18)) rather than the expected carbinolamines <88AP(321)287>, and the reductive dehalogenation of *N,N'*-dichloride (**55**) (Scheme 14), apparently proceeding via initial formation of a diazasemibullvalene and subsequent valence isomerization <92TL8047>.



Scheme 14

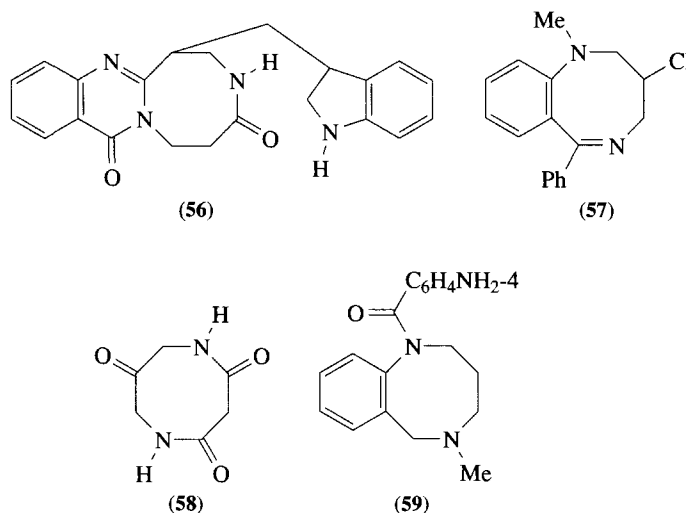
9.24.3.8 Comparison of Synthetic Routes

Clearly a large number of routes have been developed for the preparation of the diazocines and their benzo and dibenzo analogues. Several of the ring-transformation routes, in particular the transamidation of β -lactam derivatives and the reductive ring cleavage of [3.3.0] derivatives, offer often high yields and reasonable synthetic versatility, although the need for construction of appropriate precursors and the critical dependence of the latter reactions on substitution pattern may somewhat limit their general applicability. Virtually all the cyclization and condensation approaches,

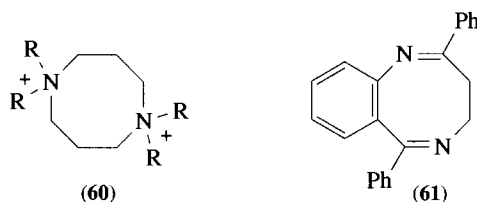
while offering access to a wide variety of diazocines, suffer from low-to-modest yields. Many routes also appear quite sensitive to substituent effects as well, further limiting their general applicability. Thus, although a plethora of synthetic routes is available, one might anticipate yield and/or generality problems to continue to somewhat restrict access to this most important class of compounds. The near absence of dibenzo[*b,g*][1,5]diazocines from the chemical literature is perhaps noteworthy and indicative of the need for additional synthetic efforts in this arena as well.

9.24.3.9 Important Compounds and Applications

Earlier reviews <87H(26)2477, 89AHC(46)1> have outlined a number of important applications of the diazocines; only practical applications since the late 1980s are discussed here. A number of diazocines have been explored as both potentially pharmacologically-active analogues of the well-known benzodiazepines and as intermediates in the synthesis of the latter via ring contraction strategies. Fused-ring (56) has been explored as a cholecystokinin (CCK) antagonist <89JAP(K)61176588>, and benzodiazocines (36) <90JMC450>, (48) <90GEP(O)3907390>, and (57) <92MIP9204025> have all been developed as intermediates for the synthesis of benzodiazepine-based CCK antagonists, of use in, for example, the treatment of pain, panic disorder, and drug and alcohol dependence. Camptothecin derivatives esterified with *N*-carboxy-1,5-diazocane have been explored as pro-drugs for cancer chemotherapy <91MI 924-02>, and other diazocines (e.g. (17) <89JPR(331)700>, (58) <87MI 924-02>) and benzodiazocines (e.g. (59) <91MIP9105549>) display a variety of biological activities. Various 6,12-diaryldibenzo[*b,f*][1,5]diazocines are anti-gonadotropic, hypotensive, blood-cholesterol lowering, and estrogenic agents <86S324, 88JHC459, 90JC48>.



1,5-Diazocane has been used as a hardening agent for epoxy resins <89EGP266361>, and both its nickel complex <87JAP(K)62131258> and a variety of *N,N'*-disubstituted derivatives add light stability to color photographic, textile, and printing ink dyes <88JAP(K)63205651>. 1,5-Bis(dichloroacetyl)-1,5-diazocane reduces the phytotoxicity of benzoate and haloacetamide herbicides toward crop plants <91EUP436483, 92EUP480902>. Quaternary salts (60; R = Et, Bu) and related electrolytes have found application in double-layer capacitors <86JAP(K)63127521>, while benzodiazocine (61) has been used in electroluminescent devices <91USP5077142>.



Quinazolone-type diazocines related to (13) have been incorporated into ladder polymers of good thermal and oxidative stability <92MI 924-01>. The polynitro 1,5-diazocanes are well-known high-

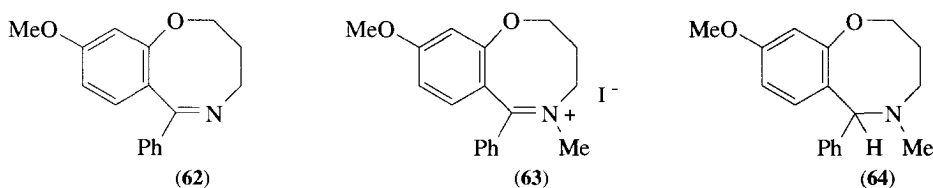
energy solid oxidizers with appropriate explosive and pyrotechnic applications <86MI 924-01, 87IZV576, 88MI 924-02, 88MI 924-04>. Metal complexes of the diazocines and their derivatives may display a range of useful properties <87MI 924-04, 92CCR133>; the intramolecular C—H bond activation chemistry displayed by a cobalt complex of *N,N'*-diacetic acid derivative (**19**; $R^1 = R^2 = \text{CH}_2\text{CO}_2\text{H}$) <86TH924-01> provides an intriguing glimpse of the potential practical importance of this coordination chemistry.

9.24.4 RINGS WITH ONE NITROGEN AND ONE OXYGEN (1,5-OXAZOCINES)

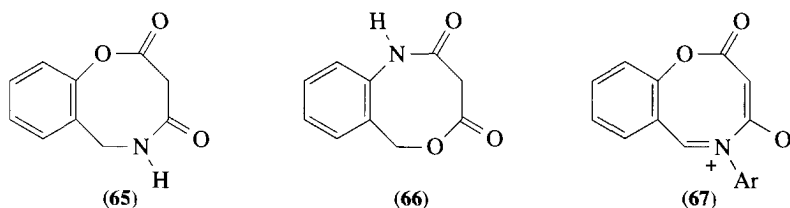
The 1,5-oxazocines received only cursory attention in CHEC-I, with two brief synthetic examples presented in Section 9.24.5.19.5. However, a comprehensive review of the oxazocines, which, with the exception of the 1,4-positional isomers, remain a comparatively scarce class of diheterocins, appeared in 1982 <82H(19)709>, and this section thus focuses on literature accounts appearing since the preparation of this review.

9.24.4.1 Experimental Structural Methods

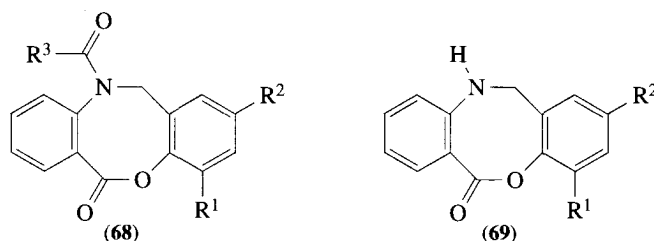
Proton NMR chemical shifts reported for 6-phenyl-1,5-benzoxazocine (**62**) and its methylation (**63**) and reduction (**64**) products are in accord with the functionalities present, although the benzylic proton in (**64**) appears at somewhat lower field (5.30 ppm) than in the corresponding benzoxazepin <84AJC129>.



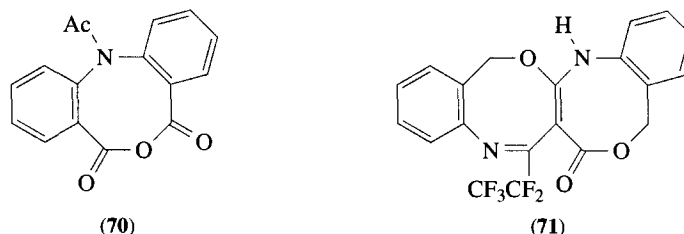
Positional isomers 5,6-dihydro-2*H*-1,5-benzoxazocin-2,4(3*H*)-dione (**65**) and 1,6-dihydro-2*H*-5,1-benzoxazocin-2,4(3*H*)-dione (**66**) display very similar ^1H NMR spectra, with no unusual chemical shifts <92G485>. In contrast, 1,5-benzoxazocin-2,4-dione analogues (**67**; $\text{Ar} = 4\text{-RC}_6\text{H}_4$, $\text{R} = \text{H}$, Me , OMe) display two low-field single-proton resonances (near 9 ppm), assigned to the oxazocine ring protons and consistent with the indicated mesoionic structure <84H(22)2587>.



The ring methylene group of *N*-acyl-6*H*-dibenz[*b,f*]oxazocin-6-one derivatives (**68**; $R^1 = R^2 = \text{Cl}$, $R^3 = \text{Me}$, Pr^i ; $R^1 = R^2 = R^3 = \text{Me}$; $R^1 = \text{H}$, $R^2 = \text{Me}$, $R^3 = \text{Pr}^i$, CHEt_2) <89JHC1383> gives rise to an AB quartet (at ca. 4.5 and 5.4 ppm), indicative of the slow conformational equilibria of these derivatives (see below) <89T6857>. Nonacylated analogues (**69**; $R^2 = \text{Me}$, $R^1 = \text{H}$, Me) undergo more rapid equilibration, and display only a broadened singlet (at ca. 4.3 ppm) for the methylene protons <89T6857>.

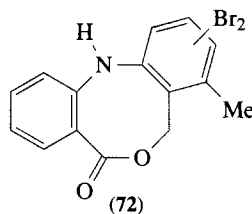


5*H*-Dibenz[*c,f*]oxazocin-5,7(12*H*)-dione (**70**) <81AQ(C)183> and benzoxazocino[4,3-*b*][5,1]benzoxazocin-7-one (**71**) <81JFC(18)447> display unremarkable ^1H chemical shifts, although only a single methylene resonance was reported for the latter.



Routine ^{13}C NMR spectral data have been reported for several oxazocines <84AJC129, 89JHC1383, 89T6857>, and two-dimensional ^1H – ^{13}C correlated spectra together with homonuclear coupling analyses allowed the complete assignment of the ^1H and ^{13}C NMR spectra of (**68**; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{Pr}^i$) <89JHC1383>. Fluorine-19 NMR spectral data demonstrated the presence of the perfluoroethyl side chain in (**71**) <81JFC(18)447>.

Mass spectral data for the 1,5-oxazocines are rather scarce. 1,5-Benzoxazocines (**67**; $\text{Ar} = 4\text{-RC}_6\text{H}_4$, $\text{R} = \text{H}$, Me , OMe) yield $\text{M}-\text{C}_3\text{O}_2$ ions, representing cleavage of carbon-heteroatom bonds of the oxazocine ring, in addition to the parent ions upon electron impact ionization <84H(22)2587>. Tetrahydro derivative (**64**) similarly yields significant fragment ions resulting from $\text{C}-\text{O}$ and $\text{C}-\text{N}$ cleavage, while dehydro analogue (**62**) displays a rather distinct fragmentation pattern <84AJC129>. Dibenz[*b,f*]oxazocines (**68**; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{Pr}^i$) <89JHC1383> and (**69**; $\text{R}^1 = \text{R}^2 = \text{Me}$) <89T6857> yield significant parent ions as well as a number of fragments, including one which may correspond to cleavage of the two aryl-heteroatom bonds of the oxazocine ring ($m/z = 120 = \text{C}_6\text{H}_4\text{CO}_2$). Parent ions, with no fragmentation data, were provided for fused “dimer” (**71**) <81JFC(18)447> and dibromide (**72**), for which no assignment of substitution pattern was provided <87MI 924-01>.



Dibromide (**72**) is pale-yellow, displaying absorption features at 276 nm and 371 nm in methanolic solution <87MI 924-01>. No other absorption spectroscopic data of oxazocines were reported, although conjugated derivatives (**67**; $\text{Ar} = 4\text{-RC}_6\text{H}_4$, $\text{R} = \text{H}$, Me , OMe) are all yellow <84H(22)2587>, while diones (**65**) and (**66**) are colorless <92G485>.

Reported IR spectral data for the oxazocines has focused primarily on the “obvious” functional groups present. The $\text{C}=\text{N}$ double bond of dihydro derivative (**62**) appears at 1600 cm^{-1} <84AJC129>, while monobenzo derivatives (**65**) and (**66**) <92G485> and dibenzo compounds (**68**; $\text{R}^1 = \text{R}^2 = \text{Cl}$, $\text{R}^3 = \text{Me}$, Pr^i ; $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Me}$; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{Pr}^i$, CHEt_2) <89JHC1383> display ester and amide-type carbonyl stretching modes at $1740\text{--}1780$ and $1640\text{--}1680\text{ cm}^{-1}$, respectively. Dibenzoxazocinones (**69**; $\text{R}^2 = \text{Me}$, $\text{R}^1 = \text{H}$, Me) <89T6857> and (**72**) <87MI 924-01> display lactone carbonyl modes at $1700\text{--}1720\text{ cm}^{-1}$ <87MI 924-01, 89T6857>. Curiously, dibenz[*c,f*]oxazocin dione (**70**) is reported to display, in addition to a typical amide carbonyl band at 1595 cm^{-1} and a $\text{C}-\text{O}-\text{C}$ mode at 1150 cm^{-1} , only a single carbonyl stretching band for the anhydride functionality <81AQ(C)183>. Mesoionic derivatives (**67**; $\text{Ar} = 4\text{-RC}_6\text{H}_4$, $\text{R} = \text{H}$, Me , OMe) also display a single carbonyl stretching band, at rather remarkable energy ($1770\text{--}1790\text{ cm}^{-1}$) <84H(22)2587>.

9.24.4.2 Thermodynamic Aspects

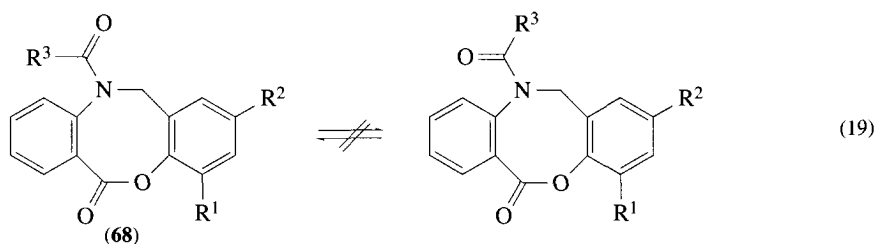
In general, the benzo- and dibenzoxazocines are rather high-melting solids, with melting points in excess of 150°C <81AQ(C)183, 87MI 924-01, 89JHC1383, 89T6857, 92G485>. Although no solid-state structural analyses have been carried out, precluding direct evaluation of intermolecular interactions,

consideration of the varied structures of the derivatives for which melting behavior has been reported suggests *H*-bonding (e.g. (65) <92G485>, (66) <92G485>, (69; $R^2 = \text{Me}$, $R^1 = \text{H}$, Me) <89T6857>, (72) <87MI 924-01>), dipolar (e.g. (68) <89JHC1383>, (70) <81AQ(C)183>), and/or aromatic π -stacking interactions may all contribute to solid-state phase stability. The exceptions to the general trend toward high melting points are perhaps most revealing. Thus, comparatively simple benzoxazocine (62) and its reduced analogue (64), lacking highly polar functional groups and *H*-bonding capability, are both noncrystalline gums <84AJC129>. Putative dimer (71) displays a perhaps surprisingly low melting point (91 °C) <81JFC(18)447>. Mesoionic derivatives (67; $\text{Ar} = 4\text{-RC}_6\text{H}_4$, $\text{R} = \text{H}$, Me , OMe) display a rather remarkable dependence of melting point on the aromatic substituent, with the phenyl derivative melting at 120 °C, the *p*-tolyl derivative at 150 °C, and the *p*-anisoyl at 170 °C <84H(22)2587>.

The various oxazocines discussed above appear to display typical solubility behavior, dissolving in solvents of moderate polarity, such as chloroform <84AJC129, 84H(22)2587, 89JHC1383, 89T6857> and dioxane <81AQ(C)183>. Both reported dibenz[*c,f*]oxazocines <81AQ(C)183, 87MI 924-01> display at best modest solubility in ethanol, from which (72) was recrystallized <87MI 924-01>. Dimethyl sulfoxide appears to be required to dissolve several of the most polar derivatives <81AQ(C)183, 92G485>. Perhaps in accord with the low melting point of fluoroalkyl derivative (71) is its reported recrystallization from cyclohexane <81JFC(18)447>.

Only the mesoionic derivatives (67; $\text{Ar} = 4\text{-RC}_6\text{H}_4$, $\text{R} = \text{H}$, Me , OMe) offer the potential for complete conjugation throughout the oxazocine ring. Although the ring protons appear at quite low field in the ^1H NMR spectra of (67), this is presumably due to their chemical environment rather than to any ring current anisotropy effects. These derivatives certainly display no chemical evidence for aromatic stabilization, and in fact are prone to facile rearrangement to isomeric coumarin derivatives <84H(22)2587>.

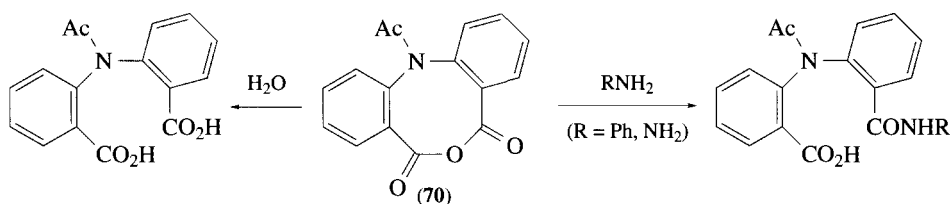
In contrast to the rather heavy focus on conformational issues pertaining to many of the other classes of diheterocins, only a single detailed analysis of the conformational preferences of the 1,5-oxazocines has appeared. Variable temperature NMR spectral analyses of several *N*-acyl-11,12-dihydrodibenz[*b,f*]oxazocin-6-ones revealed the presence of two conformations in solution at room temperature, in a 50:1 ratio for (68; $R^1 = \text{H}$, $R^2 = \text{Me}$, $R^3 = \text{Pr}^i$) <89T6857>. Molecular mechanics calculations suggest the major conformer to be boat-like, while the minor conformer represents either a pseudo-chair or twist-boat-like form. The boat conformation is revealed in part by the comparative lack of deshielding of the aromatic protons adjacent to the carbonyl group in (68), which appear at substantially higher field than analogous protons in related benzoxazinones <89JHC1383>. At higher temperatures, interconversion of conformational diastereomers through a bond rotation mechanism and of conformational enantiomers through a ring inversion process are observed. The exocyclic *N*-acyl groups remain locked in a sterically-disfavored orientation, apparently as a result of dipole-dipole interactions (Equation (19)). Compounds (69), lacking the *N*-acyl group, are conformationally much more mobile, undergoing rapid ring inversion at room temperature.



9.24.4.3 Reactivity of Fully Conjugated Rings

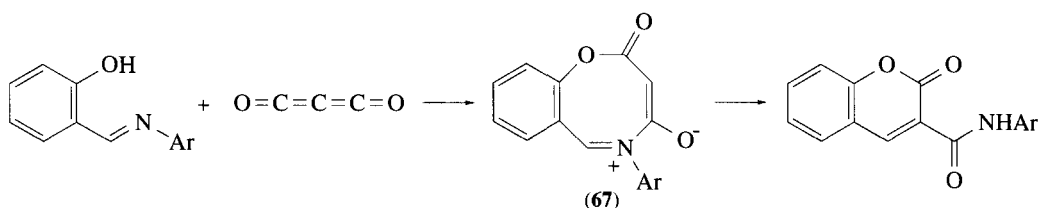
Given the bonding constraints of the 1,5-oxazocine ring system, little has been reported regarding the chemistry of derivatives which may be considered fully conjugated. Anhydride (70) (Scheme 15) undergoes hydrolytic ring cleavage in refluxing aqueous dioxane; the corresponding amides are formed upon treatment with aniline in dioxane or hydrazine hydrate in ethanol <81AQ(C)183>.

Following the report of a high-yield synthesis of mesoionic derivatives (67; $\text{Ar} = 4\text{-RC}_6\text{H}_4$, $\text{R} = \text{H}$, Me , OMe) by Bonsignore *et al.* <82CC850>, several refutations appeared, in which formation of isomeric coumarin derivatives was claimed (Scheme 16) <82CC1328, 85JHC157>. Re-analysis by Bonsignore *et al.* led to the conclusion that the oxazocines are indeed formed, although in much lower yield than previously reported, but that they undergo facile isomerization to the coumarins, both



Scheme 15

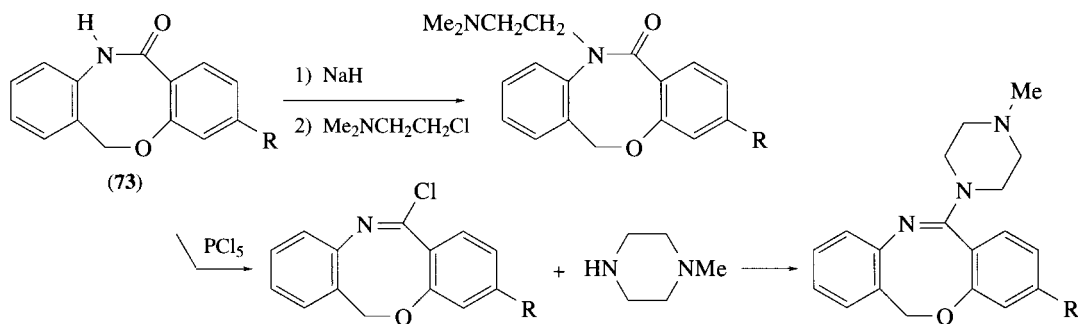
thermally (upon heating beyond the melting point) and under acid catalysis $\langle 84\text{H}(22)2587 \rangle$. Given these contradictory claims as well as the curious melting behavior discussed above, additional investigation of these reaction systems would perhaps be in order.



Scheme 16

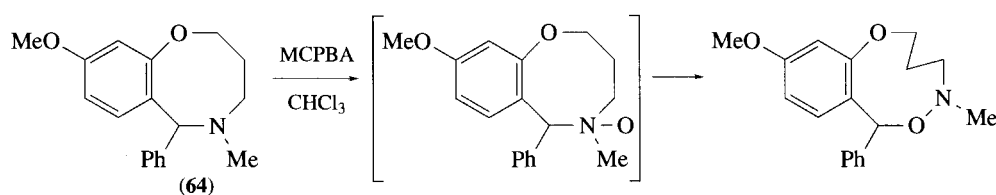
9.24.4.4 Reactivity of Nonconjugated Rings

Alkylation of the ring nitrogen of benzoxazocine (62), affording (63), is effected in high yield upon treatment with methyl iodide at elevated temperatures $\langle 84\text{AJC}129 \rangle$, while *N*-alkylation of lactam derivatives such as (73; $\text{R} = \text{H}$) has been effected by deprotonation with sodium hydride, followed by treatment with alkyl halides (Scheme 17) $\langle 84\text{JAP}(\text{K})59148768 \rangle$. The lactams also undergo chlorination upon treatment with PCl_5 in refluxing toluene, and the resulting chloro derivatives undergo facile nucleophilic displacement reactions with amines or alcohols, as shown for (73; $\text{R} = \text{Me}$) $\langle 86\text{JAP}(\text{K})6183171, 86\text{JAP}(\text{K})6183172 \rangle$.



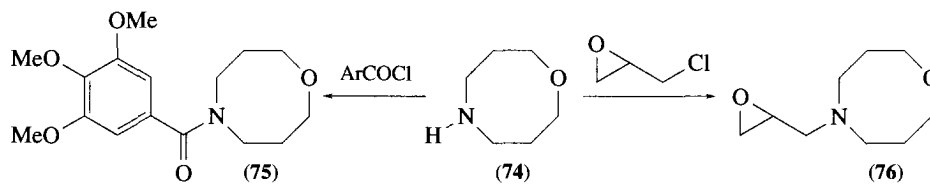
Scheme 17

Treatment of benzoxazocine (64) with *m*-chloroperbenzoic acid affords an unstable *N*-oxide which undergoes Meisenheimer rearrangement to afford the ring-expanded product in 50% yield (Scheme 18) $\langle 88\text{AJC}293 \rangle$. The major by-products of this rearrangement appear to be hydroxylamines, possibly arising from competing Cope elimination of the *N*-oxide.



Scheme 18

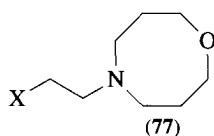
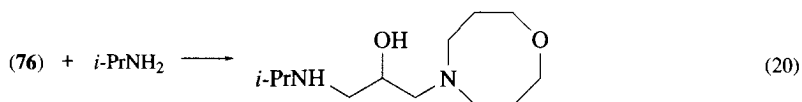
Hexahydro-1,5-oxazocine (**74**) is *N*-acylated by 3,4,5-trimethoxybenzoyl chloride (Scheme 19), forming (**75**) <85MI 924-03, 86MIP137531>, and *N*-alkylated by epichlorohydrin, giving (**76**) <85MI 924-04>.



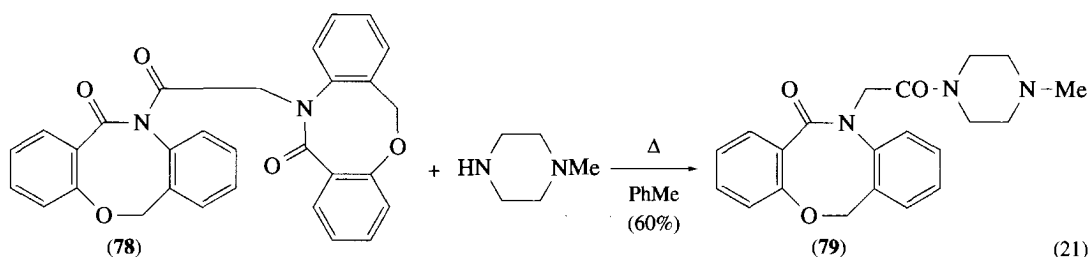
Scheme 19

9.24.4.5 Reactivity of Substituents Attached to Ring Heteroatoms

Treatment of epoxide (**76**) with isopropylamine affords the expected amino alcohol (Equation (20)) <85MI 924-04>. Other side-chain functionalities also display typical chemical reactions; thus, (**77**; X = OH) is esterified by 3,4,5-trimethoxybenzoyl chloride <84MIP121838>, and *N*-chloroethyl derivative (**77**; X = Cl) undergoes nucleophilic displacement by guanidine, affording (**77**; X = NHC(NH)NH₂) <84MI 924-01>.

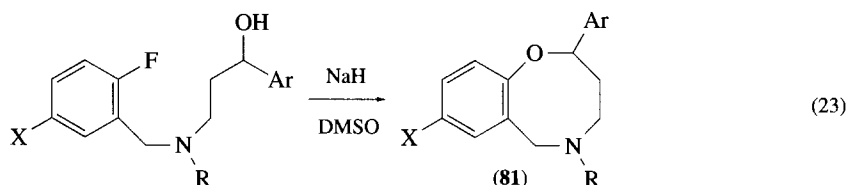
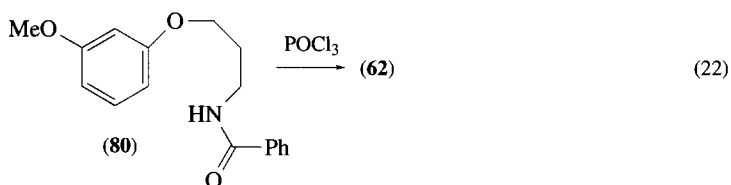


N-Acyl derivative (**78**) undergoes transamidation to (**79**) when heated with *N*-methylpiperazine (Equation (21)) <88JAP(K)63192763>.

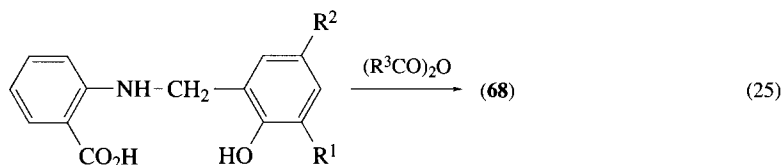
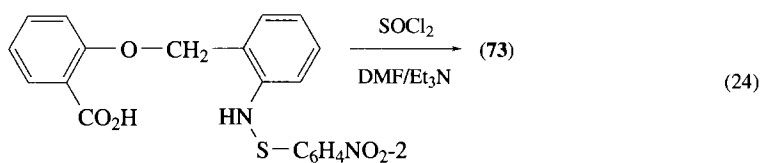


9.24.4.6 Ring Syntheses

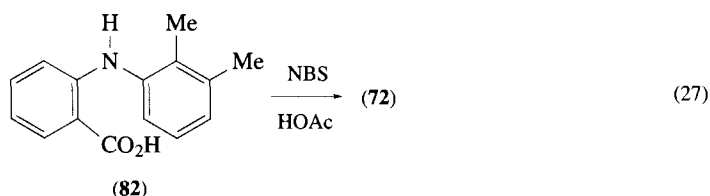
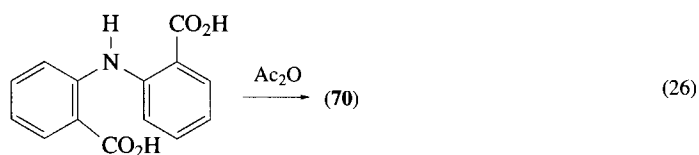
Closure of the 1,5-oxazocine ring has been effected through both unimolecular cyclization and cyclocondensation reactions. In only one case was the ring generated through formation of a C—C bond. Thus, Bischler–Napieralski cyclization of amide (**80**) under moderately dilute conditions afforded a 40% yield of benzoxazocine (**62**) (Equation (22)) <84AJC129>; higher concentrations led to inferior yields, and use of the methoxy-free analogue of (**80**) afforded no cyclization product. Intramolecular nucleophilic displacement reactions of aryl fluorides afforded tetrahydro derivatives (**81**; X = H, R = H, Et, Ar = Ph; X = H, R = Me, Ar = Ph, 4-Cl-C₆H₄; X = Cl, R = Me, Ar = Ph) (Equation (23)) <81BRP2067555>.



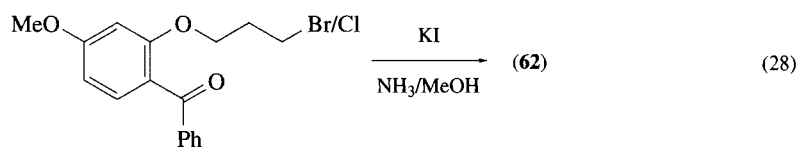
Lactamization affords 12*H*-dibenz[*b,f*]-oxazocin-12-one (**73**; R = H) in 51% yield (Equation (24)); various substituted derivatives are prepared analogously <84JAP(K)59128379>. Lactonization of appropriate hydroxy acids similarly affords 11,12-dihydro-6*H*-dibenz[*b,f*]-oxazocin-6-ones (**68**; R¹ = R² = Cl, R³ = Me, Prⁱ; R¹ = R² = R³ = Me; R¹ = H, R² = Me, R³ = Prⁱ, CHEt₂) (Equation (25)) <89JHC1383, 89T6857>. The oxazocines are obtained in high yield, although more electrophilic anhydrides and/or higher reaction temperatures tend to favor the formation of isomeric benzoxazinones <89JHC1383>.



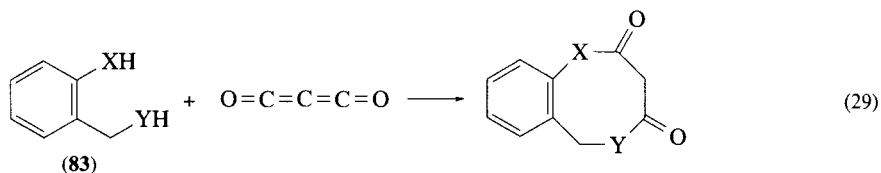
The dibenz[*c,f*]oxazocine ring system has been formed through anhydride bond construction (Equation (26)) <81AQ(C)183> and, inadvertently, by intramolecular esterification following side-chain bromination of mefenamic acid (**82**) (Equation (27)) <87MI 924-01>.



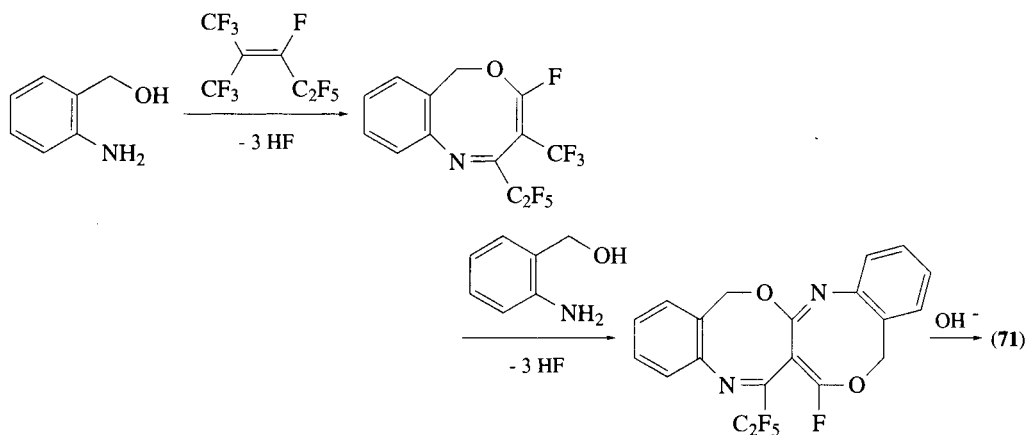
Treatment of *bis*(3-chloropropyl) ether with ammonia affords a modest (36%) yield of 3,4,5,6,7,8-hexahydro-2*H*-1,5-oxazocine (**74**) <85MI 924-04>, while nucleophilic displacement of halide by ammonia, followed by intramolecular imine formation provides a 2% yield of benzoxazocine (**62**) (Equation (28)) <84AJC129>.



Isomeric amino alcohols (**83**; X = O, Y = NH; X = NH, Y = O) react with carbon suboxide to form positional isomers (**65**) and (**66**), each in ca. 50% yield, together with lower yields of malonic acid derivatives (Equation (29)) <92G485>. Similarly, carbon suboxide is reported to react with hydroxyimines to afford mesoionic derivatives (**67**) in 9–14% yield <84H(22)2587>, although, as discussed above, others have questioned the outcome of these reactions <82CC1328, 85JHC157>.



The condensation of *o*-aminobenzyl alcohol with perfluoro-2-methyl-2-pentene affords benzoxazocino[4,3-*b*][5,1]benzoxazocin-7-one (**71**), apparently through the intermediacy of a monomeric 5,1-benzoxazocine (Scheme 71) <81JFC(18)447>.



Scheme 20

9.24.4.7 Comparison of Synthetic Routes

The oxazocine ring system clearly remains rather uncommon. The cyclization and condensation approaches both suffer from at best moderate yields, while the apparently dramatic influence of substituents on the sole C—C bond formation route perhaps does not bode well for generality of this unique cyclization approach. Anhydride-mediated lactonization represents the only high-yielding oxazocine synthesis, and the possibility of competing benzoxazine formation in these reactions may lead to difficulties in the generalization of this approach to substituted and/or nonbenzannelated analogues. Given the potential pharmacological importance of members of this class of diheterocins, elucidation of new synthetic pathways for their preparation, including routes utilizing as-yet unprecedented ring transformation reactions rather than cyclizations or condensations, would clearly be of value.

9.24.4.8 Important Compounds and Applications

A number of oxazocine derivatives display analgesic and/or antidepressant activity, including 1,5-benzoxazocines (**81**; X = H, R = H, Et, Ar = Ph; X = H, R = Me, Ar = Ph, 4-Cl-C₆H₄; X = Cl,

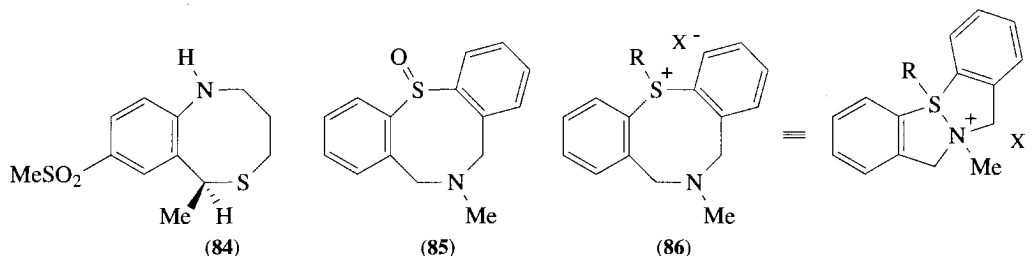
R = Me, Ar = Ph) <81BRP2067555> and a number of dibenz[*b,f*]oxazocine-6-ones <84JAP(K)59148768, 86JAP(K)6183171, 86JAP(K)6183172, 88JAP(K)63192763>. The latter also display antipyretic activity <88JAP(K)63192763> and inhibit aggression <86JAP(K)6183171>, as well as acting as sedatives. Simple *N*-acyl hexahydro-1,5-oxazocine (**75**) also displays sedative activity, with no neuroleptic or anti-depressive effects <85MI 924-03>. Hexahydro-1,5-oxazocine (**77**; X = NHC(NH)NH₂) and related compounds were prepared for examination as possible central nervous system and circulatory system active agents <84MI 924-01, 85MI 924-01, 85MI 924-02, 85MI 924-04>. In the nonmedicinal arena, several hexahydro-1,5-oxazocines have been found to serve as decoloration prevention agents for photographic materials <88JAP(K)63271-44>.

9.24.5 RINGS WITH ONE NITROGEN AND ONE SULFUR (1,5-THIAZOCINES)

Since the appearance of CHEC-I, in which the 1,5-thiazocines were briefly treated, the chemistry of this class of 1,5-diheterocins has been rather dramatically advanced. Interest in the 1,5-thiazocines has been focused primarily on the issue of transannular bonding interactions between the ring heteroatoms, but a significant number of reports have focused on the pharmacological activity of various derivatives as well. The coordination chemistry of hexahydro-1,5-thiazocines has been reviewed <92CCR133>.

9.24.5.1 Experimental Structural Methods

A number of 1,5-thiazocine derivatives have been structurally characterized by single crystal x-ray diffraction analysis. With a single exception, reduced 5,1-benzothiazocine derivative (**84**) <85CPB4856, 86CPB694, 87CPB957>, each of these structural studies was focused on the exploration of transannular N—S bonding in dibenzo[*b,g*]thiazocines, including the *S*-oxide (**85**) and various cationic derivatives (**86**; R = Me, Cl, X = PF₆⁻; R = MeO, X = SbCl₆⁻) <83JA6965, 83TL4859, 85AX(B)445, 85BCJ1946, 86JA6320>.



Thiazocine (**84**), which crystallized with two slightly different conformational forms in the asymmetric unit, displays no unusual bond lengths or angles <87CPB957>; the nitrogen and sulfur atoms, calculated to be ca. 3.76 Å apart <87CPB957>, are clearly noninteracting (sum of van der Waals radii = 3.35 Å). In contrast, the *S*-oxide (**85**) and each of the various sulfonium salts crystallographically examined display a discrete bonding interaction between the ring heteroatoms, as evidenced by both the N—S bond lengths, ranging from 2.091 Å to 2.624 Å, and the near-linearity of the N—S—R groups (Table 1) <83JA6965, 83TL4859, 85AX(B)445, 85BCJ1946, 86JA6320>. The N—S bond length correlates with sigma inductive effects of the *S*-substituent, with increased electron-withdrawing nature (R = Cl) leading to an enhanced N—S interaction and shorter N—S bond. The sulfur center in each sulfonium salt presents a distorted trigonal bipyramidal coordination geometry, with the lone pair occupying one of the equatorial positions; (**86**; R = Me) represents the first example of an isolable sulfurane with an axial alkyl substituent. Other conformational issues addressed by these solid-state structural studies are discussed later.

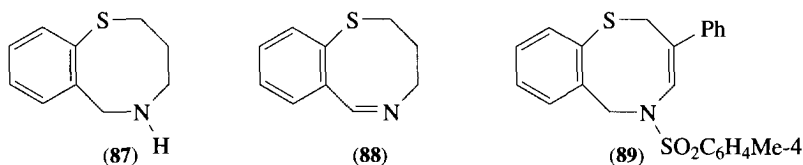
Detailed ¹H and ¹³C NMR spectral analyses of dibenzo[*b,g*]thiazocines (**85**) and (**86**; R = Me, Et, MeO, EtO, X = PF₆⁻, SbCl₆⁻) have been carried out in order to address the relevance of the solid-state structural results to their solution conformations <83TL4859, 85BCJ1946, 85TL4491, 86JA6320> and to gain additional information about the N—S interaction. An excellent correlation was found between the Hammett σ_m substituent constants for the *S*-substituent and the ¹H and ¹³C chemical shifts of the N—CH₃ (at ca. 2.5–3.1 ppm (¹H), 40–44 ppm (¹³C)), and N—CH₂ (at ca. 4.1–4.6 ppm (¹H), 56–60 ppm (¹³C)) groups in (**86**) <86JA6320>. In addition, ¹⁵N NMR analyses were carried out

Table 1 Transannular bonding structural parameters in dibenzo[*b,g*][1,5]thiazocines (**86**).

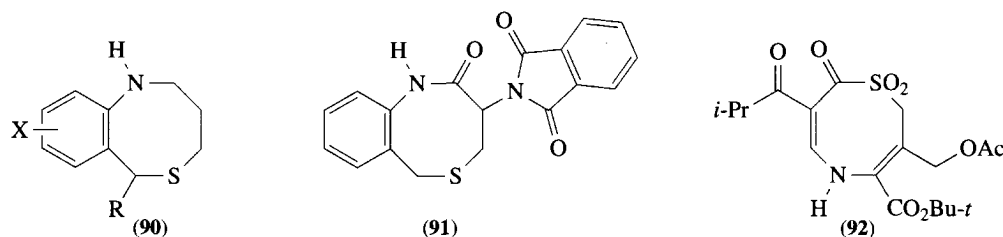
<i>R</i>	<i>X</i>	<i>N</i> — <i>S</i> (Å)	<i>R</i> — <i>S</i> — <i>N</i> (°)
O ^a		2.593	179.5
O ^a		2.624	179.1
Me	PF ₆	2.466	176.9
MeO	SbCl ₆	2.206	175.3
Cl	PF ₆	2.091	176.9

^a Values reported for each of two inequivalent molecules in the asymmetric unit.

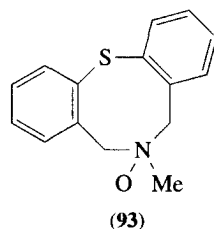
in order to assay the mechanism of demethylation of (**86**; *R* = Me, OMe) <91JA9270>. Several 1,5- and 5,1-benzothiazocine derivatives have been characterized by ¹H and, in one case, ¹³C NMR analysis. The methylene protons in tetrahydro-2*H*-1,5-benzothiazocine (**87**) appear at 2.70 (S—CH₂), 2.96 (N—CH₂), and 3.82 (Ar—CH₂—N) ppm, and at comparable chemical shifts in (**88**), the dihydro precursor to (**87**), in which the methine proton appears at characteristically low field (8.94 ppm) <87IC2963>. Rather different chemical shifts are reported for 5,6-dihydro derivative (**89**) (S—CH₂ at 3.62 ppm, Ar—CH₂—N at 4.92 ppm) <84H(22)1025>.



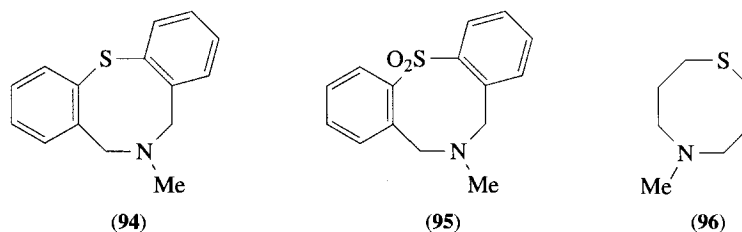
Tetrahydro-2*H*-5,1-benzothiazocine (**90**; *R* = *X* = H) displays comparable chemical shifts (2.56 (S—CH₂), 3.43 (N—CH₂), 3.97 (Ar—CH₂—S)) <84H(22)1045>. The Ar—CH₂—S protons in phthalimide derivative (**91**) similarly appear at around 3.8 ppm <88TL181>, while the methine proton in analogue (**84**) is shifted to appreciably lower field (ca. 4.9 ppm) <87CPB957>. Analysis of homonuclear coupling constants, *T*₁ values, and temperature dependence and nuclear Overhauser effects, revealed the conformational preferences of (**84**). An otherwise inexplicable lack of shielding of one of the ring protons of (**84**) revealed the presence of a different conformation in solution than that displayed in the solid state <87CPB957>. Monocyclic thiazocine (**92**), the only nonbenzannelated thiazocine for which NMR spectral data were reported, displays ¹H chemical shifts in accordance with the functionalities present; the ring methylene group appears at 4.36 ppm <91CCC2352>.



Mass spectral fragmentation data were reported only for dibenzo[*b,g*]thiazocine *S*-oxide (**85**) and isomeric *N*-oxide (**93**). Both display parent ions and *M*-16 fragments; *N*-oxide (**93**) additionally affords an *M*-46 fragment, while *S*-oxide (**85**) displays *M*-31 and *M*-60 fragments <85BCJ1946>. Dihydro derivative (**89**) displays the expected parent ion; no fragmentation data were reported <84H(22)1025>.



UV/visible absorption spectral data for the 1,5-thiazocines are largely lacking. Di- and tetrahydro-1,5-benzothiazocines (**89**) <84H(22)1025> and (**87**) <87IC2963> are both reported to be colorless, as are dibenzo[*b,g*]thiazocines (**85**), (**93**), (**94**), and (**95**) and their derived cations <85BCJ1946>. One-electron oxidation of 5-methyl-3,4,5,6,7,8-hexahydro-2*H*-1,5-thiazocine (**96**) yields a radical cation displaying an absorption band at 500 nm ($\log \epsilon$ 3.38), suggesting the presence of a transannular N—S three-electron bond <84CJC1874>.



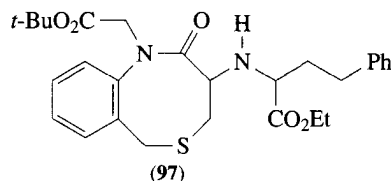
Only selected IR data has been reported for the thiazocines. Thus, dihydro derivative (**88**) displays an intra-ring C=N stretching band at 1635 cm^{-1} , absent in reduced analogue (**87**), for which only an N—H stretching mode at 3260 cm^{-1} was reported <87IC2963>. Tosyl derivative (**89**) displays the anticipated sulfonamide modes, at 1340 and 1160 cm^{-1} <84H(22)1025>. Similarly, only S—O modes are reported for sulfoxide (**85**) and sulfone (**95**), while their precursor (**94**) displays a band at 2875 cm^{-1} <85BCJ1946, 85TL4491>. An *N*-oxide vibrational mode is found at 905 cm^{-1} for (**93**) <85BCJ1946>. The partial IR data reported for cations (**86**) appears to refer only to the counteranion <85BCJ1946, 85TL4491, 86JA6320>.

9.24.5.2 Thermodynamic Aspects

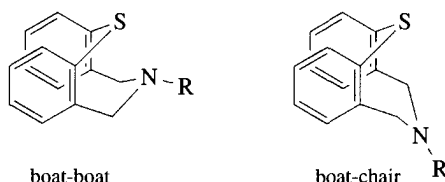
Comparison of the melting points of a series of substituted 1,3,4,6-tetrahydro-2*H*-5,1-benzothiazocines (**90**) <84H(22)1045> permits some general conclusions to be drawn. Placement of a methyl or chloro substituent on the aromatic ring tends to lower the melting point from that of the unsubstituted derivative, consistent with a reduction in molecular symmetry, while nitro or methanesulfonyl substituents significantly elevate the melting point, perhaps due to their capability to form intermolecular hydrogen bonds with the secondary amine functionality. A 6-methyl group (**90**; R = Me) slightly lowers the melting point, while a 6-phenyl substituent (**90**; R = Ph) appears to result in an increase, although data regarding the latter is comparatively limited <84H(22)1045>. Interestingly, although the unsubstituted 1,3,4,6-tetrahydro-2*H*-5,1-benzothiazocine (**90**; R = X = H) is a solid (m.p. 77°C) <84H(22)1045>, positional isomer (**87**) is apparently a liquid <87IC2963>. Reported melting points of several other 1,5-benzothiazocine derivatives <88TL181>, and of heavily substituted nonbenzannelated thiazocine (**92**) <91CCC2352> appear consistent with the functionalities and structures present. Dibenzo[*b,g*]thiazocine (**94**) is rather low-melting (65°C) <85BCJ1946>, while the corresponding sulfoxide (**85**), sulfone (**95**), and *N*-oxide (**93**) are rather higher melting (113 , 170 , and 175°C , respectively) <85BCJ1946, 85TL4491>. Consistent with their ionic character, the cationic dibenzothiazocines (**86**) are also rather high-melting, ranging from 145°C for (**86**; R = Cl, X = PF_6) to 195°C for both (**86**; R = Me, X = PF_6) and (**86**; R = Et, X = PF_6) <85BCJ1946, 86JA6320>. Only van der Waals contacts are observed in all of the dibenzothiazocine cations which have been examined crystallographically <85AX(B)445>.

The neutral monocyclic, benzo- and dibenzothiazocines discussed above display the solubilities expected for molecules bearing similar functionalities. For the most part, they appear freely soluble in solvents of moderate polarity, including chloroform (often the solvent of choice for NMR spectral studies) <84H(22)1045, 87IC2963, 88TL181, 91CCC2352>, methanol <87CPB957>, and ethyl acetate <91CCC2352>. In some cases, such as the phthalimide-containing species (**91**), DMSO appears to be required for reasonable solubility <88TL181>. The dibenzothiazocines have been recrystallized from petroleum ether (**94**), benzene/hexane (**85**), or CH_2Cl_2 /hexane ((**93**) and (**95**)) <85BCJ1946>, while the corresponding cations (**86**) are soluble in acetonitrile, from which they may be recrystallized upon addition of ether <85BCJ1946, 86JA6320, 91JA9270>. The *S*-chloro derivative is also reported to be precipitated from CH_2Cl_2 upon addition of Et_2O <85BCJ1946, 86JA6320>. Few chromatographic purifications or analyses have been reported. Silica chromatography was used to purify monocyclic derivative (**92**) <91CCC2352> and dibenzothiazocine *S*-oxide (**85**) <91JA9270>. Separation of the

diastereomers of (97), each as a racemic mixture, was also effected by chromatography, under unspecified conditions <88TL181>.



No potentially fully-conjugated 1,5-thiazocines have been reported, and potential aromaticity within the ring system appears not to have been discussed. The primary focus of stability studies of the 1,5-thiazocines has been the issue of transannular N—S interaction in dibenzo[*b,g*]thiazocine *S*-oxide (85) and the derived sulfonium salts (86). All experimental evidence points toward the importance of this interaction, which has been clearly demonstrated both in the solid state and in solution. Each of the dibenzothiazocines for which such an interaction has been documented displays a boat–boat or twist–boat–boat conformation, bringing the two ring heteroatoms into bonding distance, whereas simpler cyclooctane derivatives in which no such transannular interaction is possible tend to prefer a sterically less constrained boat–chair conformation <83JA6965, 85AX(B)445, 85BCJ1946, 85TL4491, 86JA6320>.

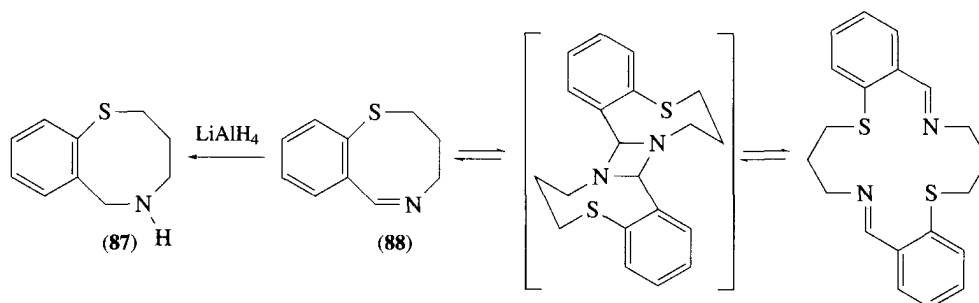


Hartree–Fock calculations using a 4-31G basis set augmented with sulfur *d*-orbitals for simple model compound (4; H₂NCH₂OCH₂SHX, X = H, Cl) reproduce the N—S interaction; omission of *d*-orbitals on sulfur leads to no predicted bonding interaction between sulfur and nitrogen, even with an extended *sp* basis set for sulfur <84CL1557>.

5,1-Benzothiazocine derivative (84) was subjected to detailed conformational analysis <87CPB957>. Although x-ray crystallographic analysis demonstrated a boat–boat-like conformation in the solid state, ¹H NMR studies were not completely consistent with the maintenance of this conformation in solution. Consideration of the full range of relaxation and shielding data acquired in the course of the NMR analyses of (84) led to the conclusion that a boat–chair conformation is adopted in solution. Additional conformational analyses of (84) and an *N*-acyl analogue have also been carried out in the course of structure–activity relationship studies for this effective gastric acid secretion-inhibition agent <85CPB4856, 86CPB694>. Benzothiazocine (97) was designed as a conformationally-restricted analogue of enalapril, an angiotensin converting-enzyme inhibitor <88TL181>.

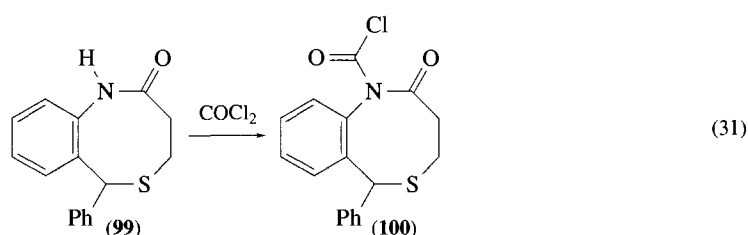
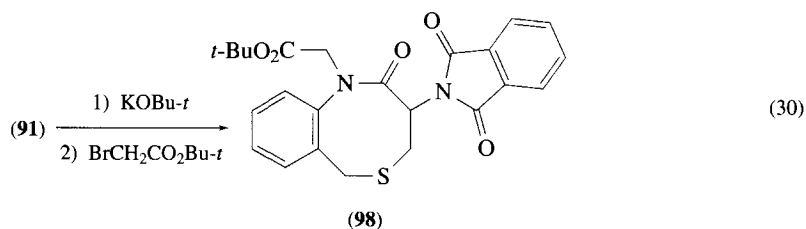
9.24.5.3 Reactivity of Nonconjugated Rings

Dihydro-1,5-benzothiazocine (88) undergoes reversible dimerization (Scheme 21), apparently via a [2 + 2] metathesis-type mechanism, upon attempted isolation as a pure liquid <87IC2963>. The imine functionality in (88) is reduced by lithium aluminum hydride, affording (87) <87IC2963>.

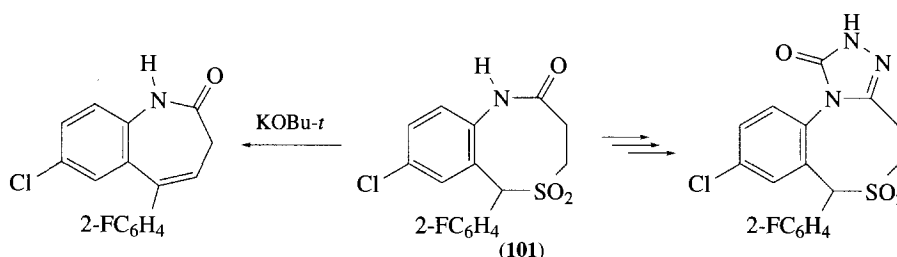


Scheme 21

N-Alkylation of lactam-type thiazocinone (**91**) under standard reaction conditions affords (**98**) (Equation (30)) <88TL181>; similarly, (**99**) reacts with phosgene to afford (**100**) (Equation (31)) <82MI 924-01>.



Related lactams such as (**101**), obtained by oxidation of substituted analogues of (**99**), undergo base-induced ring contraction (Scheme 22). Alternatively, conversion of the sulfones to the corresponding thioamides, followed by hydrazinolysis and cyclocondensation with carbonyldiimidazole, affords fused-ring triazolo derivatives <83EUP72029>.



Scheme 22

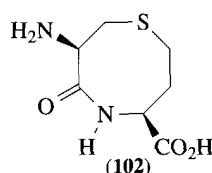
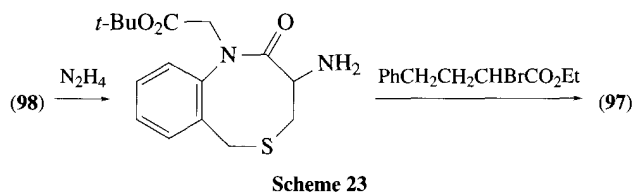
Treatment of dibenzothiazocine (**94**) with periodate affords a 72% yield of the *N*-oxide (**93**), together with a smaller amount (12%) of the *S*-oxide (**85**). The latter is the major product obtained upon oxidation of (**94**) with hypochlorite, while use of hydrogen peroxide affords sulfone (**95**) <85BCJ1946>. In contrast to the methylation of sulfoxide (**85**), discussed below, methylation of (**94**) affords only the quaternary *N*-methyl derivative <85BCJ1946>. Protonation of (**85**) with trifluoroacetic acid occurs on nitrogen, with the resulting ammonium salt apparently stabilized by an intramolecular *H*-bond to the sulfoxide <85TL4491>. Treatment of (**85**) with thionyl chloride affords the *S*-chloro sulfonium salt (**86**; R = Cl), which is converted to the *S*-methyl derivative (**86**; R = Me) by lithium dimethylcuprate <83JA6965> and to the *S*-alkoxy derivatives (**86**; R = OMe, OEt) by treatment with alcohols <86JA6320>. Preparation of other sulfonium derivatives from these precursors is discussed below.

Hexahydro-1,5-thiazocine (**96**) undergoes one-electron oxidation by Br₂⁺, generated by pulse radiolysis of KBr in aqueous phosphate buffer. The pH dependence of the first-order decay of the racial cation suggests that deprotonation represents its major mode of decomposition <84CJC1874>.

9.24.5.4 Reactivity of Substituents Attached to Ring Carbon Atoms

In the few examples of such reactions reported, side-chain functionalities appear to undergo typical chemical transformations by standard reagents, with no unusual reactivity or constraints

imposed by the presence of the thiazocine ring. Thus, phthalimide (**98**) undergoes hydrazinolysis and amine alkylation under standard conditions (Scheme 23) <88TL181>, and amino acid derivative (**102**) behaves as a typical amino acid, apparently undergoing incorporation into polypeptides under typical peptide coupling conditions <84EUP113029>.

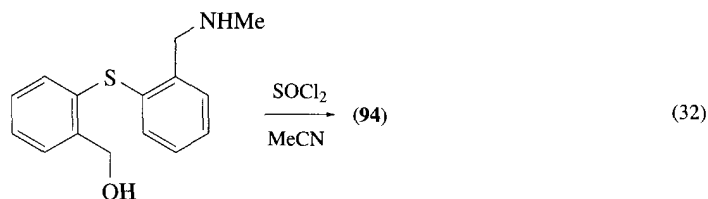


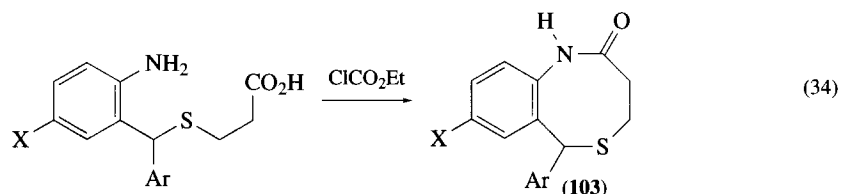
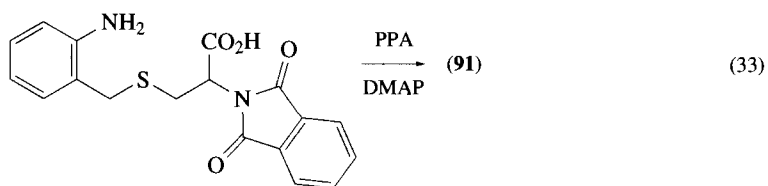
9.24.5.5 Reactivity of Substituents Attached to Ring Heteroatoms

The *t*-butyl ester in (**97**) is cleaved by anhydrous HCl in CH₂Cl₂ <88TL181>, and *N*-chlorocarbonyl derivative (**100**) is converted to various amides in aqueous acetone <82MI 924-01>, each with no apparent cleavage of the thiazocinone ring. Sulfoxide (**85**) is *O*-alkylated by Meerwein's salts, affording methoxy and ethoxy derivatives (**86**; R = MeO, EtO) <83JA6965, 86JA6320>. *S*-Methyl sulfonium salt (**86**; R = Me, X = PF₆), obtained as described above, is deprotonated by butyllithium, apparently forming an intermediate ylide, which may then be alkylated with methyl iodide to provide the *S*-ethyl sulfonium salt (**86**; R = Et, X = PF₆) <86JA6320>. The *S*-methyl and *S*-methoxy derivatives (**86**; R = Me, MeO) transfer their methyl groups to pyridine; the methoxy derivative undergoes faster demethylation than the methyl compound, despite the requirement for cleavage of a stronger O—Me bond rather than an S—Me bond, due apparently to the higher stability of sulfoxide product (**85**), stabilized relative to (**94**) by transannular bonding <86JA6320, 91JA9270>.

9.24.5.6 Ring Syntheses

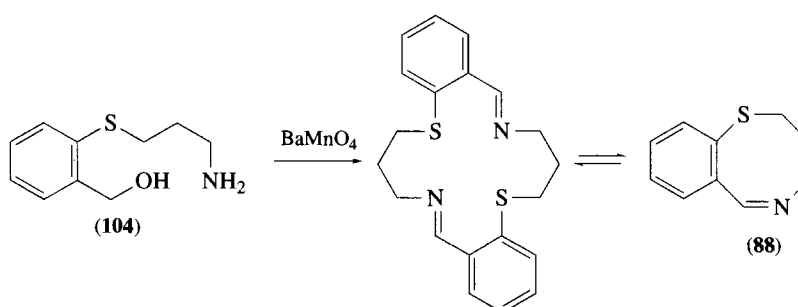
Reported syntheses of the 1,5-thiazocine ring system from acyclic precursors invariably employ unimolecular cyclization reactions. Intramolecular *N*-alkylation affords dibenzothiazocine (**94**) in ca. 80% yield (Equation (32)) <85BCJ1946>, while lactamization reactions afford phthalimide (**91**) (31%) (Equation (33)) <88TL181> and benzo derivatives (**103**; X = Br, Ar = 2-pyridyl; X = Cl, Ar = 2-ClC₆H₄, 2-FC₆H₄; X = NO₂, Ar = 2-ClC₆H₄) (Equation (34)) <83EUP72029>.





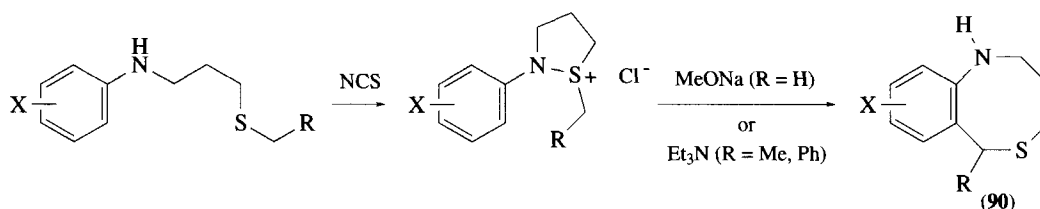
9.24.5.7 Ring Synthesis by Transformation of Another Ring

Oxidation of benzyl alcohol derivative (**104**) with BaMnO_4 affords not the expected imine (**88**), but rather a 16-membered ring dimer (Scheme 24). This dimer slowly rearranges in chloroform solution to the thiazocine; as noted above, the thiazocine dimerizes at higher concentrations, reforming its 16-membered ring precursor $\langle 87\text{IC}2963 \rangle$.



Scheme 24

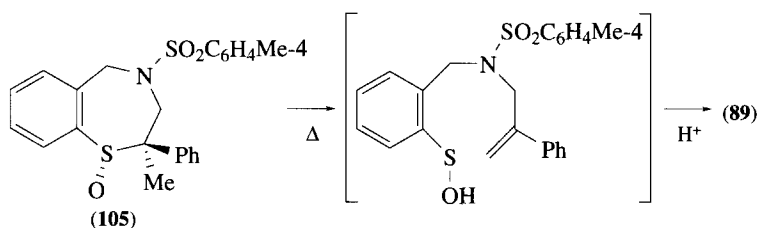
Treatment of a series of amino sulfides with *N*-chlorosuccinimide yields intermediate sulfonium salts, isolable if desired, which undergo [2,3]-sigmatropic rearrangement to the corresponding 5,1-benzothiazocines (**90**; $\text{R} = \text{H}$, $\text{X} = \text{H}$, 8-Me, 8-MeO, 7-Cl, 8-Cl, 9-Cl, 8-CN, 8-NO₂, 8-MeSO₂; $\text{R} = \text{Me}$, $\text{X} = \text{H}$, 8-Me, 8-Cl, 10-Cl, 8-F, 8-CN, 8-NO₂, 8-MeSO₂; $\text{R} = \text{Ph}$, $\text{X} = \text{H}$, 8-Cl, 8-MeO) upon treatment with base (Scheme 25); yields range from 48 to 95% $\langle 84\text{H}(22)1045, 85\text{JAP}(\text{K})60132972 \rangle$.



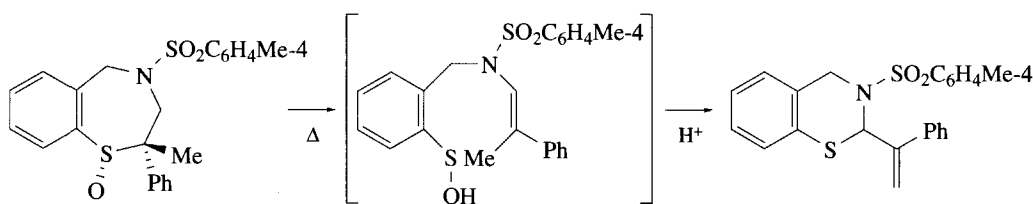
Scheme 25

Benzothiazepine 1-oxide (**105**) rearranges to thiazocine (**89**) when treated with *p*-toluenesulfonic acid at elevated temperatures, apparently via initial [2,3]-sigmatropic rearrangement to the corresponding sulfenic acid followed by acid-mediated conversion to the thiazocine (73%) (Scheme 26) $\langle 84\text{H}(22)1025 \rangle$. Interestingly, the *cis*-oxide, in which initial [2,3]-rearrangement involving the methyl substituent is geometrically prohibited, is largely unchanged under the reaction conditions, affording

mostly starting material as well as a low yield of an alternative rearrangement product (Scheme 27).

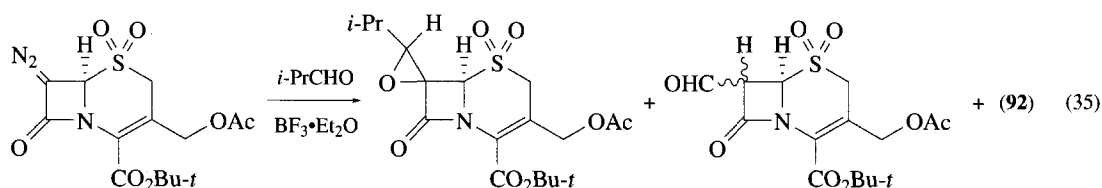


Scheme 26



Scheme 27

Thiazocine (92) is formed in less than 1% yield upon treatment of a diazo cephalosporanate derivative with 2-methylpropionaldehyde (Equation (35)); the major products of this reaction are the anticipated 6-4 ring products, and other aldehydes did not afford thiazocines in isolable quantities <91CCC2352>.



9.24.5.8 Comparison of Synthetic Routes

Cyclization approaches, thus far employing only unimolecular cyclizations, appear to offer some promise, although nonbenzannelated analogues, given the additional conformational flexibility of the cyclization precursors, may suffer from low yields. The sigmatropic rearrangement represents a rather attractive route for the preparation of a variety of 5,1-benzothiazocines in moderate-to-good yield, although electron-withdrawing substituents on the aromatic ring give diminished yields and benzyl sulfide derivatives ($R = \text{Ph}$) give competitive formation of 1,3-thiazines <84H(22)1045>. As is the case for many of the diheterocins, new synthetic approaches to the ring system would be welcome, particularly given early indications regarding their pharmacological applications.

9.24.5.9 Important Compounds and Applications

1,5-Thiazocine derivatives have been found to inhibit stomach acid secretion <84H(22)1045, 85JAP(K)60132972> and to display anticonvulsant <83EUP72029>, hypoglycemic <82MI 924-01>, and angiotensin converting-enzyme inhibitory activity <88TL181>. Cyclic peptides incorporating 1,5-thiazocine derivatives have been found to mediate the induction of epithelial cell adhesion <87B6896> and have been prepared as somatostatin analogues for the treatment of a variety of conditions, including acromegaly, diabetes, and peptic ulcers <84EUP113029>. Simple hexahydrothiazocine derivatives also serve as photofading prevention agents in color photographic film formulations <88JAP(K)63220142, 88JAP(K)63271444, 91JAP(K)03129343, 91JAP(K)03289654, 92JAP(K)0409050, 92JAP(K)04133055,

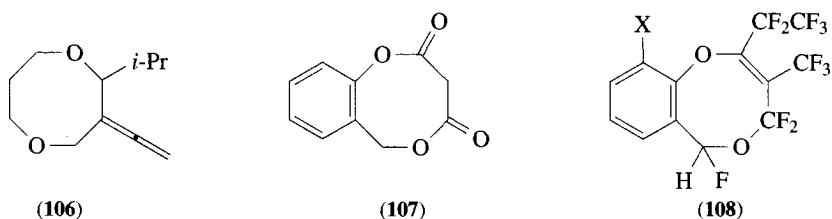
92JAP(K)0419652, 92JAP(K)0419653). Two aldolase reductase inhibitors discovered in 1991 were provocatively named thiazocin A and B (91JAN768), but apparently no structural details have been presented yet.

9.24.6 RINGS WITH TWO OXYGENS (1,5-DIOXOCINS)

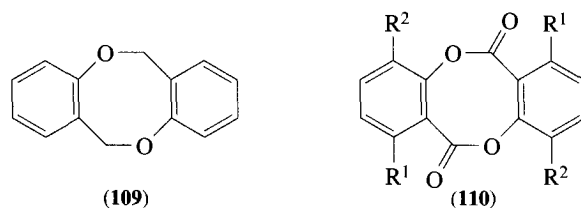
As for the previous class of 1,5-diheterocins, considerable advances have been made in the chemistry of the 1,5-dioxocins since the publication of CHEC-I in which the few known 1,5-dioxocin derivatives were reported.

9.24.6.1 Experimental Structural Methods

Dioxocane (106), the only nonbenzannelated dioxocin derivative for which ^1H NMR spectral data was reported, displays no unusual chemical shifts (88JOM(349)43). 1,5-Benzodioxocin-2,4-dione (107) displays resonances for the methylene groups at 3.30 and 4.43 ppm, quite similar to those seen for the oxazocine analogues and consistent with the proposed structure; apparently no enolization is seen (in DMSO) (92G485). Fluorinated benzodioxocin (108; X = H) displays, in addition to aromatic resonances, a fluorine-coupled doublet ($J = 56$ Hz) for the unique benzylic hydrogen; ^{19}F data was also reported for (108) (81JFC(18)447).

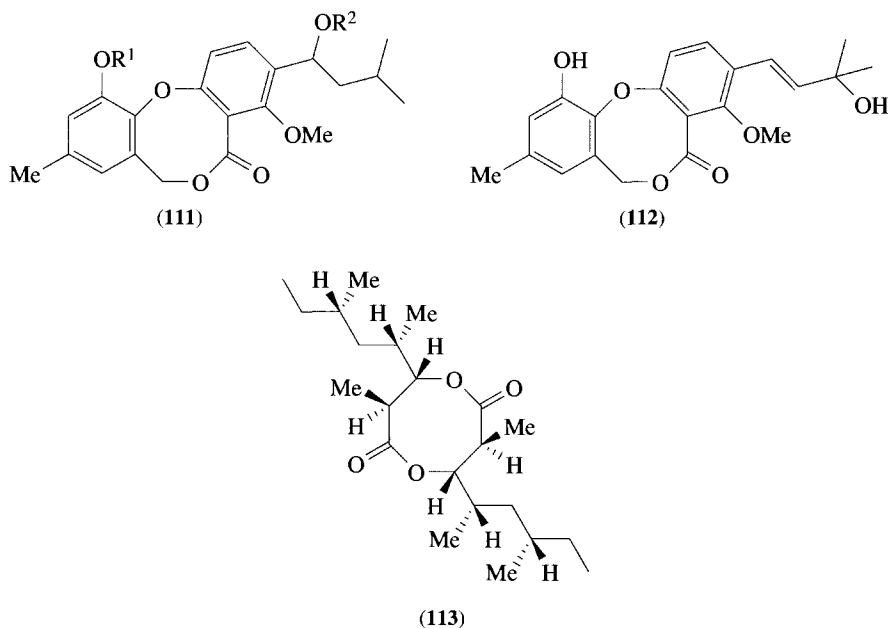


6*H*,12*H*-Dibenzo[*b,f*][1,5]dioxocin (109) gives rise to a sharp singlet for the methylene protons (4.82 ppm), consistent with rapid conformational equilibration (91P3081), while the analogous substituted 6,12-diones (110; R¹ = Me, R² = Pr^{*i*}) (di-*o*-thymotide) (82JCS(P1)1629, 91JOC4525) and (110; R¹ = Pr^{*i*}, R² = Me) (di-*o*-carvacrolide) (82JCS(P1)1629) each display temperature-dependent ^1H NMR spectra consistent with the presence of two slowly-interconverting conformers (see below).

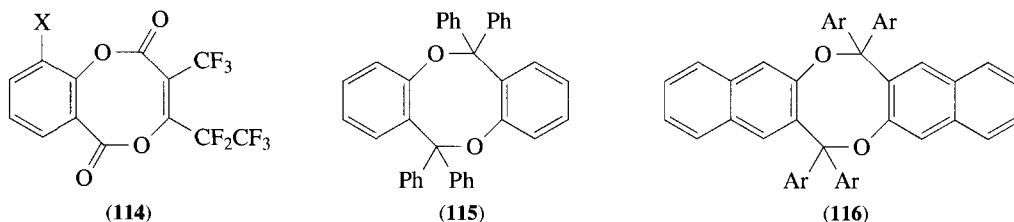


Determination of the chemical structure of dibenzo[*b,g*][1,5]dioxocin-5-one (111; R¹ = H, R² = Ac), a fungal natural product named in the literature as both purpactin A (from *Penicillium purpurogenum*) (74TL3941, 91JAN144, 91JAN152) and vermixocin B (from *P. vermiculatum*) (92JAN1268), relied heavily on multi-dimensional NMR analysis, and detailed accounts of the ^1H and ^{13}C NMR spectral features of this compound as well as several derivatives (111; R¹ = R² = H, Ac) have been reported. Related fungal extracts (from *Talaromyces derxii*) afforded (111; R¹ = R² = H) (penicillide) as well as an allied dioxocin bearing a modified side chain (112) (dehydroisopenicillide); full spectral characterizations of these natural products, as well as (111; R¹ = Me, R² = H), have also appeared (91P2096). Carbon-13 feeding experiments coupled with ^{13}C NMR studies assisted in the elucidation of the biosynthetic pathway for formation of purpactin A (92JOC1271). The symmetry apparent in

the ^{13}C NMR spectrum of the lactonic form of bourgeanic acid assisted in the assignment of this lactone as dioxocindione (**113**) <90JOC5938>.



Parent ions and “appropriate fragments” (of unspecified mass) were obtained upon mass spectral analysis of fluorinated benzodioxocins (**108**; X = H) and (**114**; X = H) <81JFC(18)447>. Unsubstituted 6*H*,12*H*-dibenzo[*b,f*][1,5]dioxocin (**109**) shows a weak parent ion (*m/z* 212), with major fragments of *m/z* 106 (representing symmetrical cleavage of the dioxocin ring) and 78 <91P3081>. Similarly, (**115**) and dinaphtho analogues (**116**; Ar = Ph, 4-FC₆H₄, 4-MeOC₆H₄) afford M/2 fragments as the base peaks in their mass spectra <82CCC838>, as does dilactone (**110**; R¹ = Me, R² = Prⁱ) <91JOC4525>.



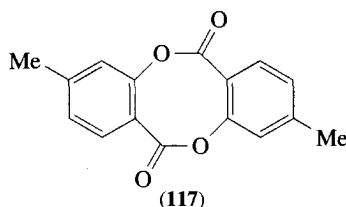
Mass spectral data has been reported for a large number of penicillide derivatives (**111**; R¹ = H, R² = H, Ac, C₃H₇CO, C₁₅H₃₁CO; R¹ = Me, Ac, R² = Ac; R¹ = THP, R² = H, Ac; R¹ = C₃H₇CO, R² = H, Ac, C₃H₇O; R¹ = C₁₅H₃₁CO, R² = H, Ac, C₁₅H₃₁CO) <74TL3941, 91JAN144, 91JAN152, 91P2096, 92JAN1268>. Aromatic side-chain cleavage appears to dominate the mass spectra of these dibenzo[*b,g*][1,5]dioxocins. In addition, with few exceptions, a C₁₃H₁₅O₃ fragment (*m/z* 219) is observed, often together with a C₁₃H₁₅O₃C₄H₈ fragment; this appears to correspond to the “right-hand side” of the penicillides, resulting from cleavage of two C—O bonds of the dioxocin ring. Only the parent ion and its dehydration fragment (M-18) were reported for related dibenzo[*b,g*][1,5]dioxocin (**112**) <91P2096>.

Benzodioxocindione (**107**) <92G485> and dibenzodioxocin (**109**) <91P3081> are colorless; the latter displays absorption maxima at 215 and 274 nm in methanolic solution. Dibenzo[*b,g*][1,5]dioxocin derivatives (**111**) all display an absorption band at ca. 280 nm; extinction coefficients of those derivatives reported by Nishida *et al.* (log ϵ ca. 3.29) <91JAN144, 91JAN152> are somewhat lower than those reported for penicillide (**111**; R¹ = R² = H) and the diacetyl analogue (**111**; R¹ = R² = Ac) (log ϵ ca. 3.70) <74TL3941, 91P2096, 92JAN1268>; it is not clear whether this difference is significant. The bathochromic shift observed for purpactin A (**111**; R¹ = H, R² = Ac) in alkaline media pointed to the phenol functionality in the original structure determinations <91JAN144, 92JAN1268>. Derivative (**112**) absorbs at slightly lower energy, 289 nm (log ϵ 3.74), consistent with the additional conjugation present; additional spectral features are observed at 267 nm (4.04) and 256 nm (4.17) <91P2096>.

Circular dichroism spectral data were reported for penicillide (**111**; $R^1 = R^2 = H$) and purpactin A (**111**; $R^1 = H$, $R^2 = Ac$); each displays a positive feature at ca. 277 nm ($\Delta\epsilon$ +0.325 and +0.379, respectively) and a negative feature at around 244 nm ($\Delta\epsilon$ -0.446 and -0.503, respectively) <92JAN1268>.

Vinylidene dioxocane (**106**) displays IR absorption bands characteristic of the allene unit, as well as a C—O mode at 1110 cm^{-1} <88JOM(349)43>. Benzodioxocin (**108**) shows a C=C mode at 1660 cm^{-1} , while related 2,6-dione (**114**; $X = H$) is reported to display a single C=O mode at perhaps surprisingly low energy (1620 cm^{-1}) <81JFC(18)447>. Simpler 2,4-dione (**107**) displays a C=O stretching band at 1730 cm^{-1} , as expected for a nonconjugated, nonenolized lactone-type carbonyl <92G485>. Infrared absorption bands at 1580, 1450, and 1360 cm^{-1} are reported for dibenzo[*b,f*][1,5]dioxocin (**109**) <91P3081>; the latter may correspond to a C—O stretching mode. Similarly, (**115**) absorbs at 1234 cm^{-1} and dinaphtho analogue (**116**; $Ar = 4\text{-MeOC}_6\text{H}_4$) at 1252 cm^{-1} <82CCC838>. No bands below 1600 cm^{-1} were reported for the dibenzo[*b,g*][1,5]dioxocins (**111**) <74TL3941, 91P2096, 92JAN1268> and (**112**) <91P2096>. Each displays the expected lactonic carbonyl band at ca. $1720\text{--}1740\text{ cm}^{-1}$, although there is some discrepancy in the IR spectral data reported for penicillide (**111**; $R^1 = R^2 = H$) <74TL3941, 92JAN1268>. Dibenzodioxocindione (**110**; $R^1 = Me$, $R^2 = Pr$) absorbs at 1760 cm^{-1} <91JOC4525>.

Dipole moments of several 6*H*,12*H*-dibenzo[*b,f*][1,5]dioxocin-6,12-diones have been measured. Disalicylide (**110**; $R^1 = R^2 = H$), di-*o*-cresotide (**110**; $R^1 = H$, $R^2 = Me$), and di-*m*-cresotide (**117**) display dipole moments of 6.26, 6.34, and 6.74 D, respectively, agreeing well with the dipole moments predicted for each in the boat conformation <82JCS(P1)1629>.



Optical rotations have been reported for penicillide (**111**; $R^1 = R^2 = H$) <91P2096, 92JAN1268> and its 11-methyl (**111**; $R^1 = Me$, $R^2 = H$) <74TL3941, 91P2096> and side-chain acetyl (purpactin A, (**111**; $R^1 = H$, $R^2 = Ac$)) derivatives <91JAN136, 92JAN1268>. Penicillide is dextrorotatory ($(\alpha)_D = +21^\circ$ (c 1, CHCl_3) <92JAN1268>, $+4.9^\circ$ (c 0.82, MeOH) <91P2096>), as is the derived anisole (**111**; $R^1 = Me$, $R^2 = H$) while purpactin A is levorotatory ($(\alpha)_D = -57.6^\circ$ <91JAN136>, -54° <92JAN1268>).

9.24.6.2 Thermodynamic Aspects

Consistent with the loss of potential intermolecular *H*-bonding interactions, the 1,5-dioxocins appear to be in general lower-melting than the *N*-containing 1,5-diheterocins. Thus, dioxocins (**108**; $X = H$, Cl) are liquids, and related diones (**114**; $X = Me$, Cl) are low-melting solids <81JFC(18)447>. Dione (**107**) is also a solid (m.p. 102°C) <92G485>; dipole-dipole interactions are presumably responsible for the higher melting points of the diones, although (**114**; $X = H$) is a liquid at room temperature <81JFC(18)447>. Dibenzodioxocin (**115**) <82CCC838> and dibenzo[*b,f*][1,5]dioxocin-6,12-diones (**110**) and (**117**) <82JCS(P1)1629, 91JOC4525>, as well as the dinaphtho analogues (**116**) <82CCC838>, are all high-melting solids, with only di-*o*-carvacrotide (**110**; $R^1 = Pr$, $R^2 = Me$) melting below 200°C <82JCS(P1)1629>; both dipole-dipole and aromatic stacking interactions presumably play roles in stabilizing the solid state of these materials. The dibenzo[*b,g*][1,5]dioxocins (**111**) are also solids, but melting points have not been reported.

All the reported dioxocins appear to display reasonable solubility. Even the symmetrical and comparatively polar dione (**107**) dissolves in acetone <92G485>, while many of the dioxocins discussed above display solubility in common organic solvents, including chloroform <82CCC838, 82JCS(P1)1629, 91JAN136, 91JAN144, 91JAN152, 91P2096, 91P3081, 92JAN1268> and alcohols <88T6169, 91JAN136, 91JAN144, 91P2096, 91P3081, 93BMC337>, as well as in nonpolar solvents such as CCl_4 ((**106**), (**111**; $R^1 = H$, $R^2 = Ac$)) <88JOM(349)43, 91JAN136>. Fluorinated dioxocins (**114**) <81JFC(18)447> and penicillide (**111**; $R^1 = R^2 = H$) <91P2096, 93BMC337> are soluble in ether, and the dibenzo- and dinaphtho[*b,f*][1,5]dioxocins (**115**) and (**116**; $Ar = Ph$, $4\text{-FC}_6\text{H}_4$) may be recrystallized from this solvent <82CCC838>. Dioxocindione (**107**) was purified by flash chromatography on silica (hexane/acetone) <92G485>; dibenzodioxocindiones such as (**110**; $R^1 = R^2 = H$) <88T6169> and (**110**; $R^1 = Me$, $R^2 = Pr$)

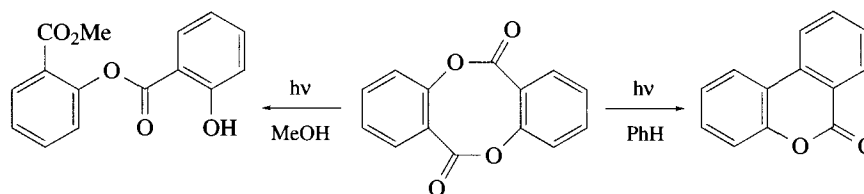
<91JOC4525> may also be chromatographed on silica. The isolation and purification of the dibenzo[*b,g*][1,5]dioxocin natural products exploited a number of chromatographic separations, including column and/or preparative thin-layer chromatography on silica, eluting with a variety of solvent mixtures of moderate polarity <91JAN136, 91JAN144, 91JAN152, 91P2096, 92JAN1268, 93BMC337>, and reversed-phase chromatography on octadecyl-derivatized silica, eluting with aqueous acetonitrile <91JAN136>; alumina was also used as a chromatographic medium in an intermediate-stage purification of purpactin A <92JAN1268>.

With the exception of the dibenzo[*b,f*][1,5]dioxocin-6,12-diones, which could display delocalized bonding were they planar (and they are not), no potentially fully-conjugated dioxocins have been reported. The potential aromaticity of the open-shell dioxocin (**3**) in the singlet and triplet states has been assayed by AM1 molecular orbital calculations <91RRC333>. Dioxocin (**3**) is much less stable than the corresponding 1,2-dioxocin, for which a classical structure may be drawn, but, in contrast to many other 1,*n*-diheterocins, does represent a minimum on the singlet potential energy surface rather than a saddle point. Interestingly, although the mesoionic structure displays more bond length equalization than the classical structures, the 1,5-dioxocin is still found to be anti-aromatic.

The conformational behavior of disalicylide (**110**; $R^1 = R^2 = H$) and several of its substituted analogues has been studied in detail by NMR spectroscopy <82JCS(P1)1629>. Each exists in the form of enantiomeric boat conformers which appear to interconvert via a pseudorotational process, proceeding through twist-boat intermediates and folded-boat transition states. Substituent steric effects are consistent with a 1,5-type interaction between the carbonyl groups and the flanking alkyl groups in the folded-boat transition state; thus, for example, di-*o*-thymotide (**110**; $R^1 = Me$, $R^2 = Pr^i$) displays a lower barrier to conformer interconversion ($\Delta G_{act} = 17.7 \text{ kcal mol}^{-1}$) than di-*o*-carvacrotide (**110**; $R^1 = Pr^i$, $R^2 = Me$, $\Delta G_{act} = 18.4 \text{ kcal mol}^{-1}$). Carbon-13 NMR spectral analysis suggested a high degree of symmetry in lactone (**113**), derived from bourgeanic acid. Analysis of the molecular structure suggested two conformers were likely, differing in the orientation of the carbonyl groups, with the *syn* isomer having overall C_2 symmetry. Molecular mechanics (MMX87) analysis revealed this conformer to be the global minimum <90JOC5938>.

9.24.6.3 Reactivity of Nonconjugated Rings

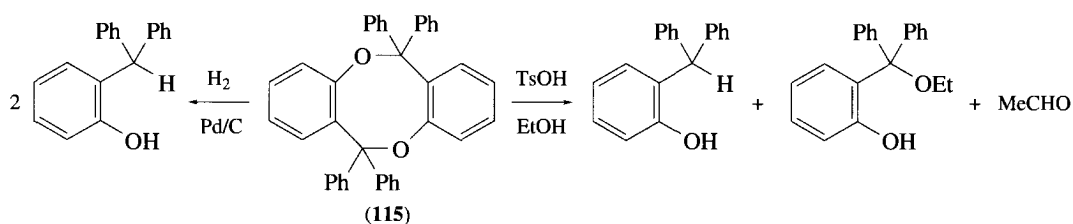
Although dibenzo[*b,f*][1,5]dioxocin-6,12-diones (**110**) could potentially display complete conjugation, their decidedly nonplanar conformations clearly argue against this, and they are thus discussed here as nonconjugated compounds. Photolysis of parent dione (**110**; $R^1 = R^2 = H$) in methanol affords predominantly the solvolysis product, while decarboxylation is effected photochemically in benzene (Scheme 28) <88T6169>.



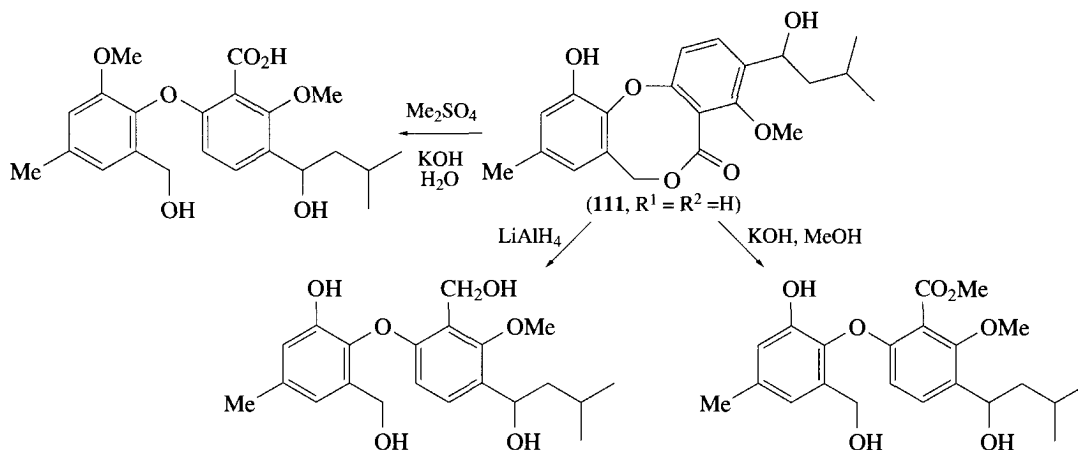
Scheme 28

Sterically-buttressed analogue (**110**; $R^1 = Me$, $R^2 = Pr^i$) displays a rather remarkable stability under a variety of reaction conditions, including hot $POCl_3$, refluxing aqueous acetic acid, and refluxing xylene, although prolonged reflux with 50% NaOH does effect ring cleavage to *o*-thymotic acid. Analogues lacking flanking substituents are appreciably less stable <91JOC4525>. Dibenzo[*b,f*][1,5]dioxocin (**115**) undergoes benzylic C—O bond hydrogenolysis and is cleaved by *p*-toluenesulfonic acid in ethanol (Scheme 29); dinaphtho derivatives (**116**) behave analogously <82CCC838>.

The dioxocin ring of penicillide (**111**; $R^1 = R^2 = H$) is hydrolytically cleaved by methanolic KOH <74TL3941> and by aqueous KOH in the presence of dimethyl sulfate <92JAN1268>; lithium aluminum hydride reduction also effects ring cleavage (Scheme 30) <92JAN1268>.



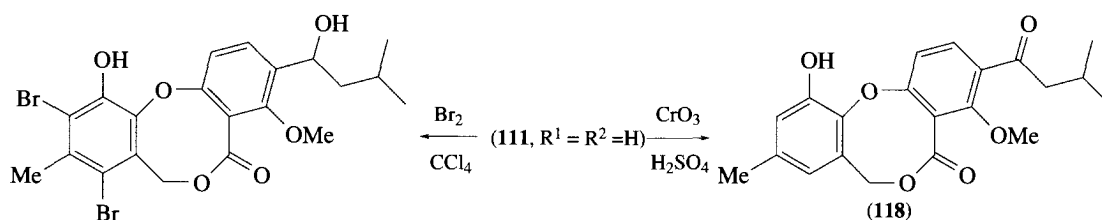
Scheme 29



Scheme 30

9.24.6.4 Reactivity of Substituents Attached to Ring Carbon Atoms

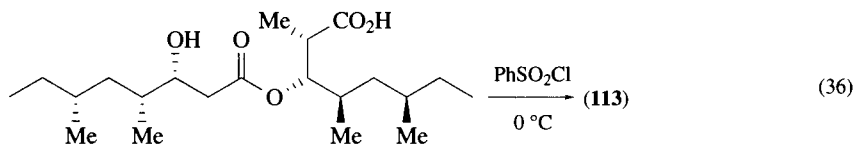
The aromatic and side-chain hydroxyl groups of penicillide (**111**; $R^1 = R^2 = H$) may be alkylated and acylated under standard reaction conditions for such reactions (91JAN144, 91JAN152, 91P2096, 92JAN1268, 93BMC337); for example, treatment of penicillide with ethereal diazomethane affords (**111**; $R^1 = Me$, $R^2 = H$) in 97% yield (91JAN144). Bromination of penicillide apparently occurs exclusively on the phenolic ring, while Jones oxidation affords the side-chain ketone (**118**) (Scheme 31) (74TL3941). Interestingly, the latter was also isolated as a minor component in a fermentation broth from *Taloromyces flavus*; the major fungal product was penicillide (93BMC337).



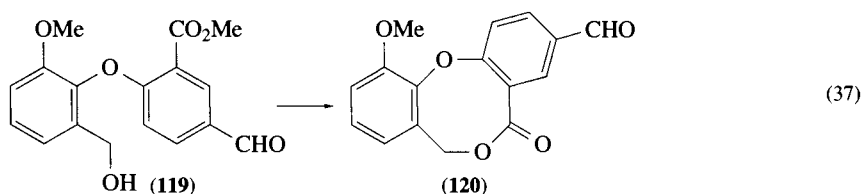
Scheme 31

9.24.6.5 Ring Syntheses

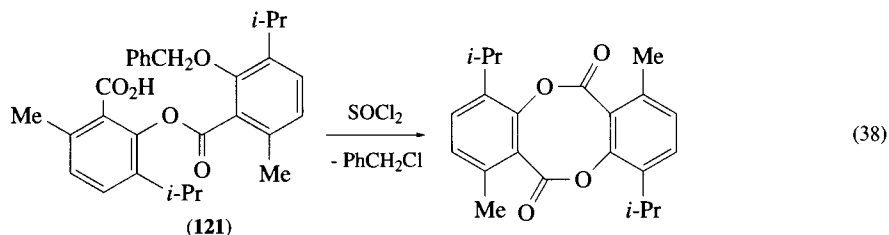
A number of cyclization and condensation reactions have been used to effect 1,5-dioxocin ring closure. Bourgeanic acid, an aliphatic depside isolated from a lichen (*Ramalina* sp.), cyclizes upon treatment with cold benzenesulfonyl chloride, affording lactone (**113**) in quantitative yield (Equation (36)) (90JOC5938).



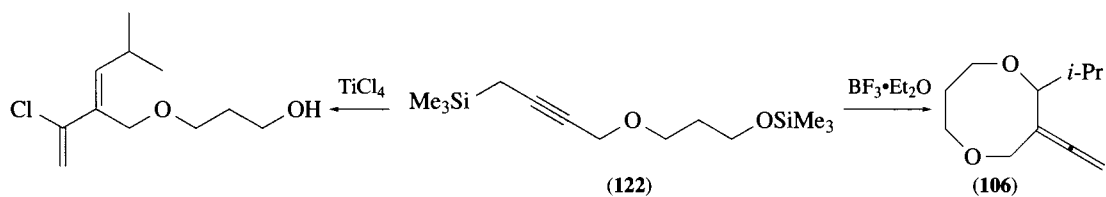
Hydroxy esters such as (119) and its substituted analogues are also reported to lactonize, affording dibenzo[*b,g*][1,5]dioxocin-5-ones (120) in unspecified yield (Equation (37)) <90GEP(O)3919255>.



Attempted formation of the acid chloride of (121) led instead to (110; $R^1 = \text{Me}$, $R^2 = \text{Pr}^i$) in 50% yield (Equation (38)), suggesting a potential rational synthetic route to unsymmetrical disalicylide derivatives <87T1519>. Other routes for the preparation of such diones, such as the pyrolysis of acetylsalicylic acid oligomers used for the preparation of disalicylide itself <82MI 924-02> and the dimerization of salicylic acid derivatives <88CZ125, 91JOC4525>, presumably would at best yield mixtures if applied to unsymmetrical analogues.

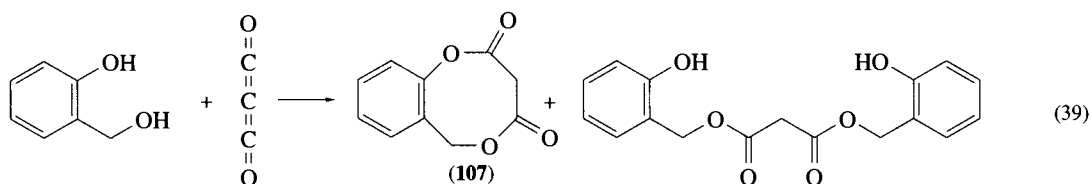


Treatment of silyl alkyne (122) with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ affords a 15% yield of vinylidene derivative (106) (Scheme 32) <88JOM(349)43>. Smaller ring analogues are formed in higher yield by treatment of analogous alkynes with TiCl_4 , but (122) affords only an acyclic diene under these reaction conditions.



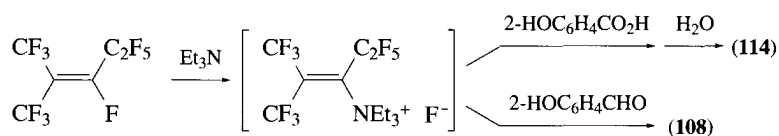
Scheme 32

Treatment of *o*-hydroxybenzyl alcohol with carbon suboxide affords a 68% yield of dioxocindione (107) (Equation (39)), together with a small amount (15%) of the acyclic malonate <92G485>.



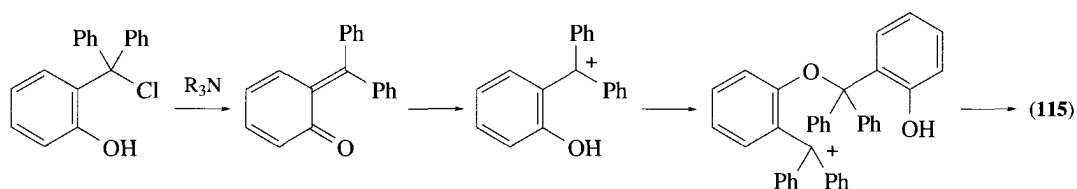
Perfluoro-2-methyl-2-pentene also serves as a three-carbon synthon, condensing with salicylic acid to form dione (114; $X = \text{H}$) and with salicylaldehyde to give (108; $X = \text{H}$) (Scheme 33); the

reactive species under the reported reaction conditions appears to be a vinyl ammonium salt formed *in situ* from the perfluoroalkene and triethylamine <81JFC(18)447>.



Scheme 33

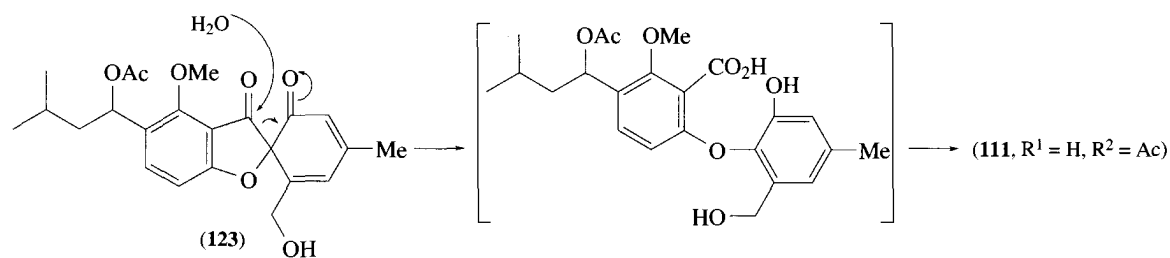
Dimerization of *o*-fuchsones, generated from *o*-hydroxybenzyl halides by treatment with either triethylamine or a diethylamino-derivatized polymer, affords dibenzo[*b,f*][1,5]dioxocin (**115**) and dinaphtho analogues (**116**; Ar = Ph, 4-FC₆H₄, 4-MeOC₆H₄) in unspecified yield (Scheme 34). These reactions are reported to follow a stepwise, ionic pathway rather than radical or concerted [$\pi 8s + \pi 8a$] thermal cycloaddition paths <82CCC838>. Curiously, no [4 + 2] dimers are formed in these reactions, although such products are favored for simpler *o*-quinone methides.



Scheme 34

9.24.6.6 Ring Synthesis by Transformation of Another Ring

No designed ring transformation approaches to the 1,5-dioxocin ring system appear to have been reported. However, purpactin A (**111**; R¹ = H, R² = Ac) is apparently formed nonenzymatically from a related fungal natural product, purpactin B (**123**), via hydrolysis of the spiroidone of the latter followed by spontaneous lactonization (Scheme 35) <91JAN144, 92JOC1271>.



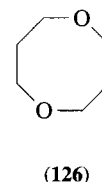
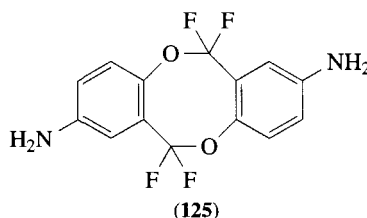
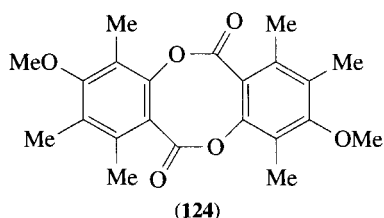
Scheme 35

9.24.6.7 Comparison of Synthetic Routes

Lactonization and salicylic acid derivative dimerization both represent reasonably effective approaches to the 1,5-dioxocin ring system. The latter is in general useful only for the preparation of symmetrical dimers, although some promise is offered above for the preparation of unsymmetrical analogues, and often trimeric structures are formed competitively as well. The lactonization strategy will most likely require conformationally-constrained precursors for reasonable yields, although the near-spontaneous and quantitative cyclization of bourgeanic acid is noteworthy. The other condensation and cyclization routes noted above may offer promise of some additional generality. The comparative absence of synthetic approaches to simple, nonbenzannelated 1,5-dioxocins suggests that additional synthetic studies are needed in this area.

9.24.6.8 Important Compounds and Applications

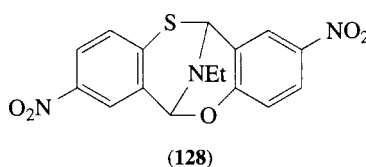
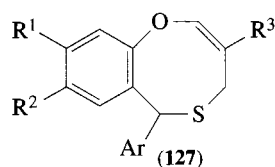
Nature's use of the 1,5-dioxocin ring system in the dibenzo[*b,g*][1,5]dioxocin fungal natural products perhaps sets the stage for anticipated biological activity. Indeed, (109) displays modest antihypertensive activity <91P3081>, while purpactin A and its derivatives are acyl-CoA: cholesterol acyltransferase inhibitors <91JAN136, 91JAN152, 91JAP(K)0352884>, of possible use in, for example, the treatment of atherosclerosis and hypercholesterolemia. Various penicillide derivatives also display cytotoxic activity *in vitro* against leukemia cells <92JAN1268>, serve as oxytocin antagonists <93BMC337>, and have been reported as potential antihypertensive and antiarrhythmic agents and for the treatment of cardiac insufficiency <90GEP(O)3919255>. Disalicylide derivative (124), derived from *Mortierella vinacea* culture broths, may be a calmodulin-dependent phosphodiesterase inhibitor <89MI 924-01>, while disalicylide itself has been suggested as a monomer for surgical suture preparation <82JST(55)261> and, in the form of its gas clathrates, as an imaging contrast agent for x-ray, NMR, and sonographic imaging studies <90EUP357163>. Dibenzo[*b,f*]dioxocin derivatives such as (125) have been incorporated in poly(imide) polymers <92GEP(O)4141624>, while 1,5-dioxocane (126) has been employed as a solvent for the preparation of partially-saponified poly(vinyl esters) <90JAP(K)02145604, 90JAP(K)02173004>. Far-ultraviolet sensitive-positive-photoresist materials incorporating the 1,5-dioxocin ring system have also been reported <88JAP(K)63163340>.



9.24.7 RINGS WITH ONE OXYGEN AND ONE SULFUR (1,5-OXATHIOCINS)

9.24.7.1 Experimental Structural Methods

Proton and carbon-13 NMR data have been reported for benzoxathiocins (127; Ar = Ph, R¹ = R² = R³ = H <91JCS(P1)959>; Ar = 2-furyl, R¹ = R³ = H, R² = Me <92CC600>). The alkenic protons in each fall at ca. 4.6 and 6.3 ppm, while the benzylic proton appears near 5.7 ppm. The allylic carbon, at ca. 24 ppm, appears upfield from the benzylic carbon, at ca. 45 ppm. All other proton and carbon resonances are in accordance with the functionality present in these derivatives. The benzylic protons in bridged dibenzo[*b,f*][1,5]oxathiocin (128) also appear between 5.5 and 6.0 ppm <92JOU331>. Proton resonances for the *N*-ethyl group in this oxathiocin appear normal, suggesting it is not subject to any unusual anisotropy effects.



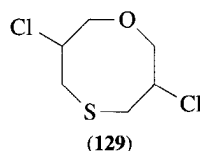
Both (127; Ar = Ph, R¹ = R² = R³ = H) <91JCS(P1)959> and (127; Ar = 2-furyl, R¹ = R³ = H, R² = Me) <92CC600> afford parent ions and M-SH fragments upon electron impact mass spectral analysis; however, the base peaks for each (M-73 and M-47, respectively) appear to result from dissimilar cleavages.

No visible absorption spectral data for the oxathiocins have been reported. The pale-yellow color of (128) <92JOU331> presumably is due to the nitroaromatic groups.

The IR spectrum of benzoxathiocin (127; Ar = Ph, R¹ = R² = R³ = H) reveals a C=C stretching mode at 1648 cm⁻¹ and an alkene C-H mode at 705 cm⁻¹ <91JCS(P1)959>, while only aromatic and nitro modes are reported for dibenzo derivative (128) <92JOU331>.

9.24.7.2 Thermodynamic Aspects

The limited data available suggest that the oxathiocins display only weak intermolecular interactions; (**127**; Ar = Ph, $R^1 = R^2 = R^3 = H$) <91JCS(P1)959> and its substituted analogues (**127**; Ar = Ph, $R^1 = MeO$, $R^2 = H$, $R^3 = H$, Me, Cl) are all liquids at room temperature <89TL189>. Nonbenzannelated oxathiocin (**129**) is also low-melting <69BRP1141492>, while bridged dibenzo derivative (**128**), presumably as a result of its comparative symmetry and the presence of polar functionalities, melts at 215°C <92JOU331>.

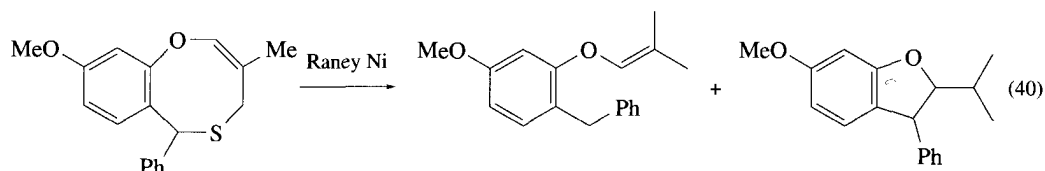


The benzoxathiocins are soluble in chloroform and aromatic solvents, and may be chromatographed on silica; (**127**; Ar = Ph, $R^1 = R^2 = R^3 = H$) is eluted with 1:1 CH_2Cl_2 /hexane <91JCS(P1)959>. Bridged compound (**128**) is also soluble in chloroform, and may be recrystallized from isopropanol/acetonitrile <92JOU331>, while (**129**) crystallizes from ethanol <69BRP1141492>.

Given the rarity of the oxathiocins and the lack of complete conjugation inherent in the ring system, no discussions of the conformations and/or potential aromaticity of oxathiocin derivatives have appeared.

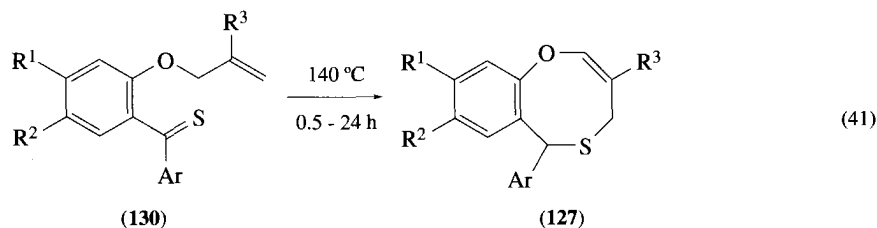
9.24.7.3 Reactivity of Nonconjugated Rings

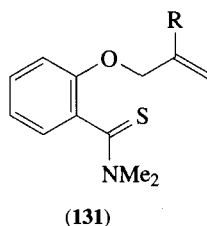
Treatment of benzoxathiocin (**127**; Ar = Ph, $R^1 = MeO$, $R^2 = H$, $R^3 = Me$) with Raney nickel W-2 affords both the expected desulfurization product and a ring-contracted benzofuran (Equation (40)) <89TL189>.



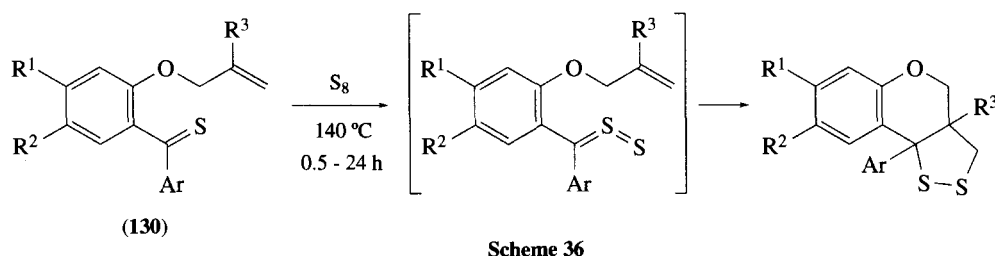
9.24.7.4 Ring Syntheses

Intramolecular ene reactions of allyloxy thioketones (**130**) afford benzoxathiocins (**127**; Ar = Ph, $R^1 = H$, OMe, $R^2 = H$, $R^3 = H$, Me, Cl; Ar = 4-ClC₆H₄, 4-MeC₆H₄, $R^1 = R^3 = H$, $R^2 = Me$; Ar = 2-furyl, 2-thienyl, $R^1 = H$, $R^2 = Me$, $R^3 = H$, Me, Cl) in 78–100% yield (Equation (41)) <89TL189, 91JCS(P1)959>. The reaction is quite general, although very electron-rich thioketones (e.g. **130**; Ar = 4-Me₂NC₆H₄, $R^1 = R^3 = H$, $R^2 = Me$, and **131**; R = H, Me) undergo Claisen rearrangement rather than the ene reaction <91JCS(P1)959>.

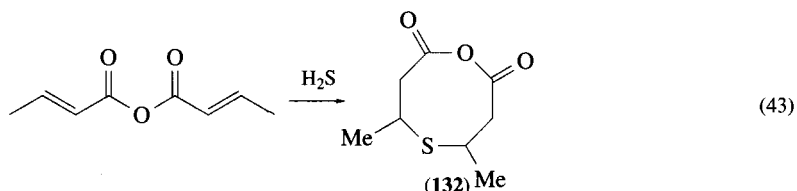
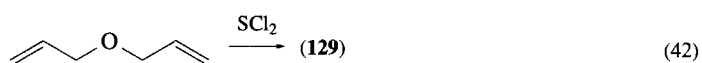




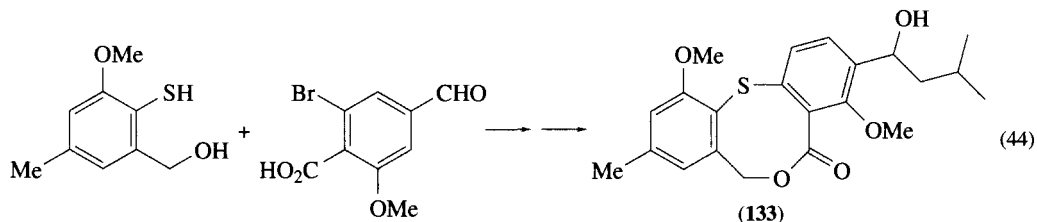
If the rearrangement is carried out in the presence of elemental sulfur, diminished yields of benzoxathiocins are obtained; under these conditions, formation of thiocarbonyl *S*-sulfides (thio-sulfines), which are trapped via intramolecular cycloaddition, accounts for the major products formed (Scheme 36) <92CC600>.



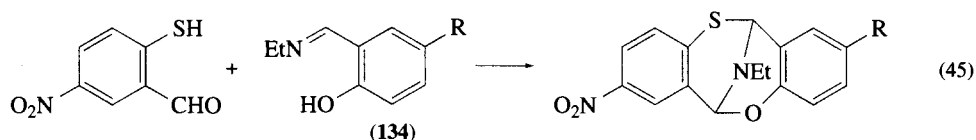
Diallyl ether reacts with SCl₂ to afford oxathiocin (129) (Equation (42)) <69BRP1141492>, while crotonic anhydride undergoes double Michael addition of hydrogen sulfide to afford oxathioindione (132) (Equation (43)) <65BRP1002328>.



Condensation of *o*-bromobenzoic acid derivatives with *o*-thiolbenzyl alcohols affords dibenz[*c,f*][1,5]oxathiocinones analogous to the dioxocinone natural products (penicillides) discussed earlier; the synthesis of (133) is illustrative (Equation (44)) <92EUP490219>.



Electron-deficient hydroxyimine (134; R = NO₂) reacts with 5-nitro-2-mercaptobenzaldehyde to afford bridged dibenzo compound (128); more electron-rich imines (e.g. 134; R = H, Br) do not yield oxathiocins (Equation (45)) <92JOU331>.



9.24.7.5 Comparison of Synthetic Routes

The intermolecular ene reaction affords access to a number of 6-phenyl-1,5-benzoxathiocins in good yield. Unfortunately, the reaction is rather sensitive to substituent effects, and attempted introduction of electron-rich aryl groups into the 6-position shuts down the ene reaction. Similarly, use of 2-furyl and 2-thienyl thioketones as cyclization precursors allows the preparation of the corresponding benzoxathiocins in only rather modest yield, with competitive alternative cyclization pathways dominating the reaction. The condensation route to dibenz[*c,f*]oxathiocinones appears to represent a reasonably general approach to this ring system, although the nature of the reaction suggests that it may be quite sensitive to substituent effects as well. Other reported preparations of the oxathiocin ring system represent rather special cases of presumably limited general applicability. Additional routes to this ring system are clearly desirable; given the developing interest in the pharmacologically interesting dioxocins, it seems likely that further developments in the oxathiocin arena will follow.

9.24.7.6 Important Compounds and Applications

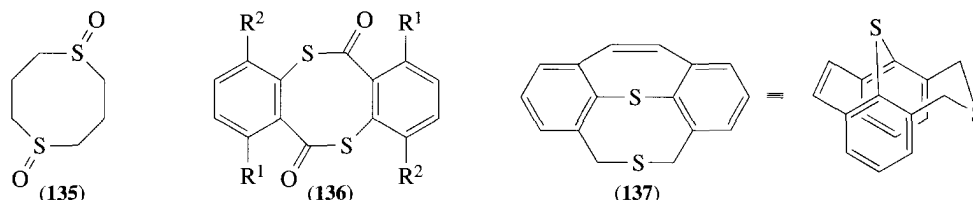
Thus far, only the dibenz[*c,f*][1,5]oxathiocins have received attention as potential biologically active agents; those compounds reported <92EUP490219> were clearly designed to mimic the structural features of purpactin A, the dioxocinone fungal natural product (111) discussed in Section 9.24.6.

9.24.8 RINGS WITH TWO SULFURS (1,5-DITHIOCINS)

The preparation and reaction chemistry of the 1,5-dithiocanes was surveyed in CHEC-I. The metal ion coordination chemistry of 1,5-dithiocane (5) and its derivatives has been reviewed <92CCR133>, as has the chemistry of transannularly-bonded dicationic derivatives <80ACR200, 89JST(55)261, 92RHA263>.

9.24.8.1 Experimental Structural Methods

A number of 1,5-dithiocin derivatives have been structurally characterized by single crystal x-ray diffraction analysis. The relatively large body of such structural data for the dithiocins, standing in stark contrast to the paucity of x-ray structural studies of most of the other classes of 1,5-diheterocins, appears to stem from a high level of interest in both the elucidation of the structural and chemical implications of transannular S—S bonding and in the exploration of the metal coordination chemistry of the 1,5-dithiocanes. 1,5-Dithiocane-1,5-dioxide (135), structurally characterized as its *cis* isomer <92JA3015, 92JA3021>, displays typical sulfoxide metrical parameters; the two ring sulfurs, separated by 4.182 Å, are clearly noninteracting (sum of van der Waals radii = 3.5–3.7 Å). Similarly, 6*H*,12*H*-dibenzo[*b,f*][1,5]dithiocin-6,12-dione (136; R¹ = R² = H, “dithiosalicylide”) displays no unusual structural features. The nearly-identical aryl–sulfur and carbonyl–sulfur bond lengths of around 1.78 Å, C=O bond length of 1.20 Å, and intra-ring bond angles at sulfur (106°) and the carbonyl group (120°) all suggest no significant delocalization in this decidedly nonplanar compound <83AX(C)1136>. Polycyclic dibenzo[*b,g*][1,5]dithiocin (137) is also highly nonplanar, adopting a conformation in which the two sulfurs are clearly noninteracting <89TL2805>.

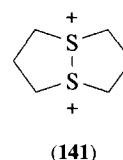
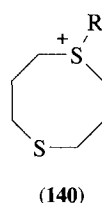
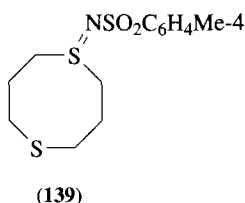
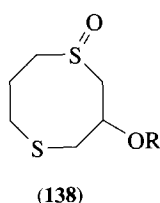


In contrast, 1,5-dithiocane derivatives in which one sulfur is oxidized universally display structures consistent with the formation of a transannular bond between the ring sulfurs. Thus, 1,5-dithiocane-1-oxide derivatives (*cis*-(138; R = H) and *trans*-(138; R = Me)) <83JOC3707>, imide (139) <87AX(C)80>, 1-methyl-1,5-dithiocanium iodide (140; R = Me) <83AX(C)887>, and acetonyl analogue (140; R = CH₂COCH₃) all display S—S distances and S—S—R(X) (X = O, N) angles (Table 2) suggestive

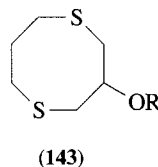
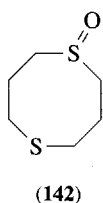
of their formulation as dithiabicyclo[3.3.0]octanes. Related dication (**141**) is also best described as a dithiabicyclo[3.3.0]octane <92RHA263>. These structural studies have been reviewed <80ACR200, 89JST(55)261, 92RHA263>.

Table 2 Transannular bonding structural parameters in 1,5-dithiocanes.

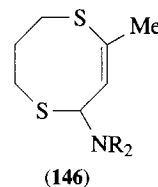
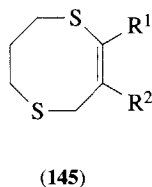
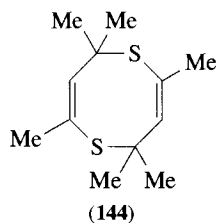
Compound	S—S (Å)	S—S—R(X) (°)
<i>cis</i> -(138 ; R = H)	3.135	175.4
<i>trans</i> -(138 ; R = Me)	3.175	176.9
(139)	3.143	177.8
(140 ; R = Me)	3.259	174.2
(140 ; R = CH ₂ COCH ₃)	3.121	178.9
(141)	2.126	



Numerous metal complexes of 1,5-dithiocane (**5**) <82JA5567, 91IC440, 91IC1297, 91TH924-01> and its derivatives, 1,5-dithiocane-1-oxide (**142**) <91IC440, 91TH1>, 3-hydroxy-1,5-dithiocane (**143**; R = H) <84AX(C)1172, 84IC1764, 87AX(C)1890, 91TH1>, and 3-methoxy-1,5-dithiocane (**143**; R = Me) <84IC3266> have been structurally characterized; these studies have been reviewed <92CCR133>. Conformational features of the dithiocane ring in these metal complexes are addressed below. In each, whether the ligand is mono-, bi-, or tridentate, the intramolecular S—S distance is clearly incompatible with any interaction between them.

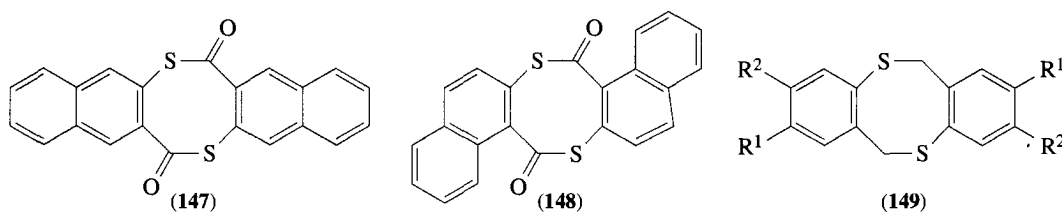


The rare nonbenzannelated unsaturated dithiocins for which NMR spectral data has been reported, 2*H*,6*H*-1,5-dithiocin (**144**) <81T3839> and 7,8-dihydro-2*H*,6*H*-1,5-dithiocins (**145**; R¹ = R² = H, Me) <85CC1266, 85JOC4218>, (**145**; R¹ = Me, Bu^t, TMS, R² = H) <89JCS(P1)1853> and (**146**; R = Me, Et) <88JOU75>, display ¹H and ¹³C chemical shifts in accordance with the proposed structures; vinylic protons appear at ca. 5.5–6 ppm <81T3839, 89JCS(P1)1853>, shifted upfield to ca. 4.1–4.5 ppm in electron-rich derivatives (**146**; R = Me, Et) <88JOU75>, allylic CH₂S groups at ca. 3.5–3.7 ppm <85JOC4218, 89JCS(P1)1853>, and simple CH₂S groups at ca. 3 ppm <85JOC4218, 88JOU75, 89JCS(P1)1853>; alkene carbon resonances in the range typical of simple alkenes (ca. 120–140 ppm) are reported for those derivatives characterized by ¹³C NMR <85JOC4218, 89JCS(P1)1853>.

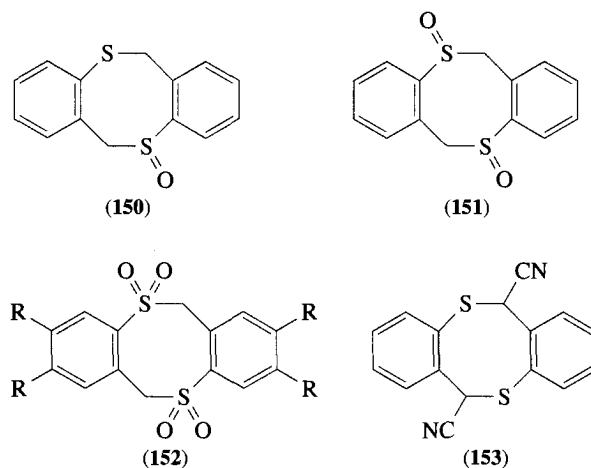


Dibenzo[*b,f*][1,5]dithiocin-6,12-diones (**136**; R¹ = H, R² = H, Me; R¹ = Me, R² = H, Me, Prⁱ) <82JCS(P1)1637, 87JOC3838> and dinaphtho analogues (**147**) and (**148**) <87JOC3838> display no unusual

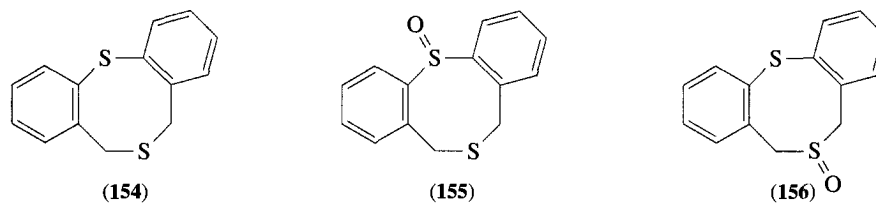
chemical shifts; variable temperature behavior consistent with conformational equilibration is observed $\langle 82\text{JCS(P1)1637} \rangle$. Dibenzo[*b,f*][1,5]dithiocins (**149**; $\text{R}^1 = \text{R}^2 = \text{H}$; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{F}$) display broad singlets at around 4.4 ppm for the ring methylene protons at room temperature $\langle 81\text{CCC2222}$, 82CCC72 , $83\text{JOC881} \rangle$; at lower temperatures, this resolves into two AB systems for (**149**; $\text{R}^1 = \text{R}^2 = \text{H}$), assigned to the boat and chair conformers of the dithiocin $\langle 83\text{JOC881} \rangle$. Analogues (**149**; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$; $\text{R}^1 = \text{R}^2 = \text{OMe}$, OEt) display very broad methylene resonances at room temperature, while each displays a singlet for the methylene protons at $> 100^\circ\text{C}$, consistent with rapid conformational equilibration at these elevated temperatures $\langle 89\text{MRC760} \rangle$. The methylene carbons appear at ca. 39 ppm in the ^{13}C NMR spectra of the latter derivatives $\langle 89\text{MRC760} \rangle$.



Oxidation of the ring sulfurs, as in 5-oxide (**150**) $\langle 87\text{JOC4254} \rangle$, 5,11-dioxide (**151**) $\langle 83\text{JOC3071} \rangle$, and 5,5,11,11-tetroxide (**152**; $\text{R} = \text{OMe}$) $\langle 89\text{MRC760} \rangle$, gives the expected downfield shift of the ring methylene protons, as does ring substitution with electron-withdrawing cyano groups as in (**153**) $\langle 88\text{JCS(P1)3375} \rangle$. *S*-Oxidation also tends to lead to restricted conformational interconversion $\langle 89\text{MRC760} \rangle$.

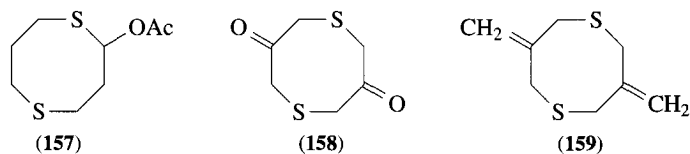


Similar NMR spectral observations have been reported for dibenzo[*b,g*][1,5]dithiocin (**154**) and its various *S*-oxides $\langle 85\text{TL5049}$, 85TL4491 , 87JCR(S)204 , $87\text{JOC4254} \rangle$ and for chloro analogues (**161**) and (**162**) $\langle 90\text{JST(238)307} \rangle$. Interestingly, whereas the 12-oxide (**155**) displays rapid conformational interconversion at room temperature, the 6-oxide (**156**) experiences restricted equilibration, and both boat–chair and a twist–boat conformer are observed spectrally at room temperature $\langle 85\text{TL4491}$, $85\text{TL5049} \rangle$.

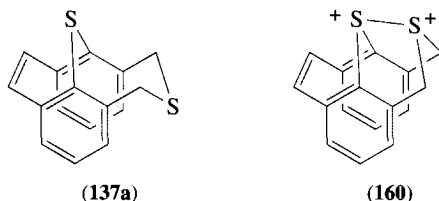


A variety of monocyclic dithiocanes, including the parent dithiocane (**5**) $\langle 85\text{IC1464}$, 92JA3015 , $92\text{JA3021} \rangle$ and its 1-oxide (**142**) $\langle 84\text{CC1151}$, 87BCJ4451 , 92JA3015 , $92\text{JA3021} \rangle$, 1,5-dioxide (**135**) $\langle 92\text{JA3015}$, $92\text{JA3021} \rangle$, and 1-imine (**139**) $\langle 84\text{CC1151} \rangle$, as well as 2-acetoxy-1,5-dithiocane (**157**) $\langle 85\text{CC1266} \rangle$, 3-ol

derivatives (**143**; R = H, Me) <83JOC3707, 84IC3266>, 3,7-dione (**158**) <90JOC2078>, and 3,7-bis(methylene) derivative (**159**) <86JOU1261>, display no unusual ^1H or ^{13}C NMR spectral features.

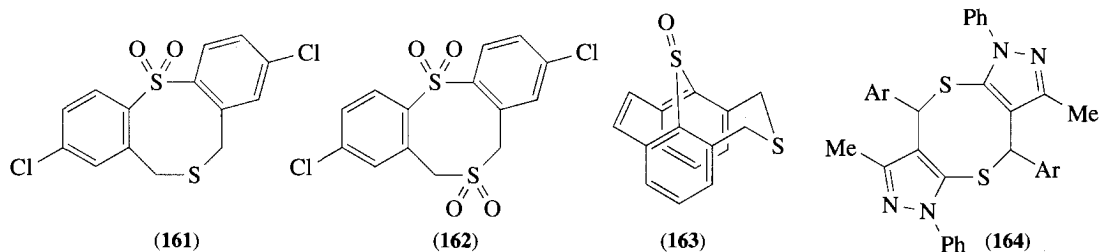


NMR Spectral data has also been presented for a series of polycyclic dithiocins; most notable is the shift of the alkene carbon resonances from 126 ppm for neutral, (**137a**), to 138 ppm in the derived dication (**160**), consistent with interaction of the alkene group with the adjacent cationic sulfur <89TL2805>.



1,5-Dithiocane (**5**) yields a significant parent ion upon electron impact mass spectral analysis <85IC1464>, together with fragments which appear to result from predominant C—S bond cleavage <86JPS285>; 3-hydroxy analogue (**143**; R = H) similarly affords both a parent ion and C—S cleavage fragments ($\text{C}_3\text{H}_6\text{S}_2$ and $\text{C}_3\text{H}_6\text{S}_2\text{O}$) <83JOC3707>. A highly complex fragmentation pattern is displayed by 3,7-dione (**158**) <90JOC2078>, while only parent ions and fragments arising from side-chain loss are reported for dihydro derivatives (**145**; $\text{R}^1 = \text{Me}, \text{Bu}^t, \text{R}^2 = \text{H}$) <89JCS(P1)1853>. Parent ions were also reported for (**145**; $\text{R}^1 = \text{TMS}, \text{R}^2 = \text{H}$) <89JCS(P1)1853>, (**145**; $\text{R}^1 = \text{R}^2 = \text{H}$) <85CC1266>, and (**159**) <86JOU1261>, and for cationic derivative (**140**; R = Cl) upon secondary ion mass spectral analysis <87BCJ4451>.

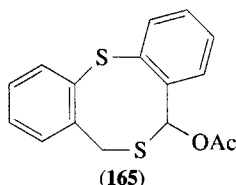
The dibenzo[*b,f*][1,5]dithiocins, seemingly regardless of oxidation state, yield both parent ions and M/2 fragments corresponding to symmetrical cleavage of the dithiocin ring <81CCC2222, 82CCC72, 83JOC3071, 87JOC3838, 89MRC760>; such cleavage is observed upon field desorption mass spectral analysis of dinaphtho derivatives (**147**) and (**148**) as well <87JOC3838>. The M/2 fragment is conspicuously absent in the reported mass spectrum of dicyano derivative (**153**), for which loss of SH and S_2H is noted <88JCS(P1)3375>; analogous loss of SH is reported to represent a relatively minor fragmentation path for dibenzo derivatives (**149**; $\text{R}^1 = \text{R}^2 = \text{OMe}, \text{OEt}$) <89MRC760>. Dibenzo[*b,g*] sulfone (**161**) displays a parent ion, together with a base peak assigned as $\text{M}-\text{HS}_2\text{O}_2\text{Cl}$, unarguably designated as resulting from “complicated fragmentation mechanisms” <90JST(238)307>. Related *bis*(sulfone) (**162**) displays a parent ion, a major fragment corresponding to loss of SO_2 , and other fragments again arising from clearly complex fragmentation processes <90JST(238)307>. Parent ions have also been reported for dibenzo[*b,g*][1,5]dithiocin-6-oxide (**156**) and 12-oxide (**155**) <85TL5049>, for polycyclic derivative (**137**) and its *S*-oxide (**163**) <89TL2805>, and for fused polycyclic derivative (**164**; Ar = 4-Me $_2\text{NC}_6\text{H}_4$) <85ZC402>.



Extremely limited data is available regarding the electronic absorption spectra of the 1,5-dithiocins. Dibenzo[*b,f*][1,5]dithiocin (**149**; $\text{R}^1 = \text{R}^2 = \text{H}$) displays absorption maxima at 225 (inflection, $\log \epsilon$ 4.30), 248 (3.91), 259 (3.84), and 283 (3.46) nm <82CCC72>, and *bis*(pyrazolo) derivative (**164**; Ar = 4-Me $_2\text{NC}_6\text{H}_4$) displays a not dissimilar spectrum, with absorptions at 265 (4.24) nm and 293 (4.12) nm <85ZC402>. Dione (**158**) is, as expected, colorless <90JOC2078>. The cation radical resulting

from one-electron oxidation of 1,5-dithiocane (**5**) is lemon-yellow <86JA6063>, displaying an absorption maximum at ca. 400 nm <85NJC5, 92TL1721>.

Infrared spectral data reported for many of the 1,5-dithiocins tends to focus on the “obvious” functional groups. Thus, for example, only S=O modes (generally at ca. 1000–1100 cm⁻¹) are reported for 1,5-dithiocane-1-oxide (**142**) <87BCJ4451> and dibenzo[*b,f*] and dibenzo[*b,g*] derivatives (**150**) <87JOC4254>, (**151**) <83JOC3071>, (**155**), and (**156**) <85TL4491, 85TL5049, 87JOC4254>, and only modes associated with the sulfonylsulfilimine group in (**139**) <84CC1151, 87JOC4254> and ester groups in (**143**; R = PhCO) <83JOC3707>, (**157**) <85CC1266>, and (**165**) <87JCR(S)204>.



Sulfoxide stretching frequencies in the same region have been reported for a number of other derivatives for which more complete spectral data was also presented, including the polycyclic compound (**137**) <89TL2805> and 3-ol derivatives (**143**; R = H, Me) <83JOC3707>. The carbonyl groups in diones (**136**), (**147**), and (**148**) absorb at around 1680 cm⁻¹ <87JOC3838>. Other bands reported for these derivatives, and, indeed, for all other dithiocin derivatives for which more complete IR spectral data has been presented, are difficult to assign with certainty to specific vibrational modes. Most revealing may be the simple nonbenzannelated derivatives, including dihydrodithiocins (**145**; R¹ = R² = Me <85JOC4218>; R¹ = TMS, R² = H <89JCS(P1)1853>) and tetrahydrodithiocins (**158**) <90JOC2078> and (**159**) <86JOU1261>, in which aromatic vibrational modes do not complicate the spectra; each displays a number of relatively low-energy ring vibrational modes. Similar spectral behavior is seen for the dibenzo[*b,f*] derivatives (**149**; R¹ = R² = H) <82CCC72, 91TL2013> and (**153**) <88JCS(P1)3375>.

1,5-Dithiocane and its cation radical and dication have been examined by resonance Raman spectroscopy, complemented by molecular mechanics and normal coordinate analyses <88JPC1747, 89JPC6052>. The neutral dithiocane (**5**) displays a higher-energy C—S stretching frequency than the dication (**141**), which displays a prominent Raman-active mode at around 450 cm⁻¹ assigned to the transannular S—S bond. Two sets of Raman bands are observed, consistent with the presence of two conformers, one a distorted chair–chair, the other a twist–boat–boat <89JPC6052>. The cation radical displays a low-energy transannular S—S Raman mode (118 cm⁻¹) as well as a number of skeletal deformation modes below 500 cm⁻¹ <89JPC6052>.

The He(I) photoelectron spectrum of 1,5-dithiocane reveals a large (0.43 eV) splitting of the sulfur lone-pair orbitals, suggesting the lone pairs are directed toward one another <81T2743>. Coupled with molecular mechanics calculations and semiempirical molecular orbital calculations of the expected orbital splittings for each low-energy conformation, this splitting suggests a probable boat–chair conformation of the dithiocane ring, but a twisted chair–chair conformation is not completely ruled out by the data.

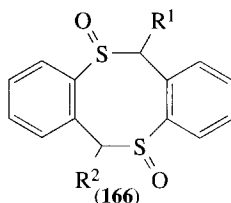
Electron-spin resonance (ESR) studies of the cation radical derived from 1,5-dithiocane <86JA6063> reveal a rather static, monomeric structure, susceptible to solvent effects, which is proposed to be a boat–chair conformer with a transannular S—S bond <81JPC3767>. Observation of coupling to four equivalent hydrogens is consistent with a related twist–boat–chair conformation in a CFCl₃ matrix <88CJC3050>. This matrix study yielded a value of *g*_{iso} intermediate to the limiting values observed in solution, and it was suggested that, unlike in solution, close approach of the ring sulfurs is not possible in the Freon matrix.

9.24.8.2 Thermodynamic Aspects

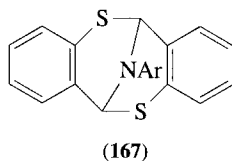
The simple dithiocins, lacking both significantly polar functionality and the capability of intermolecular *H*-bonding, are rather low-melting, and indeed the parent 1,5-dithiocane (**5**) <85IC1464, 92JA3015> and its 3-hydroxy derivatives (**143**; R = H, Me) <84IC3266>, as well as unsaturated derivatives (**145**; R¹ = R² = Me) <85JOC4218>, (**145**; R¹ = Me, Bu^t, TMS, R² = H) <89JCS(P1)1853>, and (**159**) <86JOU1261> are all liquids at room temperature. *S*-Oxidation results in an increased melting point, consistent with increased dipole–dipole interactions, although even *S*-oxide (**142**) melts at only 27 °C

<87BCJ4451, 92JA3015>; the *cis*-1,5-dioxide (**135**) melts at 151°C <92JA3015>. Similarly, *cis*-3-hydroxy-1-oxide (**138**; R = H) (m.p. 142°C) and *trans*-3-methoxy-1-oxide (**138**; R = Me) (m.p. 89°C) are higher melting than the unoxidized derivatives (**143**; R = H, Me) <83JOC3707>. Side-chain polarity appears to exert a smaller influence; benzoate (**143**; R = PhCO) melts at 45°C <83JOC3707>, while 2-acetoxy derivative (**157**) melts at 30.5°C <85CC1266>. Interestingly, although only van der Waals-type intermolecular contacts are revealed by the x-ray crystallographic analysis of imine (**139**) <87AX(C)80>, it displays a comparatively high melting point (175°C) <84CC1151, 87JOC4254>.

5*H*,7*H*-Dibenzo[*b,g*][1,5]dithiocin (**154**) melts at around 130°C, while its 6-oxide ((**156**) ca. 180°C) and 12-oxide ((**155**) ca. 200°C) again are higher-melting <85TL4491, 85TL5049, 87JOC4254>. However, it would appear the balance between dipolar and other solid-state packing effects is rather precarious. Thus, in rather startling contrast, 6*H*,12*H*-dibenzo[*b,f*][1,5]dithiocin (**149**; R¹ = R² = H) is high-melting (ca. 170°C) <82CCC72, 83JOC881, 87JOC4254>, while the corresponding 5-oxide (**150**) displays a “depressed” melting point (119°C) <87JOC4254>. The corresponding 5,11-dioxide (**151**), as a 70 : 30 mixture of *cis* and *trans* isomers, is reported to melt at around 170°C <83JOC3071>. Methylation and dimethylation of this 5,11-dioxide gives lower melting ((**166**; R¹ = Me, R² = H) and (**166**; R¹ = R² = Me) 141 and 149°C, respectively) <92TL2053>. For polycyclic dithiocin (**137**), again the *S*-oxide ((**163**) 226°C) is higher-melting than the unoxidized derivative (198°C) <89TL2805>.

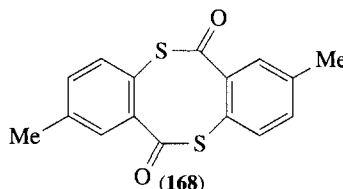


Other dibenzo[*b,f*][1,5]dithiocins, for which melting behavior was reported, include difluoro derivative (**149**; R¹ = H, R² = F), obtained in two crystalline polymorphs (m.p. 146 and 244°C) <81CCC2222>, dimethyl analogue (**149**; R¹ = Me, R² = H) (189°C) <89MRC760>, and dialkoxy derivatives (**149**; R¹ = R² = OMe, OEt) (250 and 204°C, respectively) <89MRC760>. The disulfone derived from (**149**; R¹ = Me, R² = H) melts at 292°C <89MRC760>. Similarly, mono- and disulfones (**161**) and (**162**) are quite high-melting (218 and >305°C, respectively) <90JST(238)307>. Dithiosalicylide (**136**; R¹ = R² = H) melts at around 175°C, while dinaphtho analogues (**147**) and (**148**) each melt above 300°C <87JOC3838>. Alkyl substituents, as in dithiosalicylide derivatives (**136**; R¹ = H, R² = Me; R¹ = Me, R² = H, Me, Prⁱ) result in a ca. ±20°C change in melting point from the unsubstituted derivative <82JCS(P1)1637>. The solid-state structure of dithiosalicylide suggests that aromatic π -stacking interactions are responsible for the rather high stability of the solid state for these dibenzo derivatives <83AX(C)1136>. Fused polycyclic derivative (**164**) melts at 191°C <85ZC402>, and bridged derivatives (**167**; Ar = 2-MeC₆H₄, 4-MeOC₆H₄) also melt at this temperature; curiously, (**167**; Ar = 3-MeC₆H₄) is reported to be much lower-melting (65°C) <84AG(E)244>.



The monocyclic dithiocins and their *S*-oxides uniformly display good solubility in common organic solvents, including CH₂Cl₂ <81JPC3767, 89JCS(P1)1853>, CHCl₃ <83JOC3707, 84CC1151, 84IC3266, 85CC1266, 87CC930, 89JCS(P1)1853, 90JOC2078>, CCl₄ <86JOU1261>, and ethereal solvents <83JOC3707, 84IC3266, 85IC1464, 85JOC4218>. Solubility in methanol <84IC3266, 92JA3015>, benzene <85JOC4218>, and nitromethane <92TL1721> has also been reported. The cation radical of 1,5-dithiocane was generated by γ -radiolysis of a frozen solution of 1,5-dithiocane in CFCl₃, while dissolution of 1,5-dithiocane-1-oxide (**142**) or the corresponding imide (**139**) in concentrated H₂SO₄ affords the bicyclic disulfide dication (**141**) <81JPC3767, 84CC1151>. The dibenzodithiocins and derived *S*-oxides display similar solubility behavior, with chlorinated hydrocarbons again most often used to prepare solutions <82JCS(P1)1637, 83JOC881, 83JOC3071, 85TL4491, 87JCR(S)204, 87JOC3838, 87JOC4254, 88JCS(P1)3375, 89TL2805, 90JST(238)307, 92TL2053>, although overall solubilities appear somewhat lower than for the monocyclic dithiocins. Thus, for example, dithiosalicylide derivative (**168**) may be recrystallized from CHCl₃.

<82JCS(P1)1637>, while dibenzo[*b,f*][1,5]dithiocin (**149**; $R^1 = R^2 = H$) crystallizes from benzene/ethanol <82CCC72> and dicyano dibenzo[*b,f*]derivative (**153**) is insoluble in both benzene and diethyl ether <88JCS(P1)3375>. Methoxy derivative (**149**; $R^1 = R^2 = OMe$) is quite insoluble, requiring DMSO for NMR spectroscopy <89MRC760>. Several other dithiosalicylide derivatives are reported to be soluble in toluene and recrystallized from methanol <82JCS(P1)1637>; dithiosalicylide itself may also be recrystallized from ethyl acetate <83AX(C)1136>.



Cationic, *S*-alkylated dibenzodithiocins are generally soluble in acetonitrile <85TL4491, 86TL3257, 89TL2805>, while the bicyclic dications are soluble in concentrated H_2SO_4 , the medium in which they are prepared by dissolution of their *S*-oxide precursors <85TL4491, 89TL2805>. Fused-ring derivative (**164**), soluble in $CHCl_3$, crystallizes from acetone <85ZC402>, while bridged derivatives (**167**) may be recrystallized from petroleum ether (b.p. 60–90°C) <84AG(E)244>. Chromatographic purification of dithiocins has been effected over both silica <82JCS(P1)1637, 83JOC881, 85JOC4218, 87JCR(S)204, 89JCS(P1)1853, 92JA3015> and alumina <86JOU1261>, while the diastereomeric *cis*- and *trans*-dibenzo[*b,f*][1,5]dithiocin 5,11-dioxides (**151**) were separated by reversed-phase HPLC <83JOC3071>. 1,5-Dithiocane (**5**) and its 1-oxide (**142**) have been analyzed and purified by gas chromatography on both OV-1 <89BCJ616> and Carbowax <81JPC3767>.

A considerable amount of information is available regarding the conformational preferences of 1,5-dithiocane and several of its simple derivatives as well as of several dibenzo[*b,f*]- and dibenzo[*b,g*][1,5]dithiocins. A number of reports relate to the conformation of the dithiocane ring when coordinated to metal ions; the boat–chair conformation is most common, although the chair–chair conformation is also well represented, and these preferences are maintained regardless of whether the dithiocane is mono- or bidentate or, in the case of 3-hydroxy-1,5-dithiocane (**143**; $R = H$), tridentate <82JA5567, 84AX(C)1172, 84IC1764, 84IC3266, 87AX(C)1890, 91IC440, 91IC1297, 91TH924-01, 92CCR133>. A rare boat–boat conformation is displayed by the 1,5-dithiocane rings in *trans*- $RuCl_2(1,5\text{-dithiocane})_2$ <91IC440>.

The boat–chair conformation appears to be favored for uncomplexed 1,5-dithiocanes as well, as supported by photoelectron spectrometry measurements on 1,5-dithiocane itself <81T2743> and crystallographic analysis of (*cis*-(**138**; $R = H$) and *trans*-(**138**; $R = Me$)) <83JOC3707>, although theoretical and experimental studies led to the conclusion that chair–chair and twist–boat–boat conformations were favored <88JPC1747, 89JPC6052>. Regardless of actual conformation, both 1,5-dithiocane and its 1-oxide appear to display a transannular interaction between the ring heteroatoms <81T2743, 88JPC1747, 89JPC6052>. This interaction, which appears to exert a dominant influence on ring conformation, is also evident in imide (**139**) <87AX(C)80> and in the cation radical of 1,5-dithiocane <81JPC3767, 88CJC3050>, each of which is reported to display a boat–chair conformation, although again other studies have led to the assignment of either a twist–boat–boat or chair–chair conformation for both the cation radical and the dication <88JPC1747, 89JPC6052>. Crystallographically characterized *S*-methyl-1,5-dithiocanium iodide (**140**; $R = Me$) displays a chair–chair conformation in the solid state <83AX(C)887>.

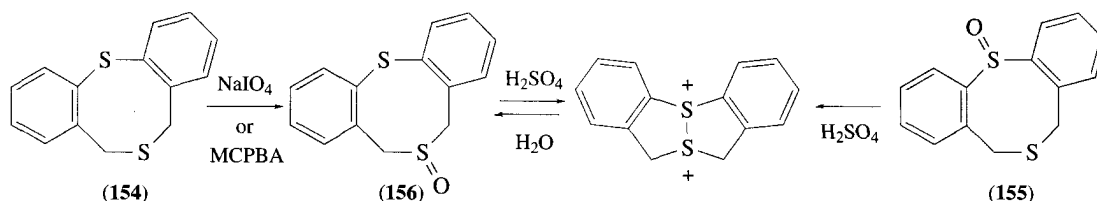
The dibenzo[*b,f*][1,5]dithiocins display tub-like conformations <89MRC760, 92TL2053>, as do the corresponding 6,12-diones (dithiosalicylides) <82JCS(P1)1637, 83AX(C)1136>. Variable temperature NMR analysis of di-*o*-thiothymotide (**136**; $R^1 = Me$, $R^2 = Pr^i$) revealed a barrier to ring inversion of enantiomeric tub conformations of 24.6 kcal mol⁻¹, much higher than that for the corresponding dilactone (**110**; $R^1 = Me$, $R^2 = Pr^i$, 17.7 kcal mol⁻¹) and consistent with enhanced resonance delocalization in the *cis*-thioester linkage over that in the *cis*-lactone <82JCS(P1)1637>. In contrast to the twist–boat thiazocine analogue (**85**), dibenzo[*b,g*][1,5]dithiocin-12-oxide (**155**) favors a boat–chair conformation, with no transannular interaction between ring sulfurs; the corresponding 6-oxide (**156**) exists as an equilibrium mixture of twist–boat and boat–chair conformers, while the derived dication, in which a transannular S—S bond exists, adopts the twist–boat form <85TL4491>. Similarly, polycyclic analogue (**137**) and its *S*-oxide (**163**) appear to exist in the boat–chair form, while conversion to the dication results in S—S bond formation and a concomitant switch to the twist–boat form <89TL2805>. NMR analysis of chlorinated mono- and bis-sulfones (**161**) and (**162**) revealed

each to display a helical-type conformation with C_2 symmetry at room temperature. Enantio-merization is observed at elevated temperatures; this process, of activation energy 20.0 and 18.2 kcal mol⁻¹ for the mono and disulfones, respectively, is proposed to proceed via a two-ring flip transition state, as the constraints of the ring system appear to preclude independent ring flips <90JST(238)307>.

9.24.8.3 Reactivity of Nonconjugated Rings

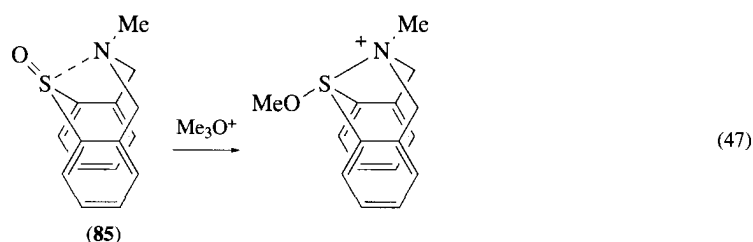
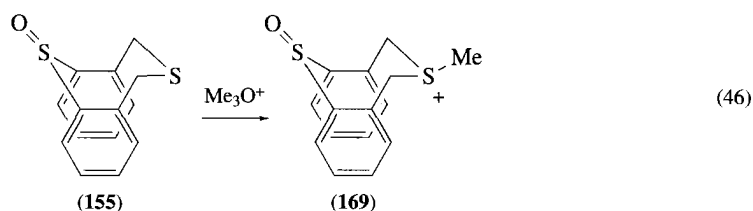
Chemical oxidation of dibenzo[*b,f*][1,5]dithiocin (**149**; $R^1 = R^2 = H$) by $NaIO_4$ or *m*-chloroperbenzoic acid is reported to yield the 5-oxide (**150**) <87JOC4254>, which is also obtained, in optically active form, through oxidation with $Bu^tOOH/Ti(OPr^i)_4/(+)$ -diethyl tartrate <92TL2053>; the latter procedure also affords the 5,11-dioxide (**151**) (*cis* and *trans* forms) as well as the 5,5,11-trioxide. Treatment of dithiocin (**149**; $R^1 = R^2 = H$) with an oxaziridine oxidant affords the 5,11-dioxide, as around a 70:30 mixture of diastereomers, in high yield <83JOC3071>, while oxidation with excess peracetic acid is reported to afford the 5,5,11,11-tetroxide in 71% yield <89MRC760>. The 5-oxide dissolves in concentrated H_2SO_4 to afford the transannularly-bonded dication <86H(24)17, 87JOC4254>. The racemic 5,11-dioxide (**151**) may be either singly or doubly deprotonated by butyllithium; methylation of the resulting anion affords (**166**; $R^1 = Me$, $R^2 = H$) and (**166**; $R^1 = R^2 = Me$), respectively, each as single diastereomers <92TL2053>.

Dibenzo[*b,g*][1,5]dithiocin (**154**) may also be oxidized by $NaIO_4$ or *m*-chloroperbenzoic acid, affording the 6-oxide (**156**) exclusively (Scheme 37) <85TL4491, 87JOC4254>, while singlet oxygen oxidation in the presence of potassium superoxide yields (**156**) as well as a trace of the 12-oxide (**155**) <85TL5049>. Dissolution of the 6-oxide in concentrated H_2SO_4 gives the corresponding dication bearing a transannular S—S bond <85TL4491, 86H(24)17, 87JOC4254>, also obtained under identical conditions from the independently-synthesized dithiocin 12-oxide <85TL4491, 87JOC4254>. When the dication is quenched with water, only the 6-oxide is formed <87JOC4254>.

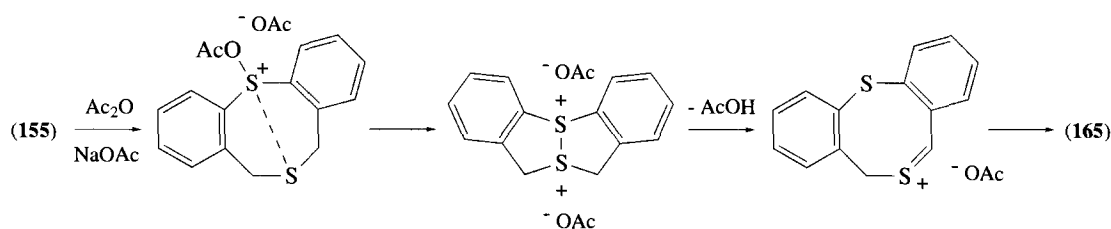


Scheme 37

Interestingly, treatment of the 12-oxide with trifluoroacetic acid results in inter- or intramolecular oxygen migration, yielding the 6-oxide, while methylation with Meerwein's reagent affords the 6-methyl cation (**169**) (Equation (46)); each of these results contrasts with the reactivity of the analogous thiazocine *S*-oxide (**85**) (Equation (47)), which is reversibly *N*-protonated by trifluoroacetic acid and *O*-methylated by Meerwein's reagent. The lack of transannular interaction in the dithiocin 12-oxide, in contrast to the apparent interaction in the thiazocine, provides a convenient rationalization of these results <85TL4491>.



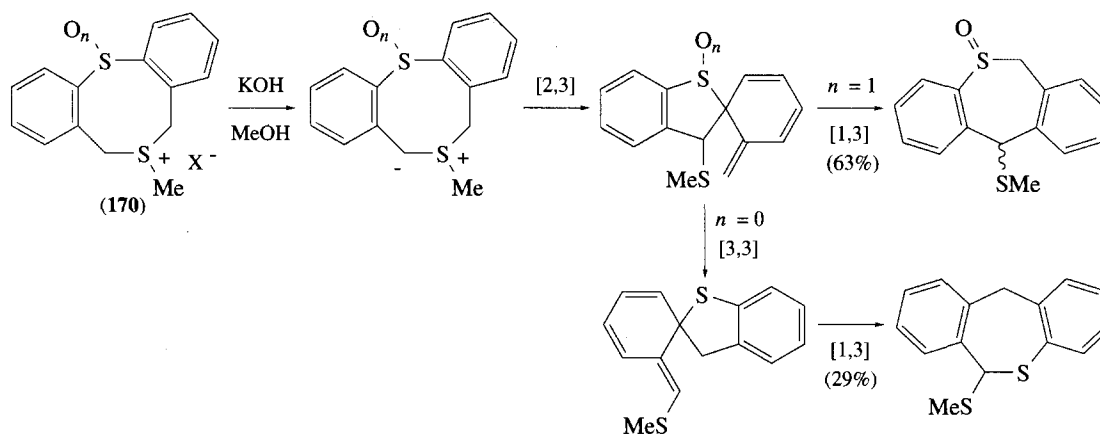
The 12-oxide undergoes a remote Pummerer reaction, apparently proceeding via the S—S-bonded dicationic intermediate, affording (**165**) (Scheme 38) <87JCR(S)204>.



Scheme 38

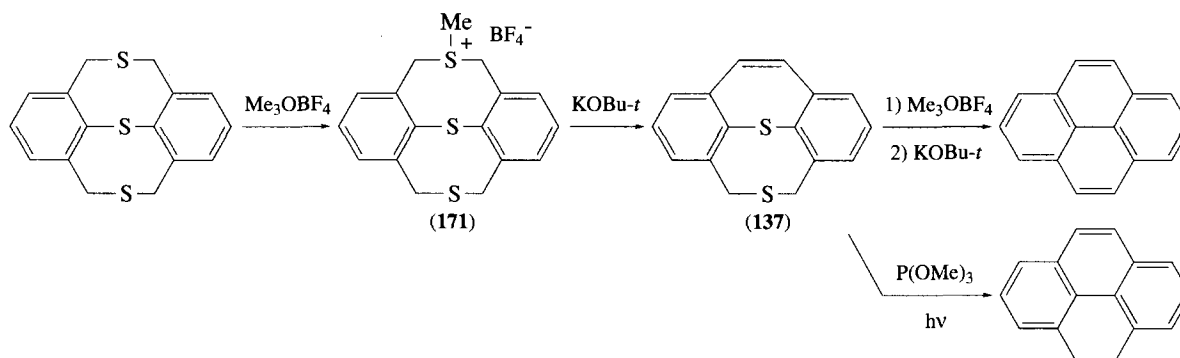
Hydrogen peroxide effects the oxidation of monosulfone (**161**) to the corresponding disulfone (**162**) (85%) <90JST(238)307>. Electrochemical oxidation of dibenzo[*b,g*]dithiocin (**154**) has also been reported <90TL2307, 91CL1649>.

S-Methylated 12-oxide (**170**; $n = 1$, $\text{X} = \text{SbCl}_6$) undergoes ring contraction when treated with KOH , affording a *cis/trans* mixture (1 : 2.3) of dibenzothiophins (Scheme 39), while the unoxidized dithiocinium salt (**170**; $n = 0$, $\text{X} = \text{BF}_4$) affords a rather different product. Competing [3,3]- and [1,3]-rearrangement of the spirocyclic intermediate presumed to arise from initial Sommelet–Hauser-type rearrangement of the first-formed ylide is proposed to account for these results <86TL3257>.



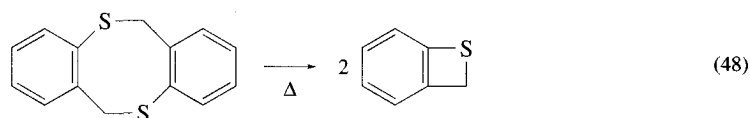
Scheme 39

Polycyclic dithiocinium salt (**171**) undergoes base-induced rearrangement/elimination to afford ring-contracted product (**137**) (Scheme 40); when the process is repeated on the remaining dithiocin ring in (**137**), both sulfurs are extruded, affording pyrene even at -80°C <89TL2805>. Photochemical desulfurization of (**137**) with $\text{P}(\text{OMe})_3$ proceeds analogously, while similar treatment of dibenzo[*b,g*][1,5]dithiocin (**154**) itself yields an intractable mixture of products <89TL7441>.

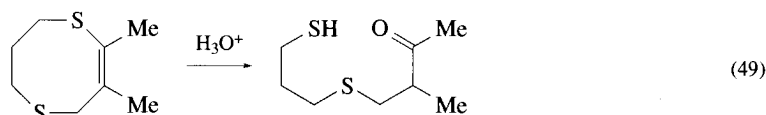


Scheme 40

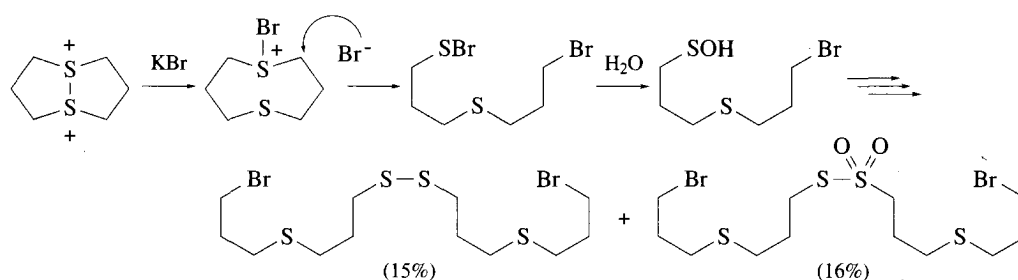
Pyrolysis of dibenzo[*b,f*][1,5]dithiocin (**149**; $R^1 = R^2 = H$) reportedly affords benzothiote (Equation (48)) <91JHC573>.



Dihydro-1,5-dithiocin (**145**; $R^1 = R^2 = Me$) is hydrolytically cleaved in aqueous sulfuric acid, affording the expected ketone in 64% yield (Equation (49)) <85JOC4218>.

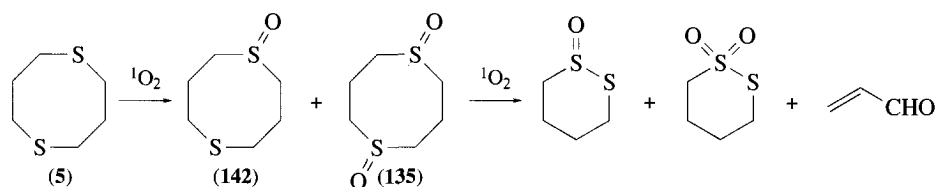


Much of the reported reaction chemistry of perhydrodithiocins concerns the generation and reactivity of the transannularly-bonded dication of 1,5-dithiocane (**141**). Comprehensive reviews of this reaction chemistry, which includes the monocyclic analogue of the remote Pummerer reaction depicted above for the dibenzo derivative <89G617>, have appeared <89JST(55)261, 92RHA263>. Since the appearance of these reviews, the cleavage of the dithiocane ring through addition of KBr to the dication (Scheme 41) has been reported <93T1605>. Also of note are the electrophilic reactions of dication (**141**) with aromatic compounds, affording (**140**; $R = 4-XC_6H_4$, $X = OH, NH_2, NPh_2$) <88CL709> and with carbanions, which effect the reduction of (**141**) to 1,5-dithiocane (**5**) <89CC147>.



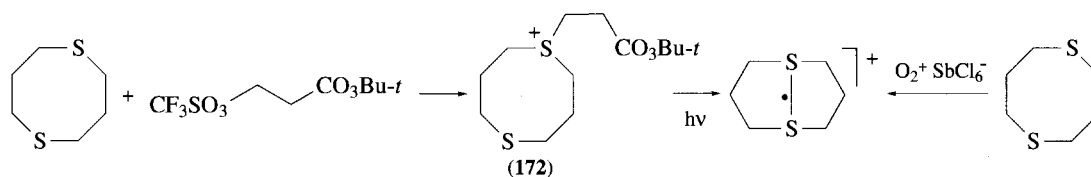
Scheme 41

Oxidation of 3-ol derivatives (**143**; $R = H, Me$) by basic iodine in aqueous methanol affords the corresponding 1-oxides (**138**) as separable mixtures of *cis* and *trans* isomers (1 : 2 *cis/trans* (**138**; $R = H$), 1 : 1 (**138**; $R = Me$)) <83JOC3707>. 1,5-Dithiocane (**5**) has been oxidized to the 1-oxide (**142**) by PhIO in the presence of iron and manganese porphyrins <83PS(16)67>, iodate, benzophenone-sensitized photooxidation <85NJC5, 86JA4214, 90TH924-02>, and singlet oxygen <92JA3015, 92JA3021>. The latter also affords the 1,5-dioxide (**135**) as a *cis/trans* mixture. When carried out in aprotic media, further oxidation, with concomitant ring cleavage, is observed (Scheme 42) <92JA3015>.



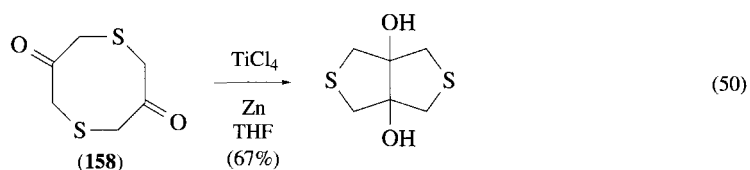
Scheme 42

1,5-Dithiocane-1-oxide (**142**) undergoes α -deuteration in basic media and is reduced to (**5**) by NaI/HClO₄ <81JPC3767>. One-electron oxidation of 1,5-dithiocane is effected by dioxygenyl hexafluoroantimonate <86JA6063>; the same cation radical is obtained upon laser flash photolysis of *S*-alkylated perester (**172**) (Scheme 43) <92TL1721>; continuous photolysis of the perester resulted in apparent photodecomposition of the cation radical.



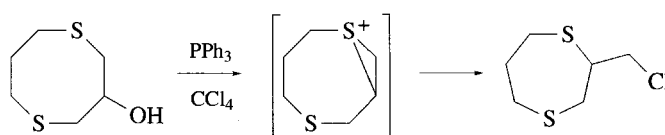
Scheme 43

Reductive treatment of 1,5-dithiocane-3,7-dione (158) with a low-valence titanium species affords the transannular pinacol (Equation (50)) <88CC959>.



9.24.8.4 Reactivity of Substituents Attached to Ring Carbon Atoms

1,5-Dithiocane-3-ol (143; $\text{R} = \text{H}$) may be methylated, affording (143; $\text{R} = \text{Me}$) <83JOC3707, 84IC3266>, and acylated, affording (143; $\text{R} = \text{PhCO}$) <83JOC3707>, but undergoes ring contraction upon attempted conversion to the corresponding chloride, apparently through formation of an intermediate episulfonium species, as often seen for β -substituted sulfides (Scheme 44) <83JOC3707>.



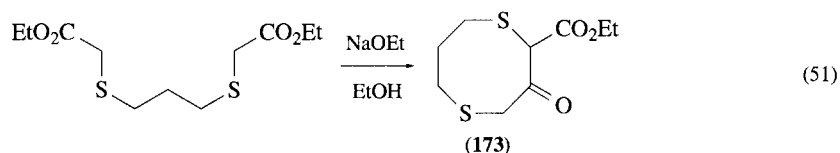
Scheme 44

9.24.8.5 Reactivity of Substituents Attached to Ring Heteroatoms

The 1,5-dithiocane dication (141) is most readily prepared by treatment of 1,5-dithiocane-1-oxide (142) with trifluoromethanesulfonic anhydride <92RHA263>. This and related reactions, although clearly involving removal of a substituent attached to a ring heteroatom, are included in the discussion of the reactivity of the dithiocane ring (see Section 9.24.8.3), as the dicationic species is clearly implicated as an intermediate in many of these reactions.

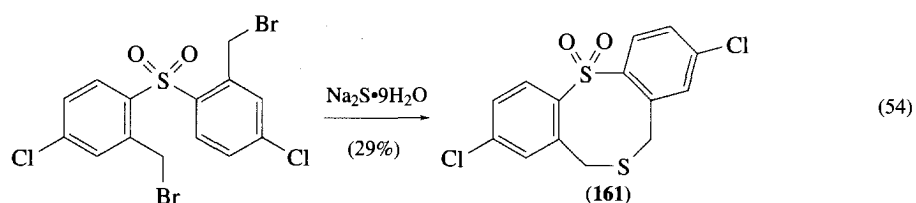
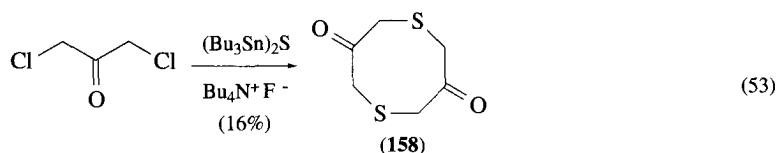
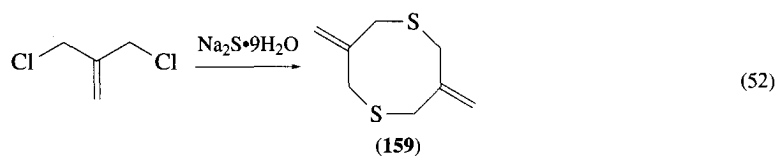
9.24.8.6 Ring Syntheses

Unimolecular cyclization remains a rare approach to the 1,5-dithiocin ring system, but has apparently been successfully applied in the form of a Dieckmann cyclization, affording dithiocane-3-one (173) (Equation (51)) <89USP4814325>.

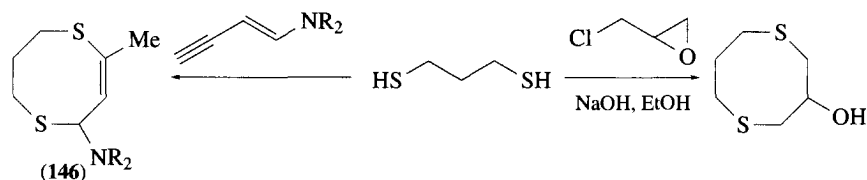


Treatment of 1,7-dielectrophiles with either sodium sulfide <86JOU1261, 90JST(238)307> or bis(tri-

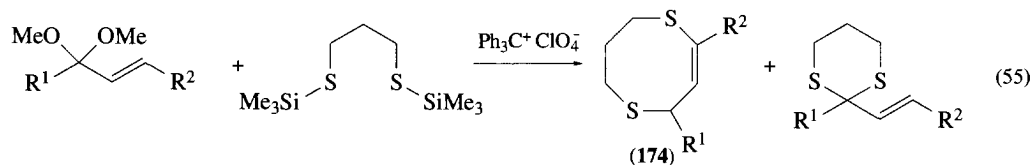
butylstannyl)sulfide <90JOC2078> has afforded access to both the 1,5-dithiocane and the dibenzo [*b,g*][1,5]dithiocin ring systems (Equations (52)–(54)).



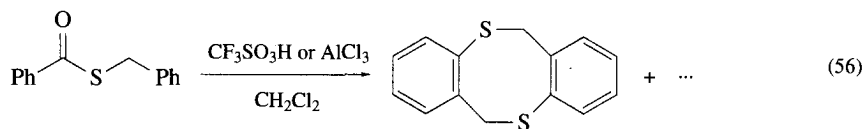
Alkylation of 1,3-propanedithiol with 1,3-dibromopropane affords the parent 1,5-dithiocane (**5**) in modest yield <92JA3015, 92JA3021>. Mass spectral analysis of the oligomeric by-products of this reaction <86JPS285> and attempted template control using caesium carbonate <85IC1464> have also been reported. Use of epichlorohydrin in place of 1,3-dibromopropane affords the 3-ol (**143**; R = H) in 29% yield <83JOC3707>, while α,β -unsaturated ketone acetals and other dielectrophiles react with 1,3-propanedithiol or its functional equivalent to afford dihydrodithiocins (**146**; R = Me, Et) (Scheme 45) <88JOU75> and (**174**; R¹ = Ph, R² = Bu^t; R¹ = Bu^t, R² = Ph) (Equation (55)) <91BCJ1108> in moderate yields. Attempted formation of (**174**; R¹ = R² = Ph), however, afforded only the dithiane.



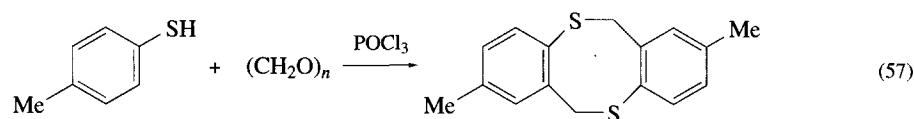
Scheme 45



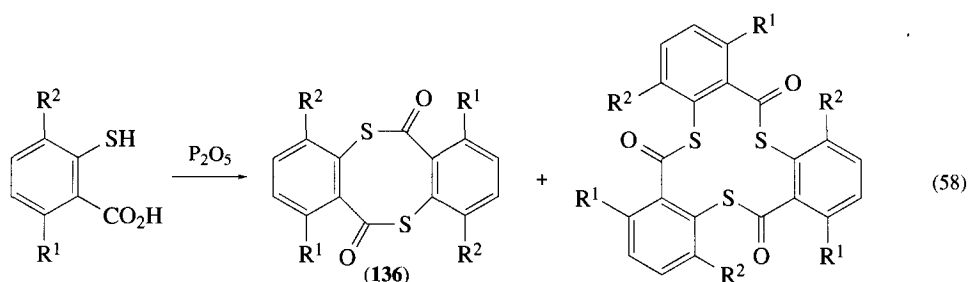
Dibenzo[*b,f*][1,5]dithiocins (**149**; R¹ = R² = H, MeO, EtO; R¹ = H, R² = Me, F) have been isolated in low yield as unexpected by-products of other reactions <81CCC2222, 82CCC72, 89MRC760>, and (**149**; R = H) has also been reported, again in low yield (<10%), as the product of several “unconventional” Friedel–Crafts reactions (Equation (56)) <91PS(61)373>.



Independent synthesis of (**149**; R = Me) was also effected, in 29% yield, through condensation of thiocresol with paraformaldehyde (Equation (57)) <89MRC760>.

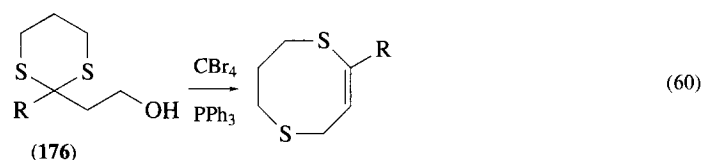
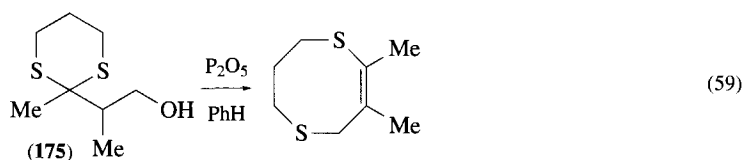


Dibenzo[*b,f*][1,5]dithiocin-6,12-diones (dithiosalicyclides) (**136**; R¹ = H, R² = H, Me; R¹ = Me, R² = H, Me, Prⁱ) and (**168**) are formed in low to modest yield, together with cyclic trimers, upon treatment of *o*-thiosalicylic acid derivatives with anhydrides (Equation (58)) <82JCS(P1)1637, 83AX(C)1136>, and (**136**; R¹ = R² = H) has also been obtained as a by-product (3%) in the DCC-mediated esterification of *o*-thiosalicylic acid <89AQ(C)39>.

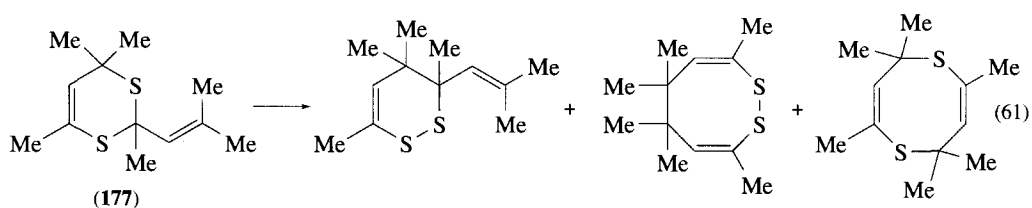


9.24.8.7 Ring Synthesis by Transformation of Another Ring

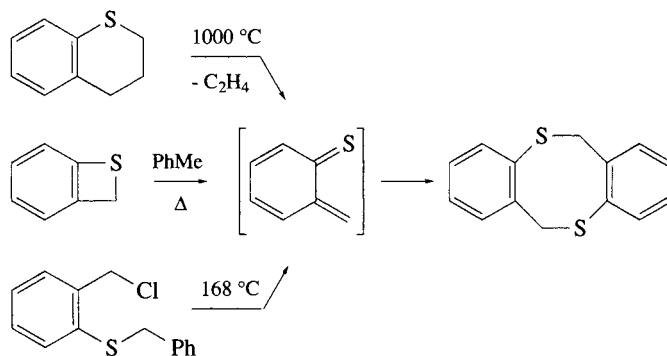
Attempted dehydration of hydroxyethyl dithiane (**175**) resulted in conversion to dihydrodithiocin (**145**; R¹ = R² = Me) in 60% yield (Equation (59)) <85JOC4218>. Analogous rearrangement occurs upon attempted conversion of dithianes (**176**; R = Me, Bu^t, TMS) to the corresponding bromides (Equation (60)) <89JCS(P1)1853>. Yields of dithiocins (**145**; R¹ = Bu^t, TMS, R² = H) are nearly quantitative, supporting the Thorpe–Ingold-type role of these substituents, while the methyl derivative (**145**; R¹ = Me, R² = H) is formed in lower yield (39–61%). Dithiane (**176**; R = H), however, affords only the bromoethyl dithiane under analogous reaction conditions.



Thermal rearrangement of vinylic dithiane (**177**) is reported to form, in addition to a 1,2-dithiane as the major product, an inseparable mixture of 1,2- and 1,5-dithiocins, in a combined yield of 2.6% (Equation (61)) <81T3839>.

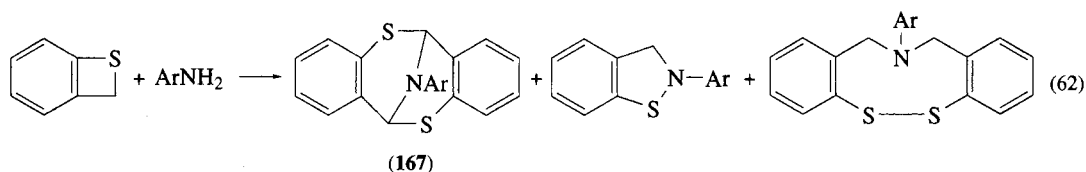


Thermolysis of benzothiete affords dibenzo[*b,f*][1,5]dithiocin (**149**; $R^1 = R^2 = H$), the [4 + 4] cyclo-dimer of *o*-thioquinone methide, in 75% yield (Scheme 46) <83JOC881>. This dibenzodithiocin is also obtained as a by-product in a number of condensation reactions of benzothiete with various dienophiles <86TL5703, 87AG(E)1046, 89CB1545, 90CB1143, 91CB377, 91JHC573>. Alternative routes for the generation of *o*-thioquinone methide, including flash vacuum pyrolysis of thiochroman <91TL2013> and pyrolysis of *o*-chloromethylphenyl benzyl sulfide <92TL2053> also afford (**149**; $R^1 = R^2 = H$).

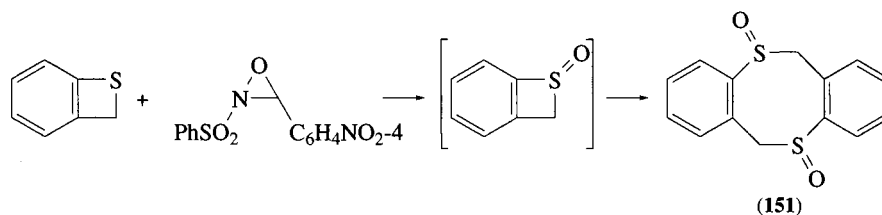


Scheme 46

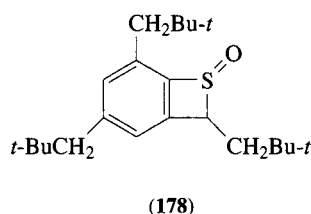
Benzothiete reacts with aromatic amines to form bridged dithiocins (**167**; Ar = 2-MeC₆H₄, 3-MeC₆H₄, 4-MeC₆H₄, 4-MeOC₆H₄) in low to modest yield (trace–31%) <84AG(E)244>, together with benisothiazoles and dibenzodithiazonines in generally comparable yields. The bridged dithiocins (**167**) are apparently not the result of addition of amines to; (**149**; $R^1 = R^2 = H$) (Equation (62)).



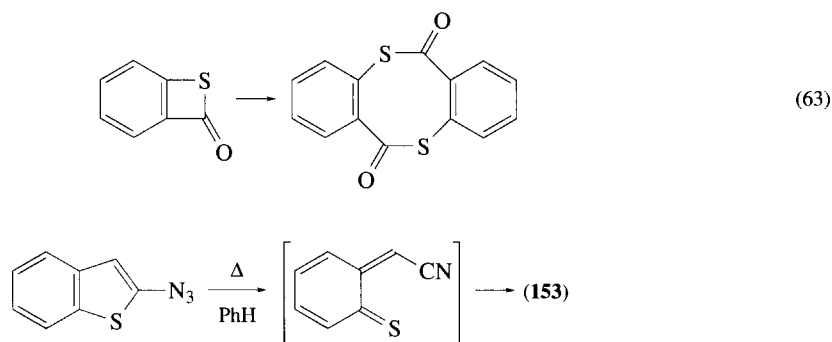
Oxidation of benzothiete similarly affords dibenzo[*b,f*][1,5]dithiocin-5,11-dioxide (**151**), apparently through ring opening and dimerization of benzothiete *S*-oxide (Scheme 47); steric protection allows isolation of substituted benzothiete *S*-oxide (**178**) <83JOC3071>.



Scheme 47

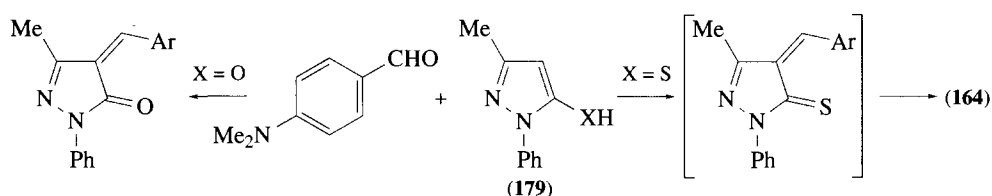


Warming benzothiet-2-one to room temperature results in formation of dibenzo[*b,f*][1,5]dithiocin-6,12-dione (**136**; $R^1 = R^2 = H$) in around 20% yield, together with a trimer and polymeric material (Equation (63)); the 1,2-naphtho and 2,3-naphtho analogues react analogously <87JOC3838>. Thermolysis of 2-azidobenzo[*b*]thiophene also appears to produce a thioquinone methide, which dimerizes to afford dicyano derivative (**153**) in high yield (Scheme 48) <88JCS(P1)3375, 90JCS(P1)2971>.



Scheme 48

Fused-ring dithiocin (**164**; Ar = 4-Me₂NC₆H₄) may also arise from dimerization of a thioquinone methide-type intermediate; use of hydroxy starting material (**179**; X = O) in place of thio compound (**179**; X = S) allows isolation of the keto analogue of this presumed intermediate (Scheme 49) <85ZC402>.



Scheme 49

9.24.8.8 Comparison of Synthetic Routes

Despite the comparatively heavy focus the 1,5-dithiocins have received, few good, reliable, and/or general synthetic routes for their preparation have been developed. Cyclization strategies appear to suffer uniformly from low yields, while the relatively less-studied dithiane ring transformation routes appear rather critically dependent on particular substitution patterns. The benzothiete and related dimerizations provide modest to good yields of benzo[*b,f*][1,5]dithiocins. The dependence of many of these routes on flash vacuum pyrolyses, either for the dithiocin-forming reaction or for the preparation of the benzothiete precursors, however, does not bode well for large-scale syntheses of these derivatives. The dearth of syntheses of unsaturated monocyclic 1,5-dithiocins and apparently complete absence of singly-benzannelated 1,5-dithiocins provide additional evidence for the need for further synthetic studies.

9.24.8.9 Important Compounds And Applications

Perhaps as a consequence of their current synthetic inaccessibility, few applications of the 1,5-dithiocins have yet been reported. Phosphoric and phosphorothioic acid derivatives derived from synthetic elaboration of (**173**) have been reported as pesticides <89USP4814325>, while both 1,5-dithiocane (**5**) and 1,5-dithiocan-3-ol (**143**; R = H) improve the stability of color developer solutions for silver halide photographic materials <88JAP(K)63214750>. 1,5-Dithiocane serves as a quencher for photoexcited aromatic systems, facilitating intrasystem crossing via exciplex formation <83JPC40>, and 1-methyl-1,5-dithiocanium salts (**140**; R = Me) serve as promoters for the Darzen's-type formation of epoxides from aromatic aldehydes and benzyl halides <87NKK1353>. The palladium(II) complex of 1,5-dithiocane promotes the hydrolysis of methionine-containing peptides <92IC3994, 93JA4566>, while the Ru(III) complex serves as a rather effective inorganic oxidant, given the

significant stabilization of Ru(II) relative to Ru(III) by the 1,5-dithiocane ligand <85IC1464>. The bis(ruthenium pentammine) complex of 1,5-dithiocane-1-oxide (**142**) represents an interesting case of 'molecular hysteresis,' in which generation of the mixed-valence state by reduction affords a different species than that afforded by oxidation <91JA2327>.

9.25

Eight-membered Rings with Three Heteroatoms

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9.25.1 INTRODUCTION

Eight-membered heterocyclic rings were reviewed in the first edition of *Comprehensive Heterocyclic Chemistry* CHEC-I (84CHEC-I(7)653). This chapter aims to cover the chemistry of eight-membered rings with three heteroatoms reported since the publication of CHEC-I. More specifically,

the preparation, reactivity, and applications of triazocines, eight-membered rings containing three nitrogens, have formed part of a review <90AHC(50)1>.

A large number of eight-membered heterocycles containing three heteroatoms are known. The various ring systems and their fused derivatives discussed in this chapter are listed in Scheme 1 and are surveyed, beginning with rings containing three identical heteroatoms and in the order of nitrogen, oxygen, and sulfur.

9.25.2 THEORETICAL METHODS

Molecular orbital and molecular mechanical calculations have been used to investigate the conformational preferences of the various eight-membered heterocycles, which consist of four low-energy conformational families categorized as the boat-chair, crown, boat, and chair forms (see Section 9.25.4.1). The predicted energy minimized conformations *in vacuo* can be compared to those observed in the solid state by x-ray diffraction analysis. Molecular dynamics calculations are used to simulate solution conformations which in turn can be compared to those determined experimentally by NMR spectral studies.

9.25.2.1 Trioxocanes

Conformational calculations indicate the boat-chair-1,3,6 form (C_1 symmetry) of 1,3,6-trioxocane to be the minimum-energy conformer, followed by the boat-chair-1,4,6 (C_s), boat-chair-2,4,7 (C_1), and boat-boat (C_1) conformers <92MI 925-1>. Strauss and co-workers have described a geometrical model, together with a potential energy function, that predicts relative energies and geometries of the various 1,3,6-trioxocane conformers consistent with NMR structural results and low-frequency vibrational spectra <81JPC2469, 81JPC2476>.

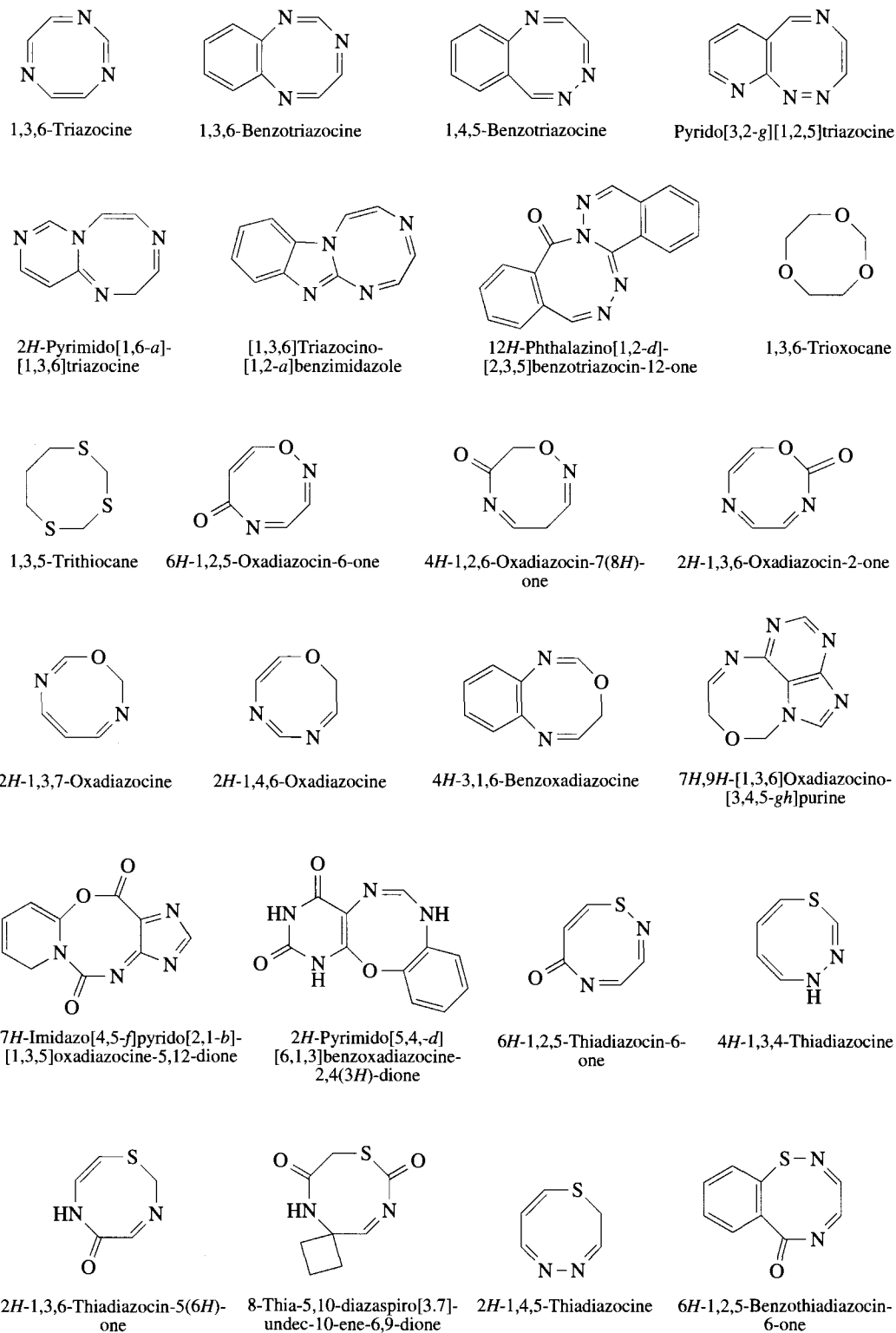
A conformational analysis of the two disaccharides (1) and (3), each of which contains a 1,3,6-trioxocane unit as a 3,2'-*O*-isopropylidene acetal, was carried out using molecular mechanical (MM2) calculations <89JCS(P2)1867>. The geometrical angles for the low energy conformations of (1) and (3), calculated to be preferred over other conformers by over 30 kJ mol⁻¹, are compared in Table 1 with the angles found in the solid state for the analogue (2) and those predicted for a boat-chair (BC) configuration. The 1,3,6-trioxocane moiety in (1) can be described as a tub-chair similar to that found in the crystal structure of (2) (see Section 9.25.4.1.1), whilst the geometry of the trioxocane ring of (3) closely resembles that calculated for the boat-chair conformation.

9.25.2.2 Oxadiazocines

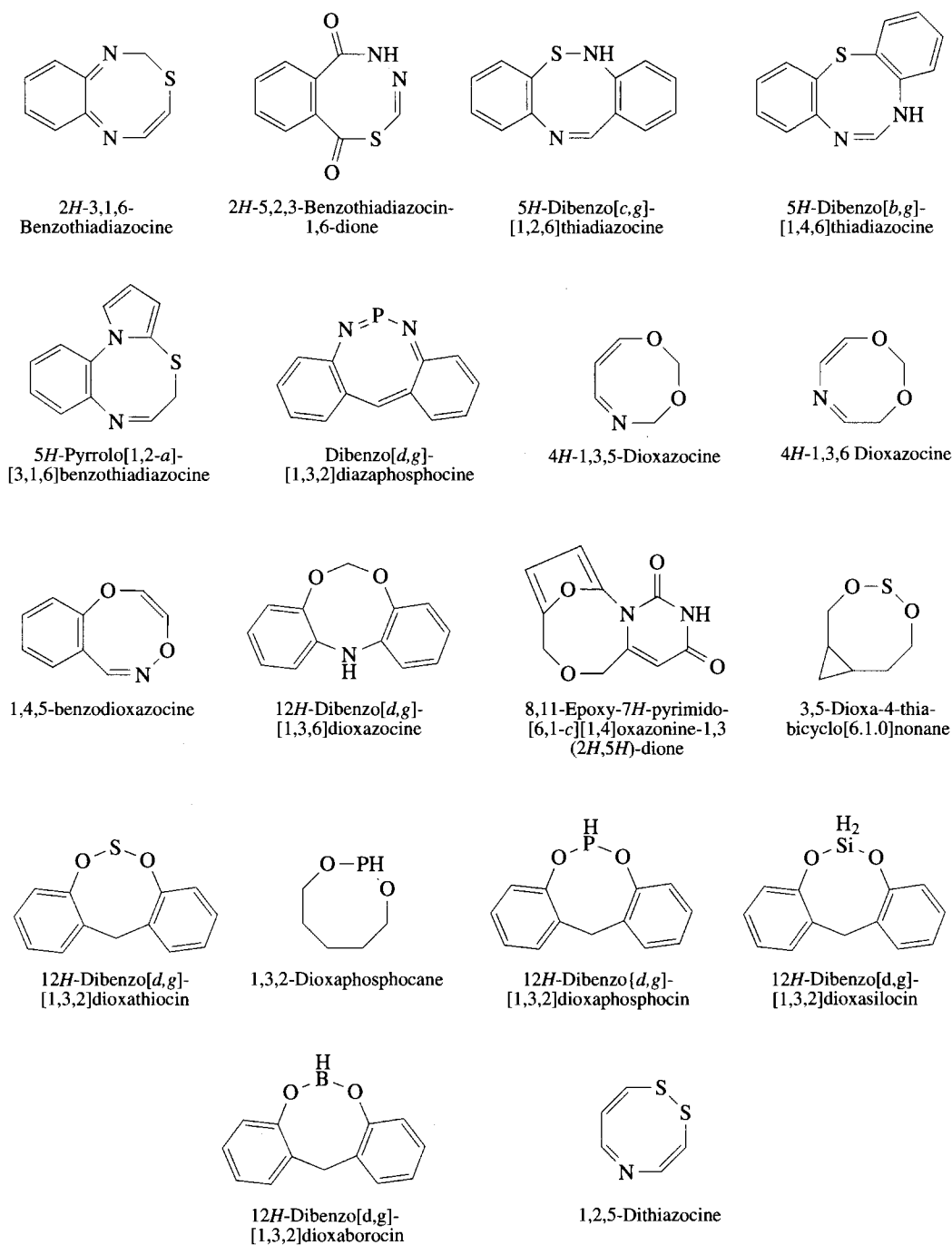
Semiempirical MNDO quantum theoretical calculations on the heats of formation of the 5,6,7,8-tetrahydro-4*H*-1,3,6-oxadiazocin-2-one ring skeleton were performed by Yamada and co-workers <92JHC1529> and the boat-chair conformation (4a) was favored over the chair-chair (4b) and boat-boat (4c) configurations by 2.9 and 7.7 kJ mol⁻¹, respectively.

9.25.2.3 Thiadiazocines

Molecular mechanical MM2 energy minimization calculations on the 5,6,8-tricyclic 5,6-dihydro-pyrrolo[1,2-*a*][3,1,6]benzothiadiazocine system (5) carried out by Varvounis and co-workers <92JHC295> produced a structure in agreement with the twisted boat conformation (5a) determined in the solid state by x-ray crystallography (see Section 9.25.3.1). In order to mimic the solvent effect, the energy minimized *in vacuo* molecule was put in a bath enveloped by 35 deuteriochloroform molecules. A molecular dynamics study was carried out; the predicted solution structure (5b) has the tosyl group folded towards the three-ring system, the segments of the eight-membered ring not connected to the benzene and pyrrole rings distorted substantially from the boat conformation.



Scheme 1

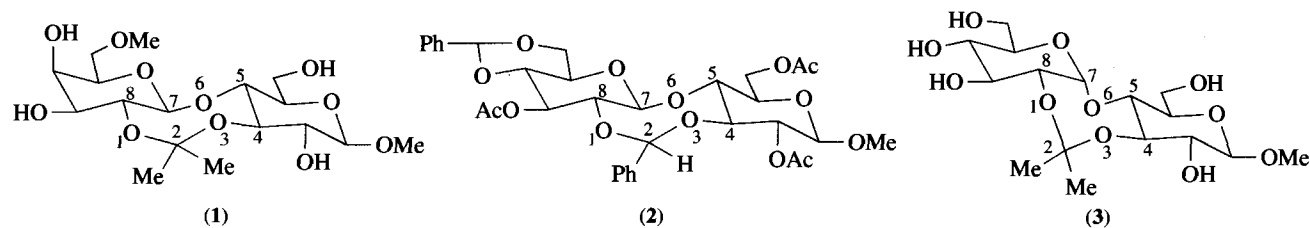


Scheme 1 (continued)

9.25.2.4 Dioxazocines

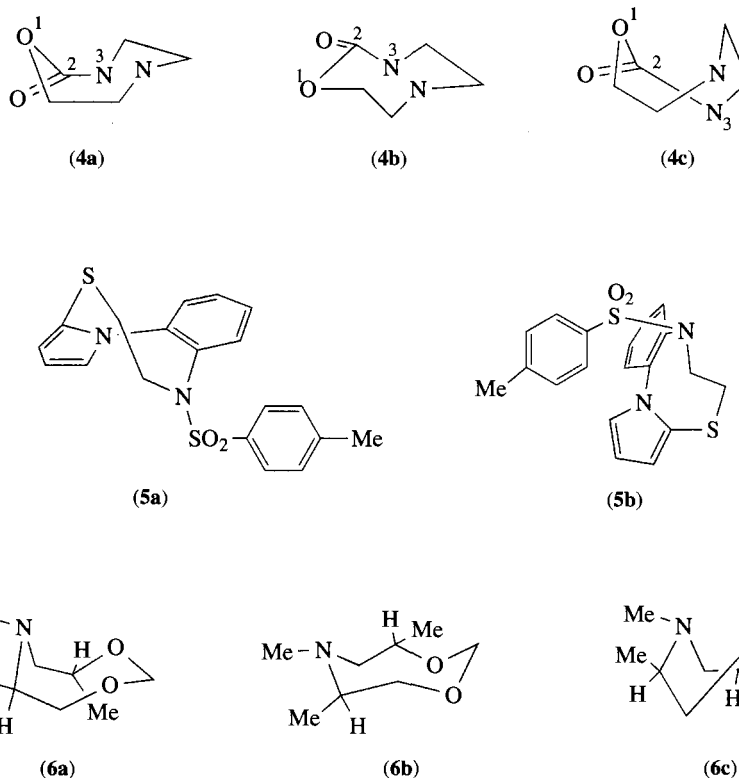
Similar molecular mechanics calculations on the conformation of 4e,6,7a-trimethyl-1,3,6-dioxazocane (**6**) predicted the boat-chair conformation (**6a**) to be favored over the crown (**6b**) and twist-boat-chair (**6c**) forms by 5.7 and 26.1 kJ mol⁻¹, respectively <92BCJ2294>.

A different conformational picture is encountered when the eight-membered ring is fused with two aromatic rings as illustrated by the conformational analysis on the dibenzo[d,g][1,3,6]dioxazocine (**7**) skeleton carried out by Farkas *et al.* <85JST131>. The possible structures can be divided into the quasi-rigid *C_s* symmetric butterfly conformation (**7a**), which has the hetero ring in the crown conformation, and two flexible conformational families with an enantiomeric relationship

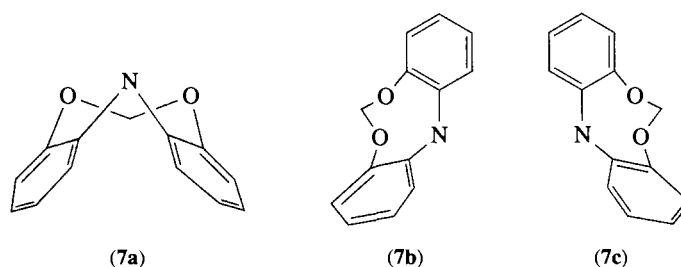
Table 1 Calculated and x-ray geometries of the eight-membered rings of disaccharide 3,2'-*O*-isopropylidene acetals.

<i>Torsion angles</i>	(1) ^a	(2) ^b	(3) ^a	BC ^c
O(1)—C(2)—O(3)—C(4)	−93.5°	−108.4°	−43.5°	−44.0°
C(2)—O(3)—C(4)—C(5)	79.9°	85.4°	111.4°	102.2°
O(3)—C(4)—C(5)—O(6)	−70.9°	−68.5°	−68.1°	−65.0°
C(4)—C(5)—O(6)—C(7)	109.1°	107.5°	62.4°	65.0°
C(5)—O(6)—C(7)—C(8)	−57.6°	−54.4°	−104.0°	−102.2°
O(6)—C(7)—C(8)—O(1)	−61.3°	−64.3°	58.5°	44.7°
C(7)—C(8)—O(1)—C(2)	85.9°	75.7°	56.0°	65.0°
C(8)—O(1)—C(2)—O(3)	9.7°	28.1°	−68.2°	−65.0°

^aTorsion angles from MM2 global minima. ^bTaken from x-ray data. ^cCalculated angles for the ideal boat-chair conformation.



represented by (7b) and (7c). The total energy of the conformers was calculated by empirical potential energy functions and then optimized as a function of the dihedral angle. Energy minimization and dipole moments were also determined by semiempirical CNDO/2 calculations. The optimized geometry and empirically calculated results both indicate the butterfly conformation (7a) to be the most stable and dominant structure. Furthermore, interconversion of the butterfly conformation (7a) with the conformational family (7b,c) requires an increase of 800 kJ mol⁻¹ over the energy minimum and would not be possible at room temperature.

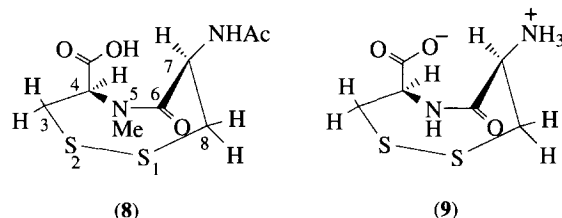


9.25.2.5 Dithiazocines

The cyclic disulfide *cyclo*-[L-cysteinyl-L-cysteine] dipeptide (9), which contains a 1,2,5-dithiazocane ring system, has attracted the interest of several research groups as the disulfide linkage introduces conformational constraint to the dipeptide unit with minimal perturbation of stereoelectronic and physicochemical properties. Researchers at Merck Laboratories have modeled the *N*-acetyl-*cyclo*-cystinyl-*N*-methyl amide (8) using molecular mechanics (MM2) <93T3449> and compared their energy minimized structure with the parameters determined by single-crystal x-ray diffraction analysis for the cyclic dipeptide (9) <77AX(B)2080> (see Section 9.25.3.1). The calculated and observed

results showed good correlation (Table 2) and were consistent with the preferred conformation of *cyclo*-[L-cysteinyl-L-cysteine] possessing a *cis* amide bond.

Table 2 Comparison of calculated and x-ray structures of *cyclo*-cysteinyl-cysteine.



Torsion angles/ atom distances	Calculated	X-ray
ψ (N(5)—C(6)—C(7)—N)	134°	156°
ω (C(4)—N(5)—C(6)—C(7))	7°	−7°
ϕ (C(3)—C(4)—N(5)—C(6))	−130°	−129°
χ (C(3)—S(2)—S(1)—C(8))	91°	94°
C(3)—C(8)	4.2 Å	4.1 Å
H(4)—H(7)	1.91 Å	2.02 Å

The solution conformation of the *N*-BOC-*t*-butyl ester dipeptide disulfide derivative was investigated by North *et al.* (93T5891). NMR analysis indicated that in chloroform two conformers exist both with *cis* amide bonds and differing mainly in the helicity of the disulfide linkage. However, energy minimization using the MM2, AMBER, and OPLSA forcefields, both *in vacuo* and in simulated chloroform and water solvents, incorrectly predicted that conformers with *trans* amide bonds would be 12–16 kJ mol^{−1} more stable. Three ring structures with *cis* amide bonds were found in the set of minimum energy conformations, two of which were compatible with the NMR data. One of these was identical to that observed for the parent dipeptide (9) in the solid state by x-ray crystallography (77AX(B)2080).

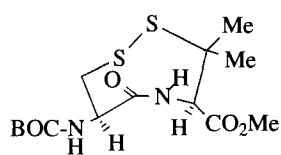
North *et al.* (93T9049) have also examined the related *cyclo*-[cysteinyl-penicillamine] dipeptide system, which differs in having *gem*-dimethyl groups on the C-terminal amino acid. NMR analysis determined that the *N*-BOC-*cyclo*-[(*R*)-cysteinyl-(*R*)-penicillamine] exists in chloroform solution as two conformers, with the major one (10a) having a *cis* amide bond. Isomeric *cyclo*-[(*R*)-cysteinyl-(*S*)-penicillamine], with the opposite absolute configuration at the C-terminal amino acid, also has two conformations in chloroform; however, the major conformer (10b) possesses a *trans* amide bond. Molecular mechanics calculations using the AMBER forcefield were unable to predict the correct relative energies of the various conformations, both in terms of amide geometry and disulfide helicity, although, as before, the experimentally observed structures were found in the set of minimum energy conformations.

Similar molecular mechanical calculations were carried out for (4*R*)-7,7-dimethyl-6-oxo-1,2,5-dithiazocane-4-carboxylic acid (11), which possesses the same ring system as the cysteinylcysteine cyclic disulfide (92JCR(S)88, 92JCR(M)735). This compound crystallizes with two independent molecules (11a,b) in the asymmetric unit, both of which have *trans* amide bonds but opposite helicities for the disulfide bonds. Torsional angles for the two conformations with the lowest calculated energy were similar to those in the solid state. The difference in stabilities between these two ring conformations and those seen for the cyclic cysteinylcysteine dipeptides, which generally possess *cis* amide bonds, was accounted for by the need to avoid high bending strains of the amide and C(7)—C(8)—S(1) bonds due to the presence of the *gem*-dimethyl group.

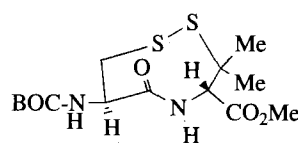
9.25.3 EXPERIMENTAL STRUCTURAL METHODS

9.25.3.1 X-ray Crystallography

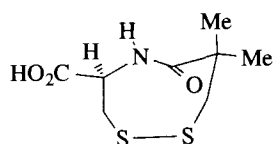
Single crystal x-ray diffraction has provided information on the solid-state geometries of various eight-membered rings with three heteroatoms. Representative bond lengths and angles for the



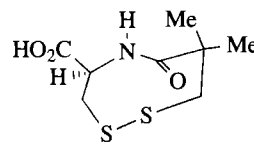
(10a)



(10b)



(11a)



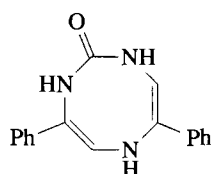
(11b)

reported x-ray crystal structures are collected in Tables 3 and 4, respectively. The various conformations adopted by the eight-membered rings in the crystal structure are discussed in Section 9.25.4.1.1.

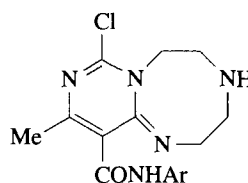
9.25.3.2 Proton NMR Spectroscopy

9.25.3.2.1 Triazocines

The ^1H NMR spectrum of the 1,3,6-triazocin-2-one (**24**) in CDCl_3 contains deuterium-exchangeable proton signals at δ 3.05 and 10.1 (in the ratio 2 : 1) arising from the three NH moieties, whilst the two alkenic proton signals appear as singlets at δ 5.15 and 6.30 <93SC2151>. The methylene protons of the pyrimido[1,6-*a*][1,3,6]triazocine (**25**) are observed as two multiplets at δ 3.6 and 4.3 <92PHA186>.



(24)



(25)

The 1,4,5-benzotriazocines have distinctive ring signals due to the methylene at C-3. The methylene protons of 1,4,5-benzotriazocin-2-one hydrochlorides (**26**) show an upfield shift of ca. δ 4.3 to 5.1 on switching from $\text{DMSO}-d_6$ to trifluoroacetic acid, with the alkenic and amide protons at δ 7.6 and 9.4, respectively <83M1231>. The methylene protons of the 1,4,5-benzotriazocinium salt (**27**) in $\text{DMSO}-d_6$ exhibit an AB pattern at δ 4.28 and 4.58 ($J = 13$ Hz) <79CPB2084>. When the methylene has an adjacent NH group, as in benzotriazocines (**28**) and (**29**), further coupling occurs and the methylene appears as a pair of unresolved quartets in an ABX system, collapsing to a pair of doublets ($\delta = 3.39$ and 3.84 , $J = 15$ Hz) on addition of D_2O or irradiation of the NH proton. Alternatively, on irradiation of the methylene protons, the NH signal, which appears as a triplet at δ 7.86 ($J = 7$ Hz) collapses to a singlet <73CPB2375>. The two methylene groups of the 1,2,5-pyridinotriazocin-6-one (**30**) were reported to be isochronous when observed at 80 MHz in $\text{DMSO}-d_6$, appearing as a 4H singlet at δ 3.1 <85PJC1115>.

9.25.3.2.2 Trioxocanes

The C-2 methylene protons of 1,3,6-trioxocane in CDCl_3 appear as a singlet <72JA1389>. On cooling, two conformers are seen as the signal broadens and splits with a ratio of 1 : 1 into a quartet ($\Delta\nu_{\text{AB}} = 89$ Hz, $J = 8$ Hz) and a single line, with a coalescence temperature of -50°C ; the other

Table 3 X-ray structure bond lengths of eight-membered rings with three heteroatoms.

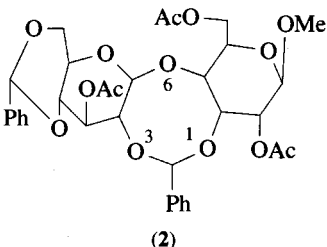
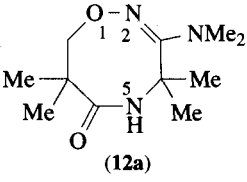
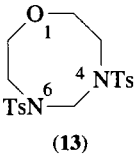
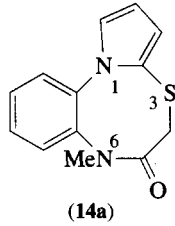
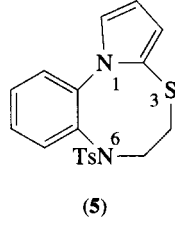
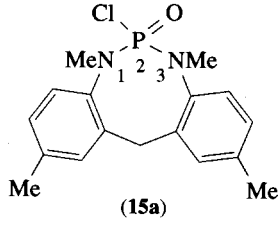
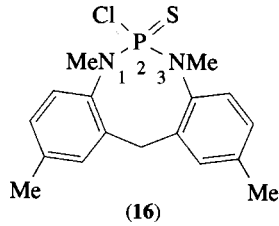
Compound	Bond lengths (Å)								Ref.
	1—2	2—3	3—4	4—5	5—6	6—7	7—8	8—1	
 (2)	1.408	1.451	1.418	1.539	1.407	1.454	1.507	1.433	80JCR(S)190
 (12a)	1.448	1.297	1.556	1.484	1.381	1.531	1.554	1.437	86HCA298
 (13)	1.415	1.505	1.462	1.434	1.450	1.484	1.501	1.400	87AX(C)2167
 (14a)	1.736	1.830	1.502	1.355	1.431		1.427		92JHC295
 (5)	1.746	1.819	1.514	1.473	1.435				92JHC295
 (15a)	1.650	1.637	1.433				1.455		86PS(26)185
 (16)	1.636	1.634	1.435		1.54	1.57	1.443		86PS(26)185

Table 3 (continued)

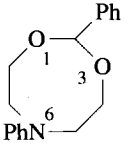
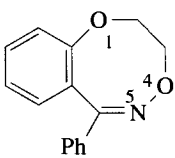
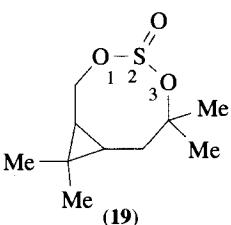
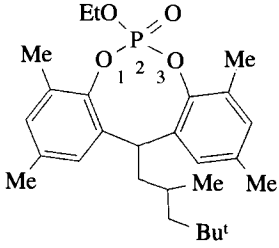
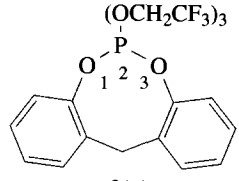
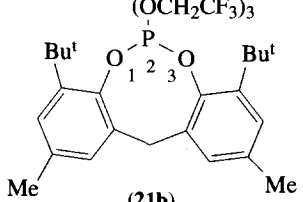
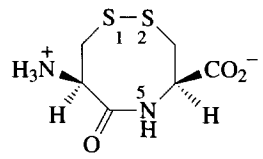
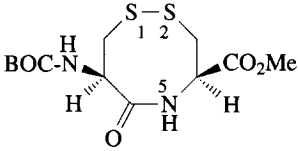
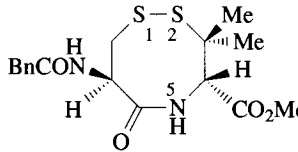
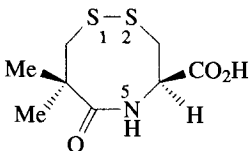
Compound	Bond lengths (Å)								Ref.
	1—2	2—3	3—4	4—5	5—6	6—7	7—8	8—1	
 (17)	1.415	1.422	1.435	1.491	1.472	1.447	1.511	1.426	88JHC1327
 (18a)	1.443	1.499	1.436	1.441	1.285	1.487	1.386	1.393	83AJC2555
 (19)	1.602	1.615	1.467	1.487	1.520	1.513	1.538	1.493	84JCS(P1)887
 (20a) ^a	1.578	1.570	1.414	<i>trans</i> 1.387	isomer 1.523	1.523	1.388	1.423	88JHC575
	1.568	1.575	1.417	<i>cis</i> 1.383	isomer 1.520	1.528	1.382	1.413	
 (21a)	1.602	1.660	1.389	1.386	1.527	1.522	1.387	1.404	92IC1913
 (21b)	1.595	1.595	1.415	1.403	1.516	1.516	1.403	1.415	92IC1913
 (9)	2.036	1.838	1.520	1.448	1.325	1.525	1.538	1.811	77AX(B)2080

Table 3 (continued)

Compound	Bond lengths (Å)								Ref.
	1—2	2—3	3—4	4—5	5—6	6—7	7—8	8—1	
 (22)	2.029	1.810	1.526	1.460	1.345	1.540	1.518	1.818	77AX(B)3561
 (23) ^b	2.057 2.066	1.861 1.855	1.565 1.477	1.459 1.454	1.367 1.386	1.516 1.529	1.500 1.479	1.814 1.823	88JCS(P1)365
 (11) ^b	2.040 2.046	1.812 1.826	1.549 1.538	1.442 1.436	1.343 1.345	1.525 1.526	1.547 1.551	1.830 1.826	92JCR(M)735

^aData given for the two isomers of dibenzo[*d,g*][1,3,2]dioxaphosphocin oxide (20a) corresponding to the ethoxy group *cis* or *trans* to the bridging alkyl group. ^bBoth cyclic lactam disulfides (23) and (11) contain two independent molecules in the crystalline asymmetric unit.

protons give a complex pattern. In CHCl_2F , the two conformers are observable at room temperature as two sharp singlets at δ 4.75 and 3.55 with relative intensities of 1 : 4, of which the downfield signal broadens to a quartet on cooling (72JA1390). The AB quartet was assigned to either a twist-chair-chair or crown conformation which undergoes slow ring inversion; whereas the singlet represents a twist-boat-chair conformation with rapid ring inversion.

The disaccharide 3,2'-*O*-isopropylidene acetals (31) each contain a trioxocane ring. Using one- and two-dimensional ^1H NMR techniques, including partially relaxed COSY and RELAY-COSY experiments, the ring protons were assigned and their values and coupling constants are shown in Table 5 (89JCS(P2)1867).

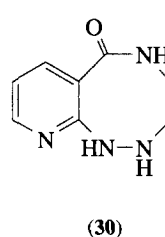
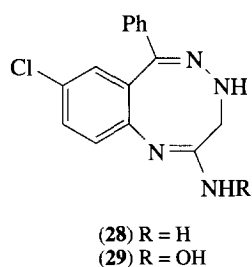
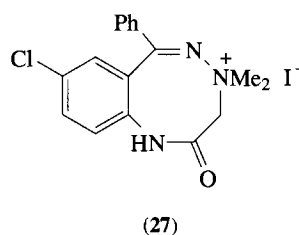
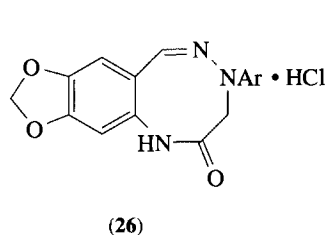


Table 4 X-ray structure bond angles of eight-membered rings with three heteroatoms.

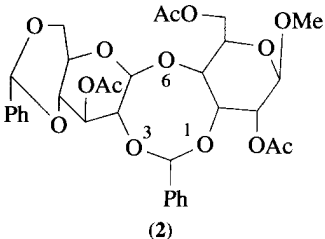
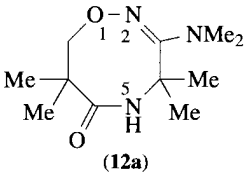
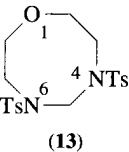
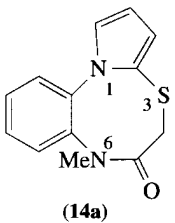
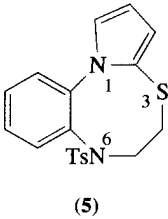
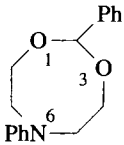
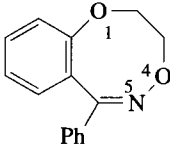
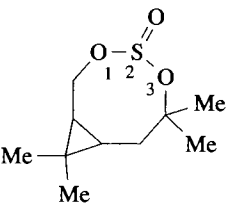
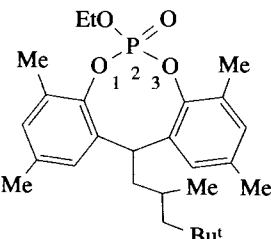
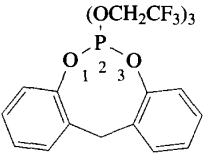
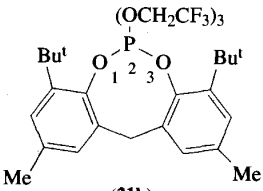
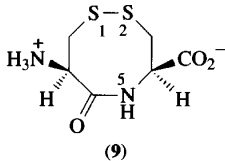
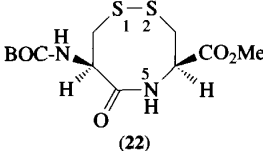
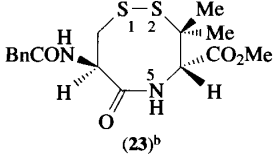
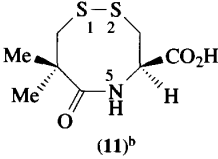
Compound	Bond angles (°)								Ref.
	8—1—2	1—2—3	2—3—4	3—4—5	4—5—6	5—6—7	6—7—8	7—8—1	
 (2)	115	110	118	112	112	118	107	112	80JCR(S)190
 (12a)	108.7	115.5	127.2	108.2	118.6	114.7	103.6	112.9	86HCA298
 (13)	117.7	112.7	115.7	118.9	113.8	119.2	113.2	114.5	87AX(C)2167
 (14a)	124.8	122.5	104.0	112.1	116.7	123.5	120.1	118.8	92JHC295
 (5)	127.0	123.2	103.8	114.2	112.3	119.0	120.1	120.8	92JHC295

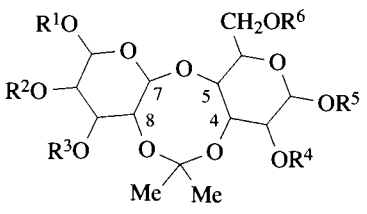
Table 4 (continued)

Compound	Bond angles (°)								Ref.
	8—1—2	1—2—3	2—3—4	3—4—5	4—5—6	5—6—7	6—7—8	7—8—1	
 (17)	116.9	109.7	118.2	112.2	114.6	116.8	115.7	115.4	88JHC1327
 (18a)	114.3	111.7	110.3	108.6	111.4	124.8	120.6	120.1	83AJC2555
 (19)	119.1	99.71	114.4	112.4	122.5	122.1	114.7	110.0	84JCS(P1)887
 (20a)^a	122.7	106.6	121.5	<i>trans</i> 118.4	<i>isomer</i> 121.2	109.2	120.1	118.4	88JHC575
	125.2	107.1	127.3	<i>cis</i> 119.1	<i>isomer</i> 121.7	108.3	121.3	119.4	

 (21a)	127.7	94.9	129.7	121.9	122.2	110.4	121.9	120.1	92IC1913
 (21b)	127.6	116.8	127.6	166.8	122.2	118.9	122.2	166.8	92IC1913
 (9)	105.5	104.2	113.2	111.8	127.6	120.0	111.8	115.0	77AX(B)2080
 (22)	103.8	103.2	113.4	111.6	126.6	119.7	112.6	119.1	77AX(B)3561
 (23)^b	108.5 107.2	110.0 110.1	106.5 106.9	109.1 110.9	123.9 122.4	114.3 113.5	107.0 107.5	115.4 116.0	88JCS(P1)365
 (11)^b	107.2 106.7	107.1 106.6	112.9 116.1	110.5 110.1	120.6 122.2	116.6 116.5	106.7 102.2	114.8 117.8	92JCR(M)735

^aData given for the two isomers of dibenzo[*d,g*][1,3,2]dioxaphosphocin oxide (**20a**) corresponding to the ethoxy group *cis* or *trans* to the bridging alkyl group. ^bBoth cyclic lactam disulfides (**23**) and (**11**) contain two independent molecules in the crystalline asymmetric unit.

Table 5 Proton NMR spectral data for disaccharide 3,2'-O-isopropylidene acetals.

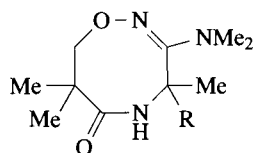
Disaccharides (31)	Substituents	δ (^1H)				J (Hz)	
		4	5	7	8	4:5	7:8
 (31)	(31a) ^a R ¹ = Bn, R ² = Bz, R ³ = Bn R ⁴ = Bn, R ⁵ = Me, R ⁶ = Bn	3.86	3.78	4.68	3.98	7.8	8.6
	(31b) ^a R ¹ = Bn, R ² = H, R ³ = Bn R ⁴ = Bn, R ⁵ = Bn, R ⁶ = Bn	3.82	3.80	4.47	4.30	8.0	8.6
	(31c) ^b R ¹ = Pr ⁱ , R ² = Pr ⁱ , R ³ = Ac R ⁴ = Ac, R ⁵ = Me, R ⁶ = Ac	3.96	3.50	5.46	3.77	8.6	3.9

^a Measured in DMSO-*d*₆. ^b Measured in CDCl₃.

9.25.3.2.3 Oxadiazocines

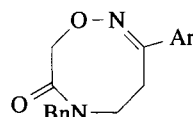
1,2,5-Oxadiazocin-6-ones (**12**) contain *gem* dimethyl groups at C-7 and two protons at C-8, which are not equivalent in CDCl₃ and appear as two singlets at ca. δ 1.1 and 1.3 and an AB system at δ 3.5 and 3.9 (J = 12 Hz), respectively <86HCA298>. The spectrum of the oxadiazocine (**12c**) containing a vinyl substituent at C-4 is an exception in this series in that the proton signals of the vinyl, C-7 methyl and C-8 methylene groups are all broad at room temperature. On warming to ca. 50°C, the peaks appear to be sharpened with the exception of the C-8 methylene group and the alkene CH, which remain broad.

In contrast, the C-8 protons of the 1,2,6-oxadiazocin-7-one (**32**) are equivalent at 20°C appearing as a singlet, whilst the protons at C-4 and C-5 give one multiplet <84LA1696>. On cooling to -50°C, the C-8 signal splits to give an AB system with doublets at δ 4.3 and 4.9 (J = 14 Hz). The C-4/C-5 multiplet resolves into a doublet of doublets for the C-5 axial proton (δ 2.71), doublet of doublets for the C-5 equatorial (δ 3.02) and C-4 axial hydrogens (δ 3.32), and a multiplet for the C-4 equatorial proton (ca. δ 4.7–5.0). Large geminal couplings ($J_{4ax;4eq}$ = 14 Hz, $J_{5ax;5eq}$ = 18 Hz), and smaller axial-equatorial (J = 6 Hz) and axial-axial couplings (J = 10 Hz) are observed.



(12)

- (a) R = Me
(b) R = Prⁱ
(c) R = CH=CH₂
(d) R = CH₂CH=CH₂
(e) R = Ph



(32)

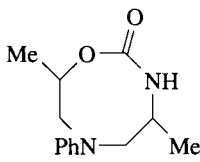
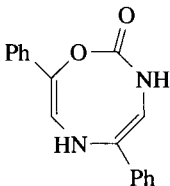
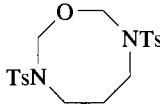
- (a) Ar = Ph
(b) Ar = *p*-Me-Ph
(c) Ar = *p*-MeO-Ph

Chemical shifts for the eight-ring heterocycle of both *cis* and *trans* isomers of the hexahydro-1,3,6-oxadiazocin-2-one (**33**) <92JHC1529>, the dihydro-1,3,6-oxadiazocin-2-one (**34**) <93SC2151>, and the symmetrical hexahydro-1,3,7-oxadiazocine (**35**) <84PJC251> are shown in Table 6.

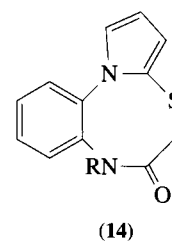
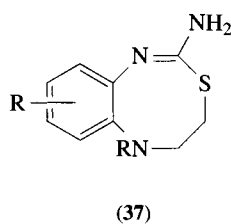
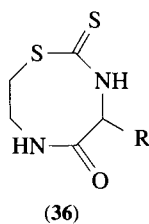
9.25.3.2.4 Thiadiazocines

The two methylene groups at C-7 and C-8 of the 2-thioxo-1,3,6-thiadiazocin-5-ones (**36**) are observed as triplets with small coupling constants (2 Hz) at about δ 4.0 and 3.0, respectively <90SC2675>. 2-Amino-3,1,6-benzothiadiazocines (**37**) possess two methylene groups at C-4 and C-5, which appear with similar chemical shifts at ca. δ 3 as triplets, unless they are isochronous in which

Table 6 Proton NMR spectral data (CDCl₃) for 1,3,6- and 1,3,7-oxadiazocines.

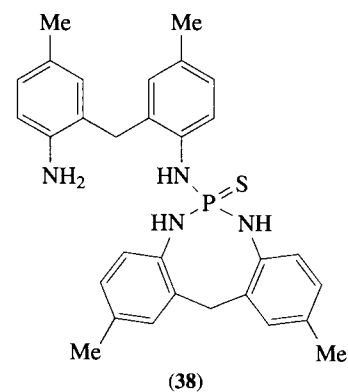
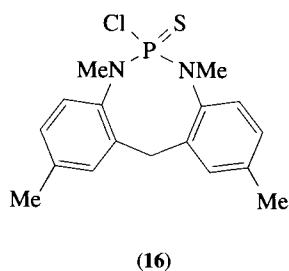
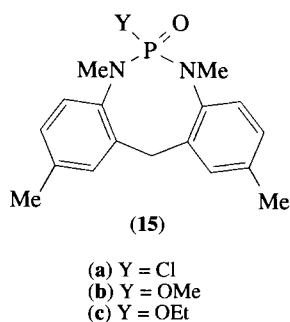
1,3,6- and 1,3,7-Oxadiazocines			δ (^1H)				
			4	5	7	8	
 (33a) <i>cis</i> (33b) <i>trans</i>	 (34)	 (35)	(33a)	3.95	3.05	2.94	4.83
			(33b)	3.82	3.27 3.12 3.95	3.73 2.98 3.87	4.79
				4	7		
				(34)	6.30	5.00	
				2/8	4/6	5	
			(35)	4.80	3.40	1.85	

case simplification to an A₄-type singlet occurs <85T2855>. The two-proton NH₂ signal indicates that the amino form is the exclusive tautomer present in solution <83T1203>. The methylene protons of the pyrrolo[1,2-*a*][3,1,6]benzothiadiazocines (**14**) are not equivalent and show a characteristic AB pattern of absorption centered at about δ 3.0 and 3.4, with a geminal coupling constant of around 11 Hz <85JHC423, 89JHC81>.



9.25.3.2.5 Diazaphosphocines

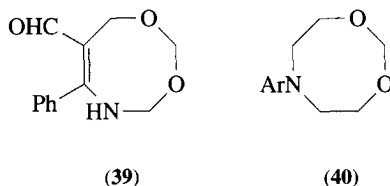
The methylene protons of 6-chloro-dibenzo[*d,g*][1,3,2]diazaphosphocines (**15a**) and (**16**) appear as AB quartets <86PS(26)185>. The ethoxy and methoxy diazaphosphocines (**15b,c**) are unusual in that their methylene signals are broadened at room temperature in CDCl₃, but revert to typical quartets when the spectra are run in 1,2-dichlorobenzene. The endocyclic methylene of the diazaphosphocine (**38**) has nonequivalent protons δ H_A 3.63, δ H_B 4.62 ($J = 12$ Hz), one of which (H_B) also exhibits a long-range through-space coupling to the phosphorus atom of 3.5 Hz <87JCS(P1)1547>.



9.25.3.2.6 Dioxazocines

The three methylene groups of the 1,3,5-dioxazocine-7-carbaldehyde (**39**) have similar chemical shifts and appear in CHCl_3 as an apparent 5H singlet at δ 4.79, and a 1H singlet at δ 4.91 attributed to one of the C-2 protons $\langle 84\text{TL}2731, 85\text{CCCC1982} \rangle$. Substitution at C-2 leads to observance of doublets for the C-4 hydrogens at ca. δ 5.2 and 4.2 ($J = 15$ Hz), a multiplet for the C-8 hydrogens overlapping with the NH at δ 4.5–5.1, and a singlet for the C-2 hydrogen, whose chemical shift depends on the substituent.

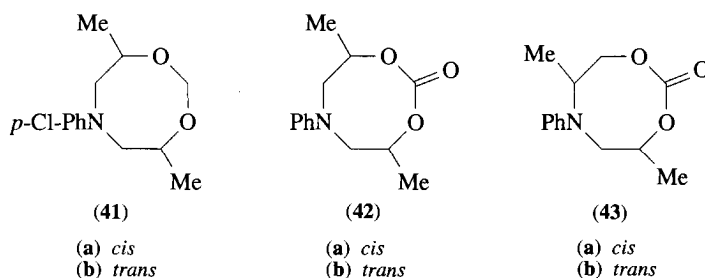
The spectral behavior of the tetrahydro-6-aryl-1,3,6-dioxazocine system has been studied by Yamada and co-workers. In the simplest case, the parent 1,3,6-dioxazocine (**40**) shows a deshielded singlet for the C-2 protons at ca. δ 4.7, with the remaining methylene protons overlapping in a multiplet at δ 3.55–3.96 $\langle 83\text{JHC}479, 91\text{JHC}1369 \rangle$.



Two alkyl substitutions at the ring result in the formation of separable *cis* and *trans* diastereoisomers, which can be distinguished by their ^1H NMR spectra. In the example of the 4,8-dimethyl-1,3,6-dioxazocine (**41**), the C-2 methylene protons of the *cis* isomer (**41a**) are observed as doublets at δ 4.38 and 5.23 ($J = 7.5$ Hz); whereas for the *trans* isomer (**41b**), the same protons appear as a singlet at δ 4.63 $\langle 83\text{JHC}479 \rangle$. The non-equivalence of the *cis* methylene was explained as a consequence of the proximity of the axial C-2 hydrogen to the nitrogen lone-pair.

4,8-Dimethyl-1,3,6-dioxazocin-2-ones (**42**) can also be separated into *cis* and *trans* isomers, which are distinguished by their H-5/H-7 axial resonances which occur at δ 3.3 ($J_{\text{gem}} = 13.5$ Hz, $J_{\text{vic}} = 5.0$ Hz) for the *cis* isomer (**42a**) and δ 3.8 ($J_{\text{gem}} = 15.5$ Hz, $J_{\text{vic}} = 3.0$ Hz) for the *trans* isomer (**42b**) $\langle 84\text{JHC}1145 \rangle$. For both isomers, the 4,8-methine protons are multiplets at ca. δ 4.7, whilst the H-5/H-7 equatorial hydrogens are seen at ca. δ 3.0 ($J_{\text{vic}} = 10$ Hz).

The *cis* isomer of 4,7-dimethyl-1,3,6-dioxazocin-2-one (**43a**) shows H-5 resonances at δ 3.0 ($J_{\text{gem}} = 15$ Hz, $J_{\text{vic}} = 10$ Hz) and δ 3.3 ($J_{\text{vic}} = 2.2$ Hz), and H-8 resonances, which occur at δ 4.0 ($J_{\text{gem}} = 11$ Hz, $J_{\text{vic}} = 5.1$ Hz) and δ 4.3 ($J_{\text{vic}} = 11$ Hz) $\langle 90\text{JHC}143 \rangle$. The corresponding *trans* isomer (**43b**) has H-5 resonances at δ 3.3 ($J_{\text{gem}} = 15$ Hz, $J_{\text{vic}} = 9$ Hz) and δ 3.4 ($J_{\text{vic}} = 3.5$ Hz), and H-8 resonances at δ 4.0 ($J_{\text{gem}} = 11$ Hz, $J_{\text{vic}} = 2.4$ Hz) and δ 4.6 ($J_{\text{vic}} = 4$ Hz). For both isomers, the H-4 methine is a multiplet at around δ 4.8, whilst the H-7 methine is a multiplet at δ 4.15 and 3.8 for the *cis* and *trans* isomers, respectively.

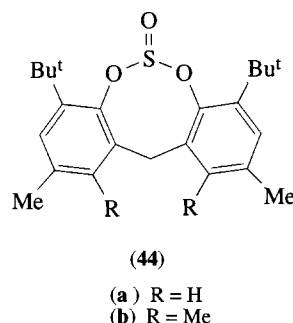
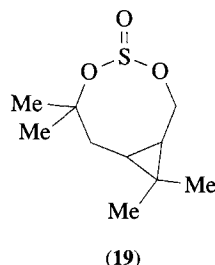


9.25.3.2.7 Dioxathiocins

The spectra of the bicyclo[6.1.0]nonane (**19**), which contains a 1,3,2-dioxathiocin ring, show two double doublets at δ 4.78 ($J = 13.4, 5.4$ Hz) and 3.88 ($J = 13.4, 7.6$ Hz) for the nonequivalent methylene protons adjacent to the oxygen atom $\langle 84\text{JCS}(\text{P}1)887 \rangle$. The two *cis* hydrogens of the cyclopropane ring are seen as two highfield peaks at δ 1.04 and 0.85, whilst the remaining methylene is observed at δ 1.87.

The geminal coupling constants for the bridging methylene protons of the dibenzo[*d,g*] [1,3,2]dioxathiocins (**44**) provide useful information on the conformation of the eight-membered

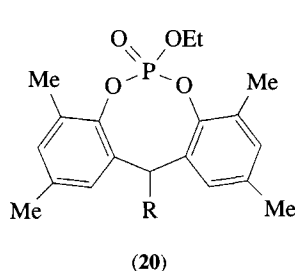
ring, since its value depends strongly on the orientation of the C—H bond relative to the π -orbitals of the two aromatic groups <90HCA618>. The measured experimental value is about 15.5 Hz, which points to a boat conformation, as opposed to the expected values for the boat–chair and boat–boat of 12.5 Hz and twist–boat of 19 Hz.



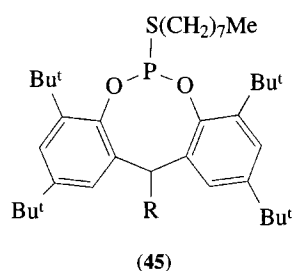
9.25.3.2.8 Dioxaphosphocins

The bridging methylene protons observed in the ^1H NMR spectra of the dibenzo[*d,g*]-[1,3,2]dioxaphosphocin (**20b**) are nonequivalent <88JHC575>. Whilst one proton is seen as a geminal doublet at δ 3.62 ($J = 13$ Hz), the downfield doublet at δ 4.23 is split further into a doublet of doublets due to an additional through-space long-range small heteronuclear coupling to the phosphorus atom ($^5J_{\text{HP}} = 3$ Hz). A similar feature was observed in the proton spectra of the dibenzo[*d,g*][1,3,2]diazaphosphocine (**38**). For the C-12 substituted dioxaphosphocins (**20a,c–e**), which are isolated as *cis* and *trans* isomers relative to the ethoxy group, only the *trans* isomers exhibit heteronuclear coupling between the phosphorus and C-12 methine proton. One explanation for the observations of nonequivalence at C-12 and heteronuclear coupling is the adoption of the heterocyclic eight-membered ring into a noninverting butterfly or tub conformation bringing one of the protons into proximity to the phosphorus atom. Similar nonequivalence for the bridging methylene protons is observed in the spectra of analogous dibenzo[*d,g*][1,3,2]dioxasilocins and boracins.

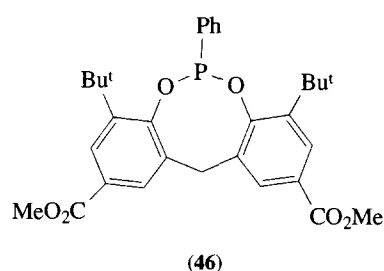
The analogous 6-octylthio- and 6-phenyl-dioxaphosphocins (**45**) and (**46**) also display the same characteristic features for the bridging methylene protons with an upfield doublet at ca. δ 3.5 ($^2J_{\text{HCH}} = 13$ Hz) and a downfield doublet of doublets at ca. δ 4.5 displaying the additional small phosphorus coupling ($^5J_{\text{HP}} = 2\text{--}3$ Hz) <83JHC1311>.



- (a) R = $\text{CH}_2\text{CHMeCH}_2\text{Bu}^t$
(b) R = H, (c) R = Me
(d) R = Et, (e) R = Pr



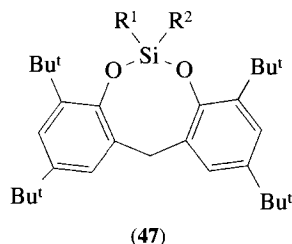
- (a) R = H
(b) R = Me
(c) R = Pr



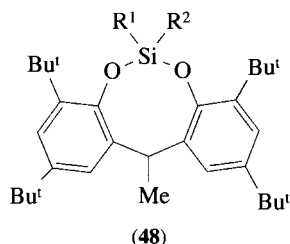
9.25.3.2.9 Dioxasilocins

At room temperature, the proton spectra of dibenzo[*d,g*][1,3,2]dioxasilocins (**47a**) and (**47b**) both show broad singlet resonances for the C-12 bridging methylenes at δ 3.97 and 4.13, respectively <84JOC1297>. On cooling to -31°C , the C-12 methylene signal of (**47b**) separated into a pair of

doublets at δ 3.61 and 4.50 with geminal coupling of 14 Hz. Taken with the nonequivalence of the silicon methyl groups, but equivalence of the two pairs of *t*-butyl groups, the data suggest that below coalescence temperature the ring adopts a noninverting conformation possessing a σ plane of symmetry passing through the C-12 carbon and silicon atoms. The spectra of (47c) and (47d) at room temperature show nonequivalence of their bridging methylenes indicating that at this temperature a single conformational isomer is observed. The spectrum of dibenzodioxasilocin (48b) also appears to be that of a single conformation at room temperature with a quartet at δ 4.82 for the C-12 methine, whereas (48a) was observed as a mixture of two unseparated *cis-trans* diastereoisomers.



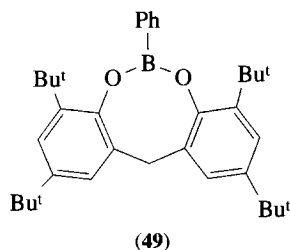
- (a) $R^1, R^2 = H$
- (b) $R^1, R^2 = Me$
- (c) $R^1, R^2 = H, Me$
- (d) $R^1, R^2 = H, Ph$



- (a) $R^1, R^2 = H, Me$
- (b) $R^1, R^2 = Me$

9.25.3.2.10 Dioxaborocins

The proton spectrum of the dibenzo[*d,g*][1,3,2]dioxaboracin (49) was similar to that of the dioxasilocins (47) with the C-12 bridging methylene protons nonequivalent and observed as a pair of doublets at δ 3.51 and 4.27 ($^2J_{HCH} = 14$ Hz) <83JHC1311>. This would indicate that the dioxaboracin also adopts a noninterconverting conformation at room temperature.



9.25.3.2.11 Dithiazocines

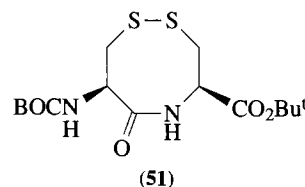
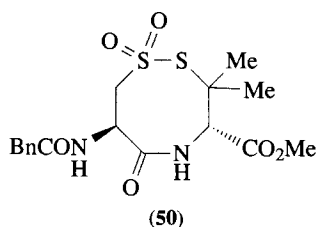
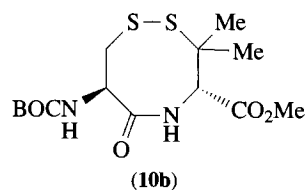
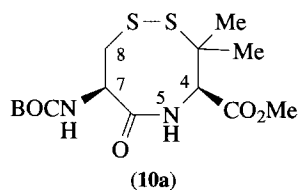
Examination of the proton spectrum of *N*-BOC-*cyclo*-[(*R*)-cysteiny]-(*R*)-penicillamine] (10a) shows that in chloroform solution two conformers are present in a ratio of ca. 92 : 8 <93T9049>. For the dominant conformer, the proton at C-4 is observed at δ 4.68 as a doublet ($J = 12.1$ Hz) coupled to the N-5 proton at δ 6.39, whilst the diastereotopic protons at C-8 are a pair of doublets of doublets at δ 2.88 and 3.01, with geminal coupling of 14.3 Hz and additional splitting of 10.8 and 2.7 Hz, respectively, to the C-7 proton at δ 4.63.

The diastereoisomer *cyclo*-[(*R*)-cysteiny]-(*S*)-penicillamine] (10b), with the opposite configuration at the *C*-terminal amino acid, also displays two conformations in its proton spectrum in a ratio of ca. 95 : 5. The chemical shifts are similar with the C-4 hydrogen assigned to the doublet at δ 4.93 ($J = 11.2$ Hz), the N-5 proton at δ 6.48, doublets of doublets for the diastereotopic C-8 protons at δ 2.92 and 3.30 ($^2J_{HCH} = 14$ Hz), coupled by 11.2 and 5 Hz to the C-7 proton at δ 4.26.

The related sulfone (50) displays a similar proton spectra with oxidation of the sulfur resulting in a deshielding effect of about δ 0.5 for the diastereotopic C-8 protons, which are observed as doublets

of doublets at δ 3.40 and 4.15 ($^2J_{\text{HCH}} = 13.9$ Hz), and the C-7 proton at δ 5.11 ($J = 11.1$ and 5.2 Hz) $\langle 88\text{JCS(P1)365} \rangle$. The C-4 hydrogen is unaltered as a doublet at δ 4.90 ($J = 11.3$ Hz) with the N-5 proton at δ 7.2.

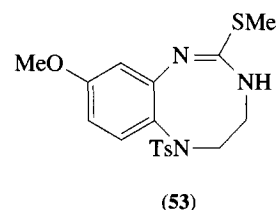
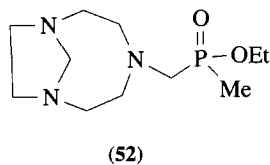
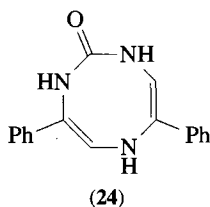
An NMR analysis indicates that *N*-BOC-*cyclo*-[(*R*)-cysteinyl-(*R*)-cysteine] *t*-butyl ester (**51**) exists in chloroform solution as two conformers in a ratio of 7:3, whose spectra suffer from peak broadening. This suggests the two forms are slowly interconverting at room temperature on the NMR time scale $\langle 93\text{T5891} \rangle$. A variable temperature study showed that on cooling to -55°C the peaks become well resolved, whereas at 60°C all the peaks are broad. The proton spectrum of the major conformer at low temperature displays features expected of the 1,2,5-dithiazocine ring. The methylene H-3 protons are observed as a doublet of doublets at δ 3.38 ($^2J_{\text{HCH}} = 13.4$ Hz), coupled to H-4 ($J = 3.7$ Hz), a doublet of triplets at δ 4.78, which itself is coupled ($J = 11.9$ Hz) to the H-5 proton, a doublet at δ 6.96. The H-8 and H-7 protons are multiplets at δ 2.94 and 4.59, respectively.



9.25.3.3 Carbon-13 NMR Spectroscopy

9.25.3.3.1 Triazocines

The 1,3,6-triazocine (**24**) shows a characteristic carbonyl signal at δ 193.0, with the remaining carbons of the eight-membered ring assigned to two signals at δ 155.0 and 133.1 $\langle 93\text{SC2151} \rangle$. The bicyclic aminomethyl phosphinic ester (**52**), containing a saturated 1,3,6-triazocine ring, gives a diagnostic ^{13}C NMR resonance for the NCH_2N carbon at δ 76.2 $\langle 90\text{CC1738} \rangle$. The spectrum of the 1,3,6-benzotriazocine (**53**) shows two close signals at δ 42.0 and 43.7 for the C-4 and C-5 methylene carbons, respectively $\langle 83\text{T1203} \rangle$.

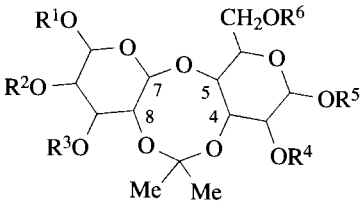


9.25.3.3.2 Trioxocanes

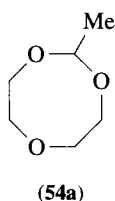
The ^{13}C NMR spectra of disaccharide 3,2'-*O*-isopropylidene acetals (**31**) were assigned through DEPT and heteronuclear correlated experiments (HETCOR and H-H-C RELAYED coherence transfer) and those of the eight-membered ring carbons are shown in Table 7 $\langle 89\text{JCS(P2)1867} \rangle$.

Carbons adjacent to one oxygen (C-4, C-5, and C-8) appear at ca. δ 75, whilst those adjacent to two oxygens (C-2 and C-7) are further deshielded by about δ 30.

Table 7 Carbon-13 NMR spectral data for disaccharide 3,2'-*O*-isopropylidene acetals.

Disaccharides (31)	Substituents	δ (^{13}C)				
		2	4	5	7	8
 (31)	(31a) $\text{R}^1 = \text{Bn}, \text{R}^2 = \text{Bz}, \text{R}^3 = \text{Bn}$ $\text{R}^4 = \text{Bn}, \text{R}^5 = \text{Me}, \text{R}^6 = \text{Bn}$	107.7	77.9	71.9	100.1	71.2
	(31b) $\text{R}^1 = \text{Bn}, \text{R}^2 = \text{H}, \text{R}^3 = \text{Bn}$ $\text{R}^4 = \text{Bn}, \text{R}^5 = \text{Bn}, \text{R}^6 = \text{Bn}$	102.8	78.3	75.9	102.9	68.3
	(31c) $\text{R}^1 = \text{Pr}^i, \text{R}^2 = \text{Pr}^i, \text{R}^3 = \text{Ac}$ $\text{R}^4 = \text{Ac}, \text{R}^5 = \text{Me}, \text{R}^6 = \text{Ac}$	101.3	74.1	79.3	98.5	72.2

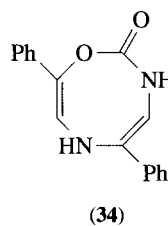
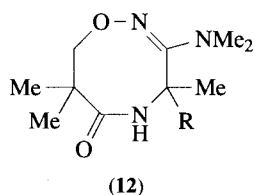
The ^{13}C NMR spectra of various sized crown ether acetals were measured at high concentrations (ca. 50% v/v) in CDCl_3 $\langle 83\text{JCS(P1)453} \rangle$. The signals for the 8-crown 2-methyl-1,3,6-trioxocane (**54a**) with chemical shifts for C-2 at δ 103.85 and those for the other ring carbons at δ 69.66 and 73.06 were deshielded by around δ 3 compared to the other crown acetals due to greater ring strain.



9.25.3.3 Oxadiazocines

Comparison of the carbon spectra of a series of 1,2,5-oxadiazocin-6-ones (**12**) showed similar chemical shifts for the heterocyclic ring including two downfield signals for the C-6 amide and C-3 amidine carbons at ca. δ 175 and 183, respectively $\langle 86\text{HCA298} \rangle$. The two quaternary carbons are observed at δ 43 for C-7 and ca. δ 60–69 for the various substituted C-4, whilst the C-8 methylene appears as a triplet at δ 80.

For the 1,2,6-oxadiazocin-2-one (**34**), the C-2 carbonyl appears at δ 191.2 with the remaining ring carbons attributed to three signals at δ 138.8, 161.1, and 164.5 $\langle 93\text{SC2151} \rangle$.

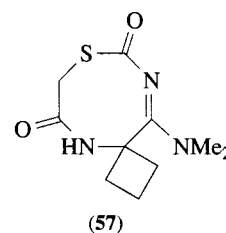
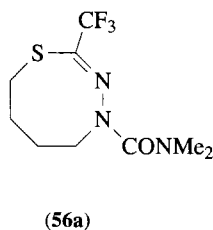
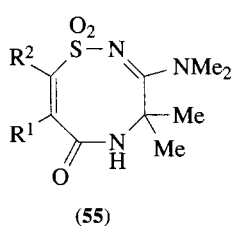


9.25.3.3.4 *Thiadiazocines*

The ^{13}C NMR chemical shift values for the heterocyclic ring of a series of 1,2,5-thiadiazocin-6-ones (**55**) showed two close downfield signals for the C-6 amide and C-3 amidine carbons at ca. δ 175, a quaternary carbon at δ 61 for the CMe_2 , and two alkenic resonances at ca. δ 138 and 150 for the C-7 and C-8 carbons, respectively $\langle 91\text{HCA}1002 \rangle$.

The carbon spectrum of the 1,3,4-thiadiazocine (**56a**) contains a downfield signal for C-2 at δ 122.2 displaying secondary splitting to fluorine with a coupling constant of 36 Hz, with the four methylene carbons at δ 45.0 (C-5), 25.4 (C-6), 30.5 (C-7) and 35.4 (C-8) $\langle 83\text{HCA}2714 \rangle$.

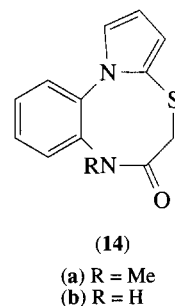
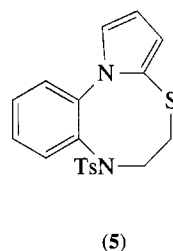
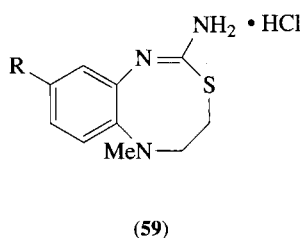
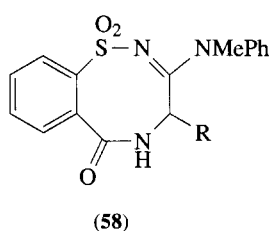
The ^{13}C NMR chemical shift values for the 1,3,6-thiadiazocin-2,7-dione (**57**) showed three downfield signals for the C-2 and C-7 amide and C-4 amidine carbons at δ 166.4, 166.6, and 170.5, a resonance at δ 52.4 for the quaternary spiro carbon, and a triplet for the methylene C-8 at δ 32.8 $\langle 90\text{HCA}1314 \rangle$.



The carbon spectra of a series of 1,2,5-benzothiadiazocin-6-ones (**58**) showed two downfield signals for the C-6 amide and C-3 amidine carbons at ca. δ 164 and 174, respectively; whilst the C-4 methine appears as a doublet at δ 44 $\langle 92\text{HCA}2270 \rangle$.

The ^{13}C NMR spectra of 3,1,6-benzothiadiazocines (**59**) exhibit diagnostic signals at ca. δ 31, 57 and 170 attributed to the $\text{S}-\text{CH}_2$, the $\text{N}-\text{CH}_2$ and the $\text{N}=\text{C}$ carbon atoms, respectively $\langle 85\text{T}2855 \rangle$.

Full assignments of the carbon spectra for the pyrrolo[1,2-*a*][3,1,6]benzothiadiazocines (**5**) and (**14**) were made by selective decoupling and carbon-carbon connectivity (2D-INADEQUATE) experiments, together with examination of carbon-proton shift correlations and long-range coupling constants $\langle 85\text{JHC}423, 92\text{JHC}295 \rangle$. The pyrrolic C-2 carbon resonates at ca. δ 120, the methylene C-4 at δ 36, and the two benzene quaternaries for C-7 and C-8 at ca. δ 138 and 141, respectively. For the pyrrolobenzothiadiazocines (**14**), the C-5 is a carbonyl at ca. δ 168; whereas for the pyrrolobenzothiadiazocine (**5**), the C-5 methylene carbon is seen at δ 54.5.

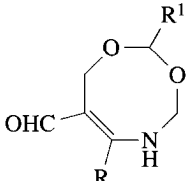
9.25.3.3.5 *Oxadiazocines*

The ^{13}C NMR spectra of a variety of 7-formyl-1,3,5-oxadiazocines have been recorded and representative examples are shown in Table 8. The signals for the methylene carbons of C-2, C-4, and C-8 are observed as triplets; whereas, those of the alkenic carbons of C-6 and C-7 are singlets.

9.25.3.3.6 *Dioxazocines*

A variety of methyl substituted *N*-aryl-1,3,6-dioxazocines have been prepared by Yamada and co-workers and the carbon spectra for representative examples are shown in Table 9 $\langle 91\text{JHC}1369 \rangle$.

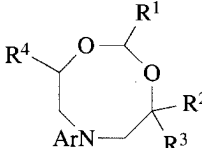
Table 8 Carbon-13 NMR spectral data for 7-formyl-1,3,5-dioxazocines.

1,3,5-Dioxazocine	Substituents	δ (^{13}C)					Ref.
		2	4	6	7	8	
	(39) ^a R = Ph; R ¹ = H	94.7	74.1	110.7	162.8	64.2	84TL2731
	(60) ^b R = 2-ClPh; R ¹ = H	96.6	74.8	112.8	162.4	66.6	90CCCC2502
	(61) ^a R = CO ₂ Me; R ¹ = H	96.2	75.8	153.4	112.6	64.2	87CCC2953
	(62) ^c R = CN; R ¹ = H	94.7	74.3	134.0	118.6	61.7	87CCC1773
	(63) ^d R = Ph; R ¹ = Ph	102.9	73.3	110.9	163.0	63.9	84TL2731

^a Measured in DMSO-*d*₆. ^b Measured in CDCl₃. ^c Measured in acetone-*d*₆.

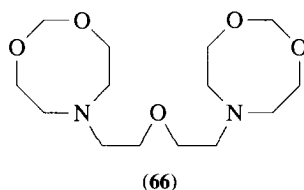
The 1,3,6-dioxazocines containing two asymmetric centers were separated into their *cis* (**41a**), (**64a**) and *trans* (**41b**), (**64b**) diastereoisomers. The *cis* diastereoisomers (**41a**), (**64a**), with the C-4/C-8 methyl groups in a diequatorial relationship, are deshielded by ca. δ 3 compared to their *trans* counterparts (**41b**), (**64b**), whose C-4/C-8 methyl groups are in interconverting axial-equatorial relationships. The upfield shift of the *trans* isomers was accounted for by a γ -gauche relationship between the axial methyl group at either C-4 or C-8 and the C-2 carbon, which does not exist in the diequatorial *trans* isomer.

Table 9 Carbon-13 NMR spectral data for 6-*p*-chlorophenyl-1,3,6-dioxazocines.

1,3,6-Dioxazocine	Substituents	δ (^{13}C)				
		2	4	5	7	8
	(40) R ¹ , R ² , R ³ , R ⁴ = H	97.5	66.4	52.0	52.0	66.4
	(41a) ^a R ¹ , R ² = H; R ³ , R ⁴ = Me	96.5	73.0	59.2	59.2	73.0
	(41b) ^b	93.6	71.3	56.8	56.8	71.3
	(64a) ^c R ² = H; R ¹ , R ³ , R ⁴ = Me	104.9	73.0	59.6	59.6	73.0
	(64b) ^d	98.2	72.9	56.4	56.4	63.7
	(65) R ¹ = H; R ² , R ³ , R ⁴ = Me	89.6	75.8	61.2	61.0	73.4

^a *Cis* isomer with eq-eq methyl groups. ^b *Trans* isomer with ax-eq methyl groups. ^c *Cis* isomer with 2,4,8-trieq methyl groups.^d *Trans* isomer with 2,4-dieq and 8 ax methyl groups.

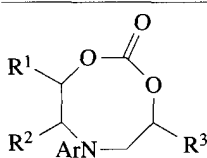
The bis(aza-8-crown-3) (**66**) shows similar resonances in its ^{13}C NMR spectrum for the 1,3,6-oxadiazocine ring, with the acetal methylene peak at δ 97.0, whilst the C-4/C-8 and C-5/C-7 are seen at δ 57.3 and 69.8, respectively <92JOC6112>.



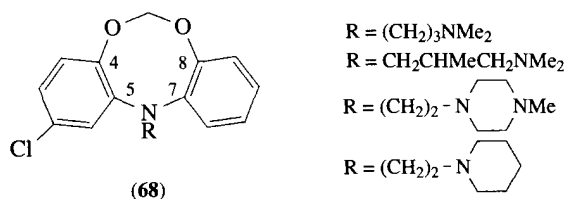
Methyl substituted *N*-aryl-1,3,6-dioxazocin-2-ones have also been studied by Yamada and co-workers and the ^{13}C NMR data for some examples are shown in Table 10. The chemical shifts for the *cis* and *trans* isomers of the 1,3,6-dioxazocin-2-ones (**42**) and (**43**) are similar and do not show the upfield shift seen in the *trans* isomers of their 1,3,6-dioxazocine (**41**) and (**64**) analogues (Table 9). This can be explained by the change in the C-2 acetal carbon being replaced by a carbonyl group removing the γ -gauche relationship between the C-4/C-8 axial methyl and C-2 hydrogen or methyl group discussed earlier.

The assigned resonances for the carbon skeleton of a series of dibenzo[*d,g*][1,3,6]dioxazocines (**68**) were all very similar ($\Delta\delta < 1$) indicating the same conformation in CDCl₃ is maintained in each case <85JST(131)131>. The acetal methylene carbon (OCH₂O) appears at a characteristic δ 95 and the aromatic C-4, C-5, C-7, and C-8 signals were found at ca. δ 148.5, 140.5, 138.0, and 150.5, respectively.

Table 10 Carbon-13 NMR spectral data for 1,3,6-dioxazocin-2-ones.

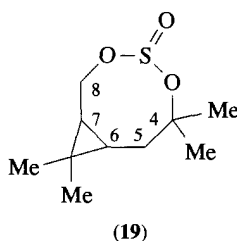
1,3,6-Dioxazocin-2-one	Substituents	δ (^{13}C)					Ref.
		2	4	5	7	8	
	(67) $\text{R}^1, \text{R}^2, \text{R}^3 = \text{H}; \text{Ar} = \text{Tol}$	155.7	68.7	52.1	52.1	68.7	84JHC1145
	(42a) ^a $\text{R}^2 = \text{H}; \text{R}^1, \text{R}^3 = \text{Me}; \text{Ar} = \text{Ph}$	154.8	76.1	58.5	58.5	76.1	84JHC1145
	(42b) ^b	154.0	77.1	58.0	58.0	77.1	
	(43a) ^c $\text{R}^1 = \text{H}; \text{R}^2, \text{R}^3 = \text{Me}; \text{Ar} = \text{Ph}$	155.2	79.9	52.4	53.9	70.5	90JHC143
	(43b) ^d	155.2	77.6	54.8	56.6	74.0	

^a *Cis* isomer with 4/8 eq-eq methyl groups. ^b *Trans* isomer with 4/8 ax-eq methyl groups. ^c *Cis* isomer with 4,7-dieq methyl groups. ^d *Trans* isomer with 4-eq and 7-ax methyl groups.



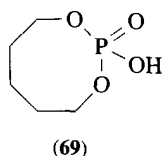
9.25.3.3.7 Dioxathiocins

The spectrum of the bicyclic 1,3,2-dioxathiocin (**19**) shows two deshielded signals for the carbons adjacent to oxygens, one at δ 82.9 for the quaternary C-4 and the other at δ 60.1 for the C-8 methylene. The other methylene at C-5 is seen at δ 36.1 and the two carbons C-6 and C-7 of the cyclopropane ring are at δ 22.1 and 25.4, respectively <84JCS(P1)887>.



9.25.3.3.8 Dioxaphosphocanes

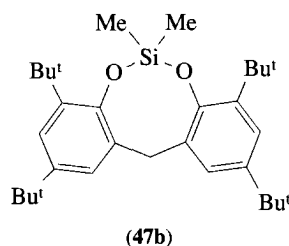
The carbon spectra in CDCl_3 of the dioxaphosphocane (**69**) revealed a small second-order phosphorus-carbon coupling of 5.86 Hz for the C-4/C-8 resonance at δ 68; whilst the C-5/C-7 and C-6 signals are at δ 29 and 23.7, respectively <84S408>.



9.25.3.3.9 Dioxasilocins

When the carbon spectrum of dibenzo[*d,g*][1,3,2]dioxasilocin (**47b**) was recorded at room temperature in CDCl_3 , a single peak at δ 0.4 was observed for the SiMe_2 <84JOC1297>. Upon cooling to -31°C , the dioxasilocin adopts a noninverting conformer possessing a σ plane of symmetry passing

through the methylene carbon and silicon atoms and two nonequivalent methyl carbons are observed at δ 0.4 and 1.6. The resonance for the methylene carbon remains unchanged at both temperatures as a single peak at δ 36.



9.25.3.3.10 Dithiazocines

The diastereoisomeric dipeptides, *N*-protected-*cyclo*-[(*R*)-cysteinyl-(*R*)-penicillamine] (**10a**) and (**70a**) and (*S*)-penicillamine (**10b**) and (**70b**), show similar resonances in their ^{13}C NMR spectra, which are listed in Table 11 <93T9049>.

Table 11 Carbon-13 NMR spectral data for *cyclo*-[(*R*)-cysteinyl-(*R* and *S*)-penicillamines].

<i>Cyclo</i> -[(<i>R</i>)-cysteinyl-(<i>R</i> and <i>S</i>)-penicillamines]		δ (^{13}C)				
		3	4	6	7	8
(10a) R = BOC (70a) R = CF₃CO	(10a)	56.25	52.54	169.46	53.19	41.86
	(10b)	57.12	52.48	167.25	54.30	46.57
	(70a)	56.29	52.43	169.05	52.75	40.65
	(70b)	57.34	52.52	168.44	52.94	45.15

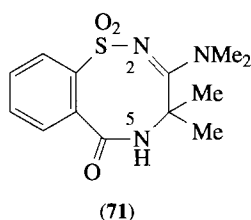
To study conformational changes, both solution and solid-state ^{13}C NMR chemical shifts were obtained for the *N*-BOC-*cyclo*-[(*R*)-cysteinyl-(*R*)-cysteine] *t*-butyl ester (**51**) and are shown in Table 12 <93T5891>. The small differences in the values indicate either that the conformers in both states are comparable or that the chemical shifts are insensitive to changes in conformation.

Table 12 Carbon-13 NMR spectral data for *N*-BOC-*cyclo*-[(*R*)-cysteinyl-(*R*)-cysteine] *t*-butyl ester (**51**).

<i>N</i> -BOC- <i>Cyclo</i> -[(<i>R</i>)-cysteinyl-(<i>R</i>)-cysteine] <i>t</i> -butyl ester (51)		δ (^{13}C)				
		3	4	6	7	8
(51)	Solution state	42.8	52.6	172.2	53.5	42.8
	Solid state	43.5	50.6	173.7	52.1	41.6

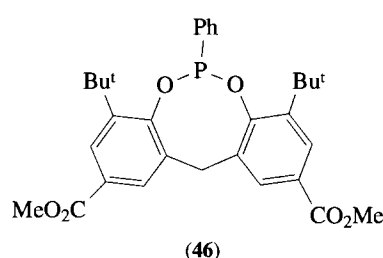
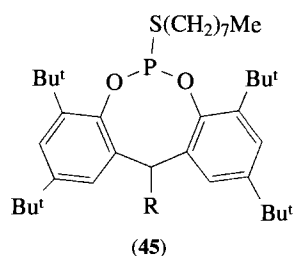
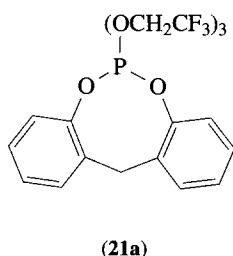
9.25.3.4 Nitrogen-15 NMR Spectroscopy

The ^{15}N NMR of the 1,2,5-benzothiadiazocin-6-one (**71**) was recorded in DMSO- d_6 and Cr(acac)₃ (the reference CH₃NO₂ was set to δ 0) and by means of ^{15}N labeling at N-5 it was determined that the N-5 nitrogen resonates at δ -239.6 as a doublet ($^1J_{\text{NH}}$ = 89 Hz), whilst the N-2 signal is a singlet at δ -189.5 <88HCA521>.



9.25.3.5 Phosphorus-31 NMR Spectroscopy

The ^{31}P NMR spectrum of the dibenzo[1,3,2]dioxaphosphocin (**21a**) was obtained by setting triphenyl phosphate at $\delta -18$ and referenced to 85% H_3PO_4 . It shows the phosphorus resonating upfield at $\delta -78.33$ in CDCl_3 $\langle 92\text{IC1913} \rangle$. The phosphorus resonances of 6-octylthio- and 6-phenyldioxaphosphocins (**45**) and (**46**) were also recorded relative to 85% H_3PO_4 and were found downfield from the standard at $\delta 170.21$, 169.2 , and 169.6 for (**45a-c**) and $\delta 166.8$ for (**46**) $\langle 83\text{JHC1311} \rangle$.

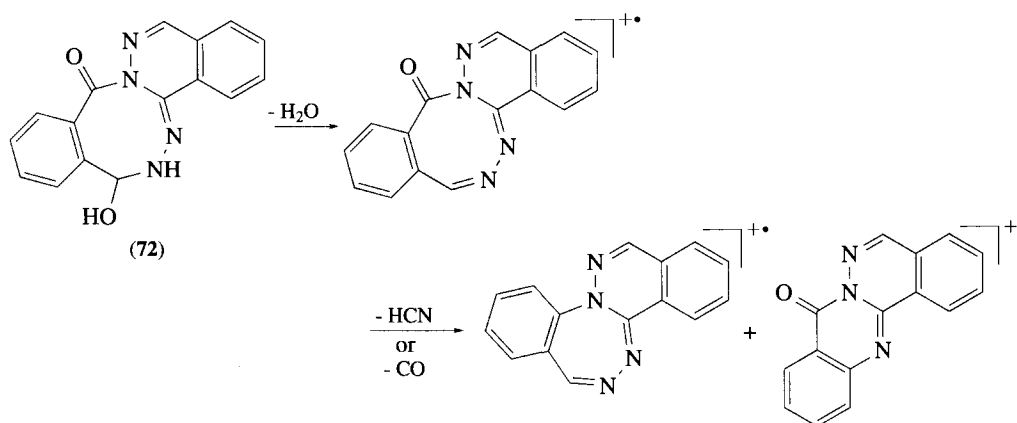


- (a) $\text{R} = \text{H}$,
 (b) $\text{R} = \text{Me}$,
 (c) $\text{R} = \text{Pr}$,

9.25.3.6 Mass Spectroscopy

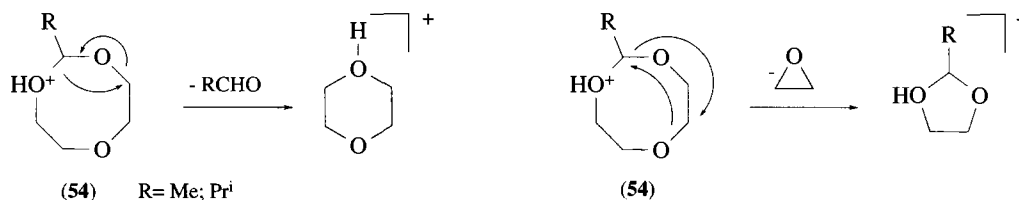
9.25.3.6.1 Triazocines

The mass spectra of 1,3,6-triazocin-2-one (**24**) $\langle 93\text{SC2151} \rangle$, the pyrimido[1,6-*a*][1,3,6]triazocine (**25**) $\langle 92\text{PHA186} \rangle$, and the bicyclic aminomethyl phosphinic ester (**52**) $\langle 90\text{CC1738} \rangle$ are reported to show molecular ion (M) $^+$ or ($M+1$) $^+$ peaks by either electron impact (EI) or chemical ionization (CI) techniques. The highest molecular ion observed in the mass spectrum of the phthalazino[1,2-*d*][2,3,5]benzotriazocine (**72**) corresponds to loss of H_2O , which is followed by extrusion of HCN and CO as shown in Scheme 2 $\langle 81\text{JHC1625} \rangle$.



9.25.3.6.2 Trioxocanes

Isobutane chemical ionization mass spectra of the 8-crown ether acetals (**54**) gave rise to prominent $(M+1)^+$ ions, which undergo elimination of an aldehyde or oxirane as shown in Scheme 3 <83OMS(18)402>.



Scheme 3

9.25.3.6.3 Oxadiazocines

1,2,5-Oxadiazocin-6-ones (**12**) show only small molecular ions ($\leq 1\%$) in their mass spectra <86HCA298>, whereas the 1,2,6-oxadiazocin-7-ones (**32**) display molecular ions with 16–38% relative intensity <84LA1696>. The macrocyclic thiourea (**73**) was reported to show a peak at m/z 86 characteristic of this class of compounds <84MI 925-01> and the simultaneous evaporation of (**74**) with either iron or cobalt acetylacetonates leads to observation of an ion–molecule cationic complex in the MS resulting from preferential attack of the metal ion at the thiourea fragment <91OMS(26)746>. The molecular ion of the *N*-methylated analogue (**74**) can be seen in its mass spectrum <84SI36>.



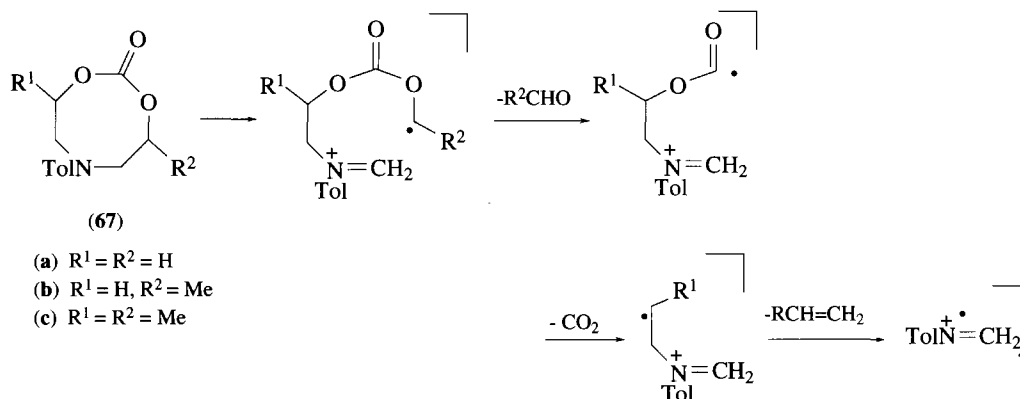
9.25.3.6.4 Thiadiazocines

The 1,2,5-thiadiazocin-6-ones (**55**) <91HCA1002> and 2-thioxo-1,3,6-thiadiazocin-5-ones (**36**) <90SC2675> are reported to show $(M+1)^+$ and $(M)^+$ ions by CI and EI mass spectroscopy, respectively. The 1,2,5-benzothiadiazocin-6-one (**58**) showed an ion corresponding to $(M+1)^+$ in its CI mass spectrum with the base peak resulting from loss of SO₂ <92HCA2270>. The fragmentation of the molecular ion of pyrrolo[1,2-*a*][3,1,6]benzothiazocine (**14a**) occurred via rupture of the eight-membered ring with loss of CHO, COCH₂, and CHOCH₂ from the parent <85JHC423, 87JHC1157>.

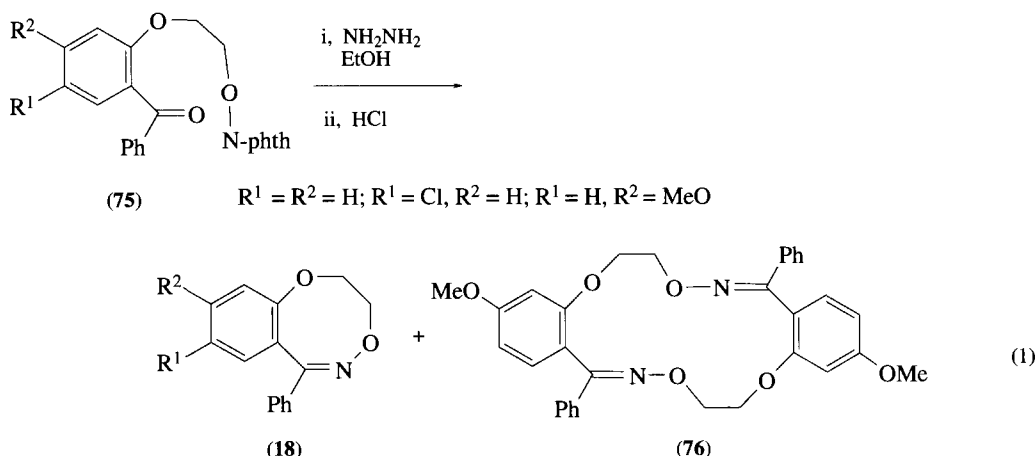
9.25.3.6.5 Dioxazocines

The major fragmentation pathway in the mass spectra of a series of methyl substituted 6-(*p*-tolyl)-1,3,6-dioxazocin-2-ones (**67**) was determined by Yamada *et al.* by metastable ion measurements <85JHC445>. As shown in Scheme 4, α -cleavage of one of the C—C bonds in the heterocyclic ring, followed by loss of aldehyde from the resulting ion, leads to the first fragment observed. Subsequent loss of CO₂ and then an alkene leads to the iminium ion corresponding to the base peak at m/e 119 common to all three dioxazocin-2-ones. The unsymmetrically substituted dioxazocin-2-one (**67b**) has two fragmentation pathways resulting from cleavage of either C—C bond. Cleavage of the C—CMe bond is favored since this leads to a more stable secondary radical (R¹ = H, R² = Me) compared to the primary radical (R¹ = Me, R² = H) (Scheme 4). This was confirmed in the mass

spectra as the peak corresponding to loss of acetaldehyde at m/e 191 was four-fold larger than that at m/e 205 resulting from loss of formaldehyde.



Mass spectrometry analysis of the 1,4,5-benzodioxazocines (**18**) obtained by cyclization of amino ketones (**75**) (Equation (1)) was used to screen for the possible presence of small amounts of cyclic dimer impurities known to contaminate similar cyclizations by competition of the intramolecular route with an intermolecular one <83AJC2555>. In one case, a trace amount of a by-product with a molecular weight of 538 was detected, which by high resolution mass spectrometry was assigned the 16-membered ring structure (**76**).

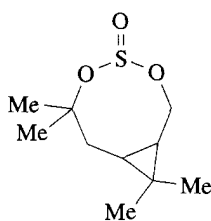


9.25.3.6.6 Dioxathiocins

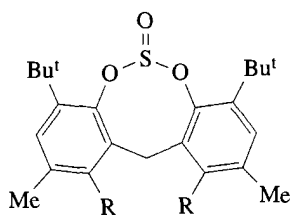
The 1,3,2-dioxathiocin *S*-oxide (**19**) fragments readily, showing only a very small (0.2%) molecular ion ($M+1$)⁺ peak in its CI mass spectrum and the loss of SO₃H constituting the base peak <84JCS(P1)887>. The dibenzo[*d,g*][1,3,2]-dioxathiocin *S*-oxides (**44**) display molecular ions and fragments due to loss of SO and SO₂ <90HCA618>. Although the dibenzodioxathiocin (**77**) also exhibits a molecular ion peak, the fragmentation occurs in a different fashion showing an ($M-28$)⁺ peak attributed to loss of CO.

9.25.3.6.7 Dioxaphosphocins

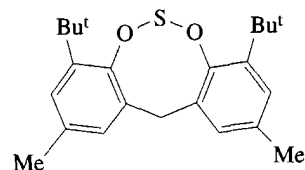
The mass spectra of the dibenzo[1,3,2]dioxaphosphocins (**20**) are extremely useful as they can be used to assign the configuration of each pair of isomers which can be separated with the ethoxy group either *cis* or *trans* to the alkyl group <88JHC575>. Both diastereoisomers of the dioxaphosphocin (**20a**), whose stereochemistry was unambiguously assigned from their x-ray structures, gave EI mass



(19)

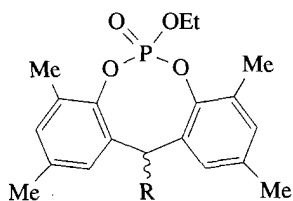


(44)

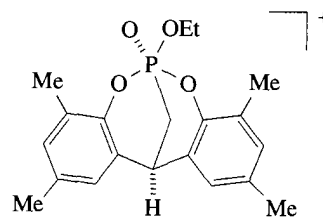


(77)

spectra with prominent molecular ion peaks, followed by weak fragmentations from loss of the alkyl radicals CH_3 , C_4H_9 , C_5H_{11} , and C_6H_{13} . The two isomers also displayed large peaks due to cleavage of the C_8H_{17} side chain, followed by loss of ethylene to give the base peak. However, the *cis* isomer exhibits a greatly enhanced propensity to eliminate the C_7H_{15} radical compared to its *trans* isomer, which can be rationalized to occur via a novel transannular cyclization of the terminal methylene radical in the side chain with the phosphorus atom to form the heterocyclic fragment (78). This formation is favored with the *cis* stereochemistry, but blocked in the *trans* isomer by the phosphorus oxygen. The assignment of other pairs of isomers in this series (20c–e) can be determined from their mass spectra using this rationale.



(20)



(78)

- (a) $\text{R} = \text{CH}_2\text{CHMeCH}_2\text{Bu}^t$
- (b) $\text{R} = \text{H}$,
- (c) $\text{R} = \text{Me}$,
- (d) $\text{R} = \text{Et}$,
- (e) $\text{R} = \text{Pr}$,

9.25.3.6.8 Dithiazocines

Molecular ions in the mass spectrum of the *cyclo*-[(*R*)-cysteinyl-(*R* and *S*)-penicillamine] (10) diastereoisomers were observed using both FAB and CI techniques (93T9049). The EI spectrum of the sulfone (50) shows fragments resulting from loss of O_2 and SO_2H .

9.25.3.7 UV Spectroscopy

The nonaromatic eight-membered rings absorb little in the accessible regions of the UV spectrum. Table 13 gives some data on reported spectra for heterocycles whose absorptions are due to either fused aromatic rings, aromatic substituents or carbonyl bonds.

9.25.3.8 IR Spectroscopy

In general, the IR absorption frequencies for the various eight-membered heterocycles are ill-defined, although detailed listings of the vibrational frequencies of 1,3,6-trioxocane and those of a

Table 13 UV spectral maxima of eight-membered heterocycles with three heteroatoms.

Heterocycle	λ_{max} (nm)(log ϵ)	Solvent	Ref.
1,4,5-Benzotriazocine (29)	266 (4.38)	<i>i</i> -propananol	73CPB2375
1,2,6-Oxadiazocin-7-one (32a)	239 (4.0)	ethanol	84LA1696
11-Methyl-1,3,6-oxadiazocino[3,4,5- <i>g,h</i>]purine (138)	284.5 (4.1)	methanol	84JHC333
Imidazo[4,5- <i>f</i>]pyrido[2,1- <i>b</i>][1,3,5]oxadiazocine-5,12-dione (85)	260 (4.09)		82CPB3088
6-Phenyl-7-formyl-1,3,5-dioxazocine (39)	296 (4.16)	methanol	84TL2731
2-Ethyl-6-phenyl-7-formyl-1,3,5-dioxazocine	236 (2.93)	methanol	86CCC2158
	299 (3.06)		
6-Cyano-7-formyl-1,3,5-dioxazocine (62)	302 (2.72)	methanol	87CCC1773
2-(4-Nitrophenoxy)-1,3,2-dioxaphosphocane-2-oxide	272	water/dioxin (55:45)	82JOC1741

1,3,5-trithiocane are provided by Dorofeeva <92MI 925-01> and Edema *et al.* <92T8065>, respectively. The characteristic absorption bands for various functional groups, such as NH, C=O, C=N, SO₂ and SiH with distinctive stretching frequencies, are listed in Table 14.

Table 14 IR absorptions of eight-membered heterocycles with three heteroatoms.

Heterocycle	Stretching frequencies (cm ⁻¹)			Ref.
	N—H	C=O ^a	C=N and/or C=C ^a	
1,3,6-Triazocin-2-one (24)	3300–3200, 3100	1690	1600	93SC2151
1,3,6-Benzotriazocin-2-one (116)	3280	1695		83T1199
1,4,5-Benzotriazocin-2-one (26)	3280	1665	1630, 1600	83M1231
1,2,5-Pyridinotriazocin-6-one (30)	3320	1670	1630	85PJC1115
1,2,5-Oxadiazocin-6-one (12)	3410, 3040–2800	1692	1510	86HCA298
1,2,6-Oxadiazocin-7-one (32)		1635	1605	84LA1696
1,3,6-Oxadiazocin-2-one (34)	3400, 3080, 2960	1750	1610	93SC2151
3,1,6-Benzoxadiazocine (104)			1700	83T479
Imidazo[4,5- <i>f</i>]pyrido[2,1- <i>b</i>][1,3,5]-oxadiazocine-5,12-dione (85)		1710, 1685		82CPB3088
1,2,5-Thiadiazocin-6-one (55)	3355, 2995	1680	1565, 1555	91HCA1002
2-Thioxo-1,3,6-thiadiazocin-5-one (36)	3216	1745		90SC2675
1,3,6-Thiadiazocin-2,7-dione (57)	3170, 3045	1650, 1575	1505	90HCA1314
1,2,5-Benzothiadiazocin-6-one (58)	3300	1665	1550, 1535	92HAC2270
2-Amino[3,1,6]benzothiadiazocine (37)	3520, 3400			83T1203
Dibenzo[<i>b,g</i>][1,4,6]thiadiazocine <i>S,S</i> -dioxide (148)	3320	1690	1330, 1150 (SO ₂)	86JOC1967
Pyrrolo[3,1,6]benzothiadiazocin-5-one (14)	3440, 3360	1720		87JHC1157
Pyrrolo[3,1,6]benzothiadiazocine <i>S</i> -oxide (87)		1655		85JHC423
Pyrrolo[3,1,6]benzothiadiazocine <i>S,S</i> -dioxide (88)		1670	1315, 1120 (SO ₂)	85JHC423
Dibenzo[<i>c,g</i>][1,2,6]thiadiazocine (89)	3220		1620	83T2073
Dibenzo[<i>d,g</i>][1,3,2]diazaphosphocine (15a)		1270 (P=O)	547 (P—Cl)	87MI 925-03
Dibenzo[<i>d,g</i>][1,3,2]diazaphosphocine (16)		790 (P=S)	525 (P—Cl)	87MI 925-03
1,3,6-Dioxazocine (41)			1580, 1500	83JHC479
1,3,6-Dioxazocin-2-one (43)		1748	1600, 1500	90JHC143
1,4,5-Benzodioxazocine (18)			1600	83AJC2555
1,3,2-Dioxathiocin (19)		1200 (S=O)		84JCS(P1)887
Dibenzo[<i>d,g</i>][1,3,2]dioxaphosphocin (46)		1720		83JHC1311
Dibenzo[<i>d,g</i>][1,3,2]dioxasilocin (47)			2200 (SiH)	84JOC1297
1,2,5-Dithiazocine (10)	3423	1742, 1703, 1668		93T9049
1,2,5-Dithiazocine <i>S,S</i> -dioxide (50)	3280	1755, 1700	1655	88JCS(P1)365

^aUnless otherwise stated.

9.25.4 THERMODYNAMIC ASPECTS

9.25.4.1 Conformations

Eight-membered rings have four low-energy conformational families, consisting of the boat–chair (boat–chair, twist–boat–chair), crown (twist–chair–chair, crown, chair–chair), boat (boat–boat,

twist-boat and boat), and chair (chair, twist-chair) forms (Figure 1). Heterocycles with three heteroatoms follow similar structural properties with the boat-chair configuration generally the most stable.

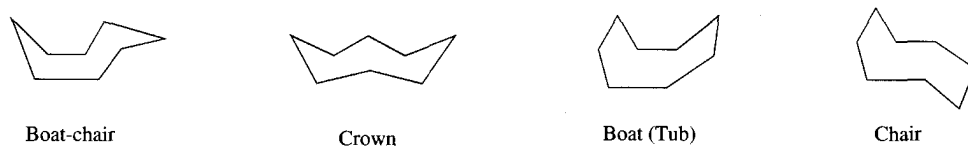
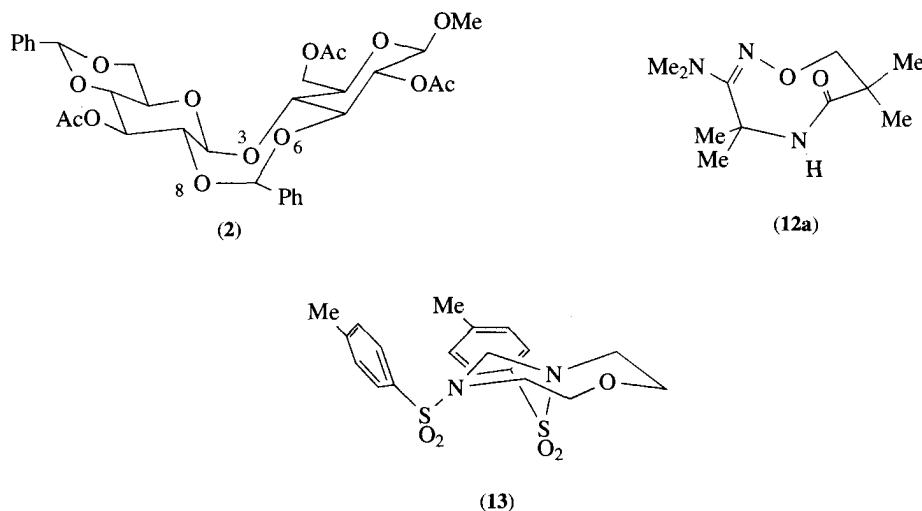


Figure 1 Conformational families.

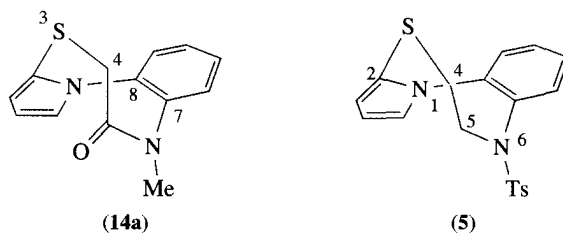
9.25.4.1.1 Solid-state conformations

Solid-state conformations are determined by x-ray crystallography. Bond lengths and angles for the heterocycles discussed are listed in Tables 3 and 4.

The trioxocane ring of the disaccharide (**2**) adopts a boat-chair configuration with an unusual 3,6,8-positioning of the heteroatoms due to the flanking glucopyranose rings, and a concave sickle shape, as viewed from above $\langle 80\text{JCR}(\text{S})190 \rangle$. The 1,2,5-oxadiazocin-6-one (**12a**) crystallizes with a *trans* configuration about the amide bond $\langle 86\text{HCA}298 \rangle$, similar to that seen for the 1,2,5-dithiazocin-6-one (**11**). The *cis* amide configuration in such heterocycles is disfavored since the presence of the C-7 *gem*-dimethyl group leads to high bending strains between amide and C(7)—C(8)—O(1) bonds. *N,N*-Ditosyl-1,4,6-oxadiazocine (**13**) is pseudosymmetric and in a crown conformation, with both nitrogen atoms sp^2 hybridized and a mean value for the torsion angles in the heterocyclic ring of $87.2^\circ \langle 87\text{AX}(\text{C})2167 \rangle$.



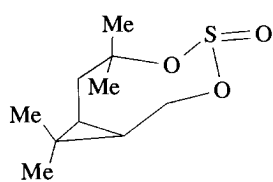
The pyrrolo[1,2-*a*][3,1,6]benzothiadiazocin-5-one (**14a**) has a slightly twisted boat configuration with the atoms S-3, C-4, C-7, and C-8 approximately co-planar $\langle 92\text{JHC}295 \rangle$. Further deviation from the boat conformation is observed in *N*-tosyl-benzothiadiazocine (**5**) by rotation around the bond C(4)—C(5), which results in atoms N-1, C-2, C-4, C-5, and N-6 being almost co-planar.



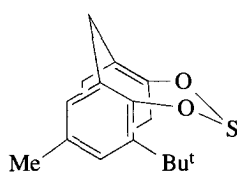
The dibenzo[*d,g*][1,3,2]diazaphosphocines (**15a**) and (**16**), whose eight-membered rings are boat-like, contain sp^2 hybridized nitrogens in trigonal planes that are twisted by between 58 and 68°

from the phenyl rings, thus strongly reducing nitrogen lone-pair delocalization into the aromatic rings <86PS(26)185>.

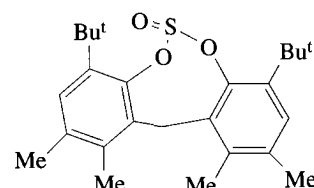
The 1,3,2-dioxathiocin (**19**) is in an approximate boat-chair conformation with both the *trans* sulfoxide and the cyclopropane ring in equatorial positions <84JCS(P1)887>. The condensed cyclopropane ring distorts the conformation of the sulfite ring in such a way that it resembles that of *cis*-cyclooctene. The preference for the sulfoxide group to be equatorial contrasts with the axial conformation normally observed in six- and seven-membered ring sulfites. Dibenzo[*d,g*][1,3,2]-dioxathiocin (**77**) adopts a boat-chair conformation similar to the dibenzo[*d,g*][1,3,2]dioxaphosphocins (**20a**) and (**21b**) with a C_s plane of symmetry passing through the sulfur atom and methylene group; whereas interaction between the methyl groups *ortho* to the methylene bridge of the dioxathiocin *S*-oxide (**44b**) forces the ring into an asymmetric boat form with the exocyclic oxygen in a pseudoaxial position <90HCA618>.



(19)

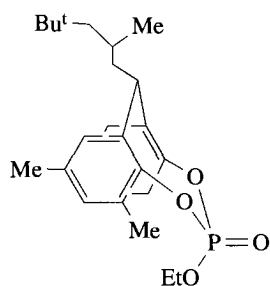
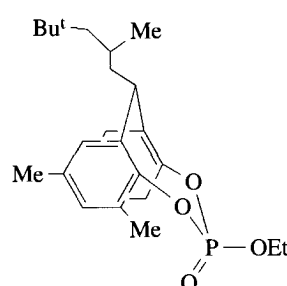
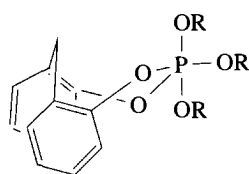


(77)

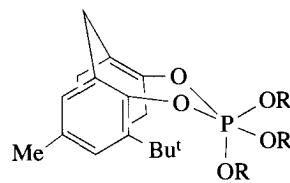


(44b)

Two isomers of the dibenzo[*d,g*][1,3,2]dioxaphosphocin oxide (**20a**) are formed with the ethoxy group either *cis* or *trans* to the bulky alkyl group at the bridging carbon, both isomers adopting a boat-chair conformation with the bulky alkyl group residing in the pseudoequatorial position <88JHC575>. In the case of the *cis* isomer, the bulky pseudoaxial ethoxy group, relative to the phosphoryl oxygen, causes a slight flattening of the eight-membered heterocycle. The dibenzo[*d,g*][1,3,2]dioxaphosphocin (**21a**) can be viewed as a very twisted boat or distorted tub with the atoms O-3, C-4, C-7, and C-8 coplanar, whereas for the *ortho* and *para* substituted analog (**21b**), a boat-chair conformation is adopted <92IC1913>.

(20a *cis*)(20a *trans*)R = OCH₂CF₃

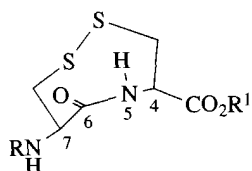
(21a)

R = OCH₂CF₃

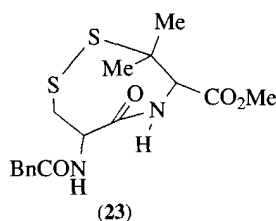
(21b)

The *cyclo*-[L-cysteinyl-L-cysteine] dipeptide (**9**), a 1,2,5-thiadiazocine, has a crystal structure with the peptide group adopting a slightly twisted *cis* conformation (torsion angle -7°), a right-handed disulfide bridge (torsion angle 94°) and the atoms C-4, N-5, C-6, and C-7 approximately co-planar <77AX(B)2080>. The *N*-BOC-[L-cysteinyl-L-cysteine] methyl ester (**22**) adopts a slightly more twisted conformation with torsion angles for the peptide and disulfide bonds of -10.8° and 95.7° ,

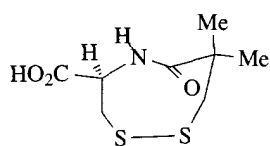
respectively $\langle 77\text{AX(B)3561} \rangle$. [L-Cysteinyl-D-penicillamine] methyl ester (**23**) crystallizes with two independent molecules in the asymmetric unit, both having *trans* amide bonds (torsion angles of -107.7° and 105.0°) and right-handed helicities for the disulfide bonds (torsion angles of -27.1° and -31.6°) $\langle 88\text{JCS(P1)365} \rangle$. (4*R*)-7,7-Dimethyl-1,2,5-dithiazocan-6-one also adopts two configurations (**11a,b**) in the crystal unit, both having *trans* amide bonds (torsion angles of -150.3° and 150.5°), but opposite helicities for the disulfide bonds (torsion angles of 86.3° and -102.4°) $\langle 92\text{JCR(M)735} \rangle$.



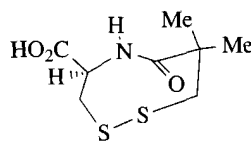
(9) $R, R^1 = \text{H}$
(22) $R = t\text{-BOC}, R^1 = \text{Me}$



(23)



(11a)

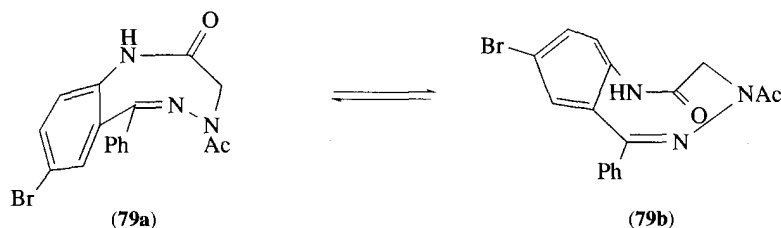


(11b)

9.25.4.1.2 Solution conformations

Conformational mobility is often observed for eight-membered heterocycles in solution with ring inversion resulting in equatorial-axial interchanges, the boat-chair form again being predominant.

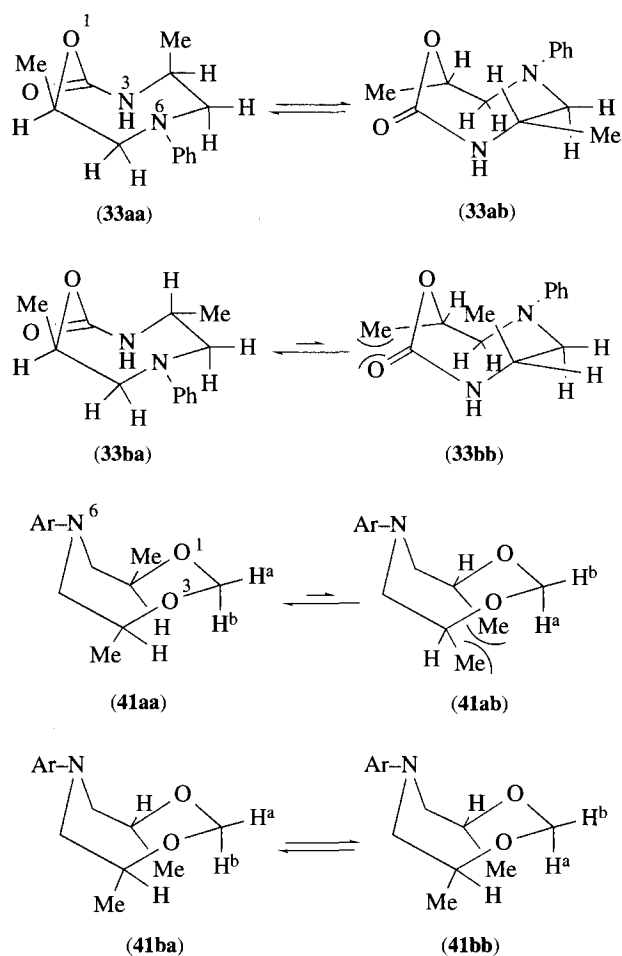
The 6-phenyl-1,4,5-benzotriazocine (**79**) undergoes ring inversion between (**79a**) and (**79b**) in DMSO with $\Delta G = 85 \text{ kJ mol}^{-1}$ as determined by dynamic ^1H NMR studies $\langle 84\text{KGS552} \rangle$.



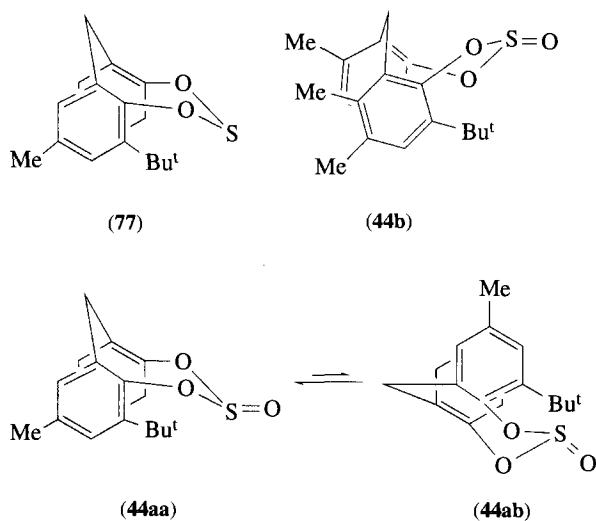
Solution conformational studies on the *cis* and *trans* isomers of 1,3,6-oxadiazocin-2-one (**33a,b**) were carried out by Yamada *et al.* involving measurement of aromatic solvent-induced shift (ASIS) and Eu-shift differences in their proton spectra $\langle 92\text{JHC1529} \rangle$. Both rings were determined to adopt 1,3,6-boat-chair conformations with the carbonyl carbon at the BC-2 position; the *cis* isomer equilibrates between the two interconverting forms (**33aa**) and (**33ab**), whereas the *trans* isomer exists solely as (**33ba**) since a *syn*-1,3 diaxial interaction between the axial methyl at the C-8 and the carbonyl group disfavors (**33bb**).

A similar study on the solution conformations of the isomers of 4,8-dimethyl-1,3,6-dioxazocine (**41**) was carried out by Yamada *et al.* and again the heterocycles were found to exist in boat-chair configurations with the nitrogen residing at the BC-1 position $\langle 91\text{JHC1369} \rangle$. In this case, the *trans* isomer equilibrates between two interconverting axial-equatorial forms (**41ba**) and (**41bb**), whereas the *cis* isomer exists solely in the diequatorial form (**41aa**) as a nonbonded interaction between 4,8-diaxial methyl groups disfavors the diaxial isomer (**41ab**). The 4,8-dimethyl-1,3,6-dioxazocin-2-one (**42**) also adopts similar boat-chair conformations in solution with the *cis* isomer existing in a diequatorial form and the *trans* isomer an axial-equatorial form $\langle 84\text{JHC1145} \rangle$.

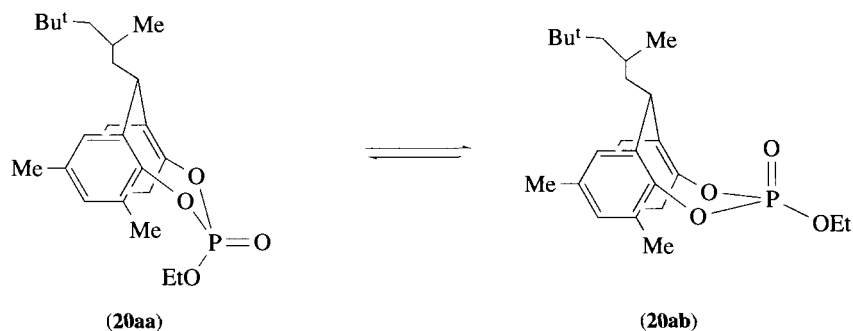
The NMR-derived solution conformations of the pyrrolo[3,1,6]benzothiadiazocines (**14a**) and (**5**), showed only slight deviations from those determined by x-ray crystallography for the solid state and are assumed to arise from the distortions in the boat conformation predicted by molecular dynamics calculations as discussed in Section 9.25.2.3 $\langle 92\text{JHC295} \rangle$.



^1H NMR indicates that the dibenzo[*d,g*][1,3,2]-dioxathiocin (**77**) possesses a boat-chair conformation in solution as it does in the solid state; however, due to the extra methyl groups, the dioxathiocin *S*-oxide (**44b**) adopts a boat form <90HCA618>. By comparison, the dioxathiocin *S*-oxide (**44a**) exists in equilibrium in solution between the equatorial-oxygen boat-chair (**44aa**) and axial boat-chair (**44ab**) conformers, which interchange through ring inversion with the equatorial form predominant.



Another equilibrium observed in solution is that for the *cis* isomer of dibenzo[*d,g*][1,3,2]-dioxaphosphocin (**20a**), which interchanges between the boat–chair conformation (**20aa**), observed in the solid state, and that of mobile boat forms such as (**20ab**) <88JHC575>. The dibenzo[*d,g*][1,3,2]-dioxasilocin (**47b**), existing either as a boat–chair or boat–boat conformation in solution, possesses a high activation energy for ring inversion ($\Delta G^\ddagger = 13.9 \text{ kJ mol}^{-1}$) as determined by variable temperature NMR <84JOC1297>.

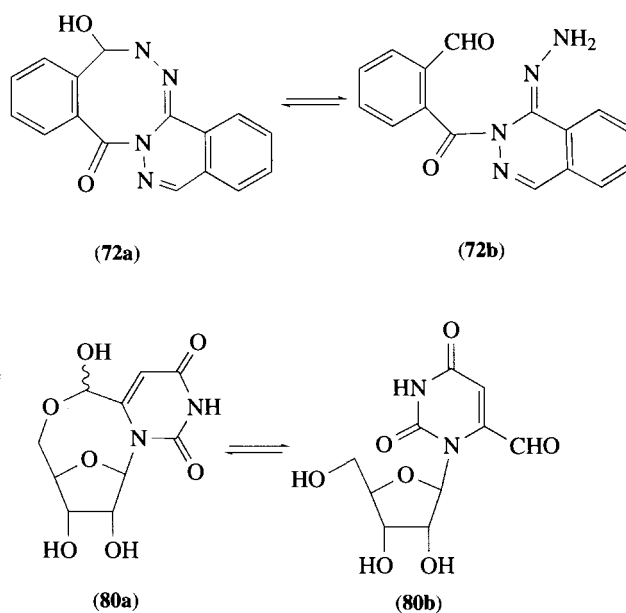


9.25.4.1.3 Theoretical conformations

In addition to x-ray crystallography and NMR solution techniques, molecular orbital and molecular mechanical calculations can be used to predict the conformational preferences of eight-membered rings. Relevant examples are discussed in Section 9.25.2.

9.25.4.2 Tautomerism

An example where ring-chain tautomerism occurs is the phthalazino[1,2-*d*][2,3,5]benzotriazocine (**72a**), which exists in equilibrium with the open-chain 2-(2-formylbenzoyl)phthalazine (**72b**) <81JHC1625>. The IR spectrum with only a weak signal for the aldehyde indicates the hemiacetal (**72a**) is the major component in the solid state; although the reverse is true in solution as the ¹H NMR spectrum in DMSO shows only aromatic and aldehyde signals corresponding to (**72b**). A similar example is the nucleoside (**80b**), which shows a strong proclivity towards existing as the 5'-cyclic hemiacetal (**80a**), 91% in DMSO solution and exclusively in the solid state <93JOC4054>.

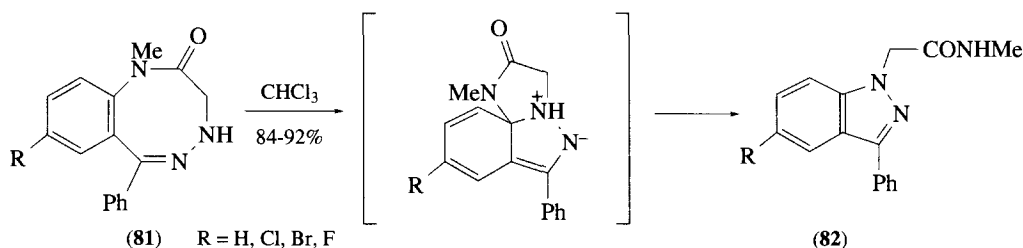


9.25.5 REACTIVITY OF NONCONJUGATED RINGS

Reports on reactivity of these eight-membered heterocycles are fairly limited and are predominantly reactions involving ring contraction, thermolysis or hydrolysis, alkylations at cyclic amides, and oxidation of ring sulfur atoms.

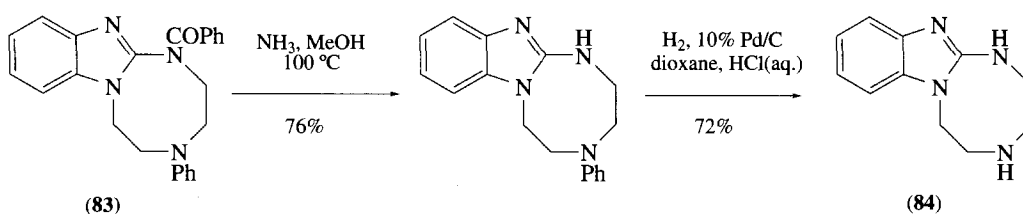
9.25.5.1 Triazocines

1-Methyl-6-phenyl-1,4,5-benzotriazocin-2-ones (**81**) readily undergo ring contraction to give 3-phenylindazole-1-acetamides (**82**) on standing as solutions in chloroform at room temperature <84CPB3252>. The ring transformation can be reasonably rationalized to occur via the spiro-type intermediate shown in Scheme 5. Other reactions of the heterocycle (**81**) include alkylations at the 4-nitrogen with alkyl halides <83KGS411> and reduction of 4-methyl-6-phenyl-1,4,5-benzotriazocin-2-one to the 1,4,5-benzotriazocine with LAH in 77% yield <79CPB2084>.



Scheme 5

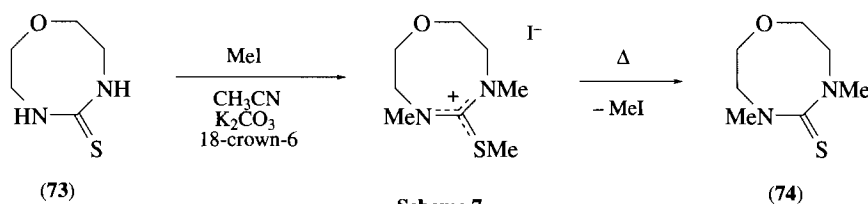
The 1,3,6-triazocino[1,2-*a*]benzimidazole (**83**) can be deprotected by heating with ammonia in a steel bomb and subsequent hydrogenation yields the parent heterocycle (**84**), as outlined in Scheme 6 <92JMC705>.



Scheme 6

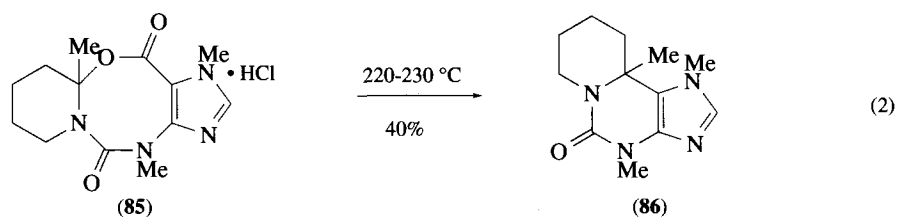
9.25.5.2 Oxadiazocines

The cyclic urea, 1,4,6-oxadiazocin-2-thione (**73**), can be methylated by treatment with methyl iodide either neat or in acetonitrile with potassium carbonate and 18-crown-6 <84S136>. The initially formed thiuronium salt undergoes thermolysis at 200°C to eliminate methyl iodide and yield the thiourea (**74**) in 60% overall yield (Scheme 7).



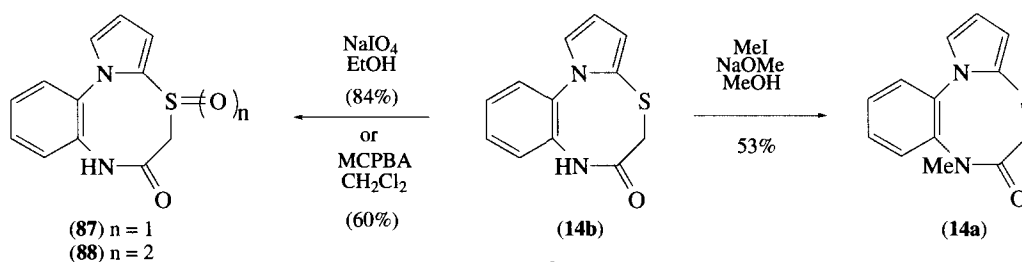
Scheme 7

Fusion of imidazo[4,5-*f*]pyrido[2,1-*b*][1,3,5]oxadiazocine-5,12-dione (**85**) at 220 – 230°C results in ring contraction with elimination of carbon dioxide to produce the pyrido[2,1-*f*]purine (**86**), as shown in Equation (2) <82CPB3088>.



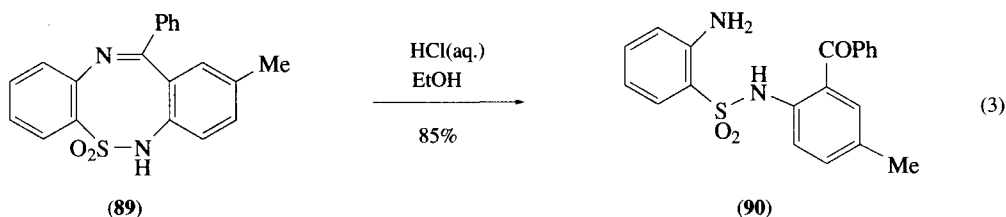
9.25.5.3 Thiadiazocines

N-Methylation of pyrrolo[1,2-*a*][3,1,6]benzothiadiazocine (**14b**) occurred under standard conditions to give (**14a**) in a moderate yield (Scheme 8) <85JHC423>. The heterocycle was stable to oxidation and thus the corresponding sulfoxide (**87**) could be obtained by oxidation with sodium metaperiodate and the sulfone (**88**) by oxidation with excess of MCPBA.



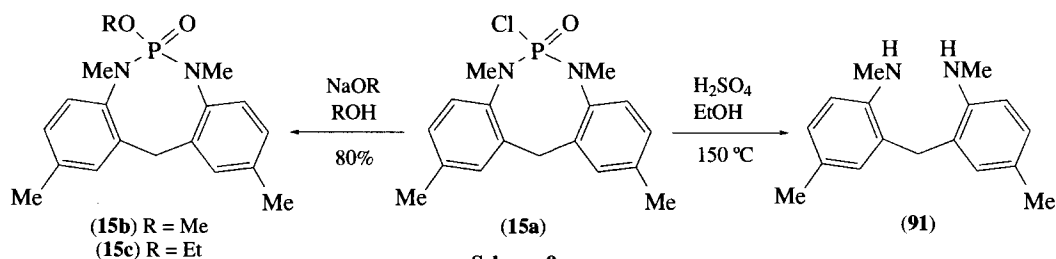
Scheme 8

The C=N bond of the dibenzo[*c,g*][1,2,6]thiadiazocine (**89**) is cleanly hydrolyzed in hydrochloric acid and ethanol resulting in formation of the acyclic sulfonamide (**90**), shown in Equation (3) <83T2073>.



9.25.5.4 Diazaphosphocines

The rather inert 6-chloro-dibenzo[*d,g*][1,3,2]-diazaphosphocine (**15a**) can be converted to the 6-alkoxy derivatives (**15b,c**) on treatment with alkoxide, but hydrolyzes only under harsh acidic conditions in a sealed tube at 150 °C for 100 h to the diamine (**91**) (Scheme 9), a process that can be reversed by treatment with phosphorus oxychloride <86PS(26)185>.

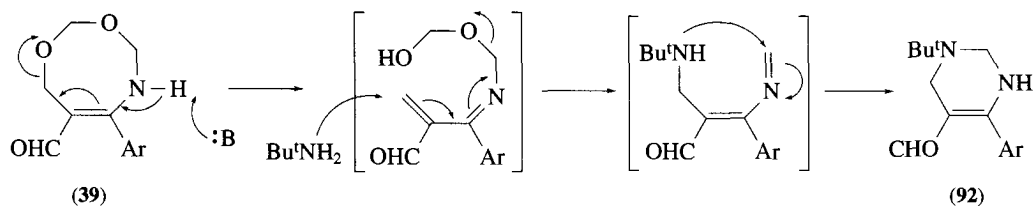


Scheme 9

9.25.5.5 Dioxazocines

The 7-formyl-1,3,5-dioxazocine (**39**) has a limited synthetic utility as it decomposes either at temperatures above 55 °C, in acid medium or in the presence of oxidative or reductive agents.

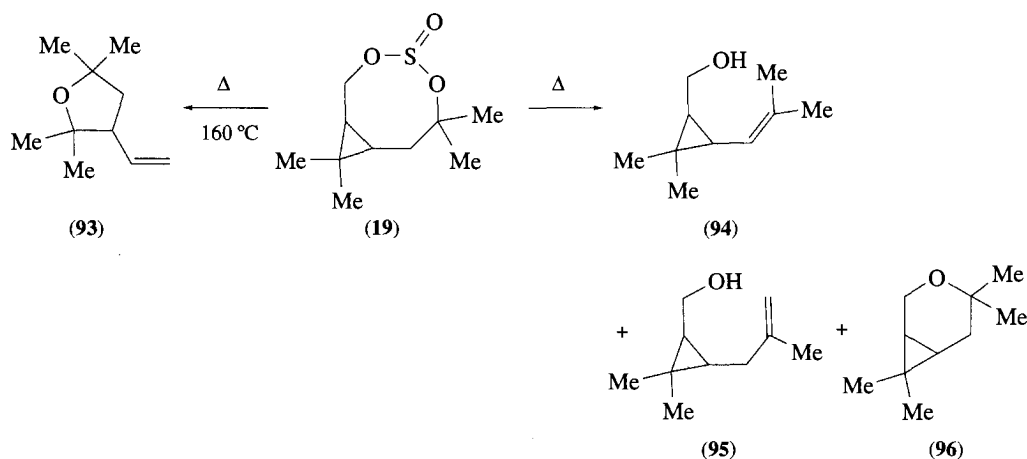
However, with an excess of *t*-butylamine in methanol at room temperature, the enaminoaldehyde 5-formyl-tetrahydropyrimidine (**92**) could be isolated in 55% yield, possibly via the mechanism outlined in Scheme 10 <90CCC2502>.



Scheme 10

9.25.5.6 Dioxathiocins

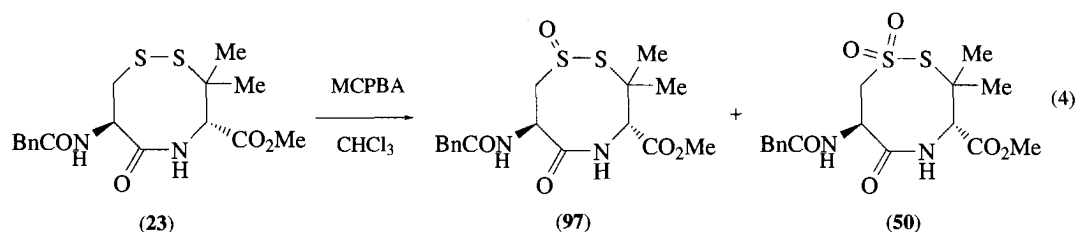
The 1,3,2-dioxathiocin *S*-oxide (**19**) gives a variety of products on thermolysis, as illustrated in Scheme 11 <84JCS(P1)887>. Heating in a sealed tube at 160°C yields the vinyltetrahydrofuran (**93**); whereas injection on to a Carbowax column programmed from 40 to 205°C results in a mixture of the isomeric chrysanthemols (**94**) and (**95**) and the tetrahydropyran (**96**).



Scheme 11

9.25.5.7 Dithiazocines

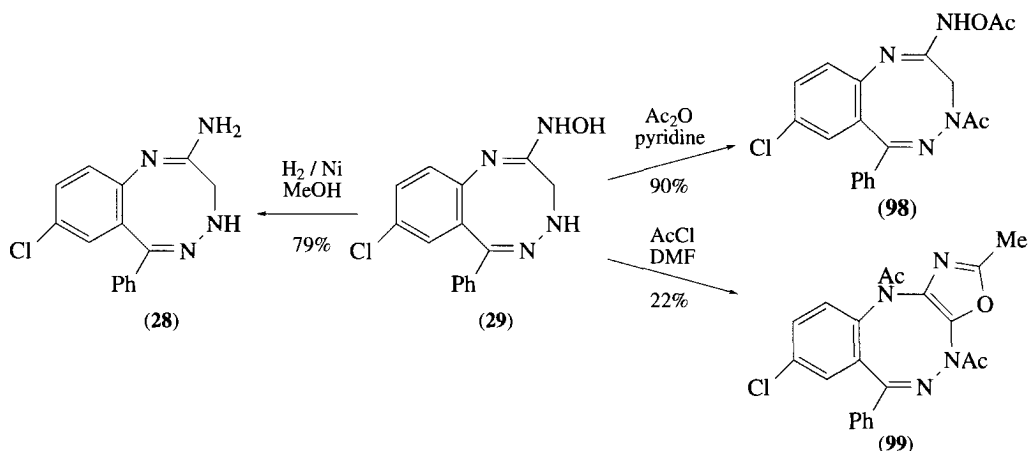
Peracid oxidation of *cyclo*-[(*R*)-cysteinyl-(*S*)-penicillamine] (**23**) occurs at the less hindered sulfur, as shown in Equation (4), to give a mixture of the sulfoxide (**97**) and sulfone (**50**) in 38 and 36% yields, respectively <88JCS(P1)365>.



9.25.6 REACTIVITY OF SUBSTITUENTS

The 2-hydroxylamino-1,4,5-benzotriazocine (**29**) was reduced by hydrogenation over Raney nickel to give the corresponding amine (**28**) <73CPB2375>. Although treatment with acetic anhydride

gave the expected bis-acetyl derivative (**98**), reaction with acetyl chloride resulted in isolation of the oxazolo[4,5-*b*][1,4,5]benzotriazocine (**99**) (Scheme 12).



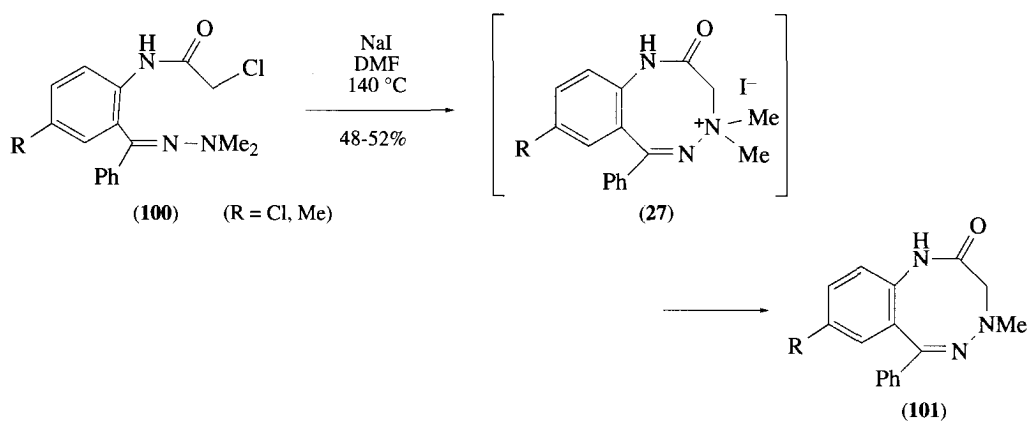
Scheme 12

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

9.25.7.1 By Intramolecular Cyclizations

9.25.7.1.1 Triazocines

6-Phenyl-4-methyl-1,4,5-benzotriazocin-2-ones (**101**) are obtained from the thermal cyclization of 2-chloroacetamidobenzophenone *N,N*-dimethylhydrazones (**100**) at 140 °C in DMF in the presence of sodium iodide <79CPB2084>. The intermediate 1,4,5-benzotriazocinium quaternary salt (**27**), shown in Scheme 13, can be isolated if the cyclization is carried out at room temperature in acetone.

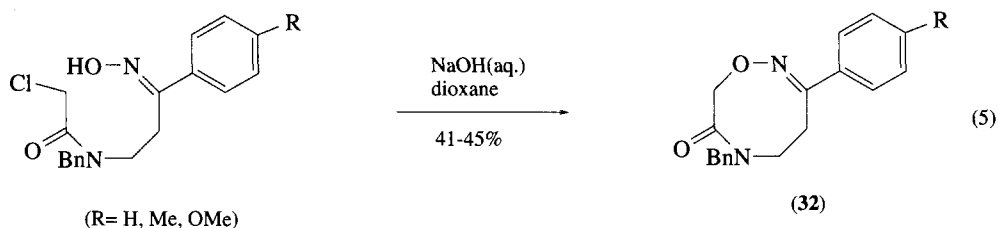
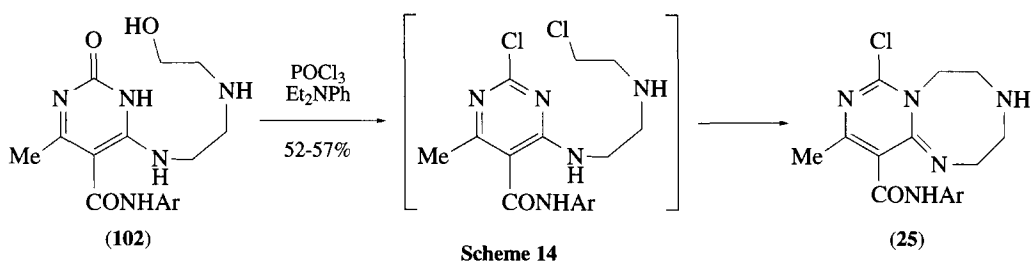


Scheme 13

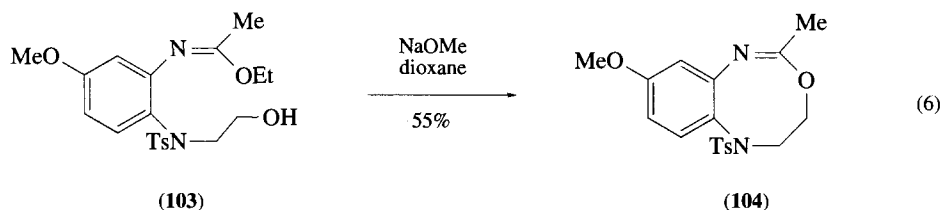
On refluxing in phosphorus oxychloride with an excess of diethylaniline, the 4[(2-(2-hydroxyethyl)amino)ethyl]aminopyrimidines (**102**) readily undergo bis-chlorination, followed by cyclization to give pyrimido[1,6-*a*][1,3,6]triazocines (**25**) (Scheme 14) <92PHA186>.

9.25.7.1.2 Oxadiazocines

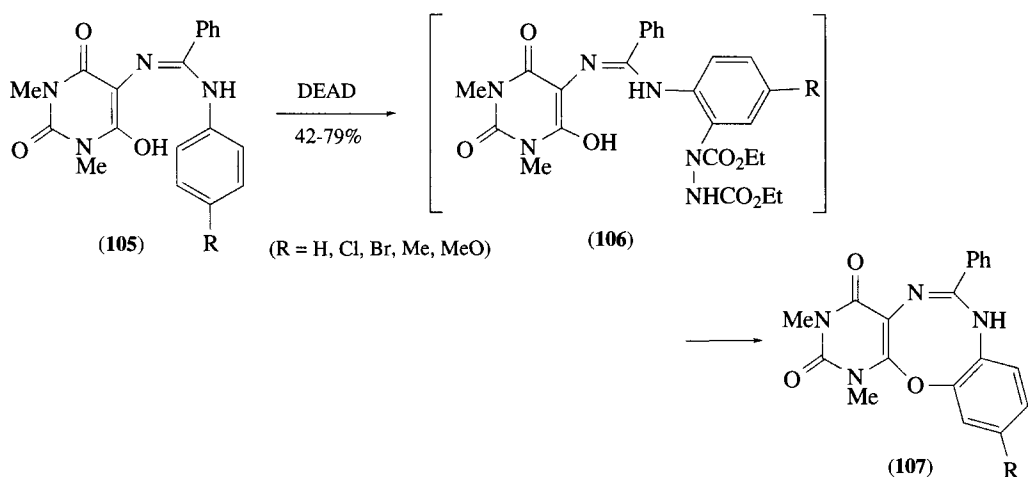
(*E*)- β -[(Chloroacetyl)amino]propiophenone oximes cyclocondense on treatment with alkali to form the 3-aryl-1,2,6-oxadiazocin-7-ones (**32**), as shown in Equation (5) <84LA1696>.



The 3,1,6-benzoxadiazocine (104) is obtained by refluxing the ethyl acetamidate (103) in anhydrous dioxane with a trace of sodium methoxide (Equation (6)) (83T479).

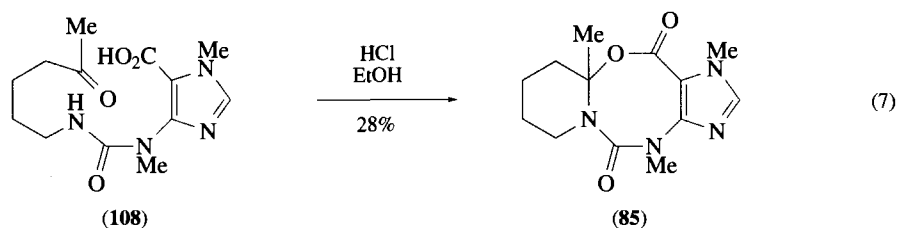


5-(*N*-Arylbenzamido)-1,3-dimethylbarbituric acids (105) undergo a dehydrogenative cyclization on treatment with diethyl azodicarboxylate to afford pyrimido[4,5-*b*][1,4,6]benzoxadiazocines (107), as illustrated in Scheme 15 (84H(22)497). The reaction is thought to proceed by initial formation of the Michael adduct (106), a mechanism that parallels the finding that 2-aminonaphthalene undergoes a Michael addition with DEAD to give 2-amino-1-(1,2-dicarbethoxyhydrazino)naphthalene.



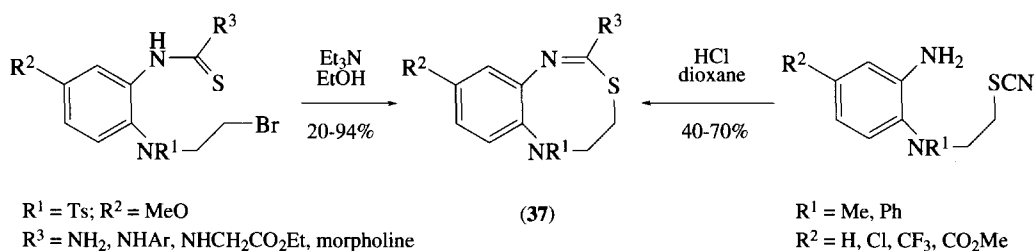
Scheme 15

The *N*-[imidazolyl]-*N'*-(hexan-5-one)urea (108) cyclizes via an acid-catalyzed intramolecular Mannich-type condensation to afford the tricyclic imidazo[4,5-*f*]pyrido[2,1-*b*][1,3,5]oxadiazocine (85), shown in Equation (7) (82CPB3088).



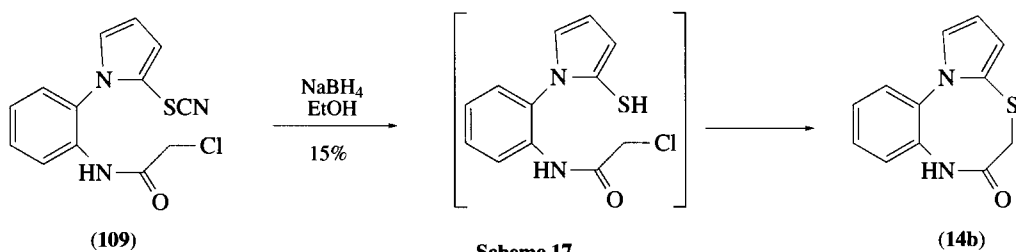
9.25.7.1.3 Thiadiazocines

Two routes to the 3,1,6-benzothiadiazocine ring system (**37**) involve intramolecular cyclization either by base-catalyzed alkylation of a thiourea <83T1203> or acid-catalyzed amine addition to a thiocyanate <85T2855>, as demonstrated in Scheme 16.



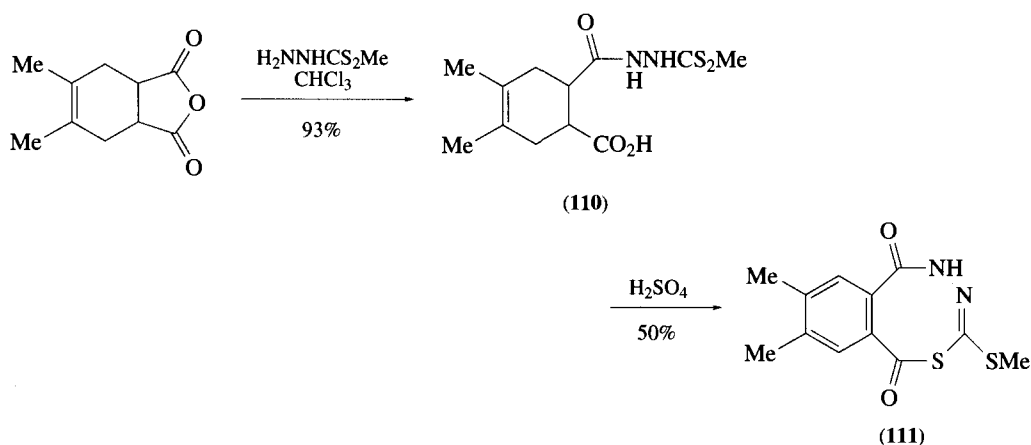
Scheme 16

The pyrrolo[1,2-*a*][3,1,6]benzothiadiazocin-5-one (**14b**) was prepared by reduction of the *N*-aryl-2-thiocyanatopyrrole (**109**) to the corresponding pyrrolo-2-thiol, which spontaneously cyclizes under the reaction conditions, as shown in Scheme 17 <85JHC423, 87JHC1157>.



Scheme 17

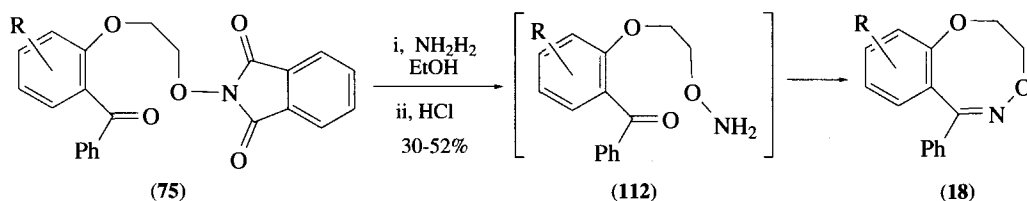
Reaction of 4,5-dimethyl-tetrahydrophthalic anhydride with methyl dithiocarbamate results in formation of hydrazide (**110**), which is cyclized in hot sulfuric acid to the 5,2,3-benzothiadiazocin-1,6-dione (**111**), as shown in Scheme 18 <88MI 925-01>. Similar cyclizations are reported to occur using 3-nitrophthalic <87MI 925-01> and quinolinic anhydrides <87MI 925-02>.



Scheme 18

9.25.7.1.4 Dioxazocines

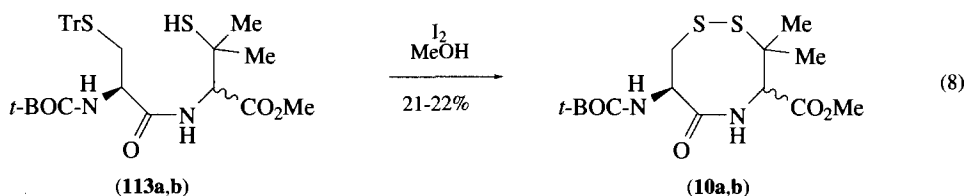
The 1,4,5-benzodiazocine ring system (**18**) can be prepared by cleavage of the *N*-phthalimido protecting group of (**75**) with hydrazine and direct cyclization of the assumed intermediate *O*-substituted hydroxyamino ketones (**112**) on acidification of the reaction medium, as demonstrated in Scheme 19 <83AJC2555>.



Scheme 19

9.25.7.1.5 Dithiazocines

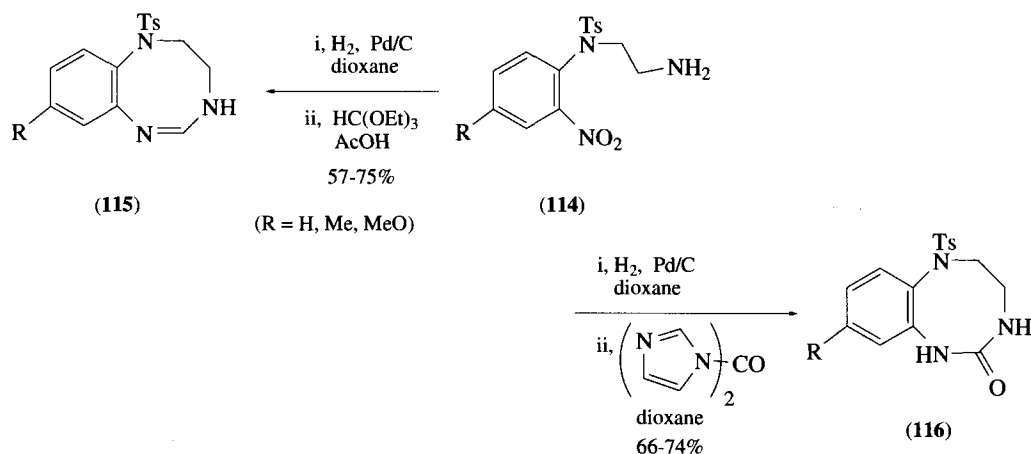
Cyclization of the dipeptides *S*-trityl-(*R*)-cysteinyl-(*R* and *S*)-penicillamines (**113a,b**) to the 1,2,5-dithiazocines (**10a,b**) was achieved by treatment with iodine in methanol under high dilution conditions, which decrease intermolecular reactions (Equation (8)) <93T9049>.



9.25.7.2 Ring Formation by [7 + 1] Cyclizations

9.25.7.2.1 Triazocines

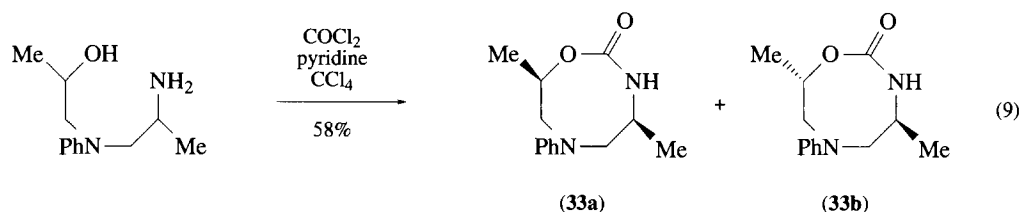
1,3,6-Benzotriazocines (**115**) and (**116**) are prepared from the common intermediate *N*-(2-aminoethyl)-2'-nitrotosylanilide (**114**) by hydrogenation to the corresponding diamine, which is not isolated, but cyclized directly with either triethyl orthoformate or carbonyl(diimidazole), as shown in Scheme 20 <83T1199>.



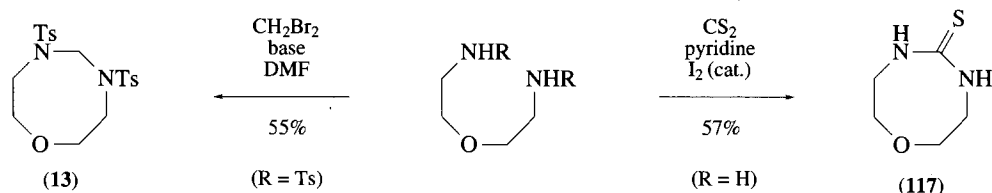
Scheme 20

9.25.7.2.2 Oxadiazocines

The cyclization of *N*-(2-aminopropyl)-*N*-(2-hydroxypropyl)aniline with phosgene affords an equimolar mixture of *cis* and *trans* isomers of 4,8-dimethyl-6-phenyl-1,3,6-oxadiazocin-2-one (**33**) (Equation (9)), which could be separated by chromatography <92JHC1529>.



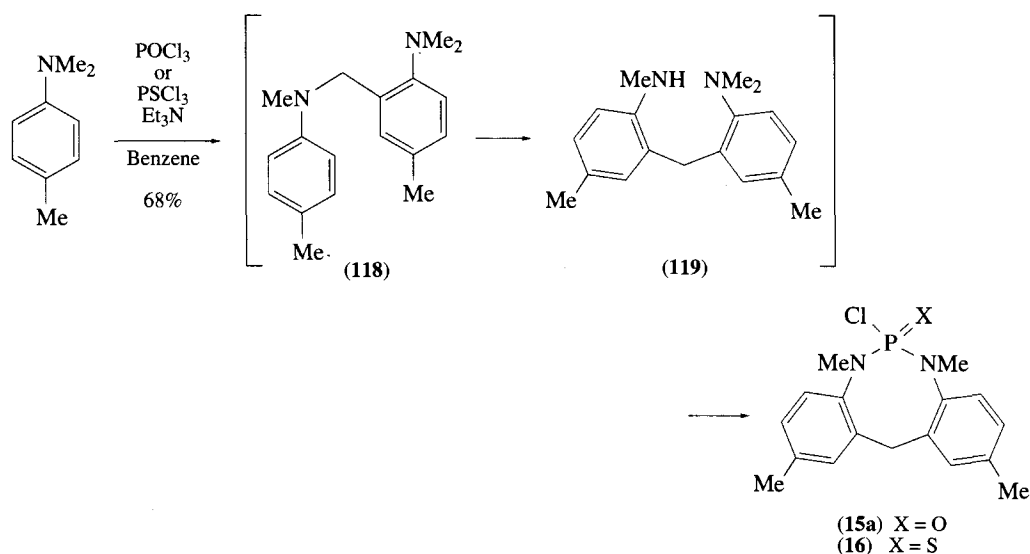
The 1,4,6-oxadiazocan-5-thione (**117**) is obtained by cyclization of bis(aminoethyl)ether with carbon disulfide in pyridine with a catalytic amount of iodine present (Scheme 21) <88MI 925-02>. Alternatively, the ditosyl derivative of bis(aminoethyl)ether can undergo condensation with dibromomethane in hot DMF with an organic base to afford *N,N*-ditosyl-1,4,6-oxadiazocane (**13**) <85MIP129814, 87AX(C)2167>.



Scheme 21

9.25.7.2.3 Diazaphosphocines

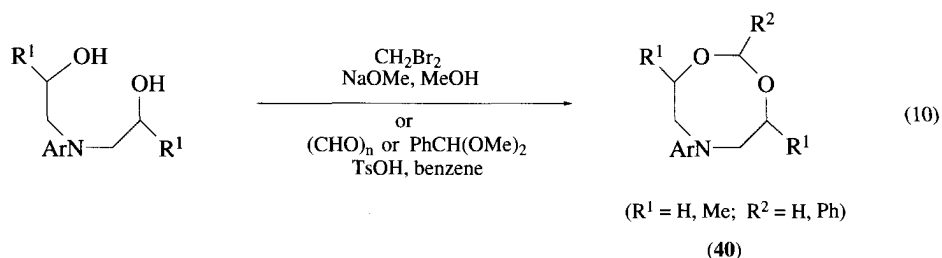
The reaction of *N,N*-dimethyl-*p*-toluidine with either phosphorus oxychloride or thioxychloride and triethylamine in refluxing benzene results in formation of the 6-chloro-dibenzo[*d,g*][1,3,2]diazaphosphocine-6-oxide (**15a**) or 6-sulfide (**16**) <87JCS(P)1547>. The complex mechanism, outlined in Scheme 22, was postulated to involve initial oxidation of the dialkylaniline by phosphorus oxychloride to give an imminium ion, which on reaction with a second toluidine molecule undergoing electrophilic substitution at the *ortho* position gives the *N*,2-methylenebis(*p*-toluidine) (**118**). Rearrangement of *N*,2-methylenebis(*p*-toluidine) (**118**) to 2,2'-methylenebis(*p*-toluidine) (**119**) and condensation of such intermediates with phosphorus oxychloride to give diazaphosphocines are known to occur.



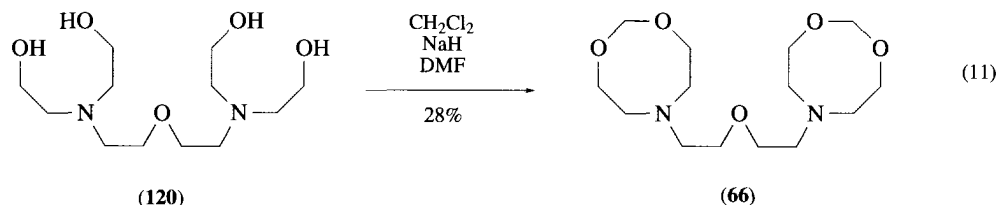
Scheme 22

9.25.7.2.4 Dioxazocines

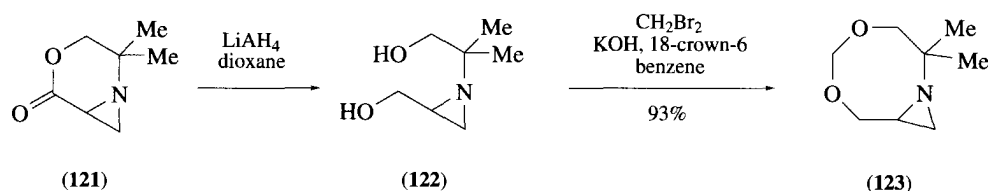
The conversion of *N*-substituted diethanolamines to 1,3,6-dioxazocines (**40**) can be carried out by cyclization with a one-carbon fragment, such as dibromomethane, paraformaldehyde or benzaldehyde dimethyl acetal, as shown in Equation (10) <83JHC479, 88JHC1327>.



An analogous cyclization was employed to prepare the bis(aza-8-crown-3) (**66**) from the tetra-alcohol (**120**) (Equation (11)), in this case using dichloromethane as the one-carbon fragment <92JOC6112>.

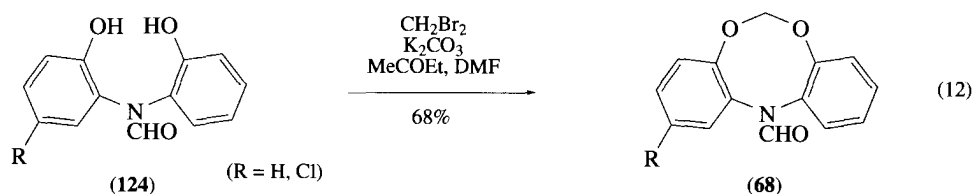


Another similar ring closure was utilized to obtain the bicyclic 1,3,6-dioxazocine (**123**), obtained in two steps from the azaoxabicycloheptanone (**121**). As outlined in Scheme 23, this proceeded by initial reduction with LAH to the 1-[(2-hydroxymethyl)-2-propyl]-2-hydroxymethylaziridine (**122**), followed by cyclization with dibromomethane <88MI 925-03>.



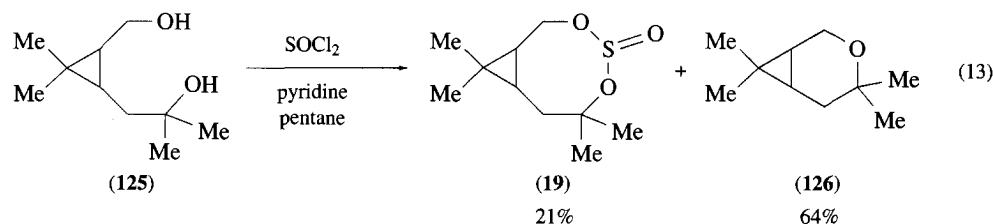
Scheme 23

Dibromomethane is also employed in the conversion of *N*-(bisphenol)-formamides (**124**) to dibenzo[*d,g*][1,3,6]dioxazocines (**68**), as exemplified in Equation (12) <85JST(131)131>.



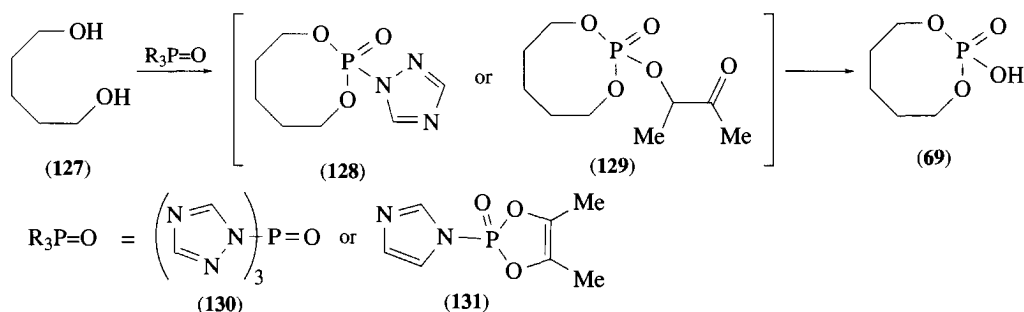
9.25.7.2.5 Dioxathiocins

The bicyclic 1,3,2-dioxathiocin (**19**) is obtained as a minor product from treatment of the cyclopropanediol (**125**) with thionyl chloride and pyridine, with the major pathway being dehydrative cyclization to the pyran (**126**), shown in Equation (13) <84JCS(P1)887>.



9.25.7.2.6 Dioxaphosphocanes

The 1,3,2-dioxaphosphocane acid (**69**) is conveniently obtained by treatment of the diol (**127**) with either phosphorylating agents (**130**) <84S408> or (**131**) <82TL5375>, as illustrated in Scheme 24. The phosphorylation with (**130**) is performed in 95% yield in either dioxane or pyridine without isolation of the intermediate (**128**), whereas the alternative route involves isolation, purification and cleavage of the intermediate (**129**) with diisopropylethylamine in acetonitrile/water to give the product in 82% yield.



Scheme 24

9.25.7.2.7 Diibenzo[d,g][1,3,2]dioxaheterocins

Condensation of biphenyl-2,2'-diols with the appropriate sulfur, phosphorus, or silane-dichloride to give the corresponding dibenzo[d,g][1,3,2]dioxaheterocins is accomplished in toluene with an organic base present, as exemplified in Table 15. Similarly, the dioxaboracin (**49**) is obtained by dehydrative cyclization of the bisphenol with phenylboric acid.

Table 15 Preparation of dibenzo[d,g][1,3,2]dioxaheterocins.

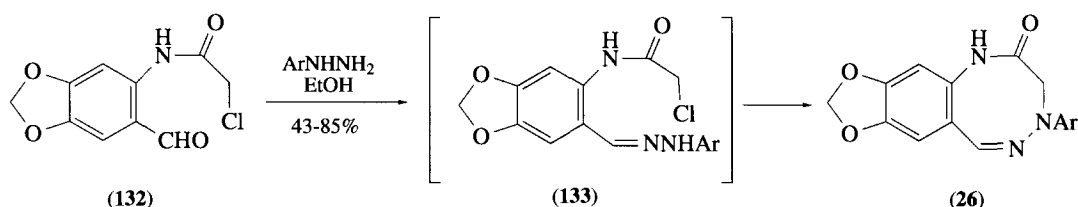
(14)

Heterocycles	$\text{R}^3\text{R}^4\text{MX}_2$	R^1, R^2	Base	Yield (%)	Ref.
Dibenzo[1,3,2]dioxathiocin (44c)	SOCl_2	Bu^t, Bu^t	pyridine	88	90HCA618
Dibenzo[1,3,2]dioxathiocin (77)	SCl_2	Me, Bu^t	pyridine	50	90HCA618
Dibenzo[1,3,2]dioxaphosphocin (46)	PhPCl_2	$\text{Bu}^t, \text{CO}_2\text{Me}$	TEA	73	83JHC1311
Dibenzo[1,3,2]dioxaphosphocin (20b)	EtOP(O)Cl_2	Me, Me	TEA/dmap	62	88JHC575
Dibenzo[1,3,2]dioxaboracin (49)	PhB(OH)_2	Bu^t, Bu^t	TsOH	61	83JHC1311
Dibenzo[1,3,2]dioxasilocin (47b)	Me_2SiCl_2	Bu^t, Bu^t	TEA	86	84JO1297

9.25.7.3 Ring Formation by [6 + 2] Cyclizations

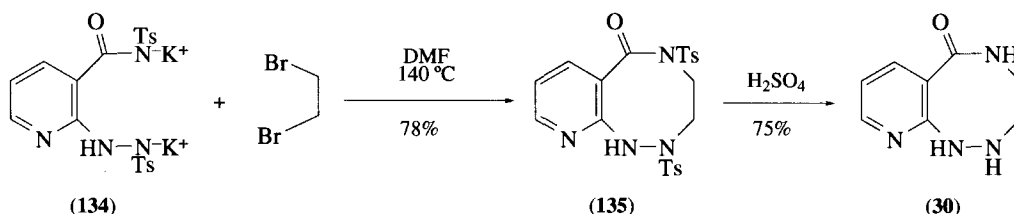
9.25.7.3.1 Triazocines

Besides direct cyclization of 2-chloroacetamidobenzophenone, *N,N*-dimethylhydrazones (**100**) (Scheme 13), 1,4,5-benzotriazocin-2-ones (**26**) can also be obtained by reaction of 6-(chloroacetamido)piperonal (**132**) with substituted phenylhydrazines without isolation of the proposed hydrazone intermediates (**133**), as shown in Scheme 25 <83M1231>.



Scheme 25

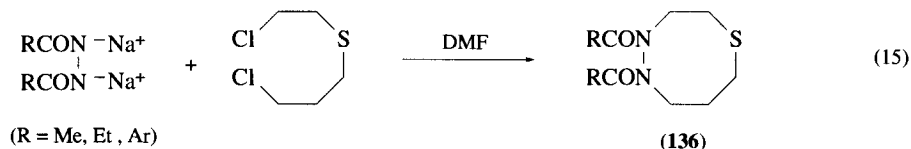
Conversion of the tosylamide of 2-(2-tosylhydrazino)nicotinic acid to its dipotassium salt (**134**) with potassium in butanol, followed by condensation with 1,2-dibromoethane, leads to cyclization to the bicyclic triazocine (**135**), which can be hydrolyzed in sulfuric acid to yield the parent pyrido[3,2-*g*][1,2,5]triazocine-6-one (**30**), as outlined in Scheme 26 <85PJC1115>.



Scheme 26

9.25.7.3.2 Thiadiazocines

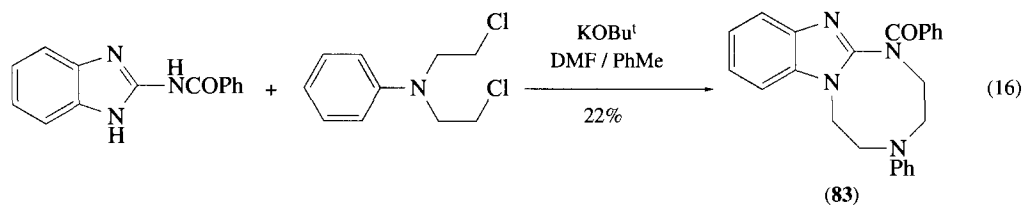
The 1,4,5-thiadiazocines (**136**) can be prepared from diacyl- and dibenzoylhydrazines by initial conversion to their disodium salts with sodium amide in benzene, followed by condensation with 2-chloroethyl-3-chloropropyl sulfide in DMF (Equation (15)) <85MI 925-01>.



9.25.7.4 Ring Formation by [5 + 3] Cyclizations

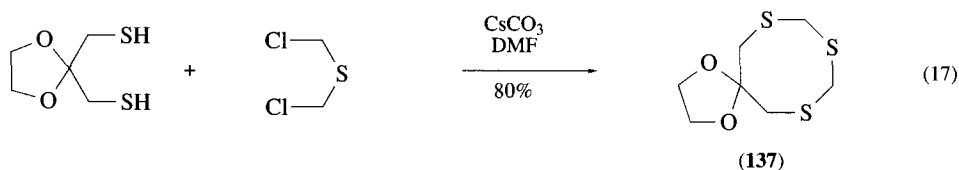
9.25.7.4.1 Triazocines

2-Benzamidobenzimidazole and *N,N*-bis(2-chloroethyl)aniline undergo condensation in the presence of potassium *t*-butoxide resulting in cyclization to the 1,3,6-triazocino[1,2-*a*]benzimidazole (**83**), shown in Equation (16) <92JMC705>.



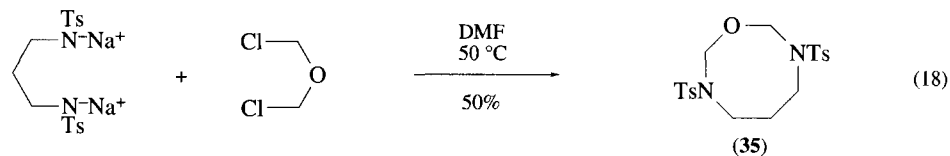
9.25.7.4.2 Trithiocanes

The 1,3,5-trithiocane (**137**), a thiacycrown ether, is obtained by a [5 + 3] heterocyclization of spiro-2,2-(1,3-dioxolane)-1,3-propanedithiol with thio(bis-chloromethane) in the presence of caesium carbonate (Equation (17)) <92T8065>.

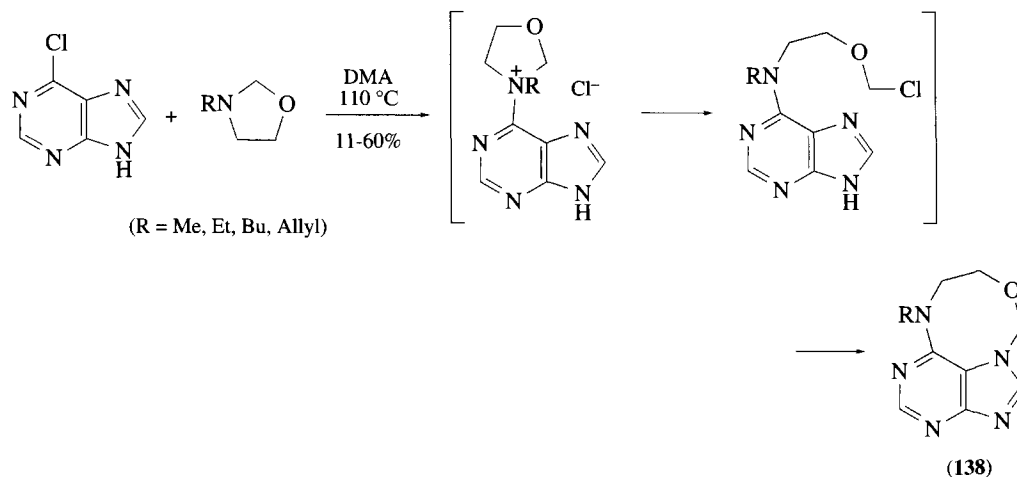


9.25.7.4.3 Oxadiazocines

N,N-Ditosyl-1,3,7-oxadiazocane (**35**) is prepared by a thermal [5 + 3] heterocyclization of the disodium salt of *N,N*-ditosyl-1,3-propanediamine, prepared from sodium methoxide in methanol with bis(chloromethyl)ether, as shown in Equation (18) <84PJC251>.



Treatment of 6-chloropurine with *N*-alkyl-1,3-oxazolidines in hot dimethyl acetamide leads to formation of tricyclic 1,3,6-oxadiazocino[3,4,5-*g,h*]purines (**138**) via the postulated intermediates shown in Scheme 27 <84JHC333>.

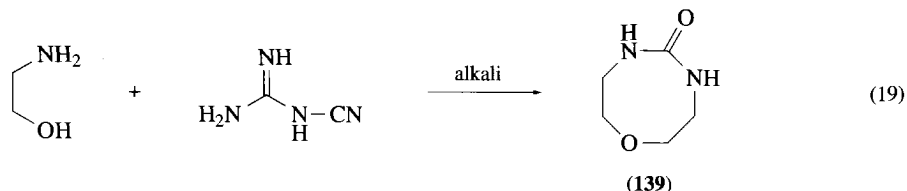


Scheme 27

9.25.7.5 Miscellaneous Routes

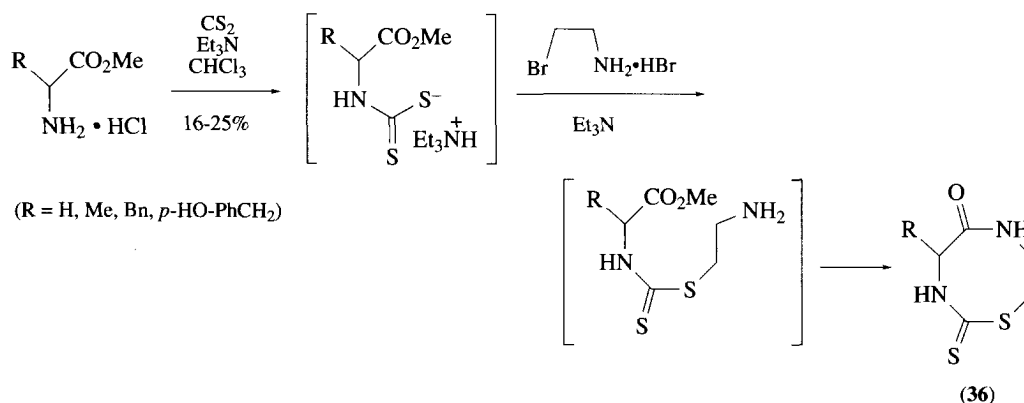
9.25.7.5.1 Oxadiazocines

Dicyanodiamide is reported to react with ethanolamine under alkaline conditions to yield 1,4,6-oxadiazocin-5-one (**139**), as illustrated in Equation (19) <85MI 925-02>.



9.25.7.5.2 Thiadiazocines

2-Thioxo-1,3,6-thiadiazocin-5-ones (**36**) are conveniently prepared from α -amino acid ester hydrochlorides in one pot by sequential treatment with carbon disulfide, followed by 2-bromoethylamine hydrobromide (Scheme 28) <90SC2675>. Starting with L-tyrosine leads to an optically active thiadiazocine indicating that racemization does not occur during the reaction.

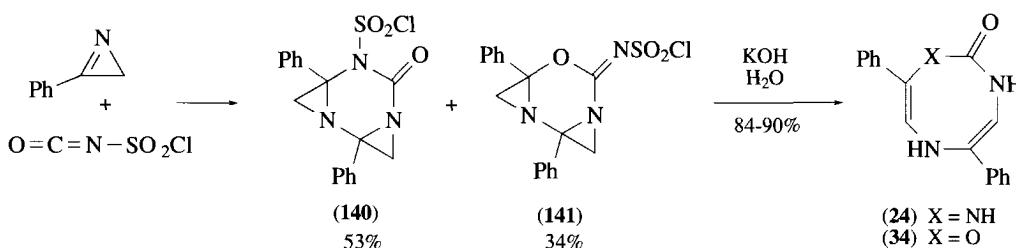


Scheme 28

9.25.8 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

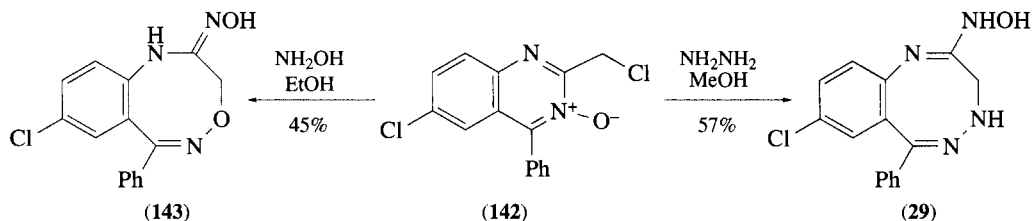
9.25.8.1 Triazocines and Oxadiazocines

Chlorosulfonyl isocyanate and 3-phenyl-2*H*-aziridine undergo a [2 + 2 + 2] cycloaddition at room temperature to yield a mixture of separable tricyclic adducts (**140**) and (**141**), which on hydrolysis undergo ring expansion to give either the 1,3,6-triazocin-2-one (**24**) or 1,3,6-oxadiazocin-2-one (**34**) (Scheme 29) <93SC2151>. The formation of the oxadiazocin-2-one (**34**) is accompanied by a second product identified as 2,5-diphenylpyrazine.



Scheme 29

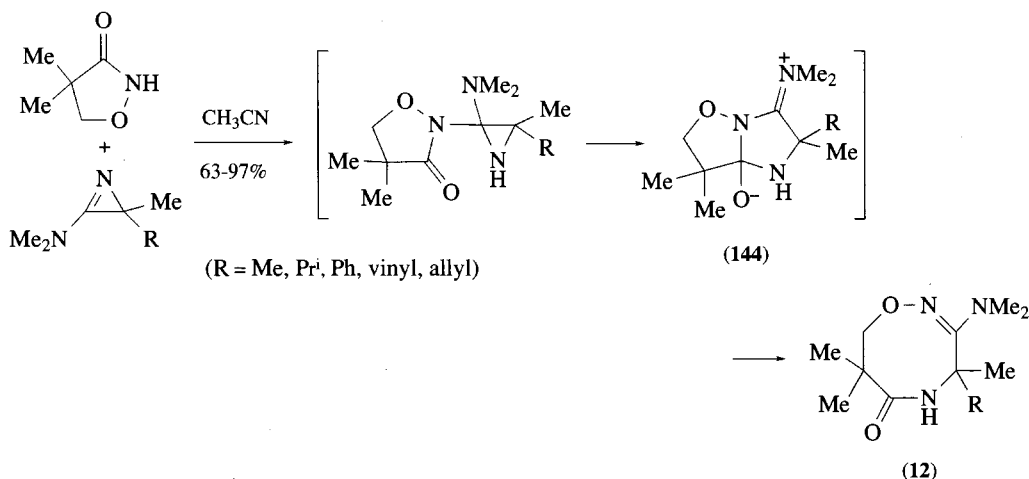
Treatment of the quinazoline 3-oxide (**142**) with hydrazine leads via fission of the N(3)—C(4) bond to the formation of the 2-hydroxyamino-1,4,5-benzotriazocine (**29**), as illustrated in Scheme 30 <73CPB2375>. A similar ring expansion was reported in the formation of 4,1,5-benzoxadiazocin-2-one oxime (**143**) by treatment of the same starting material with hydroxylamine <70JHC1429>.



Scheme 30

9.25.8.2 Oxadiazocines

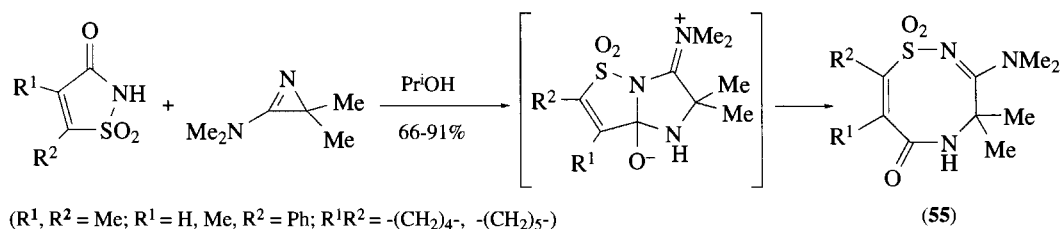
Heimgartner *et al.* have shown that 3-dimethylaminoazirines and 4,4-dimethyl-3-isoxazolidinone combine at room temperature to produce 1,2,5-oxadiazocin-6-ones (**12**) <86HCA298>. The reaction is thought to proceed, as outlined in Scheme 31, by initial addition of the oxazolidinone nitrogen across the $\text{C}=\text{N}$ of the aziridine, followed by opening of the three-membered aziridine ring and addition to the oxazolidinone carbonyl to give a bicyclic zwitterion intermediate (**144**); this ring then opens to yield oxadiazocine (**12**).



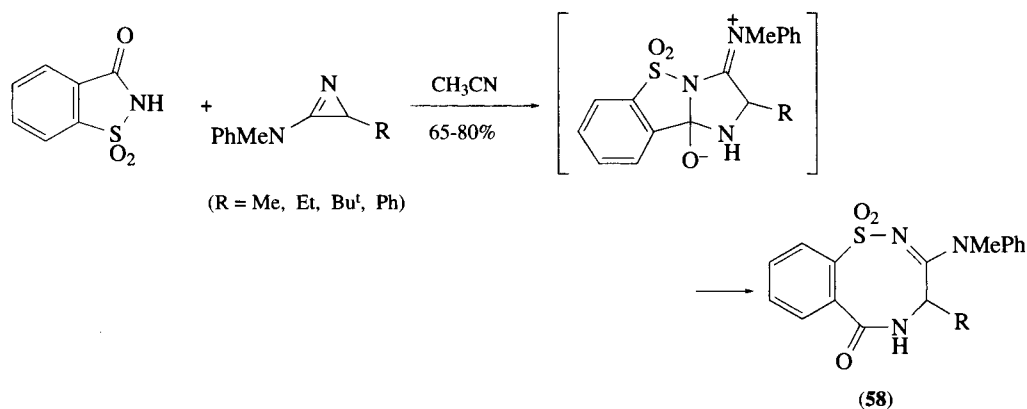
Scheme 31

9.25.8.3 Thiadiazocines

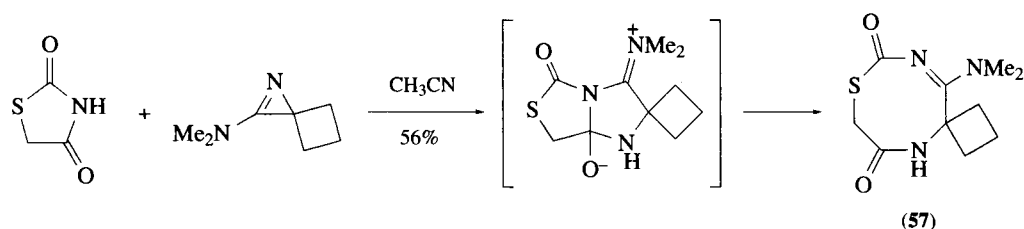
An analogous series of reactions, exemplified in Schemes 32–34, were found to occur between 3-aminoazirines and other NH-acidic heterocycles. For example, isothiazolones or isothiazolidinones 1,1-dioxides react to form the 1,2,5-thiadiazocin-6-one 1,1-dioxides (**55**) <91HCA1002>, and saccharin combines with 3-aminoazirines to yield the 1,2,5-benzothiadiazocin-6-one 1,1-dioxides (**58**) <92HCA2270>. An example was reported where 1,3-thiazolidine-2,4-dione reacted with 3-dimethylamino-2-cyclobutaneazirine to yield the 1,3,6-thiadiazocin-2,7-dione (**57**) <90HCA1314>.



Scheme 32

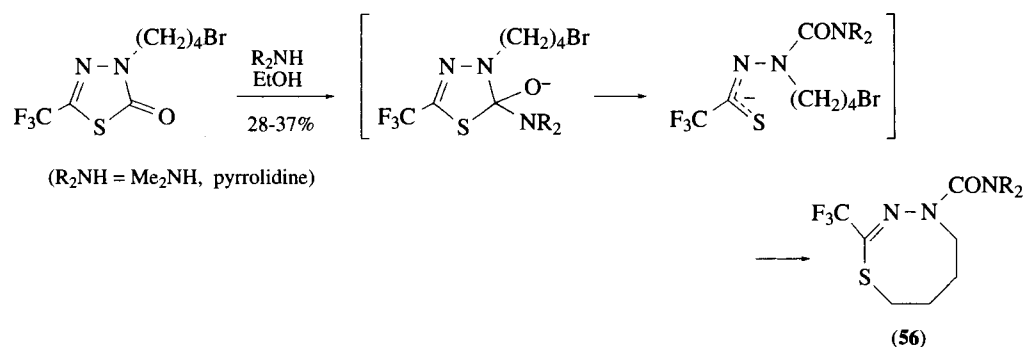


Scheme 33



Scheme 34

5-Trifluoromethyl-1,3,4-thiadiazol-2-one, with a butyl bromide side chain at N-3, undergoes a ring transformation with secondary amines to give 1,3,4-thiadiazocines (56) <83HCA2714>. The reaction is thought to occur via addition of the amine to the carbonyl of the thiadiazol-2-one, as outlined in Scheme 35. A second product in the reaction is the 3-aminobutyl-thiadiazol-2-one resulting from direct nucleophilic displacement of the bromine with the amine.

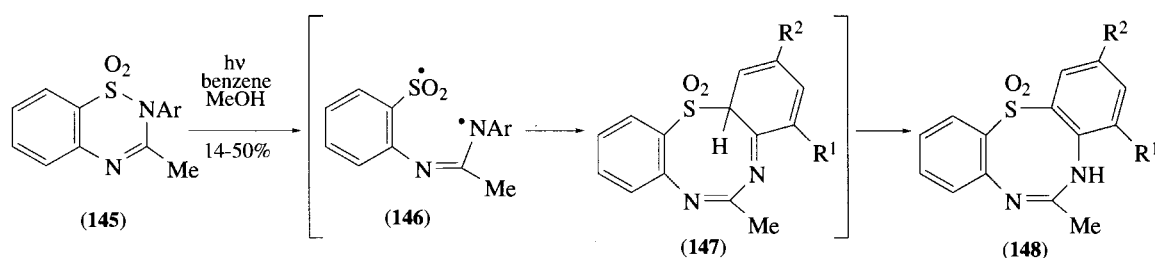


Scheme 35

Irradiation of 1,2,4-benzothiadiazine 1,1-dioxides (145) results in ring enlargement to the dibenzo[*b,g*][1,4,6]thiadiazocine 12,12-dioxides (148); possibly, as outlined in Scheme 36, via the diradical intermediates (146) leading on recombination to precursors (147) <86JOC1967>. In each case significant amounts of unreacted starting material are recovered.

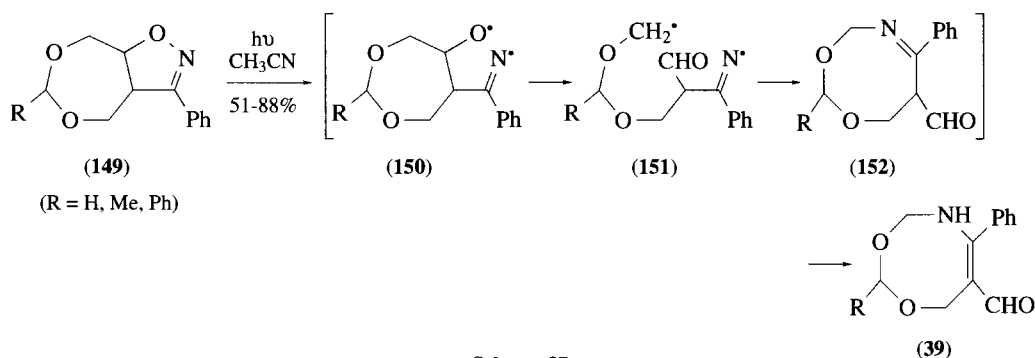
9.25.8.4 Dioxazocines

The photochemical rearrangement of various 3-phenyl-isoxazolines (149) condensed with a 1,3-dioxepane skeleton was demonstrated by Fisera *et al.* to result in formation of 7-formyl-1,3,5-dioxazocines (39) <84TL2731, 85CCCC1982, 86JPR445>. The presumed mechanism, illustrated in Scheme 37, involves initial homolysis of the N—O bond to give (150), rearrangement to the diradical (151)



Scheme 36

stabilized by the *p* electrons of the adjacent oxygen, and recombination to give the dioxazocine (152). The rearrangement was also shown to occur with 3-cyanoisoxazolines <87CCC1773> and 3-methoxycarbonylisoxazolines <87CCC2953>.



Scheme 37

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

The two most common routes to eight-membered heterocycles involve either intramolecular or [1 + 7] cyclizations. Intramolecular cyclizations are particularly useful for precursors having two components tethered *ortho* to each other on an aromatic ring, which on ring closure lead to 1,3,6-benzoheterocycles, as exemplified by Schemes 14, 16, 17 and Equation (6), and 1,4,5-benzoheterocycles, as demonstrated in Schemes 13, 19, and 25.

1,3,6-Eight-membered heterocycles are prepared by the common strategy of a [7 + 1] cyclization of a diol or diamino acyclic precursor with a one-carbon fragment such as phosgene, dihalomethane or formaldehyde (Schemes 20, 21 and 23 and Equations (9)–(12)). Other dihaloalkanes have been employed in cyclizations either with diamino compounds activated by tosylation (Scheme 26 and Equation (18)) or acylation (Equation (15)), or with dithiols (Equation (17)).

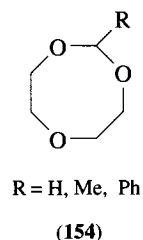
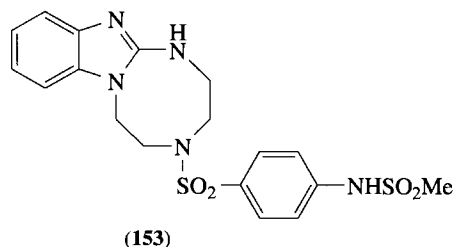
The general route to dibenzo[*d,g*][1,3,2]dioxaheterocins involves a [7 + 1] condensation of biphenyl-2-2'-diols with the appropriate sulfur, phosphorus, or silane-dichloride with an organic base (Table 15). Similar cyclizations of aliphatic diols leading to [1,3,2]dioxaheterocins are less common, but do occur (Equation (13) and Scheme 24).

9.25.10 IMPORTANT COMPOUNDS AND APPLICATIONS

The 1,3,6-triazocine[1,2-*a*]benzimidazole (153) was synthesized for evaluation as part of a series of potent antiarrhythmic agents which contain two key structural features consisting of a 2-aminobenzimidazole and a 4-(methylsulfonylamino)benzenesulfonamide group <92JMC705>. The compound, which contains these two pharmacophores linked by a conformational constraining eight-membered heterocycle, possessed efficacy approaching that of the open-chain analogues.

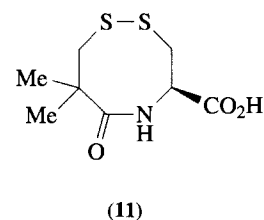
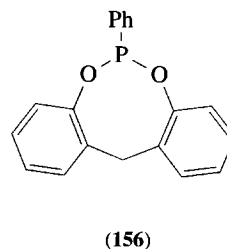
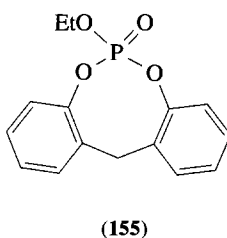
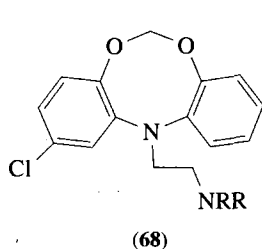
Eight-membered ring acetaldehyde, benzaldehyde, acetophenone, and benzophenone crown ether

acetals (**154**) show cation complexing properties similar to 8-crown-3 ethers <78JCS(CC)507, 83JCS(P1)453, 86BCJ3979>. They differ from crown ethers in that the crown ether acetal ring is easily cleaved by acid-catalysis, whereas crown ethers are stable under these conditions. Since the open-chain diols produced in the hydrolysis have a lower capacity for cation-binding, a useful property is thus the acid-mediated release of metal ions from such metal-crown ether acetal complexes <83JCS(P2)1121, 86JOC2131, 91JOC673>.



Dibenzo[*d,g*][1,3,6]dioxazocines (**68**), substituted at the nitrogen by tertiary aliphatic amines, are known to be biologically active in the central nervous system with a mechanism of action at the dopamine D₂ receptor site <85MI 925-03>. They have been investigated as potential antidepressants, with additional anticonvulsant and antiarrhythmic activity <89GEP3844394>, and have been evaluated as possible therapy for Parkinson's disease <87GEP3643991>. Dibenzo[*d,g*][1,3,2]dioxaphosphocins (**155**) and (**156**) have been extensively utilized as stabilizers for polymeric substrates and as antioxidants for the oil industry <83JHC1311, 88JHC575>.

The cyclic disulfide 4(*R*)-7,7-dimethyl-1,2,5-dithiazocan-6-one-4-carboxylic acid (**11**) has been evaluated as a potential hepatoprotective agent for the treatment of various liver injuries <91MI 925-01>. It has been shown to suppress increases in serum transaminase and alkaline phosphatase enzyme activities associated with tetrachloromethane and α -naphthyl isocyanate induced chronic liver damage in rodents <91MI 925-02>. It also assists in the elimination of hepatic viruses from livers of patients with chronic active hepatitis <91MI 925-03>.



9.26

Eight-membered Rings with Four or More Heteroatoms

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9.26.1 INTRODUCTION

9.26.1.1 General Considerations

This chapter is organized into eleven sections. The topic covers many different types of heterocyclic compounds, most of which are accessible by only a few synthetic routes. Therefore what would have been Section 9.26.11, "Synthesis of Particular Compounds and Critical Comparison of Various Routes Available," in the CHEC-II format is combined with Section 9.26.10, "Ring Synthesis." In general, each Section is organized by the number and type of heteroatoms in the eight-membered ring. The heterocyclic systems are arranged within each section in an order determined by the molecular weight of the total number of heteroatoms in the ring. Rings containing four like heteroatoms are discussed first in the order of nitrogen, oxygen, and sulfur. Rings containing four heteroatoms of two or more types are then discussed followed by all eight-membered rings containing five or more heteroatoms. Unsaturated ring systems appear before those of lower oxidation level.

Nomenclature consistent with IUPAC rules is used with common names and acronyms given, where appropriate.

Heterocycles containing four like heteroatoms (tetrazocanes, tetroxocanes, tetrathiocanes, and their unsaturated analogs) were reviewed from 1982 <84CHEC-I(9)653>. A discussion of these systems will continue, concentrating with material published in 1983 and later. Eight-membered rings containing five or more heteroatoms, which were not reviewed in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I), will be discussed in this chapter. An additional review on tetrazocanes appeared in 1990 <90AHC(50)1>. Bicyclic systems containing eight-membered rings, such as epitetrahiopiperazinediones and related antibiotics, will not be covered.

9.26.1.2 Occurrence of Eight-membered Rings with Four or More Heteroatoms

By far the largest compound class of eight-membered rings containing four or more heteroatoms is 1,3,5,7-tetrazocanes. This class includes tetranitrotetrazocane and related compounds, which have found application as propellants and explosives. A large body of literature exists on the properties and applications of these materials. Only papers related to the structure, reactivity, and synthesis of these systems, and those not covered in previous reviews <84CHEC-I(9)653, 90AHC(50)1> will be discussed.

Cucurbituril, a cavitand containing six tetrazocane units, has been the subject of several investigations.

The second largest class of eight-membered ring heterocycles containing four or more heteroatoms is 1,3,5,7-tetraoxocanes. The parent compound is used commercially as a monomer and substituted derivatives are useful pesticides. Again, a large body of information exists on these systems and only material related to structure, reactivity, and synthesis will be covered here. Surprisingly, few papers related to the synthesis of tetrazocanes or tetraoxocanes have appeared since 1982.

1,2,5,6-Tetrathiocanes, usually formed by the oxidative coupling of 1,2-dithiols, make up an important class of heterocycles covered in this chapter. These compounds and other polythiocanes and polythiocines are important molecules of biological interest, especially as odor and flavor components.

Of theoretical interest, 1,5-dithia-2,4,6,8-tetrazocine and its derivatives exhibit unusual electronic and structural properties.

Other eight-membered rings containing four or more heteroatoms are rare and are mentioned in the appropriate sections, as necessary.

9.26.2 THEORETICAL ASPECTS

9.26.2.1 Electronic Calculations

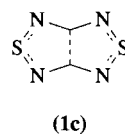
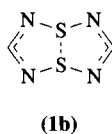
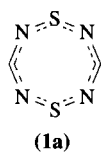
In an attempt to explain the structural dichotomy exhibited by 1,5-dithia-2,4,6,8-tetrazocines (see Section 9.26.4.2), a series of calculations have been performed on the system. Several studies have been conducted on the system (**1**) and derivatives using *ab initio* and semiempirical methods <84ICA55, 84JA312, 84JA3437, 87JCS(P2)259>. Table 1 summarizes the results of the calculations on the three possible geometries for the parent compound. The 1,5-dithia-2,4,6,8-tetrazocine system prefers to adopt a planar 10π -electron monocyclic structure (**1a**). Substituents at the carbon atoms with

π -donor capacity can induce psuedo-Jahn–Teller distortion leading to the bent, bicyclic 8- π system with a S—S transannular partial bond (**1b**). The geometry of (**1c**) is calculated to be of high energy.

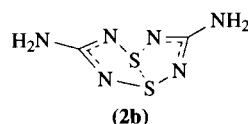
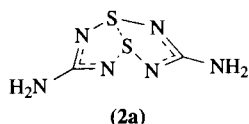
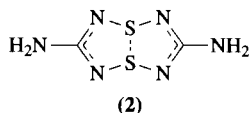
Table 1 Calculated total energies (Hartree) and relative energies (kcal mol⁻¹) of (**1a**), (**1b**), and (**1c**).

Basis	(1a)	(1b)	(1c)
STO-3G ^a	-1077.0273 0	-1077.06884 -26.0	-1077.17102 -90.1
4-31G ^a	-1088.09202 0	-1088.04742 28	-1088.02269 43.5
MNDO ^b	-58.24313 0	-58.21361 18	-58.16849 25.3

^aSTO-3G derived geometry. ^bMNDO derived geometry.



The electronic spectrum of 3,7-diamino-1,5-dithia-2,4,6,8-tetrazocine (**2**) has been computed by the CNDO-CI method for the geometries (**1a**) and (**1b**) corresponding to D_{2h} and C_{2v} symmetries, respectively. The results for the bicyclic D_{2h} structure compare well with the experimentally determined spectrum <84ICA55>.



(1)

Ab initio calculations on (**2**) estimate activation energies of amine rotation and ring inversion (**2a**) and (**2b**) to be 17.1 and 17.3 kcal mol⁻¹, respectively, which is in good agreement with values derived from NMR experiments of 17.3 ± 0.1 and 17.7 ± 0.5 kcal mol⁻¹ (Equation (1)) <94JA5167>.

9.26.2.2 Molecular Mechanics

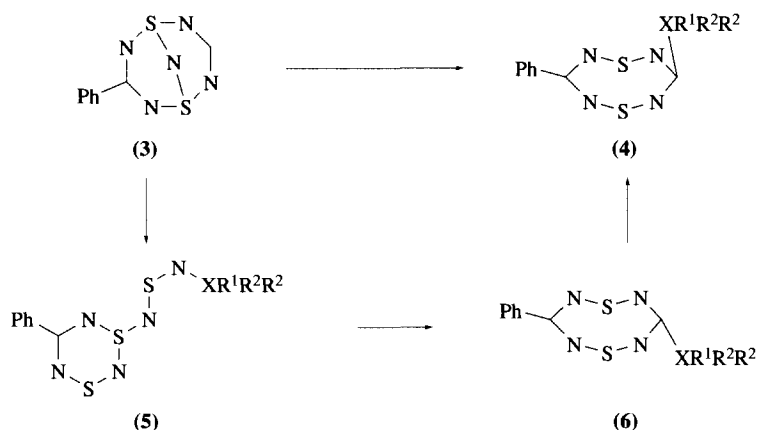
In a molecular mechanics study of C—H bond lengths and stretching frequencies, a modified version of MM3 was used to examine 1,3,5,7-tetroxocane <94JA5887>. Carbon–hydrogen stretching frequencies of 2937 cm⁻¹, 2847 cm⁻¹ (A1), 2935 cm⁻¹, and 2845 cm⁻¹ (E) were calculated and compare well with experimental values of 2290 cm⁻¹, 2780 cm⁻¹, 2920 cm⁻¹, and 2850 cm⁻¹, respectively <77SA(A)549>. In a molecular mechanics treatment of the anomeric effect, the MM2(82) program reasonably reproduced experimental geometries and energies of 1,3,5,7-tetroxocane <84MI 926-01>. Atomic displacement parameters in 1,3,5,7-tetroxocane were estimated using a lattice-dynamical calculation <93AX(B)729>.

A Urey-Bradley force field was used to calculate normal coordinates for 1,2,5,6-tetrathiocane and to confirm the temperature dependency of the S—S stretching frequencies in the molecule <86JA1271>.

9.26.3 EXPERIMENTAL STRUCTURAL METHODS

9.26.3.1 NMR Spectroscopy

Using ^{31}P and ^{15}N NMR, the kinetics of the reaction of (3) to (4) was studied. It was shown that the reaction proceeds through intermediate (5) and the kinetically favored *exo* isomer (6) (Scheme 1). In certain cases, the *exo* isomer could be isolated and was shown to slowly convert to the *endo* isomer at room temperature <87JA7781>.



Scheme 1

The ^{14}N NMR chemical shift of the nitro group of 1,3,5,7-tetranitro-1,3,5,7-tetrazocane (δ -26.9 relative to MeNO_2) was determined and correlated to its electronic environment <94JOC5623>.

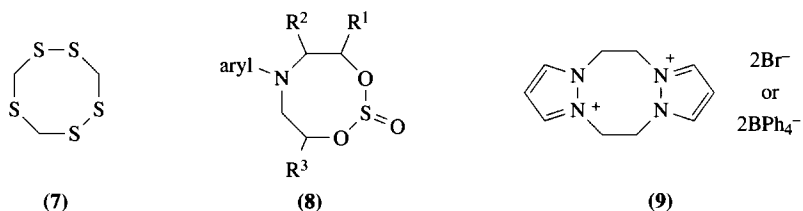
9.26.3.2 Mass Spectroscopy

Mass spectrometric techniques are very important in gaining structural information on medium sized rings containing many heteroatoms. Most of the systems described in this chapter have been subjected to mass spectral analysis and the reader is referred to the individual references for this information. Studies concentrating solely on mass spectroscopy are mentioned here.

Mass-analyzed ion kinetic energy spectrometry, collision-induced dissociation (MIKES/CID) spectral studies conducted on 1,3,5,7-tetranitro-1,3,5,7-tetrazocane (HMX) and 1,3,5,7-tetroxocane showed the presence of a series of cyclic multimers <85JA7228>.

Several other papers on the mass spectral fragmentation of tetranitrotetrazocane derivatives have been published <91OMS(26)105, 92MI 926-01, 94OMS(29)105>.

The fragmentation patterns of cyclic polysulfide, including pentathiocane (7), have been investigated using various mass spectroscopic methods <82OMS(17)165>. Three general mechanisms occur involving metastable transitions: (i) the unimolecular loss of structural parts (CH_2S , CH_x , and S_x); (ii) fragmentations that involve ring opening reactions, hydrogen migrations, and recyclizations of the product ions ($[\text{M}-\text{CH}_3]^+$, $[\text{M}-\text{CH}_3\text{S}]^+$, $[\text{M}-\text{SH}]^+$, and $[\text{M}-\text{CS}_2]^+$); and (iii) complete rearrangements preceding the fragmentations ($[\text{M}-\text{S}_2\text{H}]^+$ and $[\text{M}-\text{C}_2\text{H}_4]^+$) <82OMS(17)165>.



The mass spectral fragmentation of 4-, 5- and 4,8-disubstituted derivatives of 6-aryl-1,3-dioxo-2-thia-6-azocane 2-oxides (8) has been studied by metastable-ion measurements. The major peak appeared at m/e 119 and corresponds to that of aryl- $\text{N}=\text{CH}_2$ ion <82JHC1223>.

FAB mass spectrometry was used to identify the doubly-charged tetrazocine (9) <91BSB459>.

9.26.3.3 X-ray Crystallography

Like mass spectrometric analyses, x-ray methods have been used extensively in structure elucidation of heteroatom-rich rings. The general compound classes and the literature references for x-ray crystal structures are:

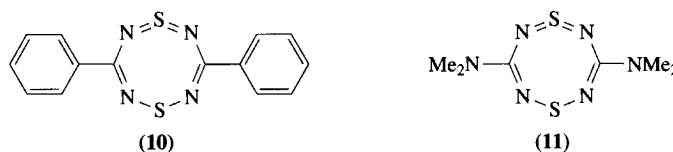
1,3,5,7-Tetrazocane <87JPR187>; cucurbituril <81JA7367> and derivatives <85JOC60, 92AG(E)1475>; 1,2,5,6-tetrazocine <91AX(C)2583>; 1,2,3,4-tetrathiocines <88PS(37)189, 89CJC1416, 90ICA245, 90JA3029, 91ICA33, 91ICA201, 91PS(62)53>; 1,2,5,6-tetrathiocane <82TL3231>; 1,2,5,6-tetrathiocine <90CC34>; 1,3-dioxa-2-thia-6-azocane <81JCS1551>; 1,5-dithia-3,7-diazocine <87JOC1810>; 1,5-dithia-2,6-diazocine <86CB1077>; 1,3-dioxa-2,6-dithiocine <89IZV1273>; 1,5-dithia-2,4,6,8-tetrazocine derivatives <81JA1540, 85AX(C)1686, 85CC655, 85MI 926-01, 86CC807, 87JA868, 93CJC473>; 1,5-dithia-2,4,6,8-tetrazocane <88H(27)2581, 90JOC6098>; 1,2,4,6-tetrathia-3,5-diazocine <83CJC1185>; 1,5-dioxa-2,6-dithia-3,7-diazocine <92ZOR1404>; 1,2,3,4,5,6,7-heptathiocane <90TL5457>; 1,3,5-trithia-2,4,6,8-tetrazocine <84AG(E)988, 86AX(C)900, 89IC4147>.

9.26.3.4 Other Spectroscopic Methods

Raman spectroscopy was used to determine the disulfide stretching frequencies and torsion angles for 1,2,5,6-tetrathiocane and its perdeutero analog <86JA1271>. A Raman and infrared study of 1,3,5,7-tetraphenyl-1,3,5,7-tetrazocane has appeared <90JPR595>.

The ultraviolet spectra of 1,5-dithia-2,4,6,8-tetrazocines (**10**) ($\lambda_{\max}$ 306.5 nm) and (**11**) ($\lambda_{\max}$ 229 nm) were instrumental in the discovery of the unusual structural dependence on substitution that exists for this class of compounds <81JA1540>.

Magnetic circular dichroism measurements of several dithiatetrazocines have been reported <86IC3194>.



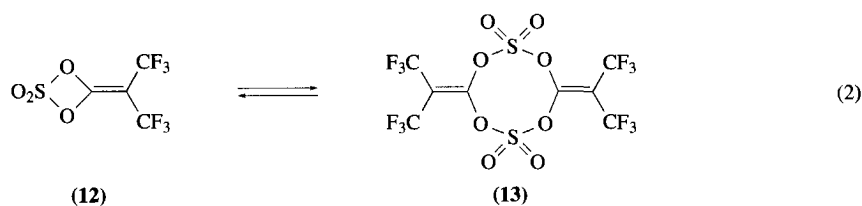
9.26.4 THERMODYNAMIC ASPECTS

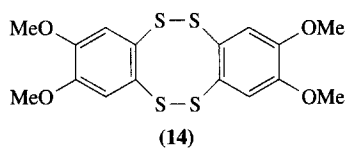
9.26.4.1 General Considerations

Melting and boiling points, when available, are given when the synthesis of individual compounds is mentioned throughout this chapter.

The ideal gas properties, C_p° , S° , $-(G^\circ - H^\circ_0)/T$, $H^\circ - H^\circ_0$, $\Delta_f H^\circ$, $\Delta_f G^\circ$, and $\log K^\circ_f$ to 1500 K, of 1,3,5,7-tetroxocane have been calculated <92MI 926-02>. The thermal properties of 1,3,5,7-tetranitro-1,3,5,7-tetrazocane have also been recently studied <84MI 926-02, 92MI 926-03, 94MI 926-01>.

Based on ^{19}F NMR data, sulfate (**12**) is believed to be in equilibrium with the dithiatetroxocane tetraoxide (**13**) (Equation (2)). A ΔH for the equilibrium was estimated to be -4 kcal mol^{-1} <70KGS1645>.

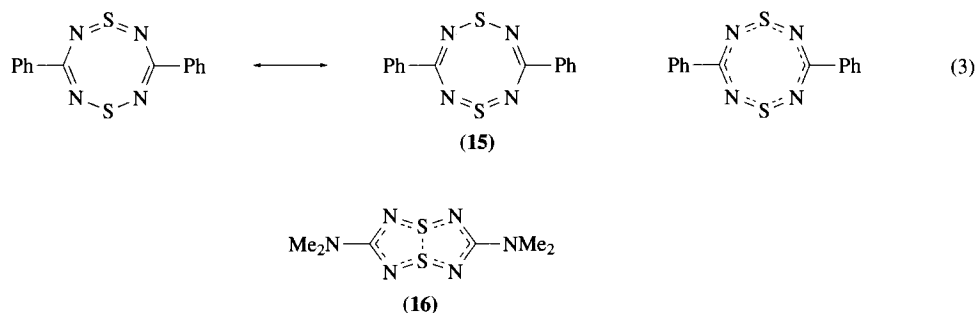




The electrochemical behavior of (14) was studied by cyclic voltammetry <85ZN(B)774>. The electrochemistry of several dithiatetrazocines has also been examined <93CJC473>.

9.26.4.2 Aromaticity of 1,5-Dithia-2,4,6,8-tetrazocine and Similar Compounds

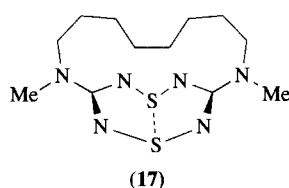
The first examples of 1,5-dithia-2,4,6,8-tetrazocine were prepared and characterized at the Woodward Research Institute <81JA1540>. An intriguing structural dichotomy was immediately apparent between compounds with varying substituents at the 3- and 7-positions. The ultraviolet spectra of 3,7-diphenyl-1,5-dithia-2,4,6,8-tetrazocine (15) ($\lambda_{\max}$ 306.5 nm) (Equation (3)) and 3,7-bis(dimethylamino)-1,5-dithia-2,4,6,8-tetrazocine (16) ($\lambda_{\max}$ 229 nm) were substantially different. X-ray crystallographic analysis of the two compounds showed (15) consisted of a nearly perfectly planar eight-membered ring; whereas, the heterocycle of (16) was folded about an axis drawn through the two sulfur atoms <81JA1540>. The S—S transannular distance in (15) is 3.79 Å and 2.428 Å in (16), which is longer than a disulfide bond (ca. 2.06 Å) but shorter than the sum of two sulfur van der Waals radii (3.6 Å) suggesting a partial bond <81JA1540>. Several crystal structures on dithiatetrazocine derivatives have been reported (see section 9.26.3.3).



The planar geometry and equal N—S bond lengths suggest that the 10- π electron systems, such as (15), have substantial aromatic character. Substituents at the carbon atoms at positions three and seven with π -donor capacity can induce pseudo-Jahn–Teller distortion leading to the bent, bicyclic 8- π system with the S—S transannular partial bond <84JA3437>.

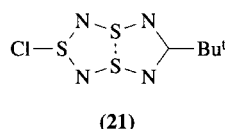
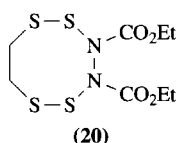
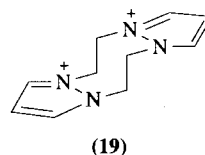
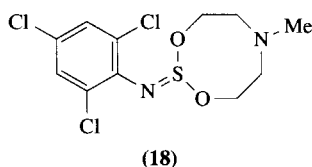
It was found that only one dimethyl amino substituent is necessary to destroy the planarity and aromaticity of dithiatetrazocines <89CC1137>.

Pascal has included these bent dithiatetrazocines in a list of “tormented aromatic compounds” <93PAC105>. In an attempt to discern the degree of aromaticity in the bent compounds, a cyclophane containing the dithiatetrazocine ring (17) was synthesized. X-ray analysis <94AX(C)108> showed the octamethylene chain passes directly over the dithiatetrazocine. Proton NMR chemical shifts of the methylene groups that are located over the internal portion of the ring fell in the range of δ 0.9–1.6 providing little evidence of ring current and aromaticity in these molecules.



9.26.4.3 Conformational Analysis

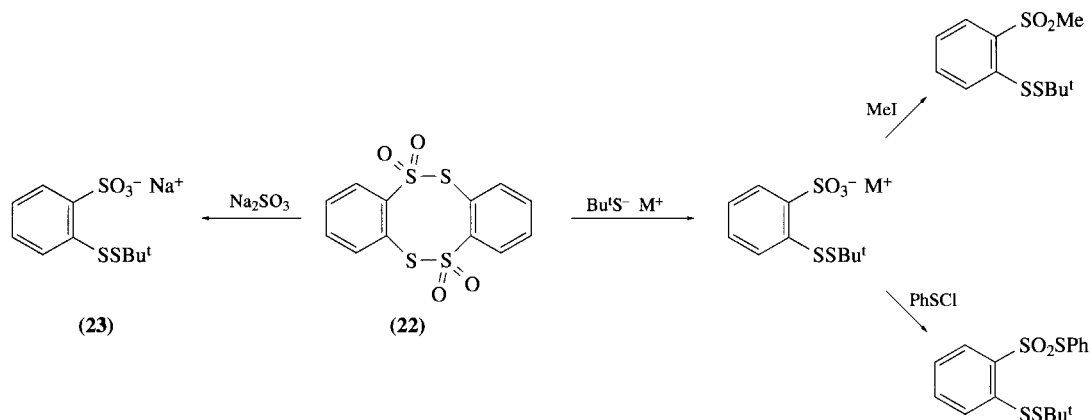
The molecular structure and conformational dynamics of dioxadithiazocane (**18**) <80NJC179> were studied by x-ray and NMR analyses. Compound (**18**) was found to exist as two pseudo-enantiomeric molecules. In the solid state, the molecule assumes two approximate boat-chair conformations with transannular sulfur–nitrogen distances of 2.94 Å and 2.99 Å. In CDCl₃ and *d*₆-benzene solutions, the material exists as an enantiomeric equilibrium of two isoenergetic boat-chair forms involving a pseudorotational path <81JCS(P2)1554>.



The dication (**19**) was found to exist in a chair conformation by x-ray analysis <91AX(C)2583> and the conformation of the 1,2,5,6-tetrathia-3,4-diazocane (**20**) was shown to be a crown in the solid state, also by x-ray crystallography <77MI 926-01>. 7-*t*-Butyl-3-chloro-1,3,5-trithia-2,4,6,8-tetrazocine (**21**) was found by x-ray analysis to have the shortest transannular S—S contact (2.378 Å) of any thiazyl compound <85AX(C)1686>.

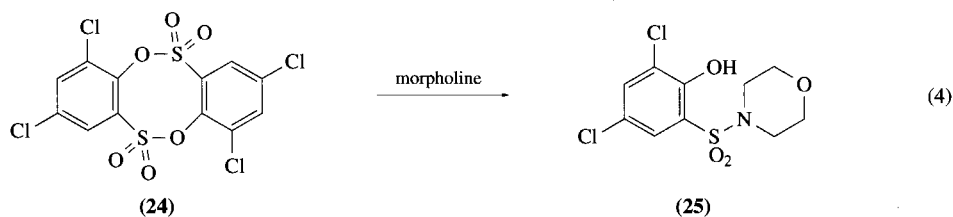
9.26.5 REACTIVITY OF FULLY CONJUGATED RINGS

Treatment of dibenzo-1,2,5,6-tetrathiocine 1,1,5,5-tetroxide (**22**) with *t*-butylthiolate gave 2-(*t*-butyldithio)benzenesulfinic acid, which was trapped with methyl iodide or benzenesulfonyl chloride in 90% and 70% yields, respectively (Scheme 2) <83JOC2943>. Reaction of (**22**) with sodium sulfite gave a quantitative yield of Bunte salt (**23**) (Scheme 2) <83JOC2943>.

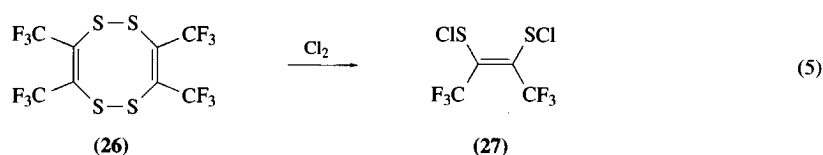


Scheme 2

Reaction of (**24**) with morpholine gave (**25**) in 72% yield (Equation (4)) <90JOC2558>.

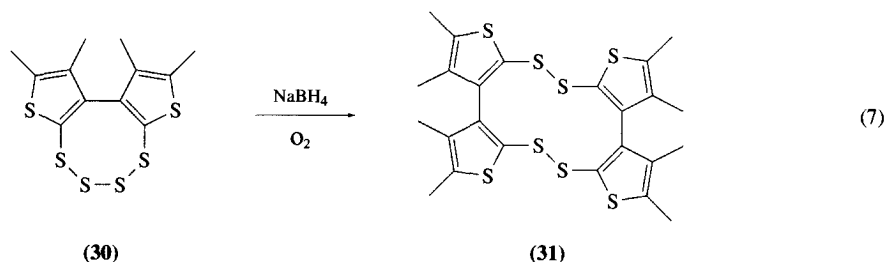
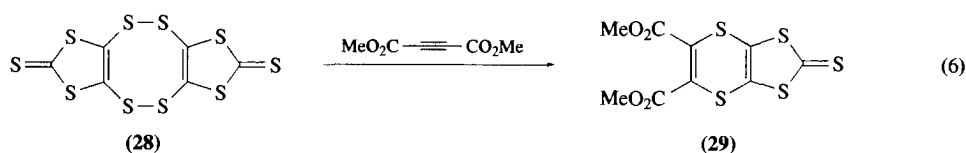


Treatment of tetrathiocine (**26**) with chlorine at low temperature gave the bis(sulfenyl) chloride (**27**) in 65% yield (Equation (5)) <94CB533>.



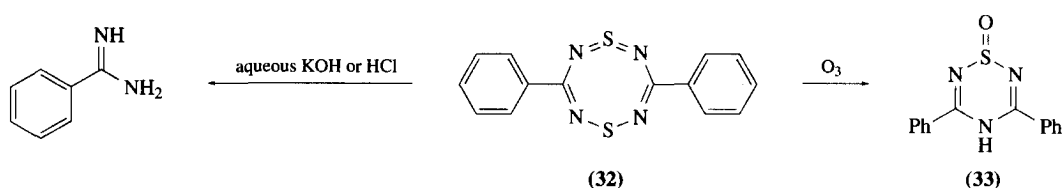
Reaction of C_6S_{10} (**28**) with dimethyl acetylenedicarboxylate gave thione (**29**) in 65% yield (Equation (6)) <90CC34>.

Treatment of (**30**) with NaBH_4 , followed by oxidative work up, gave (**31**) (mp 202°C) in 77% yield (Equation (7)) <94TL1977>.

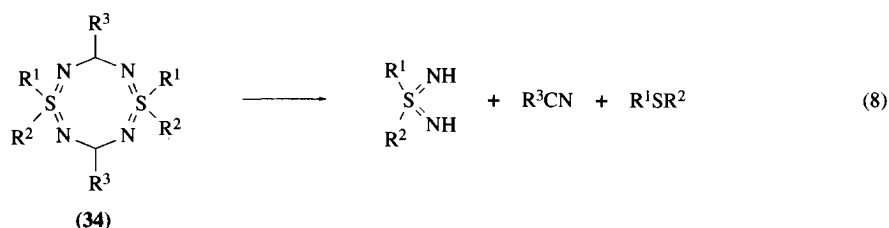


Dithiatetrazocines are quite stable due to their aromatic character (see Section 9.26.4.2), though a few reactions have been observed. Diphenyl-1,5-dithia-2,4,6,8-tetrazocine (**32**) was hydrolyzed by aqueous KOH or HCl in dioxane to benzamidine (Scheme 3) <81JA1540>. Reaction of (**32**) with ozone in dichloromethane gave thiatriazine (**33**) in 38% yield (Scheme 3) <89JCS(P1)2495>.

It has been reported that heating dithiatetrazocines (**34**) gave sulfur diimide, nitriles, and sulfides (Equation (8)) <85TL2739>.

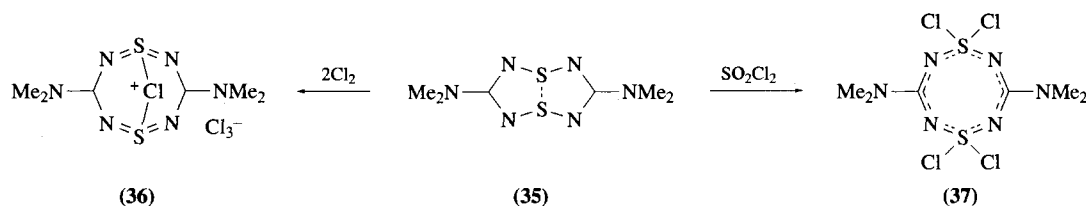


Scheme 3



Chlorination of bis(dimethylamino)-1,5-dithia-2,4,6,8-tetrazocine (**35**) gave bridged system (**36**) (mp $97-100^\circ\text{C}$ dec.) as orange, moisture sensitive crystals identified by x-ray analysis <85CC655>.

Chlorination of the same starting material with SO_2Cl_2 gave a quantitative yield of (37) (Scheme 4) <85MI 926-01, 86IC47>.



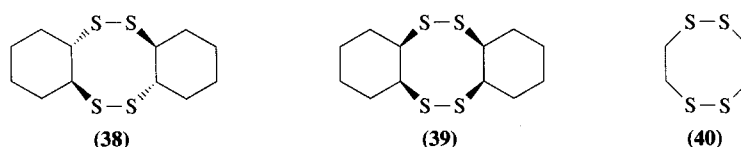
Scheme 4

A number of other oxidized derivatives of (35) have been prepared by the reaction of (35) with various oxidizing agents <87JA868>.

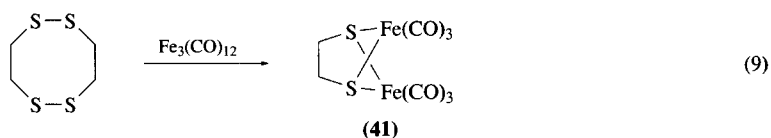
9.26.6 REACTIVITY OF NONCONJUGATED RINGS

Complexes of 1,3,5,7-tetrathiane with chromium and tungsten <83POL1363> and titanium tetrachloride <85PS(25)21> have been prepared.

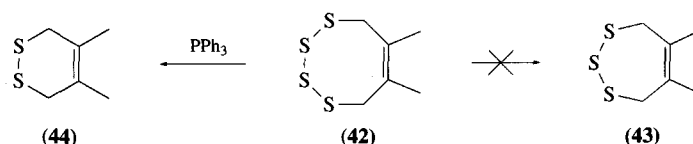
The bis(disulfide) moieties contained in 1,2,5,6-tetrathianes exhibit interesting reactivity. While eight-membered ring bis(disulfides) are uniquely stable, they rapidly polymerize at elevated temperatures <87JA6825, 89T91>. Compounds (38), (39), and (40) were found to polymerize in <15 min, when heated to their melting points in the presence of NaSMe <89T91>.



1,2,5,6-Tetrathiane reacts with $\text{Fe}_3(\text{CO})_{12}$ to give the complex $[\text{Fe}(\text{CO})_3]_2\text{-SCH}_2\text{CH}_2\text{S}$ (41), which was identified by x-ray analysis (Equation (9)) <86ICA191>.

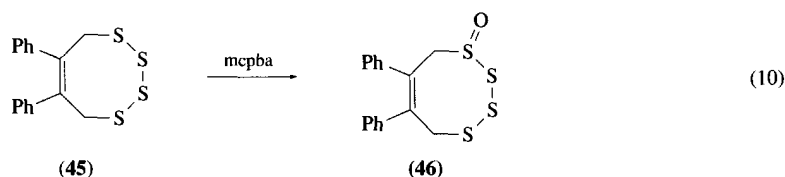


Dihydrotetrathiocine (42) was initially expected to undergo desulfurization to give the seven-membered ring (43) <81JOC2076>; however, on treatment with triphenylphosphine, (42) gave only the disulfide (44) (Scheme 5) <91TL7651, 94JOC806>.

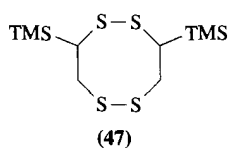


Scheme 5

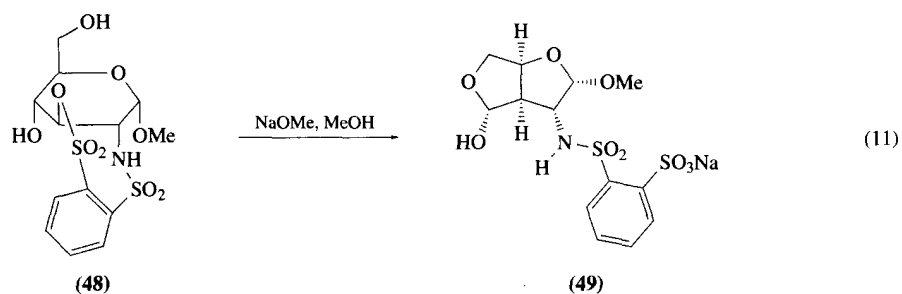
Treatment of (45) with one equivalent of *m*-chloroperbenzoic acid gave monoxide (46) (mp 135.3–137.3°C) in 35% yield (Equation (10)) <72JOC2367>. Reaction with two equivalents of oxidizing agent gave only sulfur and 3,4-diphenylthiophene due to the instability of (45) <72JOC2367>.



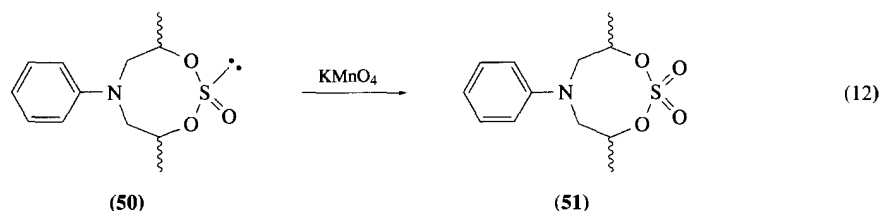
The pyrolysis of 3,8-bis(TMS)-1,2,5,6-tetrathiocane (**47**) was studied by pulse pyrolytic GC/MS. Compound (**47**) undergoes thermal decomposition via two mechanisms. The first pathway involves the formation of S_2 and trimethylvinylsilane, which reacts further to give CS_2 , SiS_2 , and lower alkanes. The second pathway involves loss of three sulfur atoms to form TMS-substituted thiophenes $\langle 85JOM(289)231 \rangle$. Compound (**47**) also undergoes reaction with $Fe_3(CO)_{12}$ to give a variety of sulfur-iron carbonyl complexes $\langle 86ZOK1540 \rangle$.



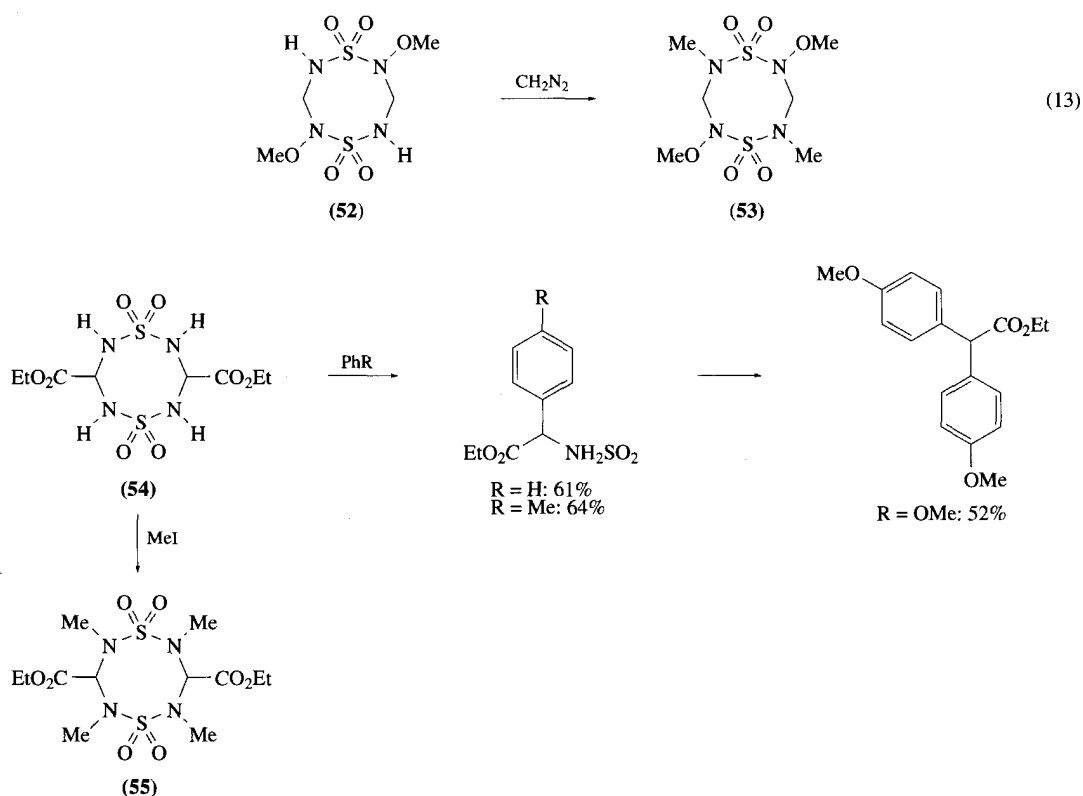
In an intriguing reaction, a dioxadithiazocine oxide moiety contained in (**48**) played two simultaneous roles as both a nitrogen protecting group and as a leaving sulfonyl group. Treatment of (**48**) with sodium methoxide in methanol at $50^\circ C$ gave the rearranged compound (**49**), as the sole product in 82% yield (Equation (11)) $\langle 82BCJ3254 \rangle$.



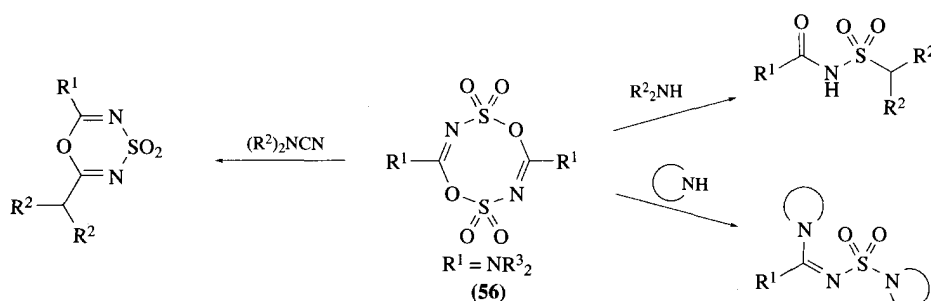
The oxidation of four isolated isomers of (**50**) (see Section 9.26.9.1.3), individually with potassium permanganate in acetone, gave two possible stereoisomers of (**51**) as the products in 35–77% yields (Equation (12)) $\langle 92BCJ2294 \rangle$.



The nitrogens of hydro-1,5-dithia-2,4,6,8-tetrazocin-1,1,5,5-tetroxide (**52**) were alkylated with diazomethane to give (**53**) (mp $202^\circ C$) (Equation (13)) $\langle 87AP(320)534 \rangle$. Compound (**54**) $\langle 90JOC6098 \rangle$ can readily be alkylated to (**55**) (mp $223\text{--}225^\circ C$) (Scheme 6) $\langle 88H(27)2581 \rangle$. Compound (**54**) is also reactive in electrophilic aromatic substitution reactions with benzene, toluene, and anisole $\langle 88H(27)2581 \rangle$. 1,5-Dioxa-2,6-dithia-3,7-diazocine 2,2,6,6-tetroxides (**56**) react with cyanamides to give oxathiadiazines in 32–95% yield; with acyclic, secondary amines to give sulfonylureas in 87–99% yield; and with cyclic amines to give sulfoguanidines in 78–93% yield (Scheme 7) $\langle 92ZOR1404 \rangle$.

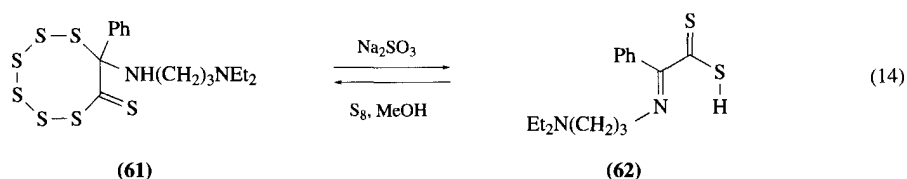


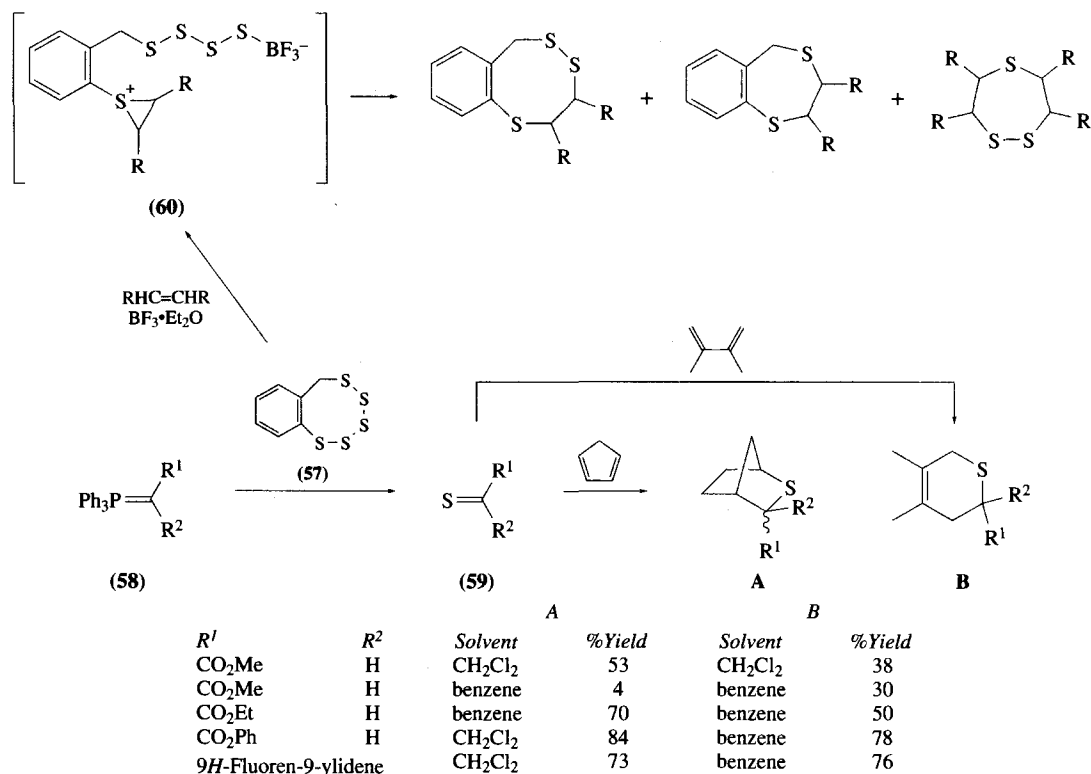
Scheme 6



Scheme 7

It has been found that pentathiocanes can act as sulfuration reactants in certain reactions. 6*H*-1,2,3,4,5-Benzopentathiocane (**57**) (BPTC) <90CL139> reacts with phosphorus ylides (**58**) to afford thiocarbonyl compounds (**59**) that have been then allowed to react *in situ* with conjugated dienes to form Diels–Alder adducts (**A**) and (**B**) (Scheme 8) <90S785>. Alkenes react with (**57**) in the presence of $\text{BF}_3\text{-Et}_2\text{O}$ to give a variety of cyclic di- and trisulfides in 13–40% yield, apparently via the episulfonium intermediates (**60**) (Scheme 8) <92TL2517>. Hexathiocane-7-thione (**61**) reacts with aqueous sodium sulfite to give dithioglyoxylic acid (**62**), which can be transformed back to the starting materials with sulfur (Equation (14)) <72M1661>.



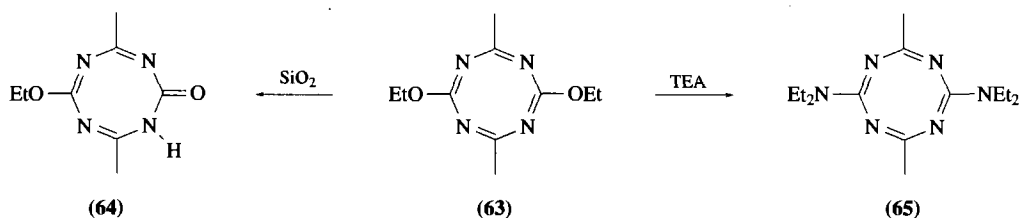


Scheme 8

9.26.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

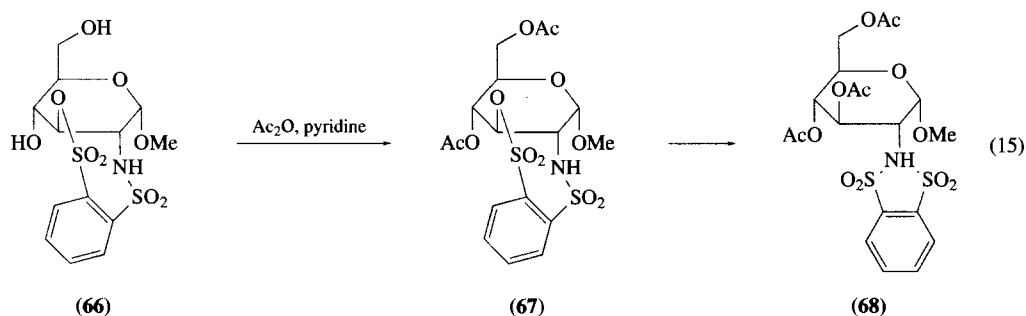
There are few examples of reactions involving substituents attached to eight-membered ring heterocycles.

A solution of tetrazocine (63), when stirred for a few days in the presence of silica gel, gave hydrolysis product (64) (mp 86°C) (Scheme 9) <83AG(E)543>. Treatment of (63) with triethylamine under refluxing conditions gave (65) (bp 130°C/0.01 torr) in 81% yield (Scheme 9) <83AG(E)543>.



Scheme 9

In a few cases, substituents have been found to undergo reactions without decomposition of the eight-membered ring. The sugar derivative (66) could be acetylated in acetic anhydride and pyridine to give the diacetate (67) in 65% yield and ring-opened product (68) in 13% yield (Equation (15)). On longer reaction time, (67) gradually converted to ring-opened (68) <82BCJ3254>.



9.26.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

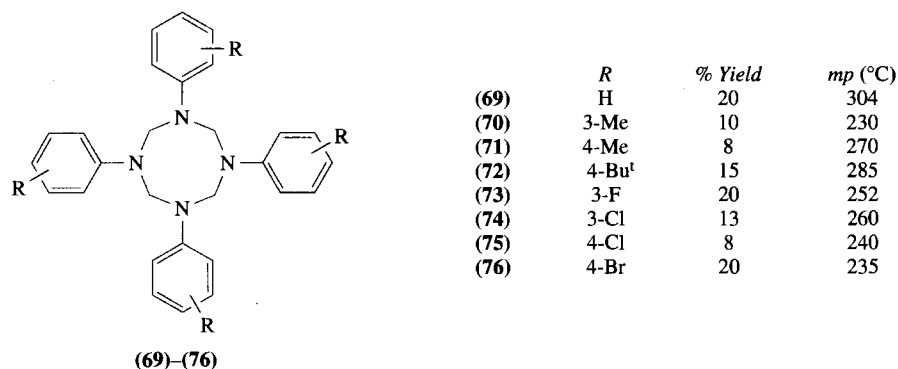
As in Section 9.26.7, there are few examples in this category. One large class of materials that should be considered here are 1,3,5,7-tetranitro-1,3,5,7-tetrazocane and derivatives. Substituents on the nitrogen atoms impart reactivity to these propellants and explosives. The reader is referred to a 1990 review on the chemistry of these materials <90AHC(50)1>.

9.26.9 RING SYNTHESSES

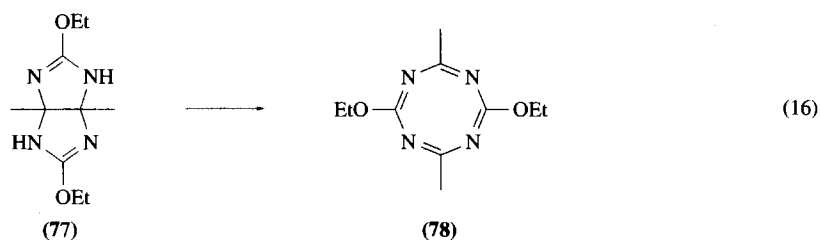
9.26.9.1 Synthesis of Rings Containing Four Heteroatoms

9.26.9.1.1 1,3,5,7-Substitution

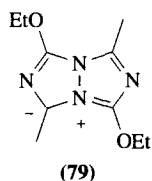
A number of 1,3,5,7-tetraaryl-1,3,5,7-tetrazocanes (**69**)–(**76**) have been synthesized by the reaction between aromatic amines and paraformaldehyde <87JPR1087>.



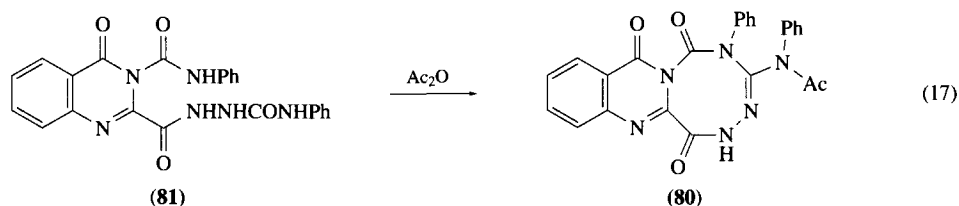
Reaction of dimethylglycoluril derivative (**77**) with *t*-butyl hypochlorite and potassium *t*-butoxide afforded (**78**) (mp 26°C) in 50% yield (Equation (16)) <83AG(E)543>.



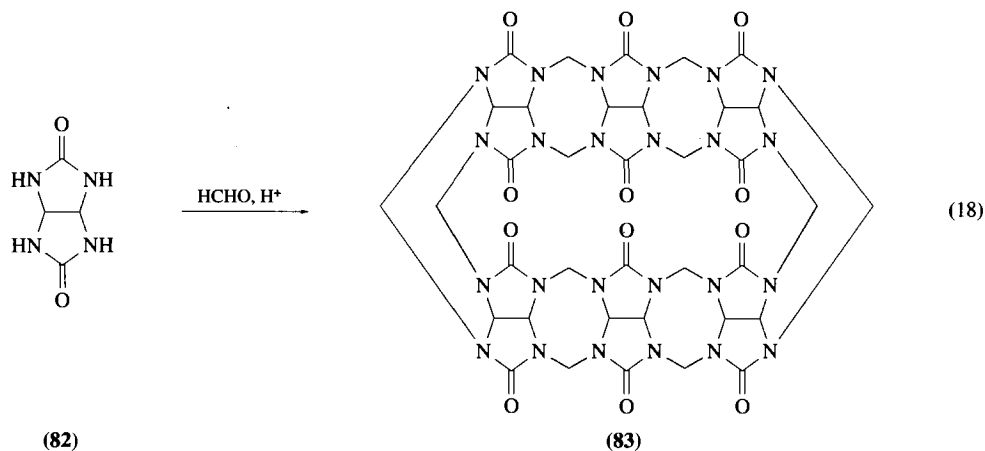
Based on NMR evidence, the involvement of tetraazapentalene (**79**) was ruled out.



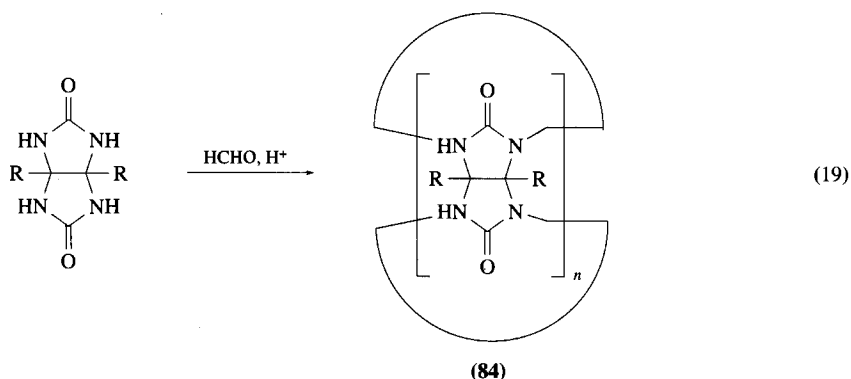
A novel tetrazocine (**80**) (mp 114°C) was prepared in 70% yield by boiling (**81**) in acetic anhydride, which induced ring closure and acetylated the exocyclic amine (Equation (17)) <93JCS577>.



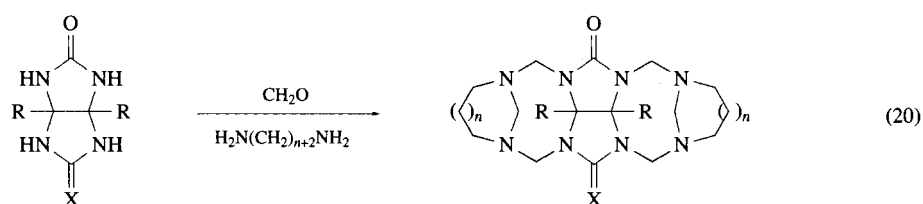
In 1905, Behrend *et al.* reported the synthesis of a white crystalline material in 40–70% yield from the acidic condensation of glycoluril (**82**) with excess formaldehyde followed by dissolution in concentrated sulfuric acid and precipitation with cold water (Equation (18)) <05LA(339)1>. This reaction was reexamined by Freeman *et al.* in 1981 and the product structure was determined by x-ray analysis of a calcium bisulfate complex <81JA7367>. The structure consists of six 1,3,5,7-tetrazocane units fusing the six glycolurils (see Section 9.26.3.3 for references on the x-ray crystallographic analysis of cucurbiturils and Section 9.26.11.1.2 for applications of the compound and its derivatives). The trivial name cucurbituril was coined for (**83**) for its gourd or pumpkin-like shape <81JA7367>.



An analog of cucurbituril consisting of five glycoluril units has been prepared from dimethylglycoluril in 16% yield and has been termed decamethylcucurbit[5]uril (**84**, R = Me, $n = 5$) (mp > 280°C) (Equation (19)) <92AG(E)1475>.

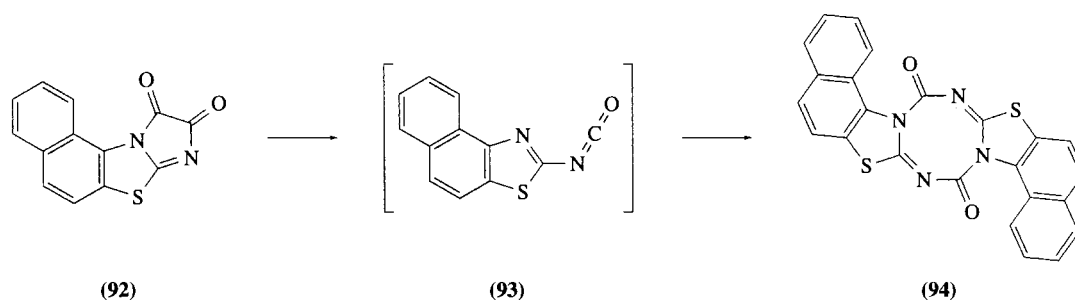


The slow addition of diamines to refluxing solutions of glycoluril derivatives and formaldehyde in methanol yielded novel heterocycles (**85**)–(**91**) related to cucurbituril (Equation (20)) <85JOC60>.



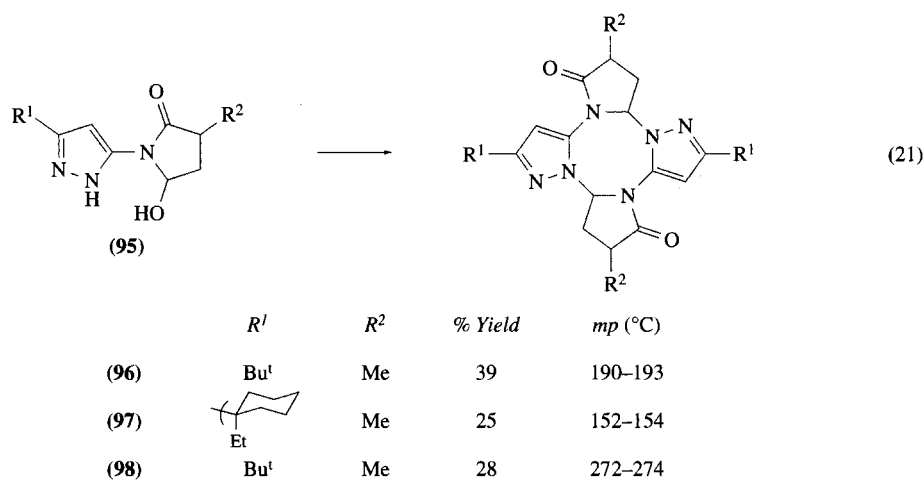
	X	R	n	% Yield	mp (°C)
(85)	O	H	0	62	256–258
(86)	O	H	1	54	273–275
(87)	O	Me	0	28	248–249
(88)	O	Me	1	70	297–299
(89)	O	Me	2	40	282–283
(90)	O	Ph	1	28	270–272
(91)	S	H	1	20	242–243

Thermolysis of (**92**) in DMF gave tetrazocane (**93**) (mp > 320°C, $\lambda_{\max}$ 267, 340, 375 nm) as yellow crystals in 85% yield, presumably via a [4 + 4] cycloaddition of intermediate (**94**) (Scheme 10) <86JHC1265>.



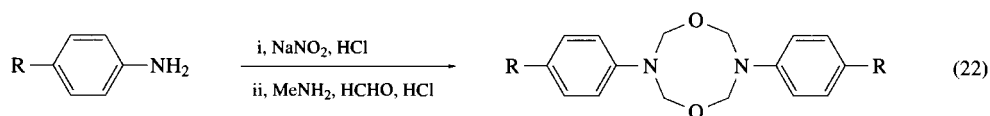
Scheme 10

Treatment of 5-hydroxypyrrolidinones (**95**) with a catalytic amount of *p*-toluene-sulfonic acid in refluxing toluene afforded tetrazocanes (**96**)–(**98**) as white solids (Equation (21)) <89JHC1713>.



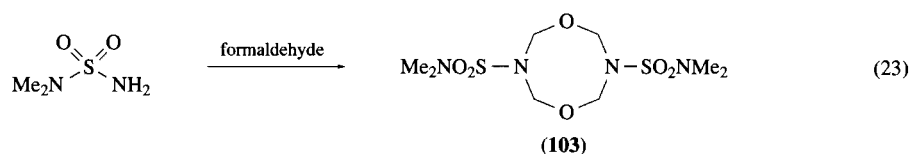
Few synthetic papers have been published on 1,3,5,7-tetraoxocanes.

4-Substituted benzenediazonium chloride, when treated with a methylamine–formaldehyde mixture at –5 to –10°C under controlled pH conditions afforded 1,5,3,7-dioxadiazocanes (**99**)–(**102**) (Equation (22)) <85TL1043>. A mechanism to account for the product was proposed <87ZN(C)41>.



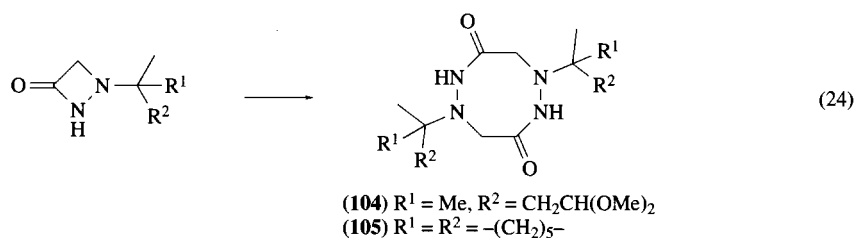
	R	% Yield	mp (°C)
(99)	CF ₃	18	195
(100)	CO ₂ Me	49	217
(101)	CN	50	227
(102)	NO ₂	53	258

Formaldehyde reacted with *N,N*-dimethylsulfamide to give (103) (mp 202°C dec.) (Equation (23)) <77AP(310)404>.



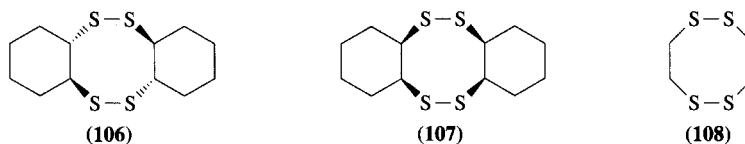
9.26.9.1.2 1,2,5,6-Substitution

1,2,-Diazetidin-3-ones substituted at N-1 dimerized on standing to give materials with the suggested structures (104) (mp 149–151°C) and (105) (mp 310–315°C) (Equation (24)) <84JOC4415>.



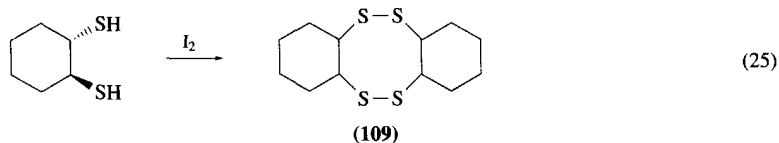
The chemistry of 1,2,5,6-tetrathiocanes is complex. Compounds having 1,2-dithiol moieties form cyclic bis(disulfides) in relatively dilute solutions (ca. 1 mM) but polymerize at high concentrations <87JA6825>.

Whitesides and co-workers have prepared, characterized, and examined the stability of several 1,2,5,6-tetrathiocanes <89T91>. The cyclic bis(disulfides) (106) (mp 178–181°C), (107) (mp 110–115°C), and (108) (mp 62–64°C) were prepared by iodine oxidation of 1,2-dithiol precursors in 21, 15, and 41% yields, respectively <89T91>.

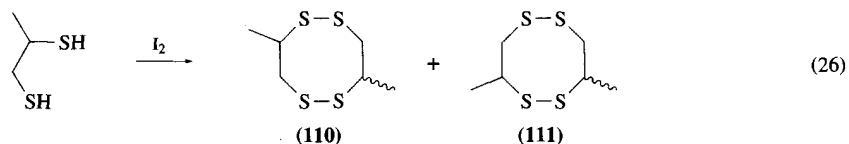


Two efficient syntheses have been reported for the parent 1,2,5,6-tetrathiocane (108). Treatment of 1,2-ethanedithiol with TEA and carbon tetrachloride reportedly gave (108) in 85% yield <89MI 926-01>. Benzyltriethylammonium tetrathiomolybdate, (BnNEt₃)₂MoS₄, a stable sulfur transfer agent, reacted with 1,2-dibromoethane to give (108) in 58% yield <94JOC1354>.

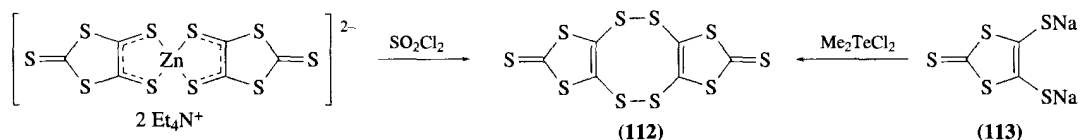
trans-1,2-Cyclohexanedithiol reacted with chlorosulfane, S₄Cl₂, under dilute conditions to give tetrathiocane (109) (mp 81–82°C) in 9% yield (Equation (25)). 1-Substituted 1,2-cyclohexanedithiols or *o*-benzenedithiols do not give cyclic compounds with S₄Cl₂ <67AG(E)703>.



A mixture of *cis/trans*-3,7- (110) and *cis/trans*-3,8-dimethyl-1,2,5,6-tetrathiocane (111) was prepared in 75% yield via the oxidation of 1,2-propanedithiol with iodine (Equation (26)) <88JA7813>.

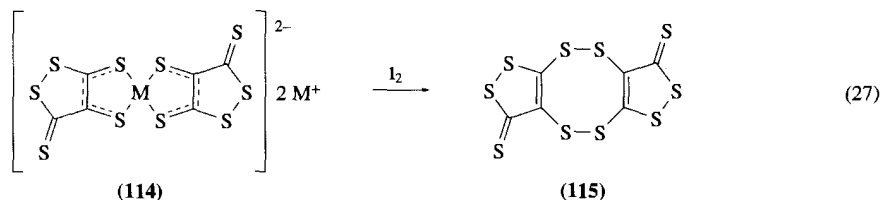


Treatment of the zinc complex $(\text{Et}_4\text{N})_2[\text{Zn}(\text{C}_3\text{S}_2)_2]$ with thionyl chloride in acetonitrile at -40°C gave C_6S_{10} (112) in 46% yield (Scheme 11) <90CC34>. Similar selenium and tellurium complexes, when oxidized with iodine in acetonitrile, also gave (112) (mp $148\text{--}149^\circ\text{C}$) <93POL2849>. Compound (112) (mp 149°C dec., λ_{max} (CH_2Cl_2) 234, 272, 372 nm), isolated as a red solid, could also be prepared by the reaction of the dithio disodium salt (113) with dimethyltellurium dichloride in methanol at room temperature in 49% yield (Scheme 11) <91JCS(P1)3341>.

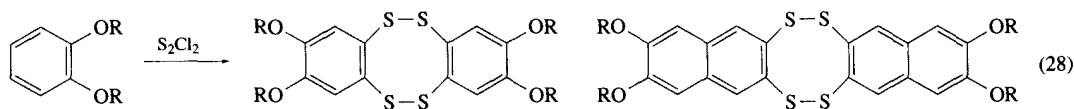


Scheme 11

Selenium and tellurium complexes (114, $\text{M} = \text{Se}$ or Te) afforded tetrathiocine (115, mp $152\text{--}154^\circ\text{C}$) in 12% yield when treated with iodine (Equation (27)) <93POL2849>.



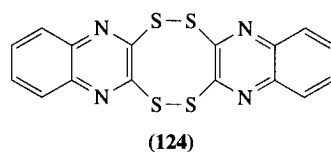
Dibenzo and dinaphthotetrathiocines (116)–(123) are formed in polar solvents by reaction of disulfur dichloride with the appropriate aromatic compound activated by alkoxy substituents (Equation (28)) <89PS(42)111>.



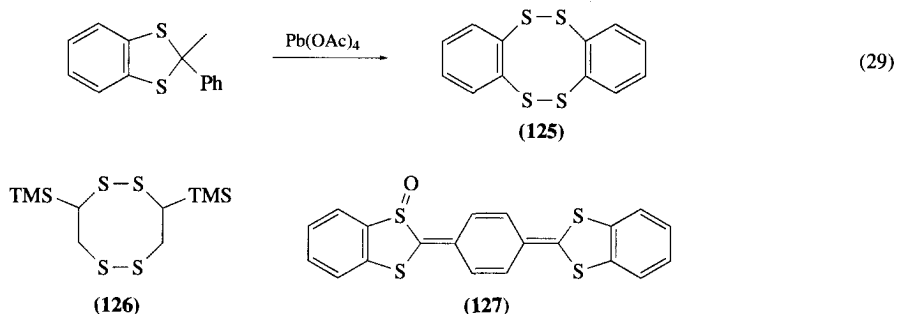
	R	% Yield	mp ($^\circ\text{C}$)		R	% Yield	mp ($^\circ\text{C}$)
(116)	Me	65	254	(122)	H	29	260 dec.
(117)	Et	16	166	(123)	Me	33	245
(118)	Pr^n	29	149				
(119)	Pr^i	65	NA				
(120)	$-\text{CH}_2-$	52	220				
(121)	$(\text{CH}_2)_2$	52	285				

Several bis(disulfide) compounds in this class are formed in low yields or as reaction byproducts. The pyrolysis of diallyl disulfide at 150°C afforded *cis/trans*-3,7- and *cis/trans*-3,8-dimethyl-1,2,5,6-tetrathiocane in trace quantities <88JA7813>. Compound (124) (mp $283\text{--}285^\circ\text{C}$ subl.) is formed as

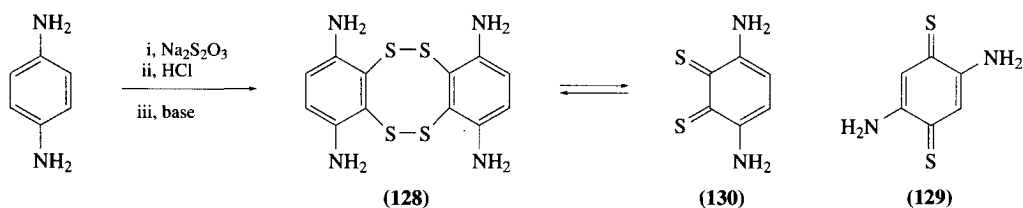
a byproduct in 39% yield of the reaction of 2,3-dimercaptoquinoxaline and methyl propiolate <85KGS862>.



Dibenzotetrathiocine (**125**) is formed in low yield on oxidation of 2-methyl-2-phenyl-1,3-benzodithiol with lead tetraacetate (Equation (29)) <83AJC2499>. The reaction of elemental sulfur, trimethylvinylsilane, and $\text{Fe}_3(\text{CO})_{12}$ gave (**126**) (mp 137–138°C) as well as a variety of other compounds <83JOM(252)133>. The regiochemistry of (**126**) was assigned by UV spectral data and by comparison with a seven-membered ring coproduct identified by x-ray structure. Reaction of 1,2-ethanedithiol with iodine and TEA gave 1,2,5,6-tetrathiocane in 10% yield along with a 16-membered ring tetrasulfide and polymer <83PS(15)27>. 1,2,5,6-Tetrathiocane has been detected by MS in the product mixture of the reaction of dithiol acetals with benzenesulfonyl chloride <84MI 926-03>. The pyrolysis of sulfone (**127**) gave dibenzo-1,2,5,6-tetrathiocine (**125**) in 14% yield <78JOC2084>.

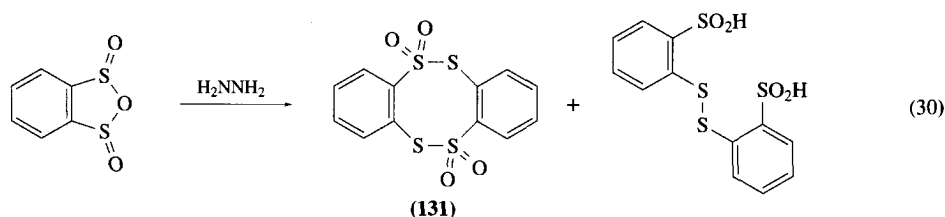


Reaction of phenylenediamine with an excess of sodium thiosulfate, followed by treatment with hydrochloric acid and then basification gave (**128**) (mp 22°C, λ_{max} 491 nm, $\log \epsilon$ 4.02) as deep red crystals (Scheme 12) <87JOC1874>. The product had originally been identified as the 1,4-dithioquinone (**129**) <03JCS1201> and then as the 1,2-dithioquinone (**130**) <68JOC2132>. The red color is thought to be due to (**130**), which is in equilibrium with (**128**) (Scheme 12) <87JOC1874>.

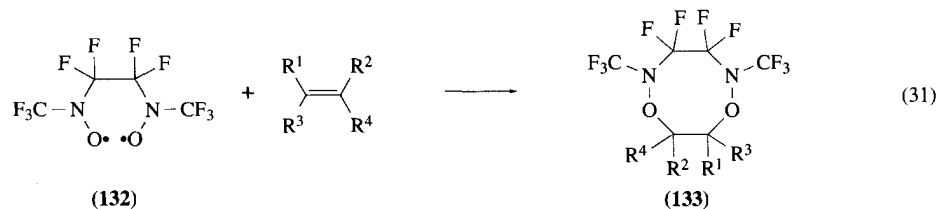


Scheme 12

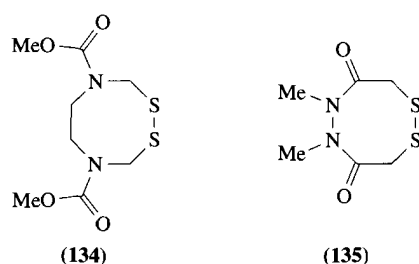
Treatment of 1,2-benzenedisulfinic anhydride with anhydrous hydrazine in acetonitrile at 10°C gave, in 55% yield, dibenzo-1,2,5,6-tetathiocin 1,1,5,5-tetroxide (**131**) (mp 265–270°C dec.) and 2,2'-dithio-bis(sulfinic acid) in 25% yield (Equation (30)) <83JOC2943>. Compound (**131**), although insoluble in most common organic solvents and only slightly soluble in DMF and DMSO, is believed to be monomeric based on the MS observation of a strong molecular ion peak at m/e 344 and no evidence of higher mass material. The reactivity of (**131**) also supports the structural assignment (see Section 9.26.5).



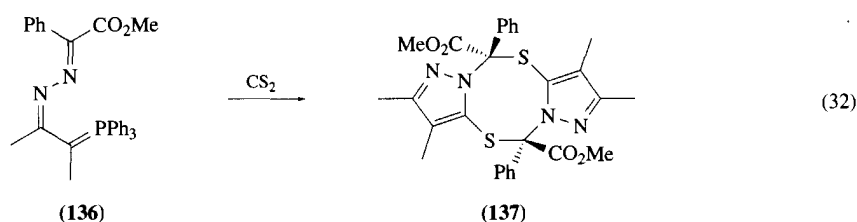
Reaction of dioxyl (**132**) with substituted alkenes gave dioxadiazocanes (**133**) in poor yields (trace–7%) in the condensed phase and in high yields (11.5–78%) in the gas phase (Equation (31)). A variety of alkene substituents (H, F, Cl, Br, Me, CF₃, COF, COCl) were examined <93JFC(65)115>.



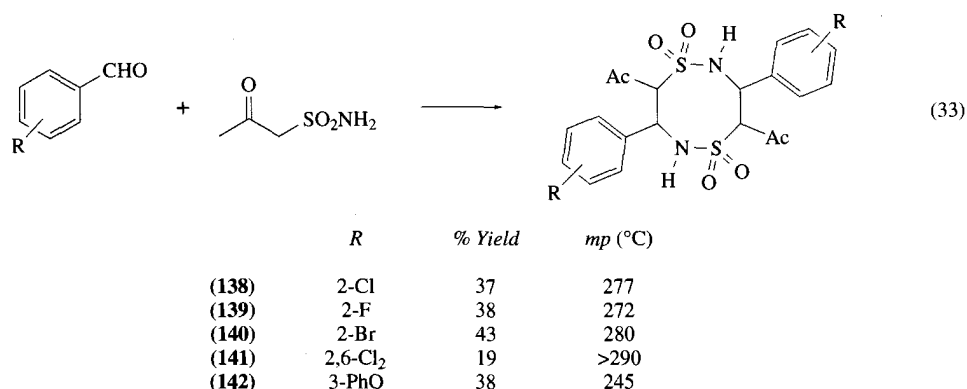
Disulfides (**134**) (oil) and (**135**) (mp 155°C) were prepared (in the dithiol forms) as alternative reagents to dithiothreitol for the reduction of disulfide linkages. The dithiol of (**135**) was found to be an acceptable replacement to dithiothreitol <93JOC633>.



The reaction of ylide (**136**) in a sealed tube in carbon disulfide at 140°C for 1.5 h gave (**137**) (mp 206–207°C) as colorless crystals in 14% yield (Equation (32)) <87JOC1810>.



Substituted benzaldehydes were reacted with 2-oxopropanesulfonamide to give dithiadiazocanes (**138**)–(**142**) (Equation (33)) <86CB1077>.

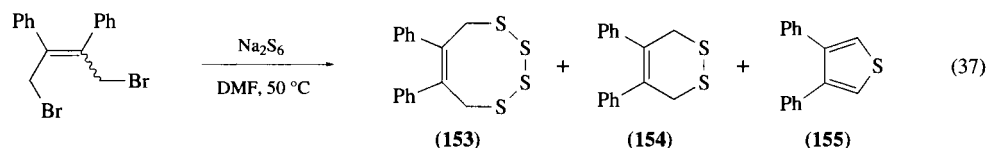


The reaction of formaldehyde, methylamine, and hydrogen sulfide was believed to have given the four-membered ring (**143**) <35JCS865>. On close examination of mass spectral and NMR evidence, the actual product was found to be dithiadiazocane (**144**) <77JOC393>.

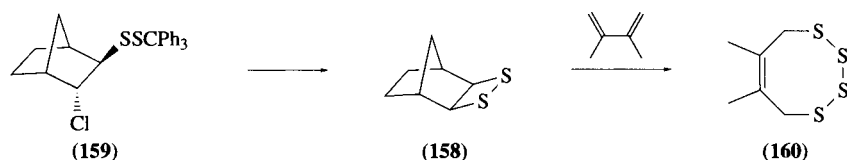
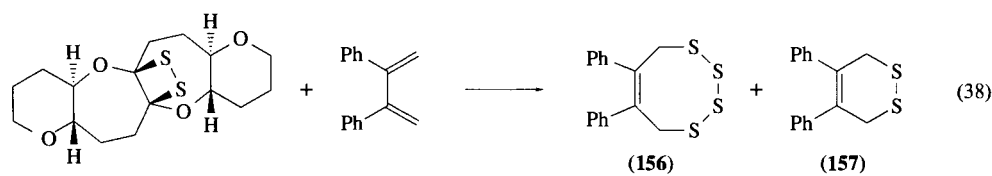
The reaction of methyl 2-amino-2-deoxy- α -D-glucopyranoside with 1,2-benzenedisulfonyl dichloride in pyridine at room temperature gave the fused ring adduct (**145**) (mp 131–132°C, $[\alpha]_D + 149^\circ$, c 1.0, acetone) in 87% yield (Equation (34)) <82BCJ3254>.

9.26.9.1.3 Other substitution patterns

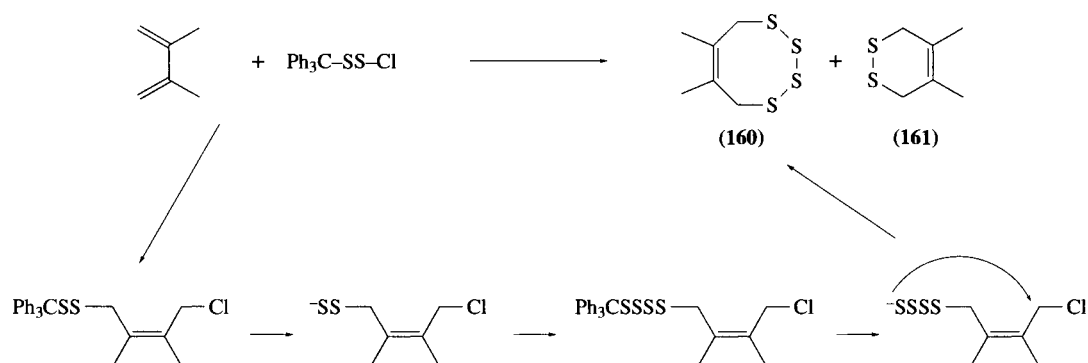
A mixture of *cis*- and *trans*-1,4-dibromo-2,3-diphenyl-2-butene, when treated with sodium polysulfides, gives dihydro-1,2,3,4-tetrathiocine (**153**) (mp 151–152°C) and side products (**154**) and (**155**) in 70–80% yield in a ratio of 1.5 : 1 : 1, respectively (Equation (37)) <72JOC2367>.



Dithiatopazine, serving as a sulfur-transfer agent, reacts with 2,3-diphenyl-1,3-butadiene to give dihydro-1,2,3,4-tetrathiocine (**156**) (mp 137–139°C) and disulfide (**157**) in 28 and 25% yield, respectively (Equation (38)) <88JA4868, 90JA3029>. Intermediate (**158**), prepared by the thermolysis of (**159**), is also a proposed sulfur-transfer agent and gave (**160**) when treated with 2,3-dimethyl-1,3-butadiene in low yield (Scheme 14) <93TL4289>. In a similar reaction sequence, chloro-(triphenylmethyl)disulfide reacted with 2,3-dimethyl-1,3-butadiene to give (**160**) and (**161**) in 35% and 30% yields, respectively, reported via the stepwise mechanism shown (Scheme 15) <91TL7651>. The tetrathiocine analog of myrcene (**162**) (yellow oil) was synthesized by treatment of bis(thio-sulfate) (**163**), prepared from disulfide (**164**), with disodium disulfide (Scheme 16) <82JCS(P1)1089>. Compound (**162**) was also observed in the product mixture obtained by the irradiation of myrcene and sulfur with sunlight or a medium-pressure mercury vapor lamp (Scheme 16) <82JCS(P1)1089>.

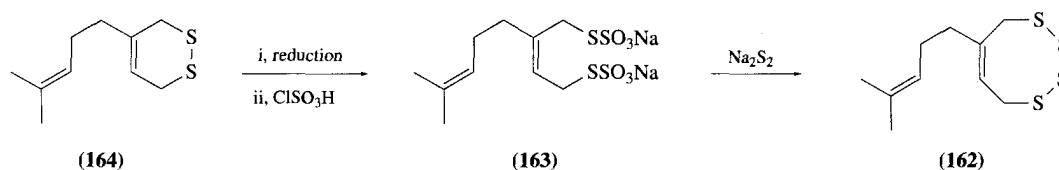


Scheme 14

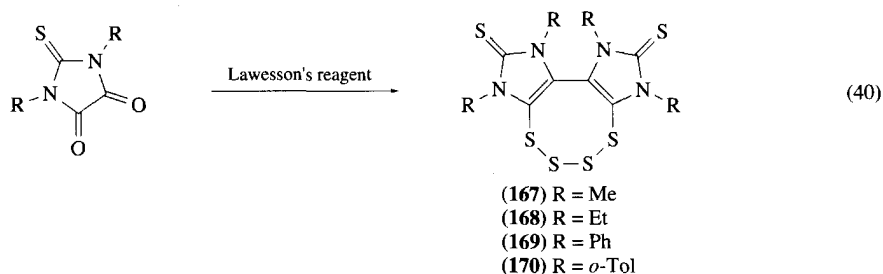
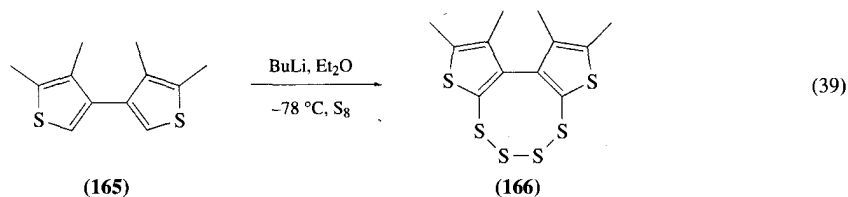


Scheme 15

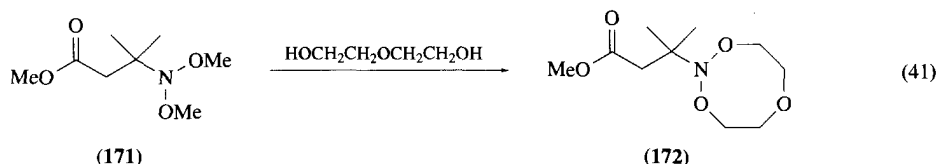
Lithiation of (**165**) and treatment with S_8 gave 1,2,3,4-tetrathiocine (**166**) in 51% yield (Equation (39)) <94TL1977>. The reaction of 1,3-disubstituted imidazolidinetrione-2-thio compounds with a slight excess of Lawesson's reagent in refluxing toluene gave the tetrathiocanes (**167**)–(**170**) in nearly quantitative yields (Equation (40)) <88PS(37)189>.



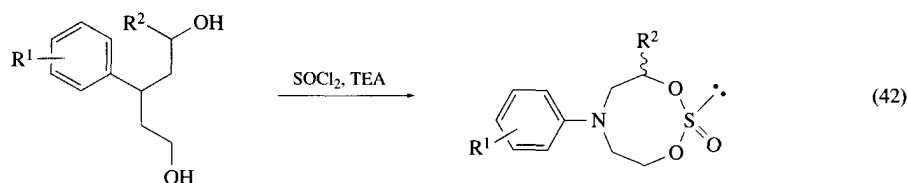
Scheme 16



The dimethoxy amine (171) was allowed to react with diethyleneglycol to give the 1,3,6-trioxa-2-azocane (172) as an oil in 30% yield (Equation (41)) <921ZV1648>.

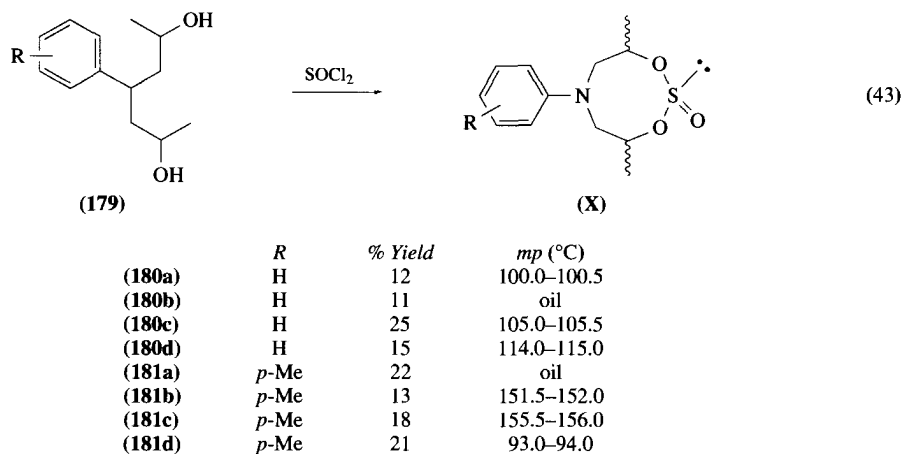


Reaction of the appropriate diol with thionyl chloride gave a variety of dioxathiazocanes (173)–(178) (Equation (42)). In each case with one substituent on the eight-ring, two isomers could be isolated by chromatography on silica gel and were found not to equilibrate at elevated temperatures. The isomers were found to be *cis* and *trans* forms based on ^{13}C and ^1H NMR data <84JHC37>.

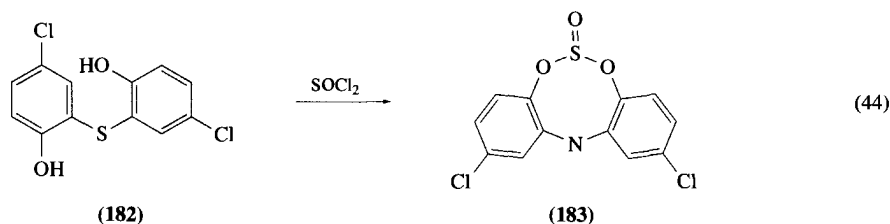


	R^1	R^2	Stereochemistry	% Yield	mp ($^\circ\text{C}$)
(173a)	<i>m</i> -Me	Me	<i>trans</i>	21	71.8–73.3
(173b)	<i>m</i> -Me	Me	<i>cis</i>	20	97.5–99.0
(174a)	<i>p</i> -Me	Me	<i>trans</i>	10	79.1–80.0
(174b)	<i>p</i> -Me	Me	<i>cis</i>	8	98.0–99.4
(175a)	<i>m</i> -Cl	Me	<i>trans</i>	15	95.8–96.8
(175b)	<i>m</i> -Cl	Me	<i>cis</i>	10	104.7–105.0
(176a)	<i>p</i> -Cl	Me	<i>trans</i>	8	90.0–91.0
(176b)	<i>p</i> -Cl	Me	<i>cis</i>	9	92.6–93.1
(177)	<i>m</i> -Me	H		40	64.5–65.2
(178)	<i>m</i> -Cl	H		25	78.8–79.4

The synthesis of dimethyl analogs of the above dioxathiazocanes has also been studied in detail. The reaction of diol (**179**) with thionyl chloride in benzene at 0–5 °C gave (**180**; R = H) or (**181**; R = Me) in 63% and 74% yields, respectively (Equation (43)). Each compound was separated into four stereoisomers and physical and spectral data were collected for each isomer <90JHC143>.

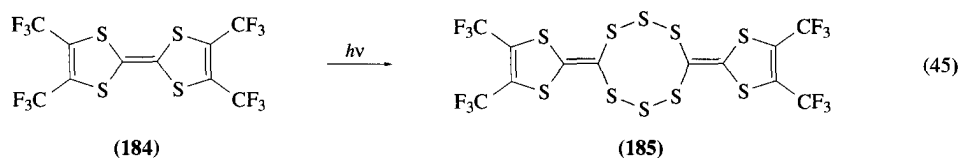


Reaction of the bis(hydroxyphenyl)sulfide (**182**) with thionyl chloride in pyridine gave (**183**) (mp 130.5–131.5 °C) in 92% yield (Equation (44)) <89IZV1273>.



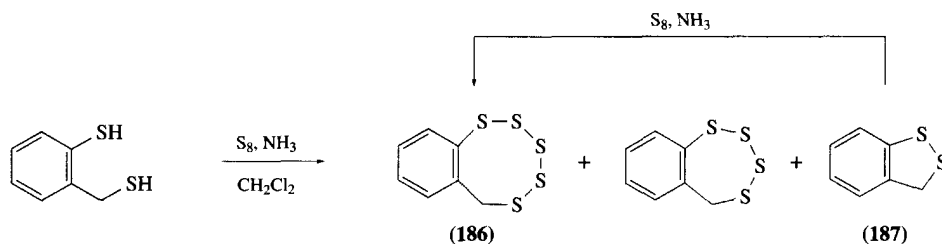
9.26.9.2 Synthesis of Rings Containing Five or More Heteroatoms

An unusual transformation took place when (**184**) was irradiated with 254 nm light; the reaction product (**185**) was formed in 36% yield (assuming a stoichiometry of 4 moles of (**184**) required for 1 mole of (**185**), or in 27% yield if 3 : 1 stoichiometry is assumed) (Equation (45)) <73JA4379>.



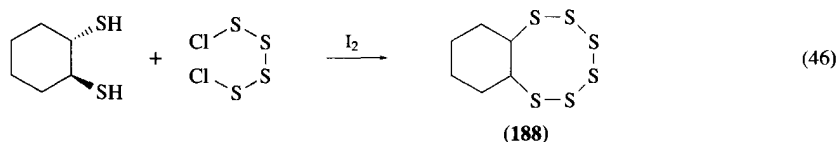
Sato *et al.*, found that treatment of 2-(thiomethyl)benzene with elemental sulfur in liquid ammonia gave 6*H*-benzo[*g*]-1,2,3,4,5-pentathiocine (**186**) (mp 61 °C) in 18% yield along with a seven-membered ring polysulfide and the five-membered ring compound (**187**) (Scheme 17) <88BCJ1647>. Compound (**187**) could be converted to (**186**) by treatment with sulfur and liquid ammonia (Scheme 17) <90CL139>.

Treatment of *trans*-1,2-cyclohexanedithiol and S₄Cl₂ with iodine under dilute conditions gave (**188**) (mp 191.5–193 °C) in 52% yield (Equation (46)) <67AG(E)703>. Compound (**188**) has also been found in the complex product mixture formed by the high temperature reaction of cyclohexene, S₈,

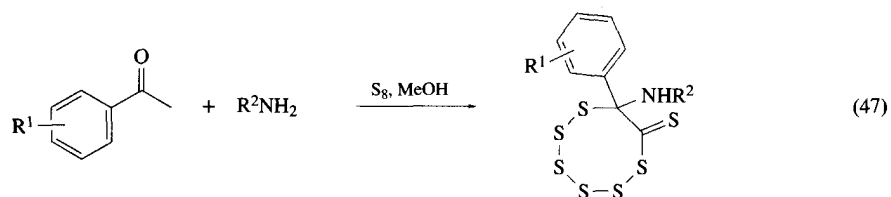


Scheme 17

and triiron dodecacarbonyl <81IZV2572>. The reaction of S_8Cl_2 with geminal dithiols gave 1,2,3,5,6,7-hexathiocanes in low yields <79ZN(B)1031>.

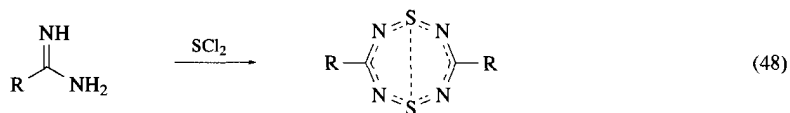


The reaction of primary aliphatic amines, sulfur, and methyl aryl ketones in methanol at room temperature reportedly afforded 1,2,3,4,5,6-hexathiocan-7-thiones (189)–(196) in reasonable yields (Equation (47)) <69LA(723)119, 72M1661>.



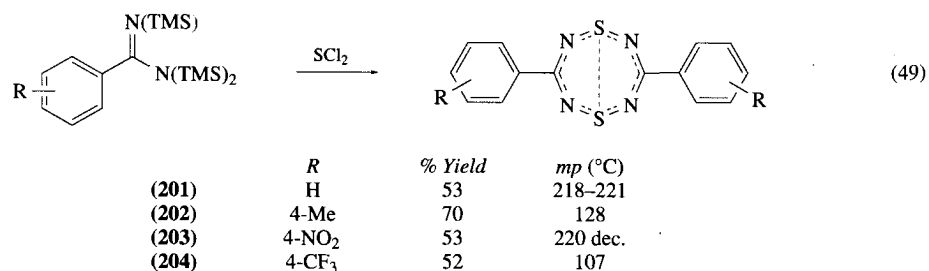
	R^1	R^2	% Yield	mp (°C)
(189)	H	$C_6H_5(CH_2)_2$	63	127.5–128
(190)	H	cyclohexyl	76	147.5–148
(191)	H	$Et_2N(CH_2)_2$	66	94.5–95
(192)	H	$Me_2N(CH_2)_3$	56	132–133
(193)	H	$Et_2N(CH_2)_2$	23	75.7–76
(194)	H	$MeO(CH_2)_2$	59	92–93
(195)	4- ClC_6H_4	$n-C_3H_7$	38	82–83
(196)	4- $MeOC_6H_4$	$n-C_3H_7$	50	84.5–85.5

In the first syntheses of 1,5-dithia-2,4,6,8-tetrazocines, benzamides were treated with sulfur dichloride to afford (197)–(199). Reaction of *N,N*-dimethylguanidine with SCl_2 gave (200) (Equation (48)) <81JA1540>.

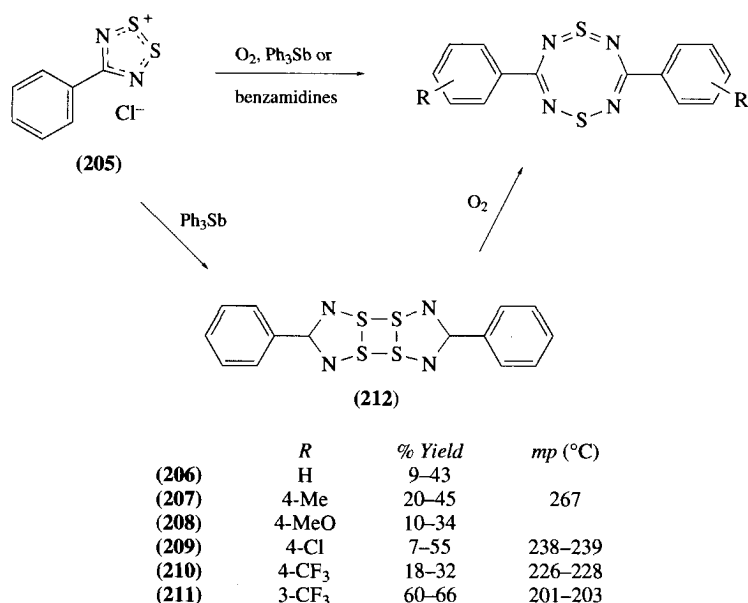


	R	% Yield	mp (°C)
(197)	Ph	7.4	225–226
(198)	$MeOC_6H_4$	3.8	268
(199)	EtO_2C	6.6	305
(200)	Me_2N	54	212 subl.

Good yields were obtained when compounds of the formula 4- $RC_6H_4CN_2(TMS)_3$ were allowed to react with sulfur dichloride giving (201)–(204) (Equation (49)) <89CB1067>.

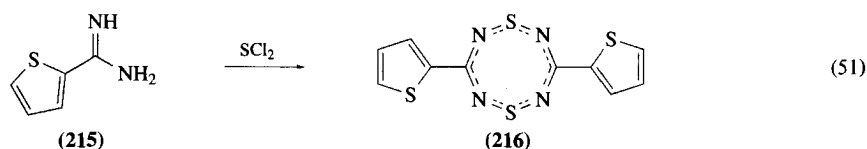
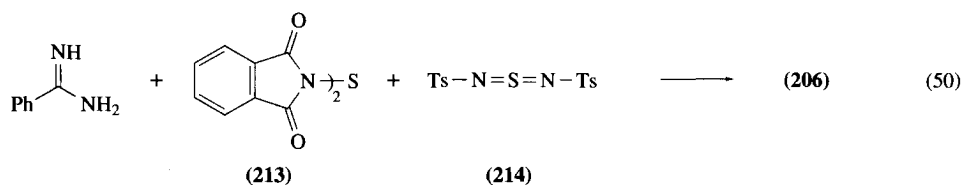


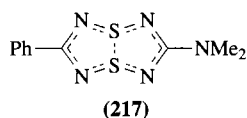
Treatment of salts **(205)** with oxygenated acetonitrile, while adding the reducing agent Ph₃Sb to stop any overoxidation, or by the treatment of **(205)** with benzamidine derivatives in acetonitrile, gave dithiatetrazocines **(206)**–**(211)** in high yields (Scheme 18). The reaction of dimer **(212)** with oxygen also gave dithiatetrazocines (Scheme 18) <93CJC473>. The authors of this study question the yields and spectral and physical data reported in a 1989 paper <89CB1067>.



Scheme 18

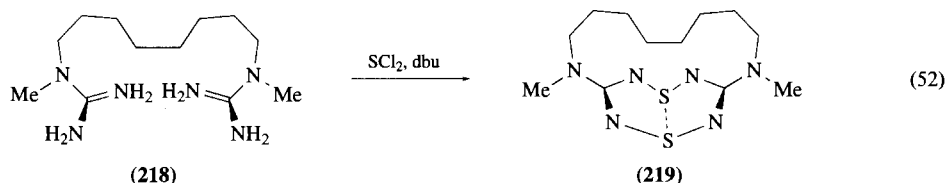
The reaction of benzamidine, sulfide **(213)**, and sulfur diimide **(214)** gave **(206)** in 10% yield with the advantage of a reportedly easy work up (Equation (50)) <89CC1137>. The use of different sulfur transfer agents for the synthesis of dithiatetrazocines has been explored <89JCS(P1)2495>. Treatment of 2-thienylamidinium **(215)** with SCl₂ gave **(216)** (mp 271–273°C) in 7% yield (Equation (51)) and treatment of a mixture of benzamidine and *N,N*-dimethylguanidine with SCl₂ gave the unsymmetrical dithiatetrazocine **(217)** (mp 182–183°C) in 3% yield as well as the symmetrical dithiatetrazocines <89CC1137, 89JCS(P1)2495>.



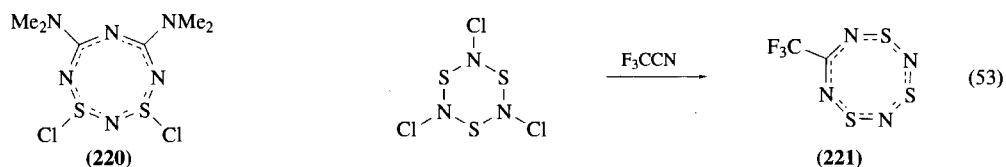


Treatment of bis(guanidine) (**218**) with sulfur dichloride and dbu gave the dithiatetrazocine cyclophane (**219**) in 1.1% yield (Equation (52)) <93PAC105>.

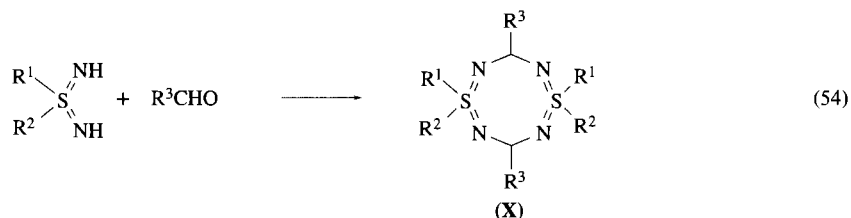
Addition of a ten-fold excess of Me_2NCN to a solution of $(\text{NSCl})_3$ gave (**220**) as moisture-sensitive yellow crystals in 90% yield <85MI 926-01, 86IC47>.



Reaction of trichlorotrithiatriazine and trifluoroacetonitrile gave (**221**) (mp 111 °C) as an ochre-colored solid in 4.3% yield along with several other products (Equation (53)) <84AG(E)988>.



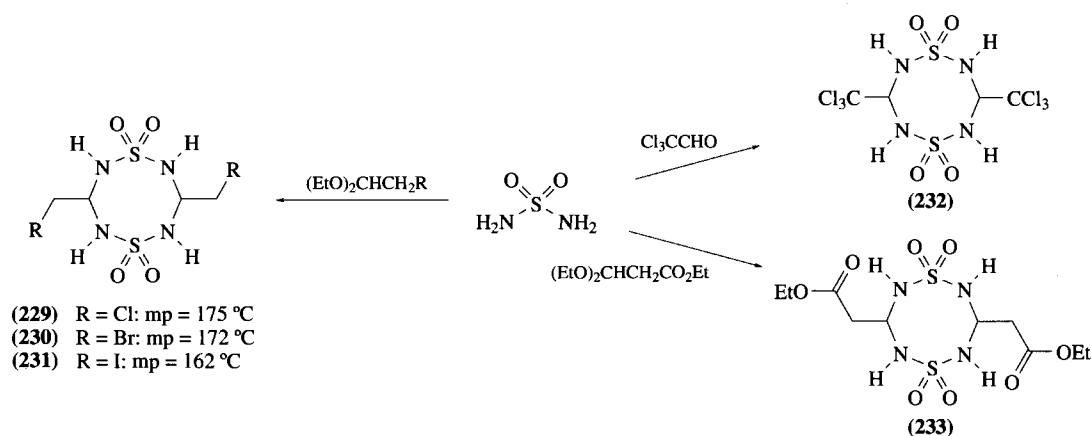
The reaction of sulfurdiimides with aldehydes at room temperature in acetonitrile gave dithiatetrazocines (**222**)–(**228**) (Equation (54)). Neither melting points nor spectral data were reported for the products <85TL2739>.



	R^1	R^2	R^3	% Yield
(222)	Me	Me	Ph	74
(223)	Me	<i>p</i> -Tolyl	Ph	31
(224)	$-(\text{CH}_2)_4-$		Ph	23
(225)	Me	Me	H	34
(226)	CH_2Ph	CH_2Ph	H	27
(227)	CH_2Ph	Et	H	16
(228)	Ph	Ph	H	43

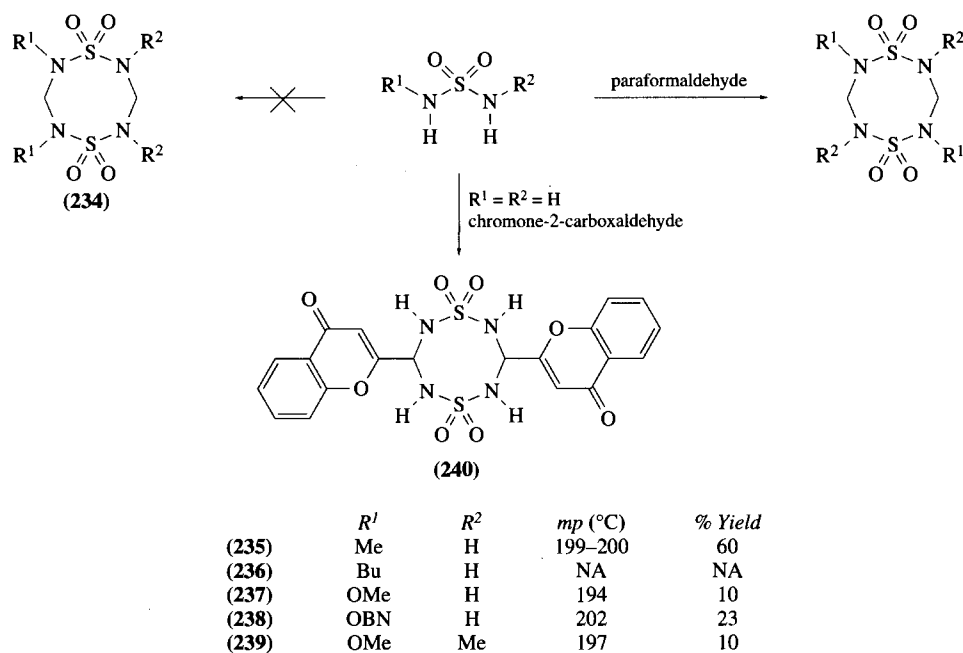
Dusemund and others have studied the reaction of sulfamide and sulfamide derivatives with aldehydes and acetals to give a variety of hydro-1,5-dithia-2,4,6,8-tetrazocin-1,1,5,5-tetroxides. The first examples, in the early 1970s, were prepared by the reaction of sulfamide with the diethyl acetals of chloro-, bromo-, and iodoacetaldehyde to give (**229**), (**230**), and (**231**) in 70%, 60%, and 40% yields, respectively (Scheme 19) <74AP(307)881>. The reaction of sulfamide with trichloroacetaldehyde gave (**232**) (mp 236–237 °C) in 43% yield <75MI095> and with ethyl 3,3-diethoxypropionate afforded (**233**) (mp 178–179 °C) (Scheme 19) <78JHC253>.

Formaldehyde reacts with sulfamide in an analogous fashion. It was originally reported that the reaction of substituted sulfamides and paraformaldehyde gave the *syn*-compounds (**234**) (Scheme 20) <77AP(310)404>. The actual products were found to be the *anti*-isomers (**235**)–(**239**) <86AP(319)826, 87AP(320)534>. Reaction of sulfamide with chromone-2-carboxaldehyde gave (**240**) (mp 143 °C dec.) in 80% yield (Scheme 20) <77AP(310)417>. Reaction of phthalaldehyde with sulfamide derivatives under basic conditions gave the (isoindolo)dithiatetrazocine (**241**; $R^1 = R^2 = \text{H}$) (mp 145 °C) in 70%

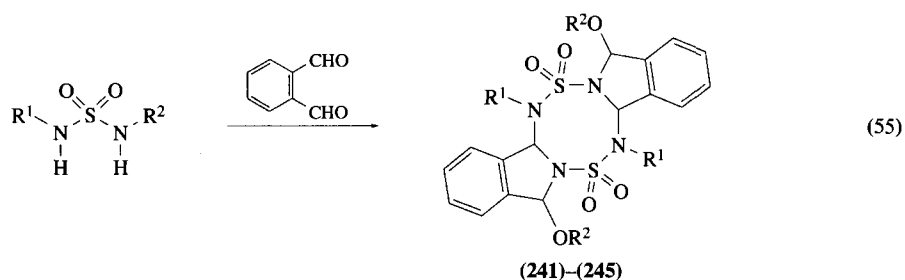


Scheme 19

yield <77AP(310)435>. Substituted analogs (**242**; R¹ = H, R² = CH₃) (mp 180 °C dec.), (**243**; R¹ = CH₃, R² = CH₃) (mp 220 °C) <77AP(310)435>, (**244**; R¹ = OCH₃, R² = H) (mp 270 °C dec.) <87AP(320)534>, and (**245**; R¹ = C₄H₉, R² = H) (mp 180 °C dec.) <77AP(310)449> were also prepared (Equation (55)).

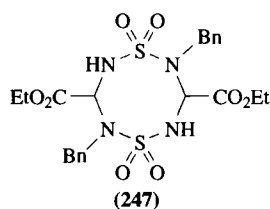
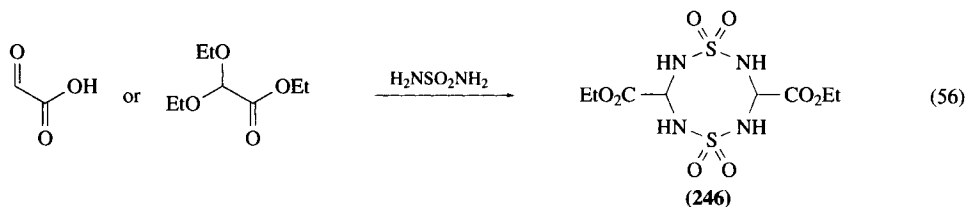


Scheme 20

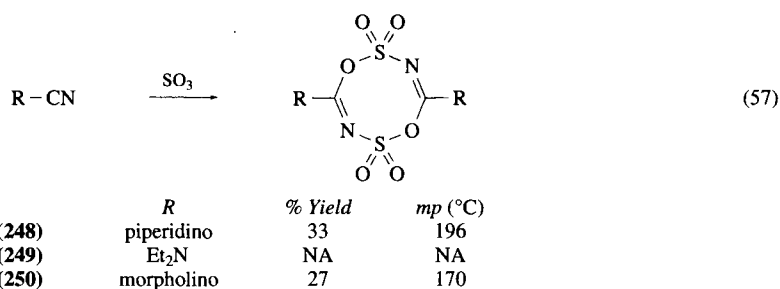


In more recent studies, from the late 1980s, on the reactions of sulfamides and aldehyde equivalents, (**246**) (mp 202–203 °C) was prepared in 29% yield from glyoxylic acid and sulfamide followed

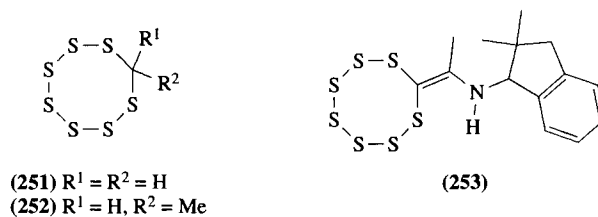
by esterification <88H(27)2581> or directly from ethyl diethoxyacetate and sulfamide in 81% yield (Equation (56)) <90JOC6098>. The benzyl derivative (**247**) (mp 216–218°C) was prepared in 74% yield from the substituted sulfamide <90JOC6098>.



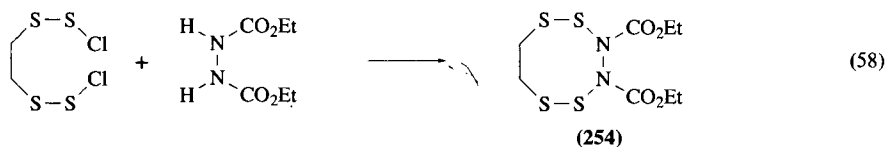
1,5-Dioxo-2,6-dithia-3,7-diazocine 2,2,6,6-tetroxides (**248**)–(**250**) were prepared by the treatment of cyanamides with sulfur trioxide (Equation (57)) <92ZOR2019>.

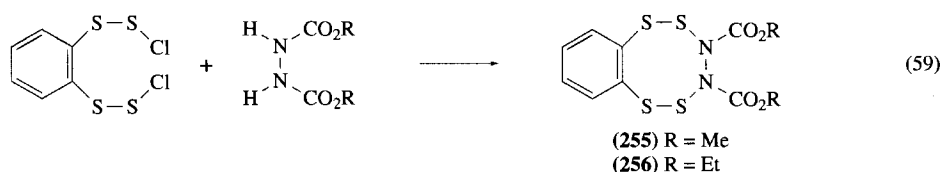


The syntheses of three heptathiocanes (**251**), (**252**), and (**253**) (mp 142–143°C) have been reported via three different methods <65ZN(B)1125, 85CZ349, 90TL5457>.

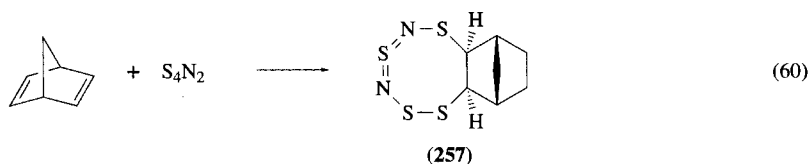


On treatment of 1,2-bis(chlorodisulfonyl)ethane with diethyl hydrazine-1,2-dicarboxylate, diethyl 1,2,5,6-tetrathio-3,4-diazocane-3,4-dicarboxylate (**254**) (mp 94–95°C) was isolated in 10% yield (Equation (58)) <71AG(E)407>. Similar reactions took place with 1,2-bis(chlorodisulfonyl)benzene to give (**255**) and (**256**) (Equation (59)) <74CB771>.

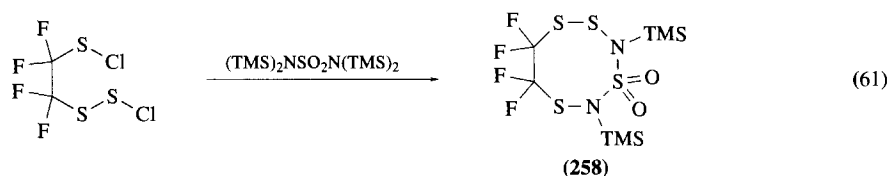




The reaction of tetrasulfur dinitride with norbornadiene produced a 1 : 1 cycloaddition adduct (**257**) (mp 92–94°C, λ_{max} 266, 362, 420 nm) as orange crystals in 12% yield (Equation (60)). This reaction represents a forbidden $[2_s + 2_s]$ process. However, the observation of free radicals in similar reactions suggests that a nonconcerted diradical mechanism is involved <83CJC1185>.

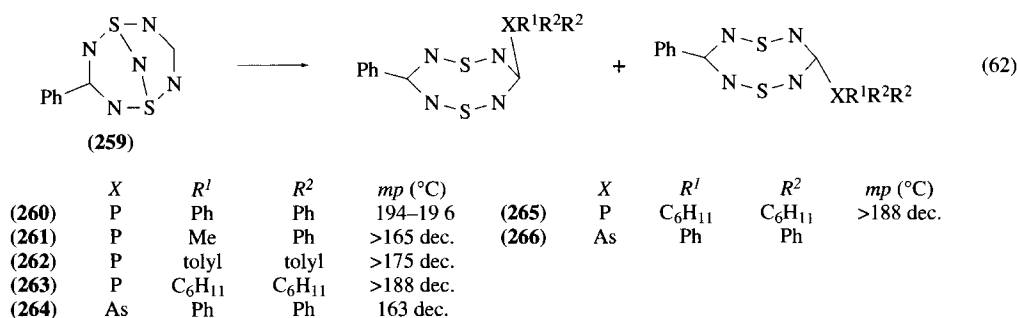


The reaction of $\text{ClSCF}_2\text{CF}_2\text{SSCl}$ and $\text{SO}_2[\text{N}(\text{SiMe}_3)_2]_2$ gave tetrathiadiazocane (**258**) (bp 126°C/0.1 torr, mp 30°C) (Equation (61)) <85CB2811>.



9.26.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

Treatment of (**259**) with tertiary phosphines and arsines gave predominantly the *endo* isomers (**260**)–(**264**) in nearly quantitative yields (Equation (62)) <87JA7781>. In certain cases, the *exo* isomers (**265**) and (**266**) could be isolated.

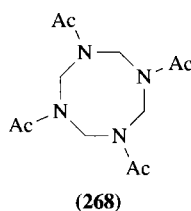
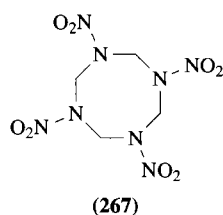


9.26.11 IMPORTANT COMPOUNDS AND APPLICATIONS

9.26.11.1 1,3,5,7-Tetrazocanes

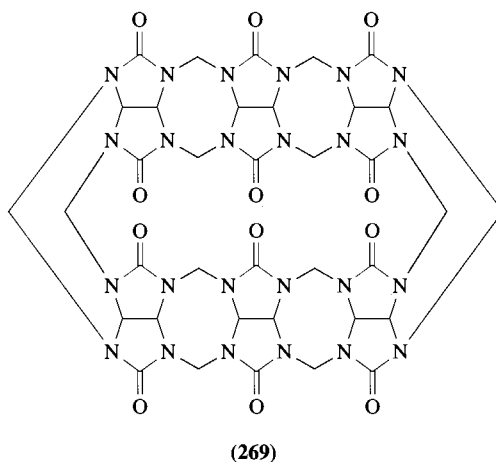
9.26.11.1.1 Tetranitrotetrazocanes and derivatives

In the chemistry of explosives and propellants 1,3,5,7-tetranitro-1,3,5,7-tetrazocane (**267**), also known as HMX and octogen; 1,3,5,7-tetraacetyl-1,3,5,7-tetrazocane (**268**), also known as TAT; and other derivatives have been reviewed <90AHC(50)1>.

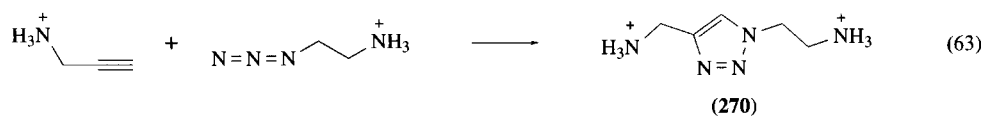


9.26.11.1.2 Cucurbituril and derivatives

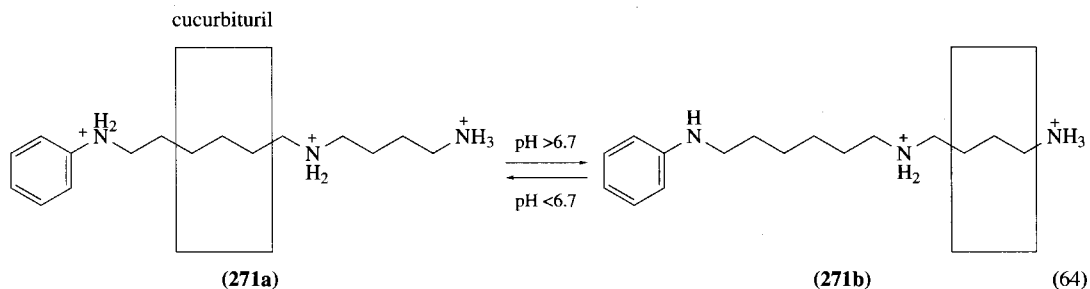
Cucurbituril (**269**) is a nonadecacyclic cage compound consisting of six tetrazocane units fusing six glycoluril moieties. It is readily synthesized from urea, glyoxal, and formaldehyde (see Section 9.26.9.1.1 for details on the synthesis of cucurbituril and derivatives, and Section 9.26.3.3 for details on structure).



Cucurbituril readily encapsulates and binds, in its internal cavity, substituted ammonium ions having dimensions smaller than a *para*-disubstituted benzene ring <83JOC3618, 88JA4706, 89JA2697>. Acting as a Pauling Principle catalyst, cucurbituril was found to accelerate a 1,3-dipolar addition reaction to form (**270**) by a factor of 5.5×10^4 (Equation (63)) <83JOC3619>.

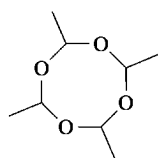


A molecular switch (**271**) has been prepared based on cucurbituril and a triamine (Equation (64)) <90CC1509>. At low pH, the cucurbituril is located proximal to the aryl group (**271a**). At high pH, the cucurbituril moves to the aliphatic portion of the molecule (**271b**). The location of the cucurbituril was determined by NMR spectroscopy <90CC1509>.

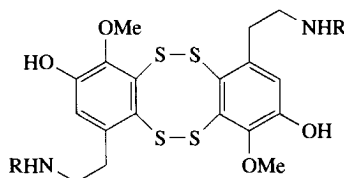


9.26.11.2 1,3,5,7-Tetraoxocanes

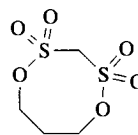
Metaldehyde (**272**), the cyclic tetramer of acetaldehyde and common active ingredient in snail and slug traps and in the chemical control of molluscs <82MI 926-01>, has been reviewed in terms of toxicity <85MI 926-02>.



(272)



(273) R = H

(274) R = COCF₃

(275)

9.26.11.3 1,2,5,6-Tetrathiocanes and Tetrathiocines

Lissochinotoxin D (**273**) (amorphous white solid) was isolated from *Lissochinum* sp. and identified as the trifluoroacetate derivative (**274**). Compound (**273**) shows antifungal activity against *Candida albicans* <94JOC6600>.

9.26.11.4 Other Tetrahetero Systems

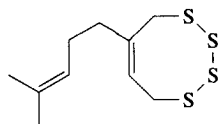
An analog of the anticancer agent cyclodisone, 1,5,2,4-dioxadithiocane-2,2,4,4-tetraoxide (**275**), was found to be active against human colon carcinoma cells <91MI 926-01>.

5,8-Dihydro-6-(4-methylpent-3-enyl)-1,2,3,4-tetrathiocine (**276**) (light yellow oil) has been observed as a component of essential oil of hops by GLC analysis <82JCS(P1)1089>.

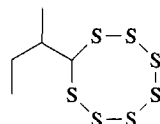
9.26.11.5 Important Systems Containing Five or More Heteroatoms

Isolated from intact cells of the sulfur-metabolizing hyperthermophilic archaea *Thermococcus tadjuricus* and *Thermococcus acidaminovorans* obtained from marine hydrothermal systems, 8-(2-butyl)-1,2,3,4,5,6,7-heptathiocane (**277**) (pale yellow oil) was identified by NMR and MS data <93LA871>. Monoalkyl-substituted heptathiocanes such as (**277**) are reported to be quite unstable towards disproportion to sulfur and disubstituted cyclic polysulfides <93LA871>.

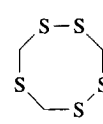
The pentathiocane (**278**) has been isolated and identified by mass spectrometry as a volatile component of Shiitake mushrooms (*Lentinus edodes* Sing.) <86MI 926-01>. The compound's genesis is believed to be via methylene disulfide <86MI 926-02>.



(276)



(277)



(278)

9.27

Nine-membered Rings

ANDREW B. HOLMES and ROSS P. McGEARY
University Chemical Laboratories, Cambridge, UK

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9.27.1 INTRODUCTION

9.27.1.1 Scope of the Chapter

In the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I), the nine-membered π -excessive heterocycles, the heteronins, were surveyed up to 1982 (Chapter 5.20 of CHEC-I). This chapter covers developments of this class of heterocycle since that time, and also covers all other nine-membered rings containing nitrogen, oxygen and sulfur, including fused and bridged systems.

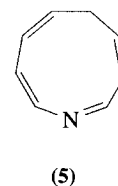
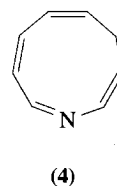
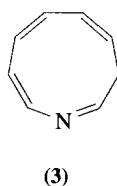
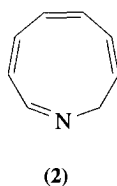
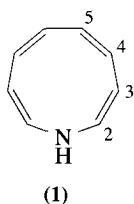
A number of reviews cover the syntheses, structures, and properties of medium-sized rings: Roxburgh has reviewed the synthesis of medium-sized carbocyclic and heterocyclic rings by ring expansion reactions <93T10749>; the synthesis of medium-ring *N*-heterocycles has been reviewed <91T9131>; Rousseau has published a comprehensive review on the synthesis, reactivity and occurrences of medium-ring lactones <95T2777>; Glass has edited an excellent book on conformational analysis of medium rings <B-88MI 927-01>; and Chaudhuri and Wiegardt have reviewed the synthesis and inorganic complexes of tridentate nine-membered heterocycles <87MI 927-01>.

9.27.1.2 Structural Types and Nomenclature

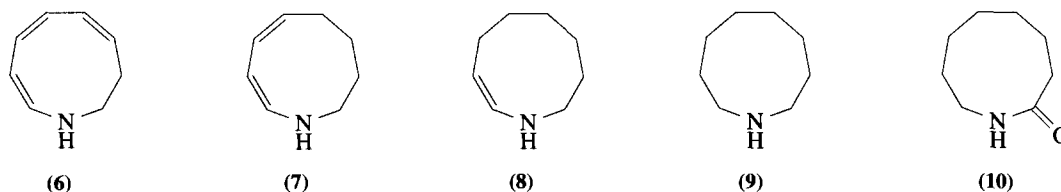
9.27.1.2.1 Rings containing one nitrogen atom

1*H*-Azonine (1) and a range of *N*-substituted derivatives are known, as well as several benzo-fused derivatives. The possibility exists for nonconjugated isomers—the 2*H* derivative (2), the 3*H* isomer (3), the 4*H* isomer (4), and the 5*H* isomer (5)—although these tautomers are unknown.

Partially reduced species are named as derivatives of their parents. For example, (6) is named 2,3-

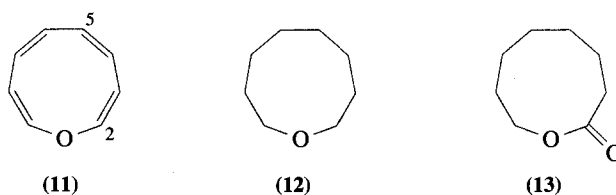


dihydro-1*H*-azonine, (7) is 2,3,4,5-tetrahydro-1*H*-azonine and (8) is named 2,3,4,5,6,7-hexahydro-1*H*-azonine. The fully saturated amine (9) is named octahydro-1*H*-azonine. Of particular importance is the lactam (10), octahydro-2*H*-azonin-2-one (trivially caprylactam).



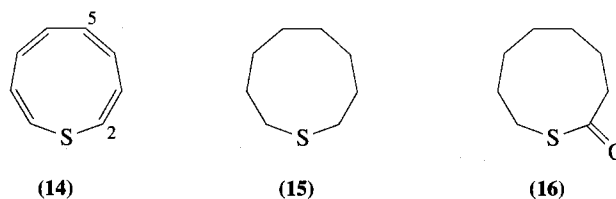
9.27.1.2.2 Rings containing one oxygen atom

Oxonin (11) is a polyenic heterocycle, even though Hückel's $4n + 2$ rule of aromaticity is formally obeyed. The naming of reduced derivatives of (11) follows a similar pattern to that of 1*H*-azonine (1), but the fully saturated oxocycle (12) is given its own name, oxonane. The lactone (13) (caprylactone) is named by IUPAC rules as 2-oxonanone.



9.27.1.2.3 Rings containing one sulfur atom

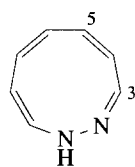
Thionin (14) remains elusive, although several of its benzo-fused derivatives have been prepared. The fully saturated heterocycle (15) is named thionane, and the 2-oxo derivative is 2-thionanone (16).



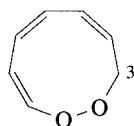
9.27.1.2.4 Rings containing two or more heteroatoms

The number of possible nine-membered rings containing more than one heteroatom is enormous, so their nomenclature is outlined here only in general terms. Introduction of another nitrogen to azonine generates a diazonine, for example 1*H*-1,2-diazonine (17). Similarly, a nine-membered ring with two oxygens is named as a dioxonin, for example 3*H*-1,2-dioxonin (18), although the fully saturated example (19) is properly named 1,2-dioxonane. Ring (20) is named 3*H*-1,2-dithionin, and the fully saturated derivative (21) is 1,2-dithionane. When two different heteroatoms are present in the ring, the numbering follows the usual priority rules, that is, $O > S > N$. Thus, structure (22) is

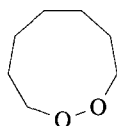
1,5-oxazonine, (**23**) is 1,5-thiazonine and (**24**) is 2*H*-1,5-oxathionin. Rings with several heteroatoms are named in the same manner, leading to 1,3,8-oxadiazonine for (**25**), and 3*H*-1,2,3,7-oxathiadiazonine for (**26**).



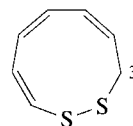
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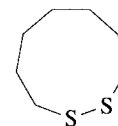
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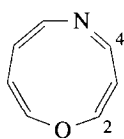
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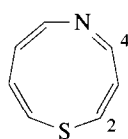
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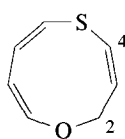
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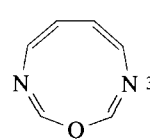
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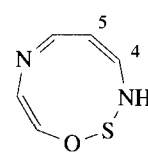
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(24)



(25)



(26)

9.27.2 THEORETICAL METHODS

Theoretical studies of the nine-membered heterocycles have centered on the question of aromaticity of the heteronins, and the conformations, transannular distances and strain energies of the nonconjugated compounds (see Section 9.27.4.1). To date, the large number of electrons in these molecules has precluded the use of *ab initio* methods, and high-level calculations have therefore been restricted to semiempirical treatments. Molecular mechanics calculations have been used extensively in the study of nine-membered heterocycles.

9.27.2.1 Semiempirical Methods

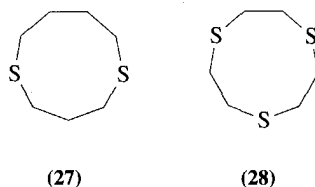
Ouamerli and Gayoso have performed MNDO calculations on 1*H*-azonine (**1**), oxonin (**11**) and thionin (**14**) <86MI 927-01>. The calculated geometry of 1*H*-azonine is in agreement with the experimental evidence that this is a planar, aromatic molecule (Table 1). The calculated geometry of oxonin, as a buckled, unsymmetrical polyenic heterocycle, is also in agreement with its known properties. The MNDO calculations on thionin indicate that this molecule is planar, which should allow effective π delocalization. Thus, thionin is predicted to have at least some aromatic character.

Table 1 Calculated geometries of the heteronins. Bond lengths (pm) and bond angles ($^\circ$) <86MI 927-01>.

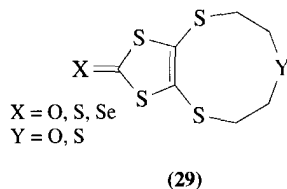
Compound	(I)	(II)	(14)
Symmetry	C_{2v}	C_s	C_{2v}
X—C-2	138.6	136.6	166.6
C-2—C-3	135.9	134.9	134.3
C-3—C-4	142.9	145.5	144.1
C-4—C-5	135.7	135.8	135.1
C-5—C-6	143.1	146.3	144.1
C-9—X—C-2	142.3	119.3	125.6
X—C-2—C-3	139.9	122.7	114.0
C-2—C-3—C-4	140.1	133.2	140.7
C-3—C-4—C-5	139.8	128.7	141.3
C-4—C-5—C-6	139.8	139.1	141.3

Both 1,5-dithionane (**27**) and 1,4,7-trithionane (**28**) have been studied by extended Hückel, MINDO/3 and SCF-CNDO/2 molecular orbital methods, as well as by molecular mechanics

analysis, and these calculations have been compared with experimental data obtained by PE spectroscopy and x-ray crystallography (81T2743). Extended Hückel and CNDO/2 calculations of the sulfur lone pair splitting of (27) are in excellent agreement with experimental results, but the splitting calculated by MINDO/3 is too large, and the calculated transannular S—S distance is much shorter than that deduced from x-ray analysis (see Section 9.27.3.1).



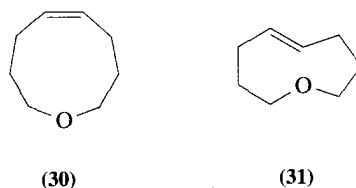
MNDO calculations have been performed on various conformations of compounds of type (29), and these values have been compared with experimental data derived from variable-temperature NMR (94JPR177). Selected conformations of caprylolactam (10), as found by a molecular mechanics search, were examined using MNDO-AM1 (90MI 927-01).



9.27.2.2 Molecular Mechanics

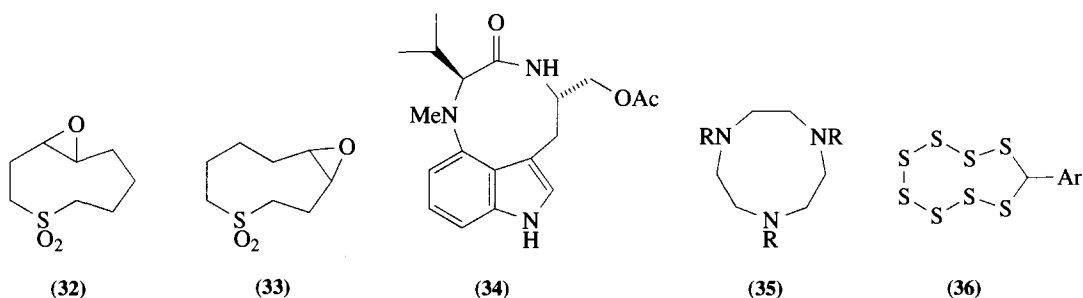
Molecular mechanics calculations have been used extensively to investigate the conformations and strain energies of nine-membered rings. Caprylolactam (10) has been the subject of an extensive comparative study where systematic, Monte Carlo, molecular dynamics, and other algorithms were examined to determine the most efficient and reliable way of conducting a complete conformational search. The systematic search was found to be far less efficient than other methods examined, but care should be exercised in extrapolating these results to other systems (90MI 927-01) (see also (92MI 927-01)). Müller and co-workers have used caprylolactam to test their algorithm for the systematic generation of conformations of macrocyclic systems (88HCA1429). Still and Galynker have used MM2 to rationalize the product distributions arising from alkylation, hydrogenation and cuprate additions to nine-membered lactones (81T3981) (see Section 9.27.6). The structure of (*Z*)-2,3,4,7,8,9-hexahydrooxonin (30) has been investigated using MM2; several low-lying conformers were found (85BCJ803). Alder *et al.* have used MM2 methods to calculate a torsional angle of 152° about the (*E*) double bond in (31) (89CC277). MM3 calculations have been performed on 6–11-membered lactones (93MI 927-01). The results for caprylolactone (13) indicate a marked preference for the *s-trans* geometry about the OC—O bond. The torsional angle for the ester bond was calculated to be 156.3° for the lowest-energy conformer, and the first *s-cis* conformer was 9.390 kcal mol⁻¹ (39.31 kJ mol⁻¹) higher in energy. However, comparisons between the calculated and experimental values of enthalpy of formation of (13) did show fairly large (6.2 kcal mol⁻¹ (26 kJ mol⁻¹)) deviations (91JA7697) (see also Section 9.27.4). *N*-Benzylcaprylolactam (121) has been the subject of an MM2 conformational search, aimed at rationalizing the sites of kinetic deprotonation with *t*-butyllithium (see Section 9.27.6.3.2) (87JA4405).

Molecular mechanics calculations of 1,5-dithionane (27) suggest a conformation of C₂ symmetry,

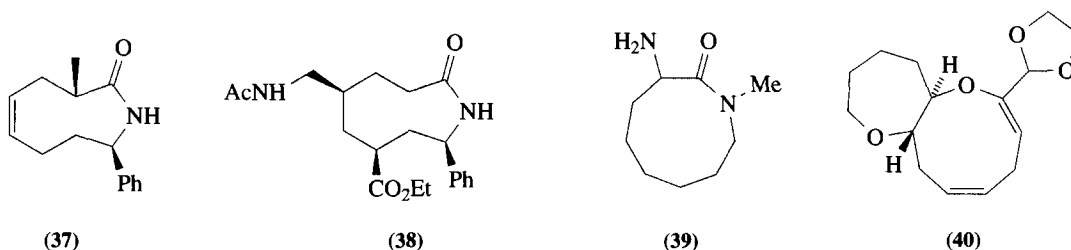


whereas PE spectroscopy and x-ray analysis indicate a more symmetrical twist-boat-chair structure for this molecule <81T2743>.

Cerè *et al.* have calculated the lowest energy conformations of (32) and (33) using the MMX force field, and have used the geometries obtained to rationalize the stereo- and regiochemistry of the products arising from carbanionic transannular epoxide ring opening <91JOC4513>. Shudo and co-workers have studied the two conformers of the indolo-fused lactam (34), caused by rotation of the amide bond, and have found good agreement between experimentally determined free energy differences and values calculated using MM2 <85TL1069, 86T5905>. Evans *et al.* have used the SYBYL program to calculate the lowest-energy conformation of trithiol (35; R = COC₆H₄SH), in which all three pendants are aligned on the same face of the nine-membered ring in an approximate threefold symmetry <92JCS(D)3229>. MMP2 calculations performed on the octathione (36; Ar = 2,4,6-tris[bis(trimethylsilyl)methyl]phenyl) converge to a geometry almost identical with the crystal structure <92CL1599>.

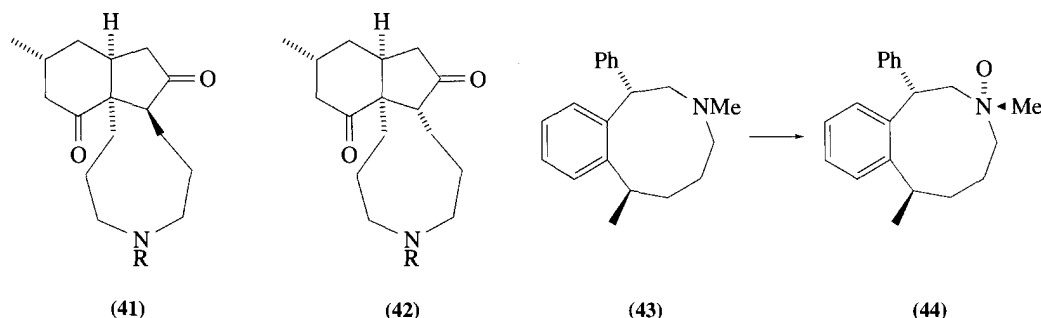


Olson *et al.* have performed molecular mechanics calculations on the disubstituted lactam (37). The lowest-energy conformer calculated using the SYBYL program showed a very close agreement with the crystal structure. The conformations of the related lactam (38) were also calculated, and the proportions of *cis*- and *trans*-amides were consistent with the ¹H NMR spectrum <90JA323>. The MM2 force field has been used to probe both the *cis* and *trans* conformers of *N*-methyl-3-aminocaprylactam (39). Examination of both global minima showed that they closely matched the crystallographically determined skeletons of caprylactam hydrochloride (46) and caprylactam (10), respectively <86JMC251>. Nicolaou and co-workers have employed molecular modeling to rationalize the unexpected relative reactivity of the disubstituted double bond of (40) towards epoxidation. The lowest-energy conformer of (40), as found using the MM2 force field, showed that the lone electron pairs of the nine-membered ring oxygen were out of plane with the *p* orbitals of the trisubstituted double bond. The calculations also suggested that the β face of the disubstituted double bond was more exposed to attack, and, indeed, epoxidation of (40) with dimethyldioxirane produced selectively the β -monoepoxide, arising from attack at the disubstituted double bond <90JA4988>.



Heathcock *et al.* have employed the MM2 force field in their study of fawcettimine (41; R = H) and derivatives <89JOC1548>. The calculated energy difference of the *N*-acetyl epimers (41) and (42) (R = Ac) was 1.4 kcal mol⁻¹ (5.9 kJ mol⁻¹), which compares with the experimentally determined value of 0.41 kcal mol⁻¹ (1.72 kJ mol⁻¹). Further calculations were consistent with the experimental data concerning the formation of intramolecular carbinolamines from both epimers: fawcettimine (41; R = H) formed a carbinolamine at the cyclohexanone ring, whereas 4-epifawcettimine (42; R = H) formed a carbinolamine at the cyclopentanone carbonyl. Maryanoff *et al.* have studied the

conformer population of (43) using the MM2 force field <86JOC3295>. To account for the highly stereoselective oxidation to (44), however, it was necessary to suppose that a minor conformer of (43) was the reactive species <90JOC760>.



9.27.2.3 Miscellaneous Methods

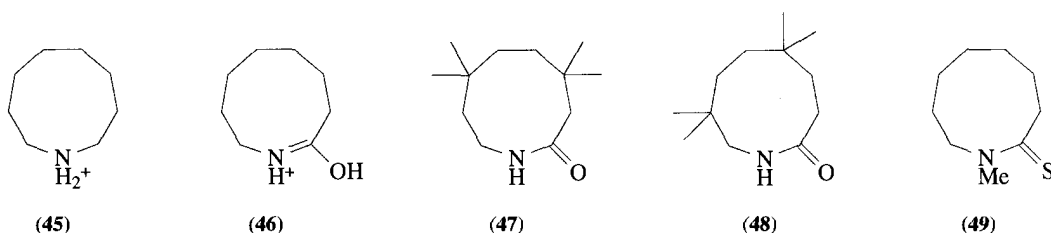
Gimarc *et al.* have calculated topological resonance energies for a series of sulfur–nitrogen rings and have suggested that the hypothetical $S_3N_6^{2+}$ species should be planar and aromatic <85ICA105>. The topological resonance energy model has also been used to study the aromatic stabilities of the heteronins. 1*H*-Azonine (1) and thionin (14) were predicted to be aromatic, whereas oxonin (11) was predicted to be nonaromatic <84JHC273>. Hückel energy levels have been calculated for the neutral S_5N_4 ring system <80PAC1443>.

9.27.3 EXPERIMENTAL STRUCTURAL METHODS

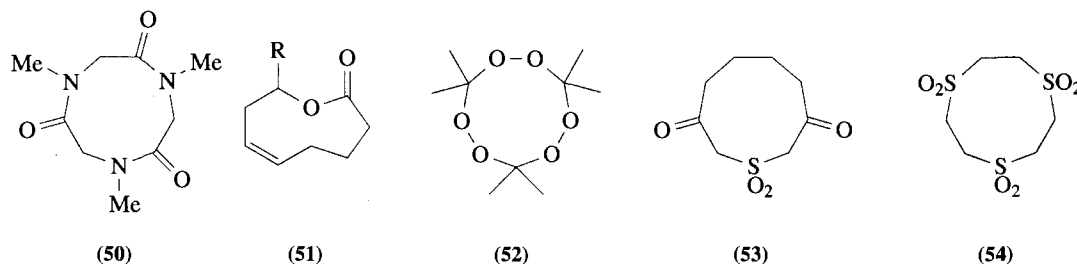
9.27.3.1 X-ray Crystallography

The structures of nine-membered heterocycles as determined by x-ray crystallography seldom show strikingly unusual bond lengths or angles compared with acyclic analogues, other than a general increase in the magnitude of the endocyclic bond angles. Rings containing *trans* C=C bonds, ester bonds or amide bonds, however, often exhibit significant deviations from planarity of these bonds.

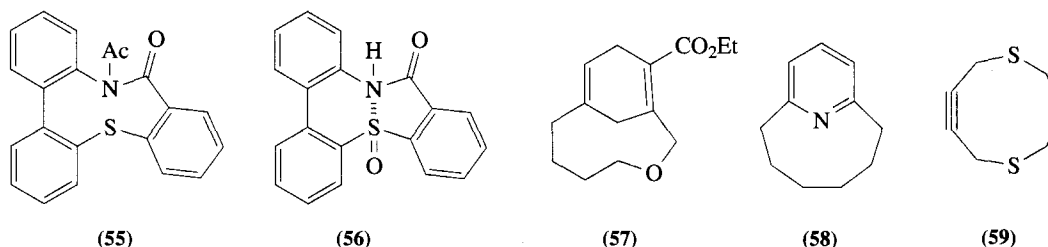
The structure of the tosylate salt (45) of octahydro-1*H*-azonine (9) has been determined. The ring adopts an unsymmetrical conformation, and none of the bond lengths or angles are unusual; the C—N bond lengths are 149.7 pm and 150.0 pm, and the C—N—C bond angle is 119.4° <77CC939>. The structures of caprylactam (10) and its hydrochloride salt (46) have been solved. In solution, (10) consists of a mixture of *cis* and *trans* conformers, but the amide bond in (10) adopts a distorted *trans* conformation in the crystal (torsion angle (τ) = 148.4°) with molecules linked by N—H···O=C hydrogen bonds. The *O*-protonated lactam (46) occurs in a near-planar *cis* conformation <75AX(B)276, 75AX(B)278>. The forces molding the geometries of nine-membered lactams appear to be finely balanced, however: 4,4,7,7-tetramethylcaprylactam (47) exists with a twisted *trans* amide bond (τ = 146.8°) <81AX(B)575>, whereas the 5,5,8,8 isomer (48) possesses a *cis* amide bond <79AX(B)1255> (see also <87AX(C)2132, 87JOC2581, 90JA323, 91JA6690>). The structure determined for the *N*-methylthiolactam (49) has a planar *cis* thioamide bond. The N-1—C-2 bond length is 131.7 pm, and the C=S bond length is 166.9 pm <72AX(B)3618>.



In the solid state the cyclic tripeptide (**50**) adopts an all *cis* "crown" conformation. Average bond lengths are 134.7 pm for the N—CO bonds, and 123.6 pm for the C=O bonds <76ACS(A)838>. The crystal structure of the marine natural product neohalicholactone has been solved, and this compound possesses an unsaturated nine-membered lactone (**51**). The *cis* double bond exhibits no deviation from planarity, but the ester group exists in a twisted *s-trans* form ($\tau = 159.7^\circ$). Extensive intermolecular hydrogen bonds exist in the crystal, which may contribute to the stability of the observed conformation in the solid state <91TL2427>. Hexamethyl-1,2,4,5,7,8-hexaoxonane (**52**) has three approximate two-fold axes of symmetry (approximately D_3 symmetry) in the crystal. The C—O bond lengths average 141.7 pm and the O—O bond lengths average 147.7 pm. The bond angle O—C—O is 112.3° and the C—O—O angle is 107.6° <69ACS1311>. The solid state conformation of thionane-3,8-dione 1,1-dioxide (**53**) is a twist-boat-chair in which the sulfur atom and the midpoint of the C-5—C-6 bond lie on a twofold axis <79JOC3496>. 1,4,7-Trithionane-1,1,4,4,7,7-hexaoxide (**54**) adopts a symmetrical [333] conformation in the crystal. The C—S bond lengths are 178.2 pm, and the C—S—C angles are 106.1° <91AX(C)2717>. The conformation of 1,5-dithionane (**27**) in the crystal is a twist-boat-chair. The C—S—C bond angles are in the normal range (average 102.8°), and average C—S bond lengths are 181.3 pm. The transannular S—S distance is 410.8 pm <81T2735>. In contrast, the transannular S—S distance in 1,4,7-trithionane (**28**) is only 345.4 pm, less than the sum of the van der Waals radii of the sulfur atoms. The molecule has C_3 symmetry, and the sulfur atoms are directed towards the center of the ring. Average C—S bond lengths are 182.2 pm, and C—S—C bond angles average 102.8° <80JA5068>.



The crystal structures of the 1,5-thiazonines (**55**) and (**56**) have been solved. The lactam amide bond of (**55**) exists in the solid state in the *cis* form, whereas (**56**) adopts a *trans* amide geometry. The S—N distance of (**56**) (278.0 pm) is much shorter than the sum of the van der Waals radii (335 pm), and the sulfur atom adopts a trigonal bipyramidal geometry <94MI 927-01>. The crystal structure of the bridged oxonane (**57**) is of interest because of its high degree of strain, which is manifested by torsional distortion of the double bonds and pyramidalization of the bridgehead carbons due to partial rehybridization with incorporation of *s* character into the *p* orbitals <86T1841>. Maryanoff *et al.* have reported the crystal structure of the unusually strong complex between saccharin and the hexahydro-3-benzazonine *N*-oxide (**44**). The conformation of the nine-membered ring in the crystal is a boat-chair <90JOC760>.



9.27.3.2 NMR Spectroscopy

NMR spectroscopy has been used extensively to probe the structures and conformational processes experienced by nine-membered rings. This is discussed further in Section 9.27.4.

9.27.3.2.1 Proton NMR spectroscopy

Borgen has published an extensive NMR study of caprylolactam (**10**) in various solvents over a range of temperatures (see also Section 9.27.3.2.2). At room temperature in most solvents both the *cis* and *trans* isomers are observed. Variable-temperature NMR measurements were used to examine conformational processes (see Section 9.27.4.1) <91MRC805>. Second-order rate constants for the proton spin-lattice relaxation of caprylolactam, catalyzed by various paramagnetic species, have been determined. The *cis*-lactam conformer experiences greater interactions from the relaxation reagents, because of more favorable steric effects <83JA7742>. The effects of lanthanide shift reagents on the ¹H NMR spectra of caprylolactam and *N*-methylcaprylolactam have been discussed in terms of the proportion of *cis* and *trans* isomers present in solution <75MI 927-01>. The effect of increased pressure on the proportions of *cis* and *trans* conformers of (**10**) has also been studied <84JCS(P2)1029>. The ¹H NMR spectrum of *N*-nitrosooctahydro-1*H*-azonine (**76**) has been subjected to line shape analysis with a view to determining the barrier to rotation about the N—N bond (see Section 9.27.4.1) <74CJC3028>.

A notable feature of the ¹H NMR spectrum of the pyridinophane (**58**) is the absence of shielding effects of the aromatic π electrons on the ansa chain, unlike the situation found in the analogous benzene derivative [6]metacyclophane. Low-temperature NMR studies of (**58**) revealed a coalescence temperature of approximately -40°C , from which the energy barrier to ring flipping was calculated as $11.0\text{ kcal mol}^{-1}$ (46.1 kJ mol^{-1}) <75JA4405>. Moriarty and Kliegman have studied the ¹H NMR effects of adding benzene or pyridine to *N*-methylcaprylolactam, either neat or as a solution in tetrachloromethane. Steady upfield shifts were observed for the CH₂N, NMe and CH₂O protons, and this was explained in terms of a solvent-solute complex which brought the aromatic ring close to the amide functional group, and hence caused diamagnetic shielding <66JOC3007>.

9.27.3.2.2 Carbon-13 NMR spectroscopy

Like ¹H NMR spectroscopy, ¹³C NMR spectroscopy is useful for studying nine-membered rings which exist in more than one conformation. The presence or absence of ring strain is sometimes apparent in the ¹³C NMR chemical shifts. The *sp* carbons of the dithiacycloalkyne (**59**) resonate at 86.5 ppm, somewhat downfield from strained cycloalkynes <93TL5277>.

Williamson and Roberts have studied the ¹³C NMR spectrum of caprylolactam (**10**) in various solvents and at various temperatures. They showed that the *trans* isomer consists of two conformers at low temperature <76JA5082>. The ¹³C NMR spectrum of caprylolactam has also been studied by Borgen using NOE-2D, HETCOR and 2D-INADEQUATE pulse sequences. Assignments for all the carbons in both the *cis* and the *trans* isomers were made in various solvents. The *trans* isomer was shown to exist in at least two conformations in solution, and low-temperature NMR measurements were used to examine conformational processes (see Section 9.27.4.1). The *cis* isomer was also shown to exist as more than one conformation <91MRC805>. The ¹³C NMR spectra of *N*-methyloctahydro-1*H*-azonine and its *N*-oxide have been assigned <77OMR(9)333>. The ¹H–¹³C coupling constant has been measured for the methyl group of *N*-methylcaprylolactam <66JOC3007>.

9.27.3.2.3 Nitrogen-15 NMR spectroscopy

The ¹⁵N NMR spectra of several lactams, including caprylolactam, have been examined in CHCl₃, DMSO and 95% ethanol. The ¹⁵N NMR chemical shifts show no apparent relationship to lactam ring size. Both *cis* and *trans* conformations of caprylolactam were observed, and the relative proportions were dependent on solvent and temperature. The ¹⁵N chemical shifts of the two conformers differ only by 2–3 ppm, and the ¹⁵N spin lattice relaxation times of both isomers are almost identical <76JA5082>. The rates of base-catalyzed N—H proton exchange in both the *cis* and the *trans* conformers of caprylolactam in DMSO have been measured by ¹⁵N NMR spectroscopy. The *cis* conformer was found to undergo proton exchange approximately 25 times faster than the *trans* isomer. The rates of proton exchange of caprylolactam have also been compared with other lactams <79NJC279>. The magnitude of the ¹⁵N–¹H coupling constants were measured as 89 Hz and 91 Hz for the *cis* and *trans* isomers, respectively <78JA5217>.

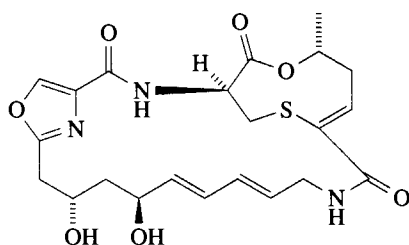
9.27.3.2.4 Oxygen-17 NMR spectroscopy

The ^{17}O NMR spectrum of caprylactam in acetonitrile has been reported. Two signals, arising from the *cis* and *trans* isomers, were observed at 335.5 ppm and 327.8 ppm. It was suggested that at the high concentration required to record the spectrum at natural abundance (0.5 M), a significant proportion of the lactam is associated, and hydrogen bonding with the carbonyl oxygen probably effects the chemical shifts $\langle 89\text{H}(29)307 \rangle$. The extent of dimerization of caprylactam has in fact been shown to be quite low (see Section 9.27.4.2).

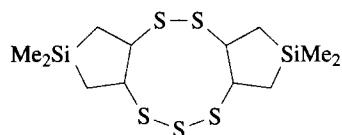
9.27.3.3 Mass Spectroscopy

Few generalizations can be drawn on the fragmentation patterns of nine-membered heterocycles, and data are confined to reports on specific compounds.

Bycroft and King have reported a very detailed analysis of the mass spectrum of the streptogramin antibiotic griseoviridin (**60**) $\langle 76\text{JCS}(P1)1996 \rangle$. Mikaya *et al.* have studied the electron impact mass spectra of several cyclic polysulfides, including the tricycle (**61**) $\langle 83\text{JOM}(256)97 \rangle$. The fragmentation patterns in the mass spectrum of *N*-nitrosooctahydro-1*H*-azonine (**76**) have been discussed $\langle 71\text{CJC}1367, 78\text{BMS}395 \rangle$.



(60)

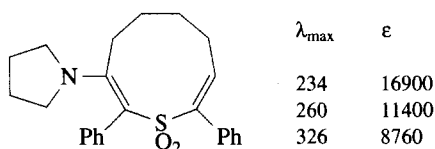


(61)

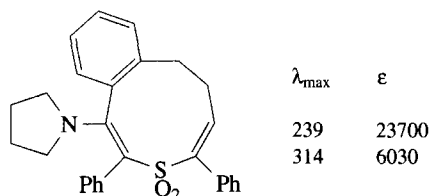
9.27.3.4 UV Spectroscopy

UV spectroscopy, so important for determining the extent of electron delocalization in the fully unsaturated heteronins (see Chapter 5.20 in CHEC-I) $\langle 72\text{ACR}281 \rangle$ has also proved useful for studying the conformations and the extent of multiple bond delocalization in other nine-membered rings.

The UV spectra of caprylactone (**13**) and several other saturated lactones have been measured in several solvents, and the energies and intensities of their $n \rightarrow \pi^*$ transitions have been interpreted in terms of the proportions of *s-cis* and *s-trans* conformers present in solution $\langle 67\text{JOC}3160 \rangle$. Comparison of the UV spectra of the tetrahydrothionin (**62**) and the benzo-fused derivative (**63**) reveals little significant difference in the values of the absorption maxima, implying that, because of steric crowding, (**63**) cannot adopt a planar conformation which would allow effective electron delocalization $\langle 74\text{JOC}3805 \rangle$.



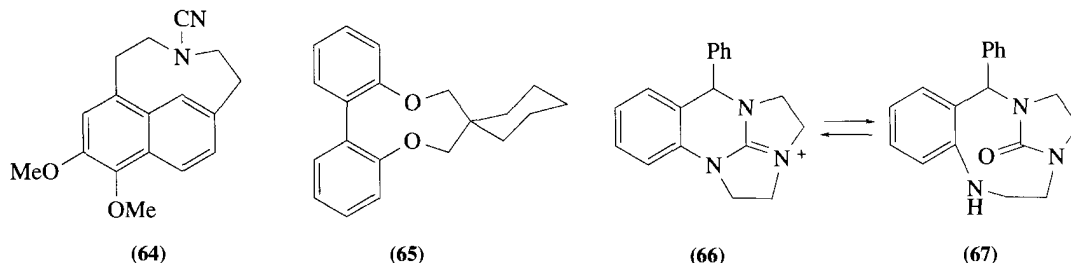
(62)



(63)

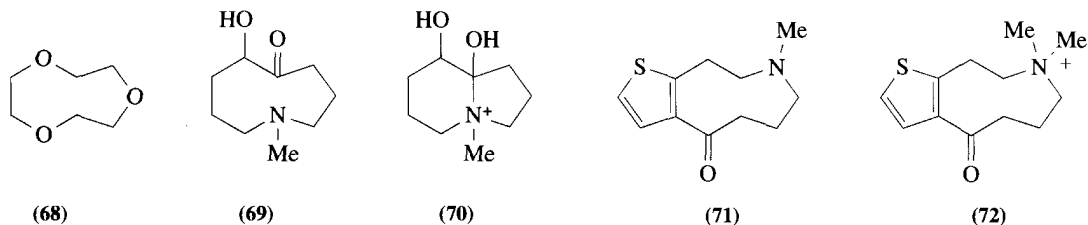
The UV spectrum of the naphthaleno-fused ring (**64**) displays a significant red shift, consistent with nonplanarity of the aromatic ring. This was confirmed by x-ray structural analysis $\langle 85\text{JA}3910 \rangle$. The UV spectrum of the nine-membered pyridinophane (**58**) also shows the effects of distortion of the aromatic ring $\langle 75\text{JA}4405 \rangle$. The UV spectra of (**65**) and some related compounds have been used

to probe the dominant conformations of these spirocycles in solution <77T1219>. Transannular effects can also be observed by UV spectroscopy. Ishikawa has shown that the ring-closed form (**66**) is favored in protic solvents, whereas the nine-membered ring-opened form (**67**) predominates in chloroform solution <80CPB2587>.



9.27.3.5 IR and Raman Spectroscopy

IR spectroscopy has not found wide application in the study of nine-membered rings, except in a few special cases. Unlike small rings, the IR frequencies of nine-membered lactones and lactams occur in the same region as their open-chain counterparts. Borgen and Dale have used IR spectroscopy to show that the crown ether (**68**) exists in an unsymmetrical conformation (see Section 9.27.4.1). They found that (**68**) exhibits the same IR spectrum in solution (35°C) as in the solid at -70°C <74CC342>. Meier and Dai have interpreted the relatively low alkyne IR stretching frequency of (**59**) (2230 cm⁻¹) as being due to ring strain <93TL5277>. Leonard *et al.* first noted the unusually low carbonyl IR stretching frequency of the aminoacyloin (**69**), and ascribed this to a transannular interaction between the amino and carbonyl groups. On protonation, the product shows no carbonyl absorption, indicating that the salt exists in the quaternary form (**70**) <54JA5708, 72JOC3489>. In the thieno-fused example (**71**), the IR carbonyl absorption occurs at 1638 cm⁻¹, suggesting a transannular interaction between the amino and carbonyl groups. On *N*-methylation, the nitrogen lone pair is no longer available to interact with the C=O bond, and the carbonyl absorption frequency of the salt (**72**) rises to 1661 cm⁻¹ <84AJC367>.



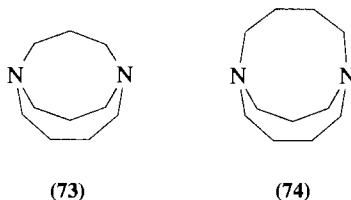
Caprylolactam (**10**) has been the subject of several IR studies, aimed at determining the proportions of *cis* and *trans* isomers present in both the crystal and in solution. The IR spectrum, in various solvents, has been interpreted as arising from as many as four solution conformations <57CB1437, 68MI 927-01, 73JPC645, 74CCC293, 94JPC3694> (cf. Section 9.27.3.2.2). An IR and near-IR study of caprylolactam, in the solid and in various solvents, has been reported. Investigations into amide group overtone and combination vibrational modes have confirmed the presence of both *cis* and *trans* conformers in solution, and only the *trans* conformer in the solid <91SA(A)193>. Detailed IR spectra of the nine-membered thiolactam and selenolactam have been reported <69JCS(A)1033, 69SA(A)1791>.

Valentini *et al.* reported the results of a preresonant Raman study of caprylolactam in the solid state, and concluded that this lactam did not show evidence for the presence of intermolecular hydrogen bonding <93JPC5535>. This conclusion has been challenged <94JPC3694>.

9.27.3.6 PE Spectroscopy

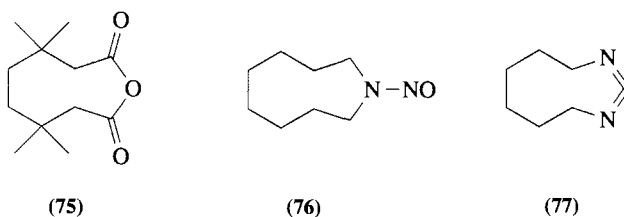
The PE spectra of 1,5-dithionane (**27**) and 1,4,7-trithionane (**28**) have been mentioned (see Section 9.27.2.1). Alder *et al.* have obtained the PE spectra of the bridged diazonines (**73**) and (**74**) and have

discussed their exceptionally low ionization energies in terms of through-space and through-bond coupling effects $\langle 81JA6137 \rangle$. The PE spectra of *N*-methyloctahydro-1*H*-azonine and *N*-tosyloctahydro-1*H*-azonine have been reported $\langle 86JCS(P2)667 \rangle$.



9.27.3.7 Dipole Moments

The dipole moments of several different-sized saturated lactones have been measured, and the results interpreted in terms of the proportions of *s-cis* and *s-trans* conformers present in solution. The dipole moment of caprylolactone in benzene is 2.25 D, and it was suggested to exist as a mixture of both conformers $\langle 58AG312, 59T253 \rangle$. The dipole moment of the crown ether (68) has been measured as 1.55 D in benzene $\langle 74CC243 \rangle$, and 4,4,7,7-tetramethyloxan-2,9-dione (75) has a dipole moment of 4.1 D in benzene $\langle 74ACS(B)13 \rangle$. The cyclic tripeptide (50) has a dipole moment of 4.66 D in benzene $\langle 69CC656 \rangle$.



9.27.4 THERMODYNAMIC ASPECTS

An investigation of the thermodynamic properties of the series of lactones of ring size 5–14 has been conducted. The enthalpies of formation, enthalpies of hydrolysis, enthalpies of reduction to the diol, enthalpies of vaporization, and strain energies of these lactones were determined. Caprylolactone (13) was found to be among the most strained of the lactones examined. The experimentally determined heat of formation of caprylolactone was compared with that calculated using the MM3 force field (unoptimized at the time for esters), and the results were useful for refining the MM3 parameters $\langle 91JA7697 \rangle$.

9.27.4.1 Conformational Studies

NMR spectroscopy has been used extensively in the study of the conformations of nine-membered rings. Fast exchange between conformers on the NMR timescale leads to spectra which represent an average of the various conformations present. When conformational equilibrium is slow at room temperature, more than one conformer may be observed in the NMR spectrum. This is often the case with nine-membered lactams, and for rings which are bridged or have other conformational constraints $\langle 72JCS(P2)2252, 76TL1163, 78JOC4831, 78TL523, 79JOC330, 81JA6137, 86JOC4739, 86TL383, 89JCS(P1)2431, 90JA323, 96JCS(P1)123 \rangle$. An intermediate exchange rate often manifests itself in broadened linewidths. These effects can often be detected by measuring NMR at several temperatures, in order to “freeze out” one or more conformers or to increase the rate of conformational equilibration, and hence improve the clarity of the NMR spectrum. Furthermore, when conformational processes can be observed by NMR, thermodynamic parameters can often be measured: the free energy of activation of a conformational process ($\Delta G^\ddagger$) may be readily calculated from the coalescence temperature, T_c $\langle B-89M1 927-01 \rangle$.

The conformations of caprylolactam have been studied using variable-temperature NMR spectroscopy. The free energy of activation for the interconversion of the *cis* and *trans* conformers was determined as 16.7 kcal mol⁻¹ (69.9 kJ mol⁻¹), approximately the same as for acyclic amides <91MRC805>. This compares with the value of 17 kcal mol⁻¹ (71 kJ mol⁻¹) determined independently <76JA5082>. In addition, two other conformational processes were found for the *trans* conformer, and one for the *cis* isomer. For the *cis* isomer this was identified as geminal ¹H exchange (interconversion of enantiomeric conformers) ($\Delta G^\ddagger = 9.6$ kcal mol⁻¹ (40 kJ mol⁻¹)). The *trans* isomer also showed geminal ¹H exchange ($\Delta G^\ddagger = 14.6$ kcal mol⁻¹ (61 kJ mol⁻¹)) as well as a poorly defined process ($\Delta G^\ddagger = 6.9$ kcal mol⁻¹ (29 kJ mol⁻¹)) <91MRC805>. The conformations of 1,4,7-trioxonane (**68**) have been probed by low-temperature NMR. This compound shows a single resonance in both its ¹H and ¹³C NMR spectra at temperatures down to -60 °C. Further cooling, however, reveals two conformational processes, one with $T_c = -94$ °C ($\Delta G^\ddagger = 7.9$ kcal mol⁻¹ (33 kJ mol⁻¹)), and the other with $T_c = -112$ °C ($\Delta G^\ddagger = 7.3$ kcal mol⁻¹ (31 kJ mol⁻¹)). An unsymmetrical conformation has been proposed to account for this behavior <74CC243>. The ¹H NMR spectrum of 4,4,7,7-tetramethyloxan-2,9-dione (**75**) shows two methyl resonances, a single resonance for the methylenes at positions 5 and 6, and a quartet for the remaining α -methylenes. This strongly suggests that (**75**) adopts a C₂ conformation in solution. Since the IR spectrum of (**75**) is the same in the solid state and in solution, the crystal form is also C₂-symmetric <74ACS(B)13>. The cyclic tripeptide (**50**) has been examined by high-temperature ¹H NMR spectroscopy. This has shown that this compound adopts a rigid all-*cis* conformation and that the coalescence temperature is not reached until about 135 °C <69CC656>. The free energy of activation of rotation about the N—N bond of *N*-nitrosooctahydro-1*H*-azonine (**76**) has been determined as 24.2 ± 1.0 kcal mol⁻¹ (101 ± 4 kJ mol⁻¹), using variable-temperature ¹H NMR spectroscopy in conjunction with total line shape analysis <74CJC3028>. The strained nine-membered carbodiimide (**77**) has been studied using low-temperature ¹H NMR spectroscopy. A conformational exchange process was noted ($\Delta G^\ddagger = 6.7 \pm 0.2$ kcal mol⁻¹ (28 ± 1 kJ mol⁻¹)), similar to the value obtained for diisopropylcarbodiimide, but the nature of the conformational process(es) in (**77**) remains unknown <80JOC1315>. The indolo-fused lactam (**34**) exists in two stable conformations in solution (*cis* and *trans* about the amide bond), the structures of which have been determined by NMR techniques. In the crystal, (**34**) exists as a single conformer, and by dissolving the crystals at low temperature, then allowing the sample to warm, the rate constant for the isomerism could be measured (5.99 × 10⁻⁴ s⁻¹ at -10 °C). The free energy difference between the two conformers was calculated as only 0.53 kcal mol⁻¹ (2.2 kJ mol⁻¹), but the free energy of activation for their interconversion at -10 °C is 19.2 kcal mol⁻¹ (80 kJ mol⁻¹). By measuring the rate constant at different temperatures, the entropy and enthalpy of activation were calculated <85TL1069, 86T5905>.

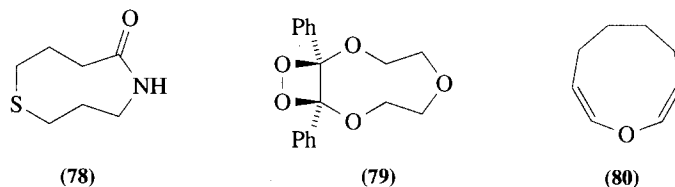
9.27.4.2 Molecular Interactions

Vapor pressure osmometry has been used to measure the extent of association (assumed to be dimerization) of a series of lactams, including caprylolactam and *N*-methylcaprylolactam, in benzene at 37 °C. A marked decrease in the dimerization constant with increasing ring size was noted, and caprylolactam was found to dimerize to the very small extent of 4.3 ± 0.3 M⁻¹. *N*-Methylcaprylolactam, which cannot associate by hydrogen bonding, showed an almost identical dimerization constant (4.1 ± 0.6 M⁻¹) <75JPC1554>.

9.27.4.3 Kinetics

A kinetics study has been performed on the aqueous iodine oxidation of the thiolactam (**78**). The rate of oxidation of (**78**) was found to be approximately 100 times that of a simple cyclic thioether, and this enhancement was ascribed to transannular anchimeric assistance provided by the nitrogen of the amide group <87JOC2581>. The thermal decomposition of the fused dioxetane (**79**) has been monitored by chemiluminescence decay, and this has been shown to follow first-order kinetics. The activation parameters have been calculated <83CL431>. Second-order rate constants for the quaternization of octahydro-1*H*-azonine (**9**) and other azacycloalkanes with iodomethane in acetonitrile and methanol have been measured <68CCCC1429>. The kinetics of the hydrogen-deuterium

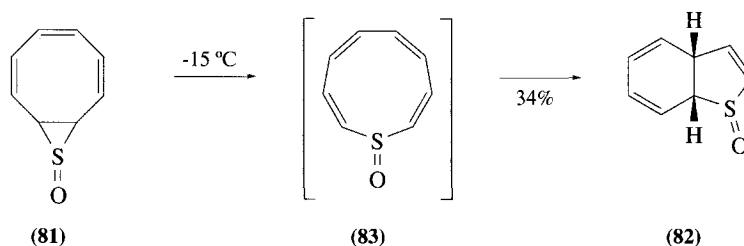
exchange for caprylolactam have been measured <69JA234>. The rates of acid-catalyzed hydrolysis of 4,5,6,7-tetrahydrooxonin (**80**) have been determined in both H₂O and D₂O. The reaction proceeds via a rate-determining proton transfer to carbon <84CJC74>.



9.27.5 REACTIVITY OF FULLY CONJUGATED RINGS

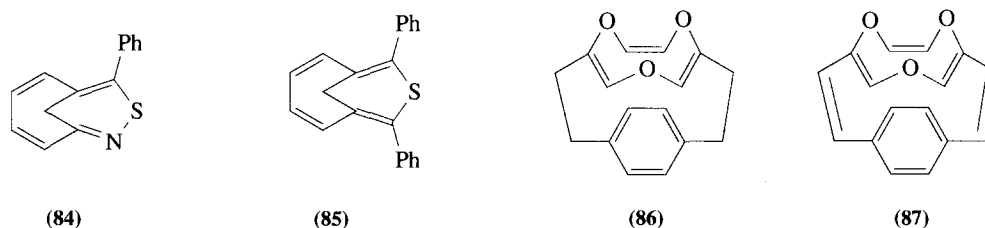
Chapter 5.20 of CHEC-I covers the chemistry of fully conjugated nine-membered rings up to 1982. Since that time there has been a diminishing interest in these heterocycles, and in most recent examples the fully conjugated nine-membered ring has been proposed as a reactive intermediate.

Quin and co-workers have described the thermal rearrangement of the sulfoxide (**81**) to the *cis*-dihydrobenzothiophene oxide (**82**), which presumably occurs via a thionin oxide (**83**) (Scheme 1) <85TL6293, 86PS(27)109>. The fact that the product has a *cis* ring fusion, rather than *trans* as expected from orbital symmetry considerations, suggests that either (**82**) is formed by epimerization of an initial *trans*-fused product, or the intermediate thionin oxide (**83**) rearranges from the initial *cis, cis, cis, trans* form to the all-*cis* isomer before ring closure.

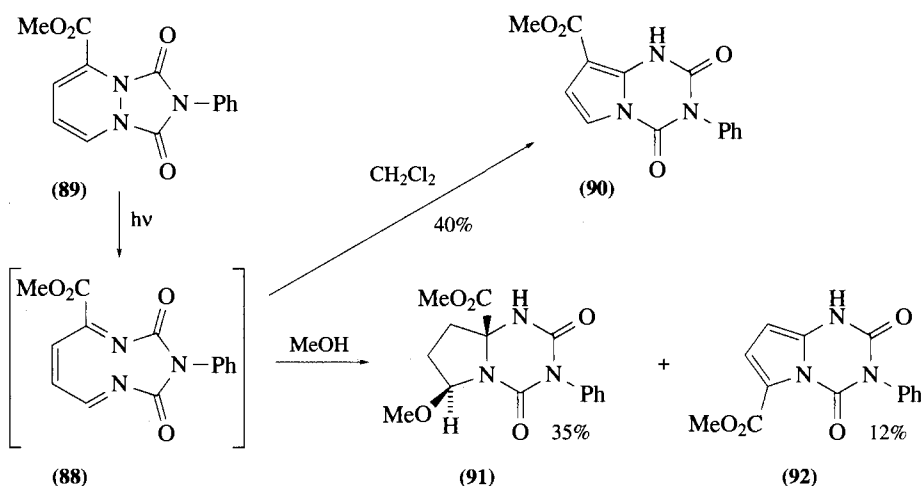


Scheme 1

Kato and Toda have synthesized (**84**), but this bridged thiazonine is too reactive to isolate. The bridged thionin (**85**), by contrast, is relatively stable once purified <82CC510>. The saturated phane-bridged 1,4,7-trioxonin (**86**) is reported to polymerize readily, either in solution or in the solid state, whereas the unsaturated analogue (**87**) may be stored at 0°C for long periods <83AG(E)867>.



Sheradsky and Moshenberg attempted the preparation of (**88**) by electrocyclic ring opening of the dione (**89**). Irradiation of (**89**) did indeed give the triazonine (**88**), but this was too reactive to be isolated. When the irradiation was conducted in dichloromethane solution, (**88**) rearranged to (**90**), but in methanol, transannular addition of the solvent to (**88**) occurred, leading ultimately to a mixture of (**91**) and (**92**) (Scheme 2) <84JOC587>.

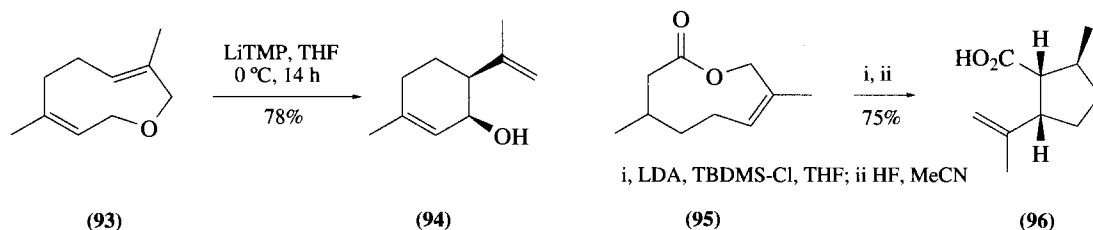


Scheme 2

9.27.6 REACTIVITY OF NONCONJUGATED RINGS

9.27.6.1 Tetrahydro Derivatives of Parent Heterocycles

The stereoselective epoxidation of the fused tetrahydrooxonin (40) has been discussed in Section 9.27.2.2. The tetrahydrooxonin (93) underwent a [2,3] Wittig ring contraction on treatment with a base to give the *cis*-cyclohexenol (94) (Scheme 3). The reaction was also examined using a homochiral base, but the asymmetric induction was low [88JOC4108].

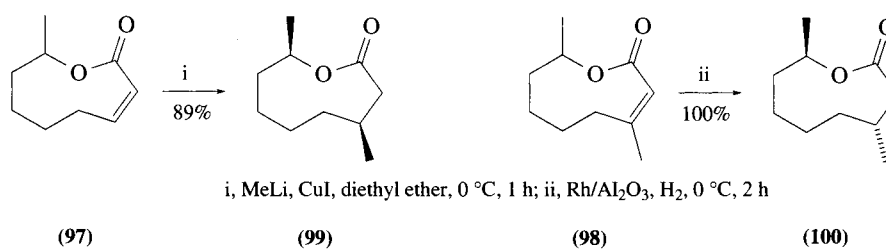


Scheme 3

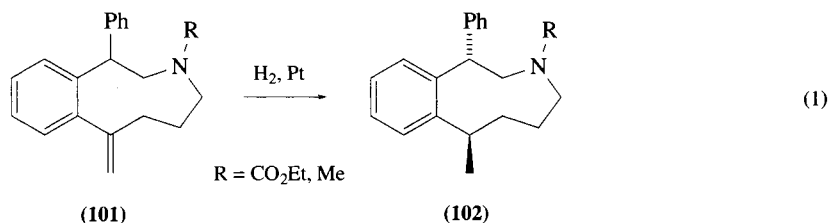
9.27.6.2 Hexahydro Derivatives of Parent Heterocycles

The Claisen rearrangement ring contractions of a range of lactone silyl ketene acetals have been examined, and the *cis* unsaturated lactone (95) has been shown to rearrange to (96) with complete diastereoselection (Scheme 3) [86T2831]. Impressive 1,5-asymmetric inductions have been achieved for the cuprate addition to (97) and for the catalytic hydrogenation of (98) (Scheme 4). The cuprate adduct (99) was obtained in very good yield, and consisted of a 99 : 1 mixture of *cis* to *trans* isomers. The isomeric product (100) was obtained as a 94 : 6 ratio of *trans* to *cis* isomers. Molecular modeling was used to rationalize the product distribution [81T3981].

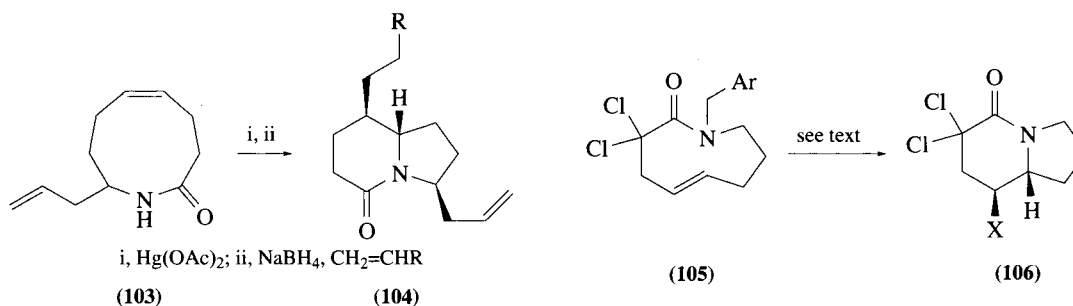
High diastereoselectivity has been noted in the formation of the *N*-oxide (44) from the corresponding tertiary amine (43) (see Section 9.27.2.2). This result was rationalized by considering the conformations of the precursor amine [90JOC760]. The same group has demonstrated high 1,4-diastereoselectivity in the hydrogenation of alkene (101) to (102) (Equation (1)). In this case, a combination of conformational analysis, ^1H NMR coupling constants and MM2 calculations was employed to determine which face of the exocyclic methylene of (101) was more accessible to attack [86JOC3295].



Scheme 4



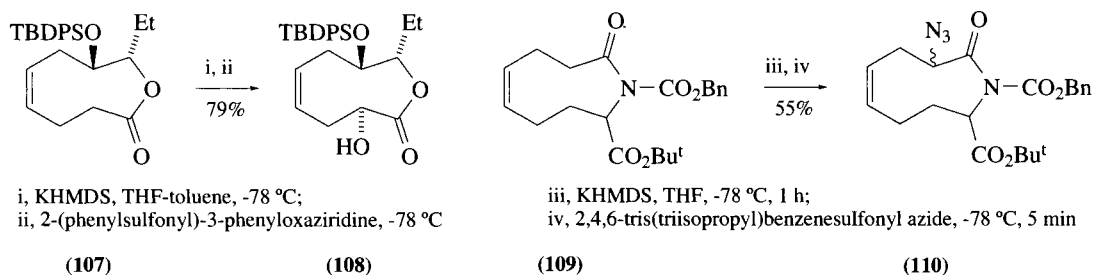
Kahn and co-workers have described an amidomercuration cyclization reaction leading from the *cis*-unsaturated lactam (**103**) to the indolizidinone (**104**). The borohydride reduction of the intermediate organomercurial product in the presence of acrylonitrile gave (**104**; R = CN) in 56% yield (86TL4841). Similarly, when methyl acrylate was employed (R = CO₂Me), a yield of 57% was achieved (Scheme 5) (87H(25)29). The treatment of the *trans*-unsaturated lactam (**105**; Ar = Ph, 4-MeOPh) with various electrophiles (I₂, TMS-I, PhSeBr) gave good yields of the indolizidinones (**106**) with complete regio- and stereoselectivity (Scheme 5) (91JA6690, 91TL5709) (see also (79TL4307)).



Scheme 5

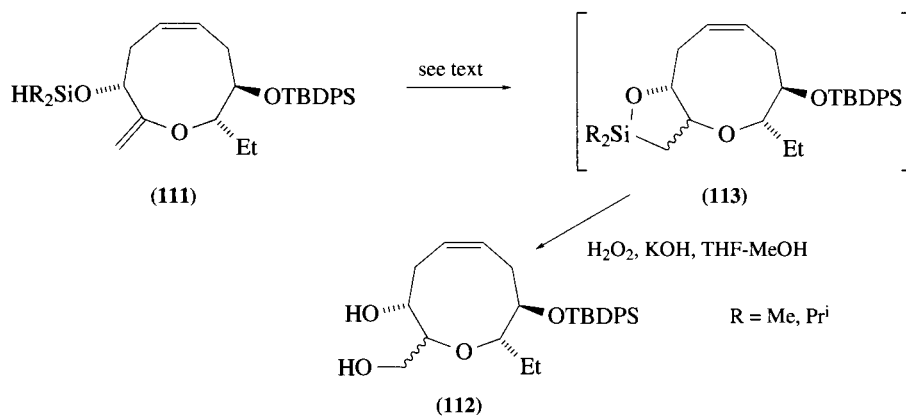
The hydroxylation of the unsaturated lactone (**107**) by the treatment of its potassium enolate with the Davis oxaziridine afforded the α -hydroxy lactone (**108**) as a single diastereoisomer (Scheme 6) (92TL671). Evans *et al.* have examined the diastereoselection of the azidation reaction of the potassium enolate derived from the unsaturated lactam (**109**). The product (**110**) was formed in only moderate yield, and as a 1 : 1.4 mixture of diastereoisomers (Scheme 6) (92TL6859).

Curtis and Holmes have examined the intramolecular hydrosilation of the enol ether (**111**).



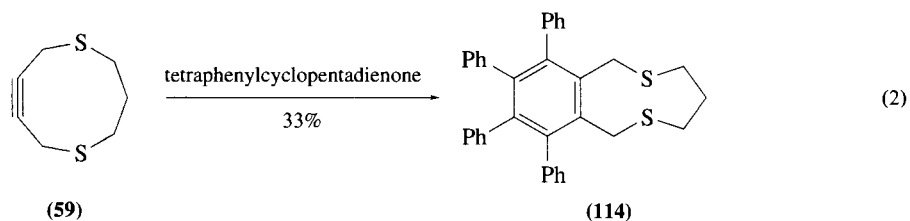
Scheme 6

Conditions were found whereby either the *cis* or the *trans* hydroxymethyl derivatives (**112**) could be formed, following oxidation of the intermediate silacycle (**113**) (Scheme 7). The *cis*-diol could be prepared with a diastereoselectivity of up to 91 : 1 ($R = \text{Pr}^i$) using 2 mol% $\text{Pt}[\{(\text{CH}_2=\text{CH})\text{Me}_2\text{Si}\}_2\text{O}]$ as the catalyst in toluene at 60°C, and the *trans* isomer could be prepared with more than 95 : 5 diastereoselectivity by the use of (acetylacetonato)(norbornadiene)rhodium(I) in refluxing THF <92TL675>.



Scheme 7

The strained dithiacycloalkyne (**59**) underwent a Diels–Alder reaction with tetraphenylcyclopentadienone to give the benzo-fused dithionane (**114**) (Equation (2)) <93TL5277>.



9.27.6.3 Octahydro Derivatives of Parent Heterocycles (Table 2)

9.27.6.3.1 Octahydro-1H-azonine and related compounds

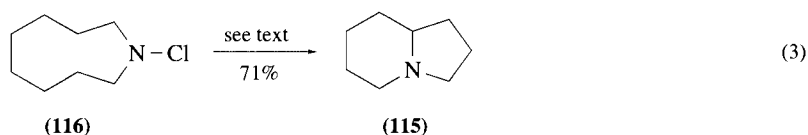
The usual route to octahydro-1H-azonine (**9**) ($\text{p}K_a$ 9.39) is by reduction (LAH, THF, 88% yield) of caprylactam; diborane in THF may also be used <74JMC1232, 84H(22)2007>. The LAH reduction of caprylactam in the presence of ethyl acetate gives *N*-ethyloctahydro-1H-azonine in 72% yield <79TL3395>. Octahydro-1H-azonine may be *N*-nitrosated (65% yield) with nitrous acid, formed *in situ* from sodium nitrite and hydrochloric acid, and this product (a carcinogen) can be reduced with LAH in ether or THF to give the corresponding hydrazine in 43% yield. The deamination of the hydrazine with nitrous acid gives (**9**) in 22% yield <49HCA544, 72CJC1167, 74JMC948>. The reductive methylation of octahydro-1H-azonine with formaldehyde and formic acid gives the *N*-methyl

Table 2 Selected physical properties of some saturated nine-membered heterocycles <35HCA1087, 49HCA544, 53M1206, 91JA7697>.

Compound	<i>m.p.</i> (°C)	<i>b.p.</i> (°C)	Density	n_D
Caprylactone		198	0.9865	
Octahydrazonine		90–92 (24 mmHg)	0.9021	1.4777
Caprylactam	77	130–135 (3 mmHg)		
Thionane		62–65 (10 mmHg)	0.9858	1.585

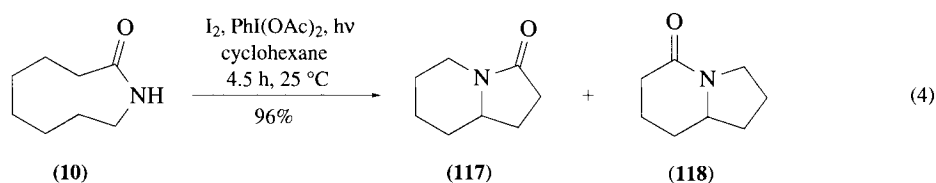
derivative, and further methylation with iodomethane in benzene yields the quaternary ammonium iodide salt $\langle 68CCC1429, 80JOC3952 \rangle$. *N*-Methyloctahydro-1*H*-azonine has also been prepared by the Wolff–Kishner reduction of *N*-methyloctahydro-1*H*-azonin-4-one $\langle 72JOC3489 \rangle$. Cerichelli *et al.* have investigated the reaction of *N,N*-dimethyloctahydro-1*H*-azoninium iodide with sodium methoxide at 130°C. A mixture of products was obtained $\langle 80JOC3952 \rangle$. The TMS derivative of octahydro-1*H*-azonine has been prepared (MeMgI, then TMS-Cl) and reacted with methoxydichlorophosphine to form the methylphosphoramidite $\langle 84TL5513 \rangle$. A number of Mannich bases have been prepared from octahydro-1*H*-azonine $\langle 67JPS1114 \rangle$.

Indolizidine (**115**) has been prepared by the silver ion-promoted cyclization of *N*-chlorooctahydro-1*H*-azonine (**116**). The *N*-chloroamine was prepared by the reaction of the free amine with dichloramine-T, and a nitrene was proposed as the reactive intermediate $\langle 65JA678 \rangle$. The same authors later found, however, that purified chloramines that were completely free of amine were inert to silver ions, and a free radical mechanism involving transannular hydrogen abstraction was proposed $\langle 72CJC1167 \rangle$. The same reaction has been found to proceed in 71% yield, by electrochemical oxidation under carefully optimized conditions (Equation (3)) $\langle 85CJC1170 \rangle$. The methiodide salt of (**115**) has been prepared by acid treatment of *N*-methyloctahydro-1*H*-azonin-5-ol $\langle 67JOC2026 \rangle$.



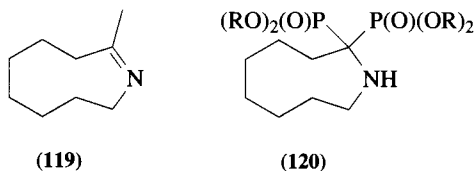
9.27.6.3.2 Caprylactam and related compounds

The ring closure of caprylactam has been accomplished by photolysis in the presence of iodine and (diacetoxyiodo)benzene. Here, an initially formed amidyl radical undergoes transannular hydrogen abstraction to afford the indolizidinones (**117**) and (**118**) in excellent combined yield (Equation (4)) $\langle 89CC1168 \rangle$. In contrast, *N*-chlorocaprylactam forms (**117**) and (**118**) in only 13% yield when heated to 80°C $\langle 65JA678 \rangle$.

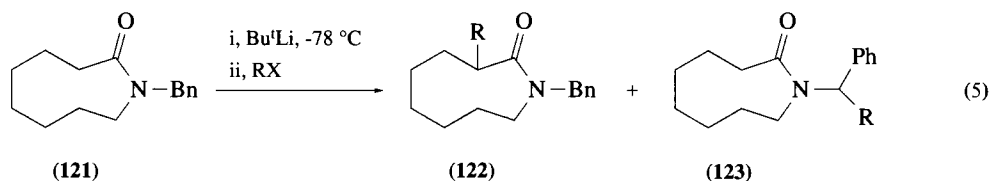


Caprylactam can be monobrominated at the 3 position using phosphorus pentabromide $\langle 86JMC251 \rangle$, and can be mono- or dibrominated with one or two molar equivalents of molecular bromine with a catalytic amount of ZnCl_2 or iodine $\langle 71JMC501 \rangle$. 3-Bromocaprylactam can be transformed to the azido derivative by treatment with LiN_3 in DMF, or with NaN_3 in aqueous ethanol. The azidolactam can then be reduced by catalytic hydrogenation to 3-aminocaprylactam $\langle 86JMC251 \rangle$. The elimination of HBr from 3,3-dibromocaprylactam can be accomplished by refluxing in piperidine for 4.5 h to give the 3-bromo- α,β -unsaturated lactam (60% yield) $\langle 84JOC5113 \rangle$. The dichlorination of caprylactam at the 3 position may be achieved using phosphorus pentachloride in chloroform–toluene, and the monochloro lactam can then be derived by catalytic hydrogenolysis $\langle 71JMC501 \rangle$. The Favorskii rearrangements of 3-bromo- and 3-chlorocaprylactam have been reported $\langle 66TL5393, 71JMC501 \rangle$ (Section 9.27.8.7). Caprylactam reacts in freon with ^{18}F -labeled fluorine (0.05% in neon) to give *N*- ^{18}F fluorocaprylactam in 33% yield $\langle 90JOC3373 \rangle$. The treatment of caprylactam with triethyloxonium tetrafluoroborate gives the ethyl lactim ether in 85% yield, and this can be hydrolyzed in 90% yield to ethyl 8-aminooctanoate $\langle 88SC1625 \rangle$. The methyl lactim of a related nine-membered lactam has similarly been prepared using trimethyloxonium tetrafluoroborate $\langle 81JA461 \rangle$; the methyl lactim ether of caprylactam may be prepared by treatment with dimethylsulfate, and with excess dimethylsulfate this can be isomerized to *N*-methylcaprylactam $\langle 73C65 \rangle$. The *N*-alkylation of caprylactam was reported using sodium hydride and alkyl halides in refluxing benzene $\langle 64JOC2748, 75CCC93 \rangle$; the *N*-alkylation of caprylactam can also be achieved with a range of electrophiles using NaOH in the presence of a phase transfer catalyst $\langle 77ZC260 \rangle$. Caprylactam reacts with TMS-Cl and Et_3N in toluene to give a 94%

yield of the *N*-TMS lactam, which reacts with MeLi to afford the nine-membered ketimine (**119**) in 85% yield <90JOC3682>. The reaction of caprylolactam with phosphorus or phosphonic acid and phosphoryl chloride in the presence of water is reported to give the diphosphonic acid derivative (**120**; R = H, alkyl) <92GEP4114586>. The anodic oxidation of caprylolactam in methanol containing tetramethylammonium tetrafluoroborate gives 9-methoxycaprylolactam in 57% yield <80S315>. Caprylolactam forms an addition product with ninhydrin which can be hydrogenated to *N*-(2-indanyl)caprylolactam <74CI(L)495>.

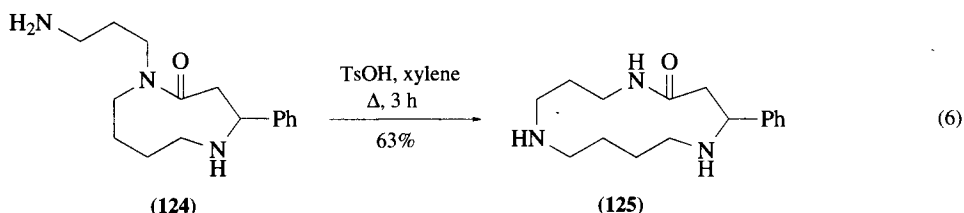


The sites of deprotonation of a series of *N*-benzyl lactams have been determined. For five- and six-membered lactams, kinetic deprotonation occurred exclusively α to the carbonyl, while seven- and eight-membered lactams gave exclusively the products arising from deprotonation at the benzylic position. The alkylation of the anion derived from (**121**), however, gave an approximately 3:1 ratio of (**122**) to (**123**) (R = Buⁿ, allyl and Bn) (Equation (5)) <87JA4405>. By contrast, the deprotonation of *N*-(BOC)caprylolactam with lithium hexamethyldisilazide in THF at -78°C gave the expected enolate, which could be alkylated with iodomethane (81% yield) or phenylselenenyl chloride (65% yield) <90SL63>.



Vilarrasa and co-workers discovered the anomalous reactivity of caprylolactam towards *N*-nitration and *N*-nitrosation. While acyclic amides and all simple lactams of ring size 5–16 gave the expected products, neither *N*-nitroso- nor *N*-nitrocaprylolactam could be obtained; caprylolactone (**13**) was instead the major decomposition product. The high reactivity of the caprylolactam derivatives was ascribed to the amide bond being unable to adopt either a truly planar *cis* or *trans* conformation, and so making them especially prone to rearrangement <89T863>. Octahydro-1*H*-azonin-2-thione has been prepared by the reaction of caprylolactam with P₄S₁₀ in refluxing xylene. Similarly, the selenolactam was prepared by the treatment of caprylolactam with red phosphorus and selenium in hot xylene <69JCS(A)1033>.

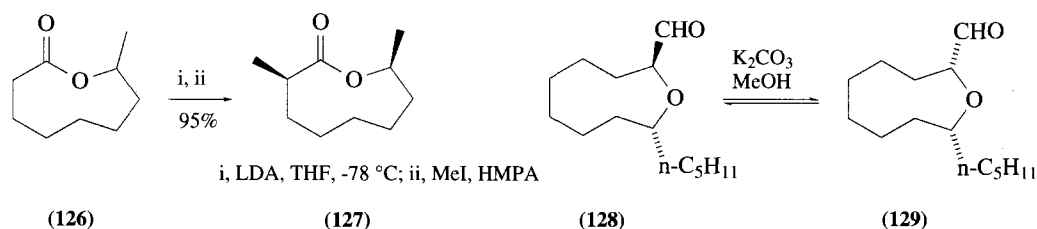
The intramolecular transamidation of nine-membered rings has been exploited in the synthesis of macrocycles. Lactam (**124**), when treated with acid catalyst in refluxing xylene, gave the 13-membered ring (**125**) (Equation (6)) <92T3775> (see also <80TL3493>).



9.27.6.3.3 Oxonane, caprylolactone, and related compounds

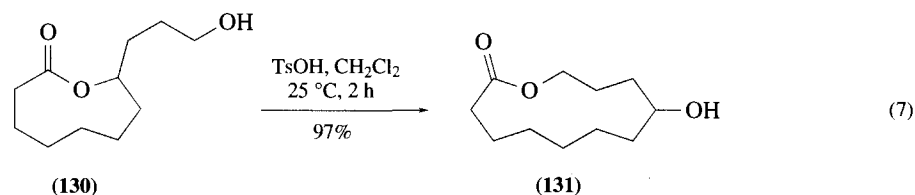
Oxonane (**12**) has been prepared, in unspecified yield, by the catalytic hydrogenation of 4,5,6,7-tetrahydrooxonin (**80**). Both (**12**) and (**80**) are reported to undergo hydrolysis and oxidation to suberic acid upon treatment with chromic acid <67TL1717>. 9-Methyloxonan-2-one (**126**) has been resolved by hydrolysis using pig liver esterase. Both the unreacted lactone and the hydroxyacid

product were obtained in high yield, and with greater than 95% *ee* <89S661>. Still and Galynker have examined the 1,4-diastereoselection of the methylation of the enolate derived from (126). They found that the product (127), obtained in 95% yield, consisted of more than 98% of the *cis* isomer (Scheme 8). The product ratio was very similar to that predicted on the basis of modeling relative strain energies of the possible (*Z*)-enolate conformations <81T3981>. The base-catalyzed equilibration of aldehyde (128) gave a 6:1 mixture of epimers, in favor of the *cis* isomer (129) <89TL6081>.

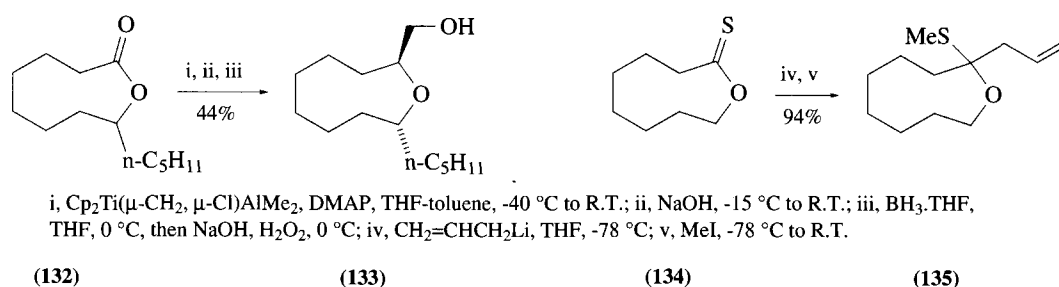


Scheme 8

The ring strain inherent in eight- and nine-membered lactones has been exploited in trans-lactonizations to form larger lactones. Thus, the treatment of the lactone (130) with a catalytic amount of acid led to its smooth conversion to the unstrained 12-membered hydroxylactone (131) (Equation (7)). This translactonization procedure, which could also be effected by base, was also used to prepare a 15-membered lactone from a nine-membered lactone <77JA7359>.

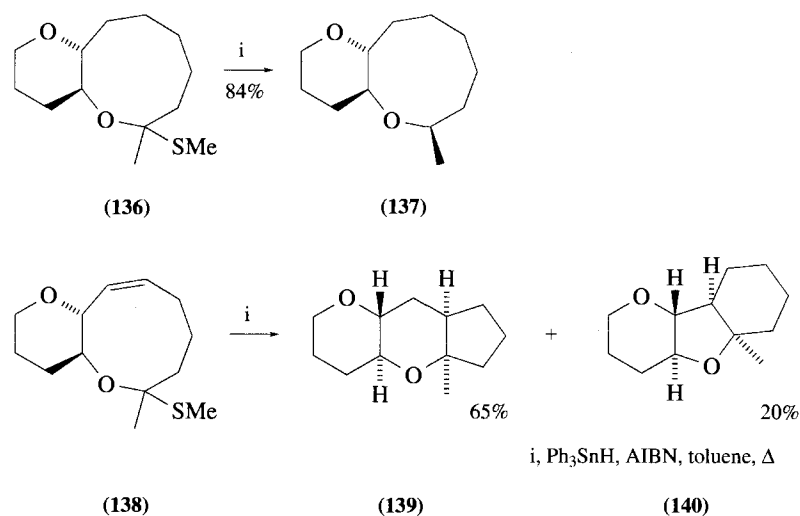


The Tebbe methylenation of the oxonan-2-one (132), followed by borane reduction of the exocyclic enol ether, led to the hydroxymethyloxonane (133) in moderate yield, and as a 9:1 ratio of *trans* to *cis* isomers (Scheme 9) <89TL6081>. Nicolaou and co-workers have shown that thionolactones react with organometallics without ring opening, and that the intermediate thiolate anion may be trapped with electrophiles. Thus, the thionolactone (134), prepared in 62% yield by the reaction of caprylactone with Lawesson's reagent, reacted with allyllithium then iodomethane to give an excellent yield of the oxonane (135) (Scheme 9) <87JA2504, 90JA6263> (see also <90JA4988>). Nine-membered exocyclic enol ethers have been prepared from thionolactone (134) by a modification of this procedure <93JOC506>.



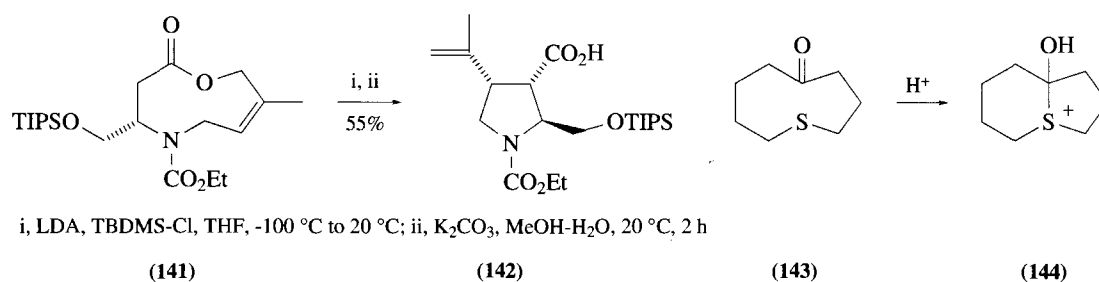
Scheme 9

The desulfurization of (136) was accomplished using triphenyltin hydride in toluene, with a catalytic amount of AIBN, to afford the epimeric fused oxonanes (137) in a 4:1 ratio, in favor of the *cis* isomer shown. When the reaction was performed on the unsaturated system (138), the radical intermediate underwent transannular closure to give a mixture of the tricycles (139) and (140) (Scheme 10) <87JA2504>.



Scheme 10

An intramolecular Claisen rearrangement was the key step in the enantiospecific synthesis of (–)- α -kainic acid. The silylation of the azalactone (**141**) gave the intermediate ketene silyl ether, which upon warming underwent a [3,3] Claisen rearrangement to furnish the pyrrolidine (**142**), via a boat-like transition state (Scheme 11) <87CC1220, 91JCS(P1)705>.



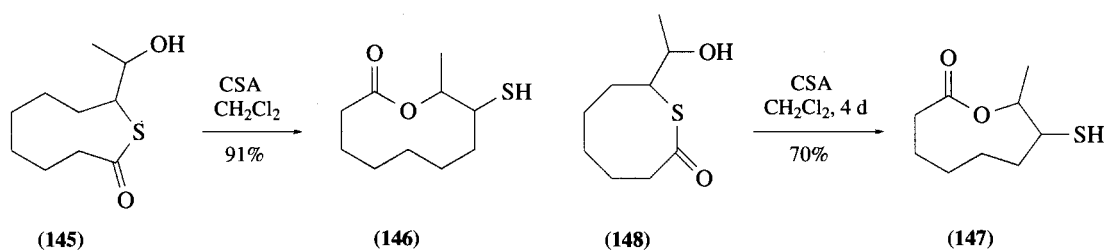
Scheme 11

9.27.6.3.4 Thionane and related compounds

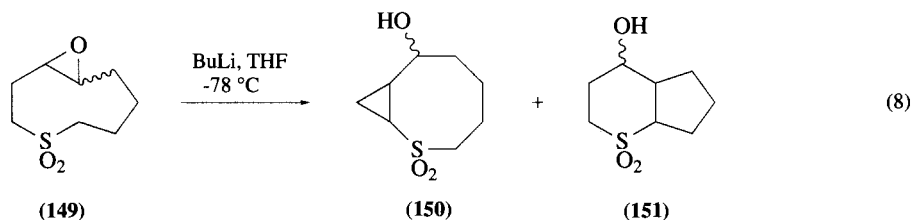
Thionane (**15**) forms a number of crystalline derivatives: a mercury addition compound (m.p. $92\text{--}93\text{ }^{\circ}\text{C}$), the sulfone (m.p. $81.5\text{--}82\text{ }^{\circ}\text{C}$) and the methiodide (m.p. $124\text{--}124.5\text{ }^{\circ}\text{C}$). With excess iodo-methane in a sealed tube, 1,9-diiodooctane is formed <53M1206>. While the IR spectrum of thionan-5-one (**143**) shows no evidence for a transannular interaction between the sulfur lone electron pairs and the carbonyl group, protonation with perchloric acid leads to the bicyclic sulfonium salt (**144**) (Scheme 11) <62JA2814>.

Vedejs and Powell employed an acid-catalyzed intramolecular S to O acyl transfer process to convert the thionan-2-one (**145**) to the 10-membered lactone (**146**) in their synthesis of phoracantholide I; the nine-membered lactone (**147**) was formed under similar conditions from (**148**) (Scheme 12) <82JA2046>.

The regio- and stereoselectivities of the anionic transannular cyclization of (*Z*)- and (*E*)-epoxy-sulfones (**149**) have been studied (Equation (8)) <91JOC4513, 92JOC1457>. The proportion of regio-isomeric products (**150**) and (**151**) was found to depend on the mode of metallation.



Scheme 12



The reaction of the octathionane (36) with triphenylphosphine to give pentathianes and stable thiobenzaldehydes has been reported <94JA7907>.

9.27.7 RING SYNTHESSES BY CYCLIZATION REACTIONS

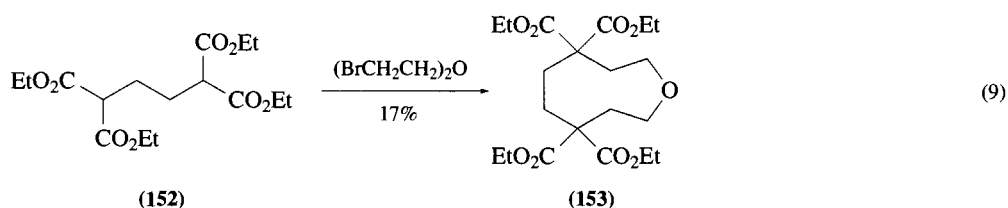
The difficulties in synthesizing medium-sized rings by cyclization methods have long been appreciated, and will not be discussed at length here <95T2777>.

9.27.7.1 C—C Bond Formations

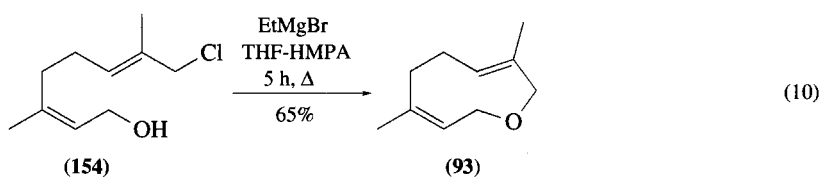
9.27.7.1.1 Ionic cyclizations

The bis-Wittig coupling procedure for the preparation of nine-membered rings has been reviewed in Chapter 5.20 of CHEC-I.

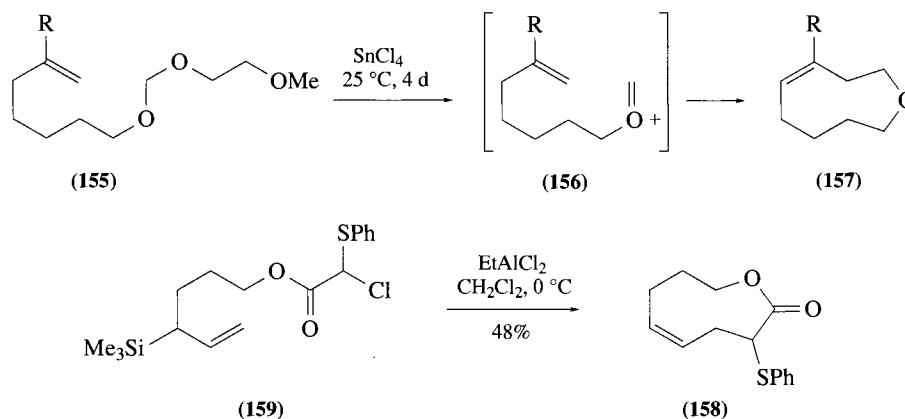
One of the first examples of a cyclization to form a nine-membered ring is that reported by Ali-Zade and Arbuzov <43MI 927-01>. The reaction of the bis-malonate (152), as its magnesium salt, with bis(bromoethyl)ether afforded the oxonane (153) (Equation (9)).



Marshall and Lebreton demonstrated that the treatment of the chloroalcohol (154) with ethylmagnesium bromide afforded the tetrahydrooxonin (93) in fair yield (Equation (10)) <88JOC4108>. The presence of two double bonds in the precursor presumably conspires to allow the cyclization to proceed without the need for high dilution. Only 3% of the dimer was formed.

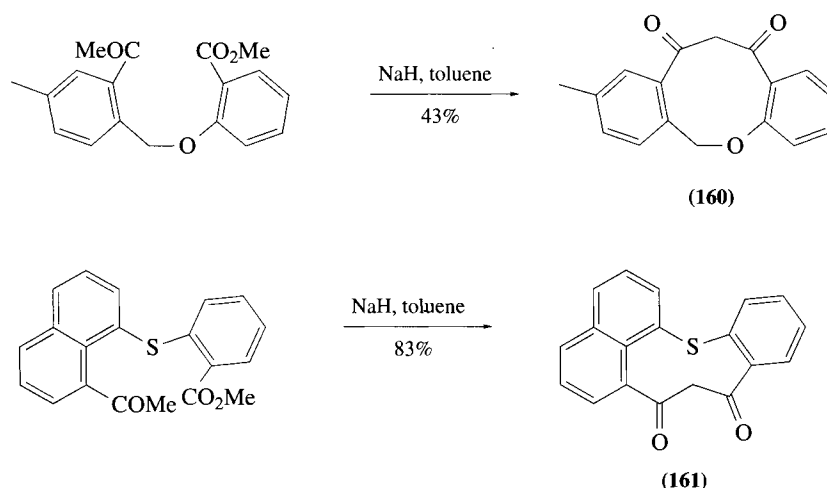


Overman and co-workers have demonstrated that unsaturated medium-ring ethers can be prepared by the Lewis acid-mediated cyclization of acetals. The treatment of (**155**; R = TMS) with tin chloride gave, via the intermediate oxocarbenium species (**156**), hexahydrooxonins (**157**; R = TMS) and (**157**; R = H), the latter product arising from the protodesilylation of the initial product (Scheme 13) <86JA3516>. Although in the original communication the yields were reported to be very good, this was found to be in error, and only low yields were in fact obtained <90JA4386>. There is evidence that this reaction proceeds by an intramolecular ene mechanism, which accounts for the high degree of regio- and stereoselectivity of the cyclization <90JA4399> (see also <91TL7689>). Wada *et al.* have prepared medium-ring lactones (**158**) in good yields (unoptimized), without the need for high dilution, by Lewis acid-promoted intramolecular condensation of α -chlorosulfides and allylsilanes (**159**) (Scheme 13) <85TL5191>.



Scheme 13

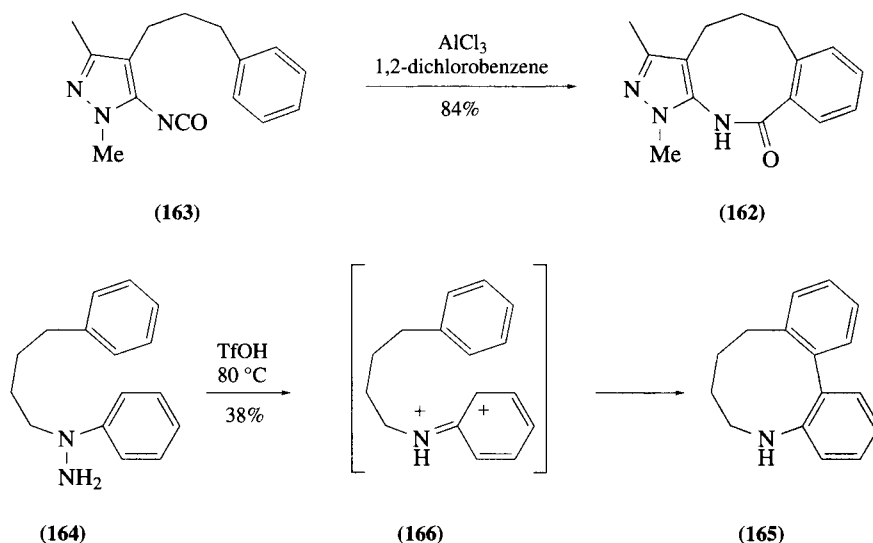
The preparation of thionan-5-one (**143**), in very poor yield, has been reported by the Dieckmann cyclization of 3-carboxyethylpropyl-4-carboxyethylbutyl sulfide <62JA2814>. The nine-membered aryl-fused rings (**160**) and (**161**) have been prepared by intramolecular condensation reactions between methyl ketones and methyl esters, using sodium hydride in boiling toluene (Scheme 14) <87CB1151>.



Scheme 14

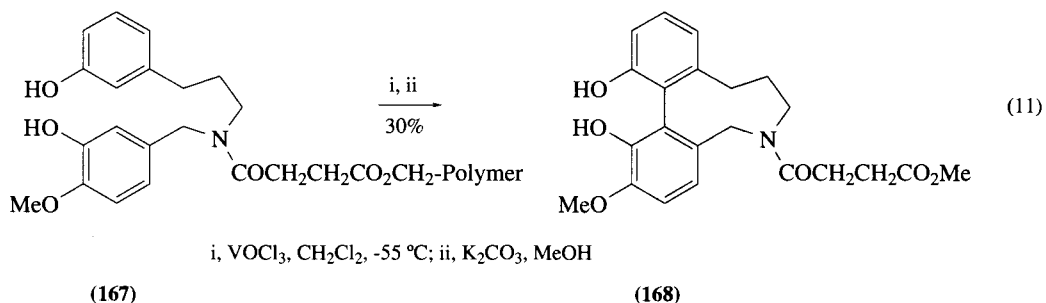
Nine-membered rings have been prepared using intramolecular Friedel–Crafts cyclizations. Butler and Alexander prepared the pyrazole-fused lactam (**162**) by the cyclization of the isocyanate (**163**) <82JHC1173>, and Shudo and co-workers have described the cyclization of *N*-amino-*N*-(phenyl-

butyl)aniline (**164**) on treatment with trifluoromethanesulfonic acid to give (**165**), presumably via the dication intermediate (**166**) (Scheme 15) <85TL5811>.

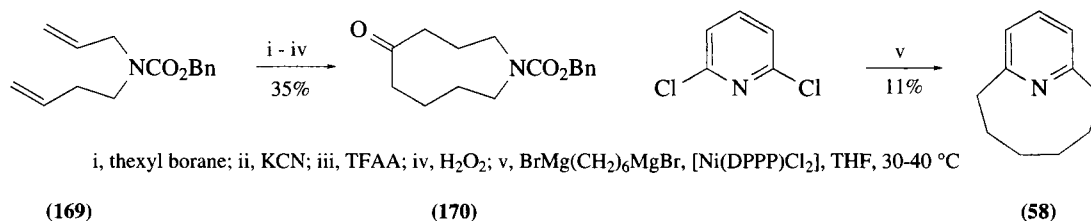


Scheme 15

Vanadium-mediated oxidative coupling of the polymer-supported diarylamine (**167**) gave, after de-anchoring from the support, a modest yield of the nine-membered ring (**168**) (Equation (11)). The orientation of the phenol coupling (*ortho, ortho*) is different to that obtained with similar substrates in solution (*ortho, para*) <82CJC368>.



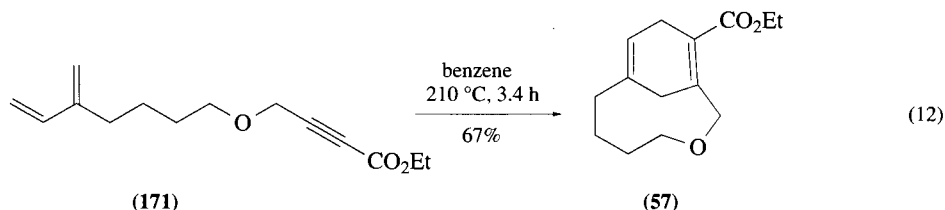
Garst and Bonfiglio have performed a hydroboration–carbonylation reaction of the bisalkenyl carbamate (**169**) to yield the ketone (**170**), without the need for high dilution <81TL2075, 82JOC1494>. Kumada and co-workers have prepared the pyridinophane (**58**), in low yield, by nickel-catalyzed cross-coupling of 2,6-dichloropyridine and a di-Grignard reagent (Scheme 16). The coordination of the magnesium to the nitrogen was considered an important factor during the cyclization <75JA4405>.



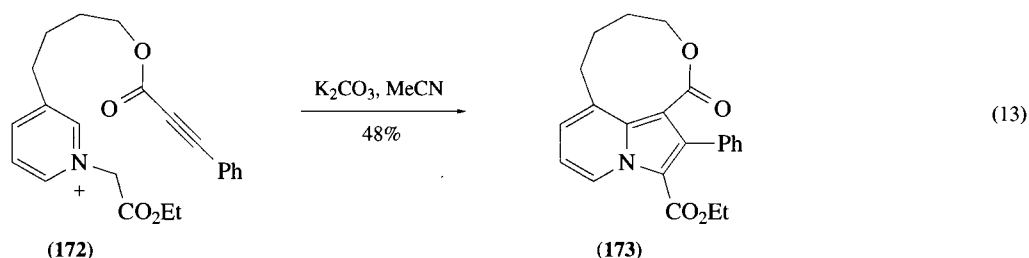
Scheme 16

9.27.7.1.2 *Pericyclic cyclizations*

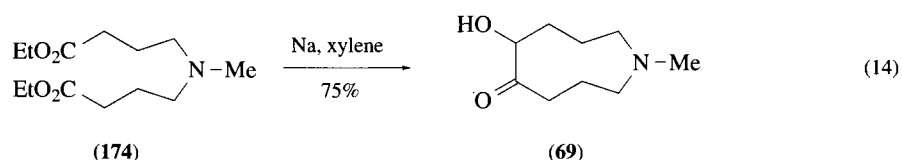
The intramolecular Diels–Alder reaction of (171) proceeds at 210°C in a sealed tube to give the strained bridgehead diene ester (57) (Equation (12)) <86T1841>. The yield is surprisingly good, considering that both a medium ring and two strained alkene bonds are formed.



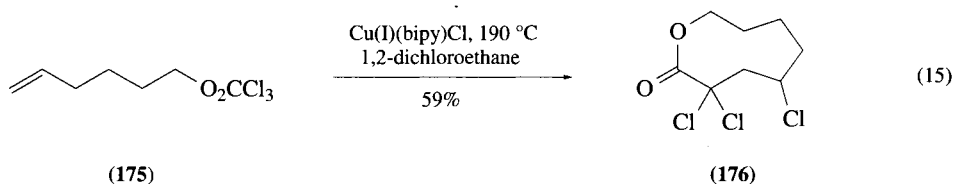
Miki *et al.* reported that the treatment of the pyridinium salt (172) with a base gave the nine-membered lactone (173), the product of an intramolecular 1,3-dipolar cycloaddition followed by aerial oxidation (Equation (13)) <85JCS(P1)379>.

9.27.7.1.3 *Radical and photochemical cyclizations*

Leonard prepared the nine-membered hydroxyketone (69) in good yield by acyloin cyclization of the aminodiester (174), utilizing high-speed stirring and high dilution (Equation (14)) <54JA5708>.

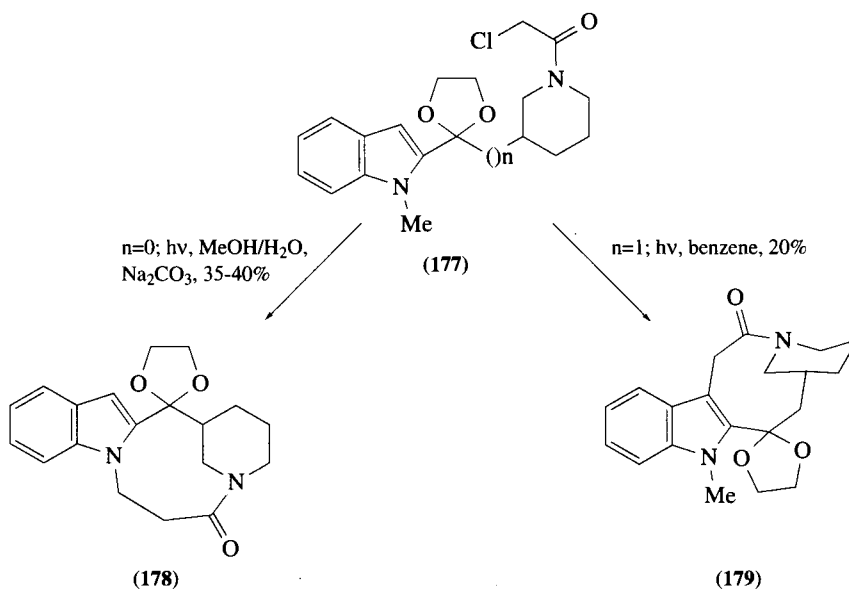


Speckamp *et al.* have reported the synthesis of medium-ring lactones by Cu(bipy)Cl-catalyzed cyclization of alkenyl trichloroacetates. In the case of 5-hexenyl trichloroacetate (175), a 0.06 M solution in a sealed tube at 190°C gave the trichlorolactone (176) in fair yield (Equation (15)) <93SL739>.



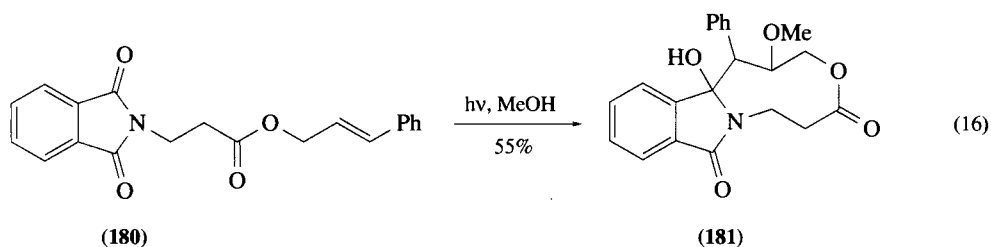
Witkop photocyclization has been applied to the preparation of indolo-fused nine-membered rings. Photolysis of *N*-chloroacetyl-piperidylindole (177; *n* = 0) in aqueous methanol gave the indole (178) <76TL1163> (see also <75TL2057>). In a related reaction, the photolysis of (177; *n* = 1) in either benzene or isopropanol gave, among other products, the nine-membered ring (179) (Scheme 17)

<75JOC2613>. Similar intramolecular insertions of photochemically derived radicals into benzene rings have also yielded nine-membered rings <69JA4591, 70JA5691, 72CPB998>.

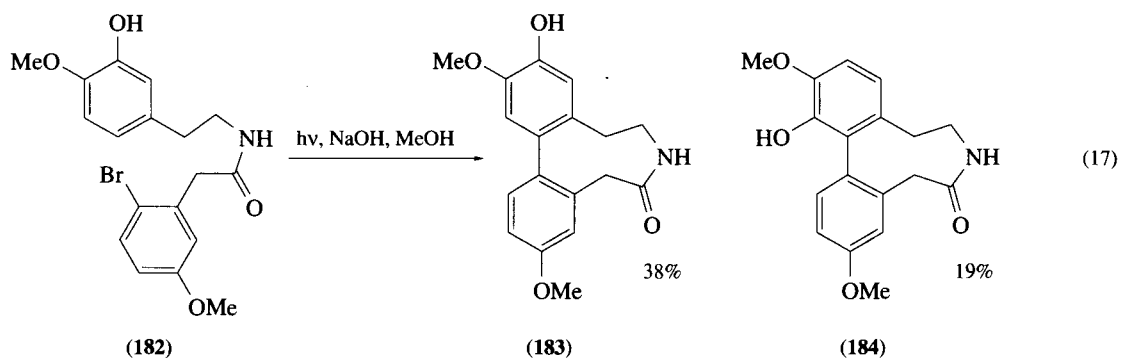


Scheme 17

Maruyama and Kubo have reported that the intramolecular photocyclization of the succinimide (180) gave the solvent-incorporated nine-membered ring (181) (Equation (16)). The mechanism has been described in terms of a photoinduced addition of methanol between electron acceptor (phthalimide moiety) and donor (alkene), involving initial single electron transfer from the alkenyl double bond to the phthalimide group <78JA7772>.

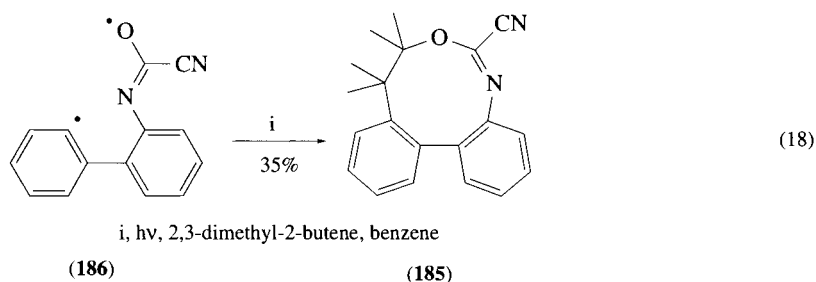


Photocyclizations have also been applied to aryl-aryl couplings. The irradiation of the bromide (182) gave a mixture of the *para* product (183) (i.e., with respect to the phenolic group of ring A), and the *ortho* product (184) (Equation (17)) <84H(22)2007>.



Albini *et al.* reported that the irradiation of 6-cyanophenanthridine *N*-oxide in the presence of

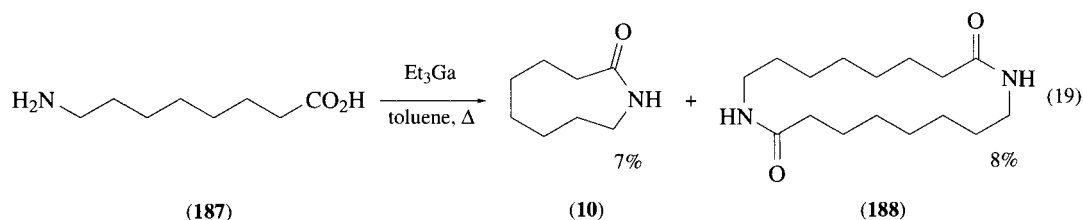
2,3-dimethyl-2-butene gave the novel photoaddition product (**185**), presumably via the diradical intermediate (**186**) (Equation (18)) <82TL4849>.



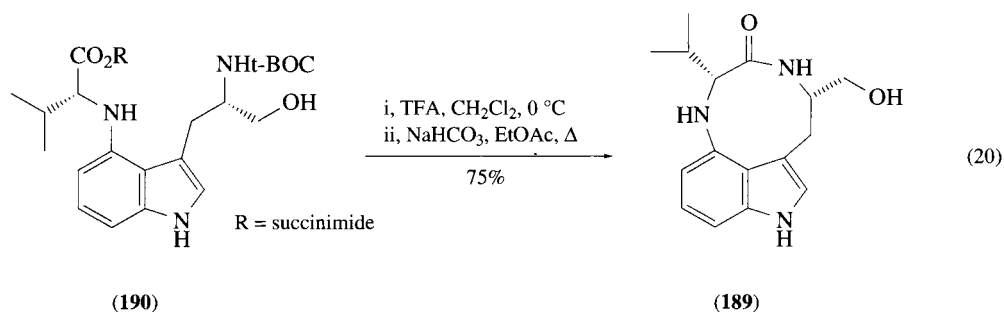
9.27.7.2 C—N Bond Formations

9.27.7.2.1 Lactamizations, acylations, and related reactions

The formation of nine-membered lactams by ring closure of ω -amino carboxylic acid derivatives generally proceeds in poor yields, if at all, and substantial amounts of dimers, oligomers, and polymers are usually obtained. The triethylgallium-mediated cyclization of the amino acid (**187**) to caprylactam and its dimer (**188**) is illustrative (Equation (19)) <89CL797> (see also <78JOC4393>). *N*-Benzylcaprylactam (**121**) has been prepared in 46% yield, along with 42% dimer, by intramolecular trapping of a ketene <94SL743>.



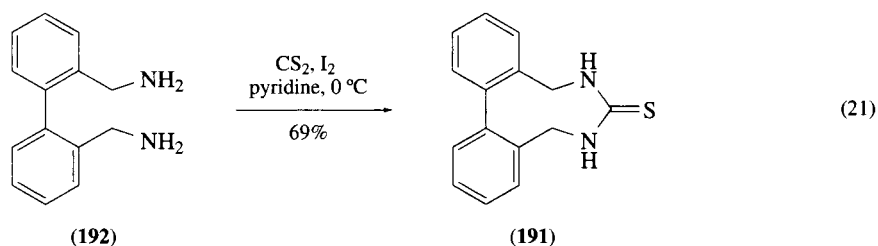
Moderate and even high yields of nine-membered lactams may be obtained from amino acid derivatives where the acyclic precursor possesses several conformational constraints which reduce the entropic penalty associated with cyclization <94MI 927-01>. An example is the preparation of (**189**) reported by Shudo and co-workers. In this instance, the conformational constraint imposed by the indole nucleus allows the smooth ring closure of deprotected (**190**) to the nine-membered lactam, without the need for excessively high dilution (Equation (20)) <86T5905> (see also <77JHC733, 93TL8119>).



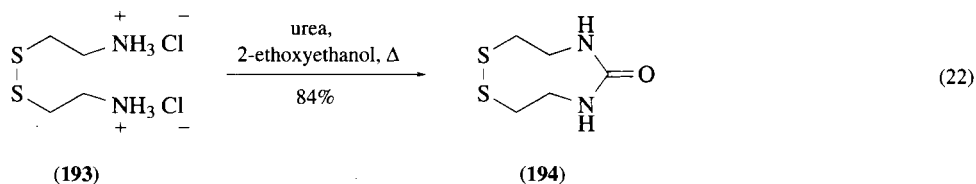
The use of high-dilution conditions for lactamizations may be effective in cases where only one conformational constraint (ring fusion, double bond, etc.) is present in the acyclic precursor <69CC656, 77LA1698, 79TL4307>.

Hiatt *et al.* prepared the thiourea (**191**) in good yield by the route shown in Equation (21). Here, the presence of two ring fusions in the diamine precursor (**192**), as well as the hindered rotation about

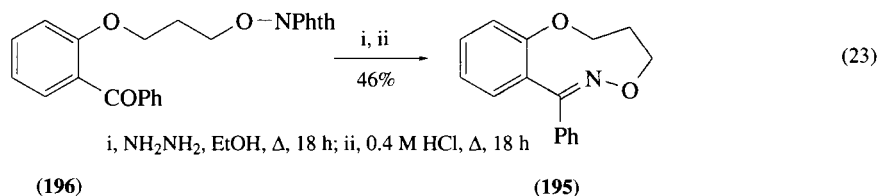
the aryl-aryl bond combine to favor an intramolecular reaction, even though high concentrations of reagents were employed. Attempts to prepare the corresponding urea were unsuccessful <79JOC3265>.



Whitesides *et al.* have reported the unusually high-yielding ring closure of the bisammonium salt (193) to form the cyclic urea (194) (Equation (22)) <77JOC332>. No mass spectrum of (194) was reported, however, and so the possibility of the product actually being an 18-membered dimer cannot be excluded.



Browne has prepared the 3,4-dihydro-2*H*-1,5,6-benzodioxazonine (195) by intramolecular imine formation from (196) (Equation (23)) <81H(16)881>.

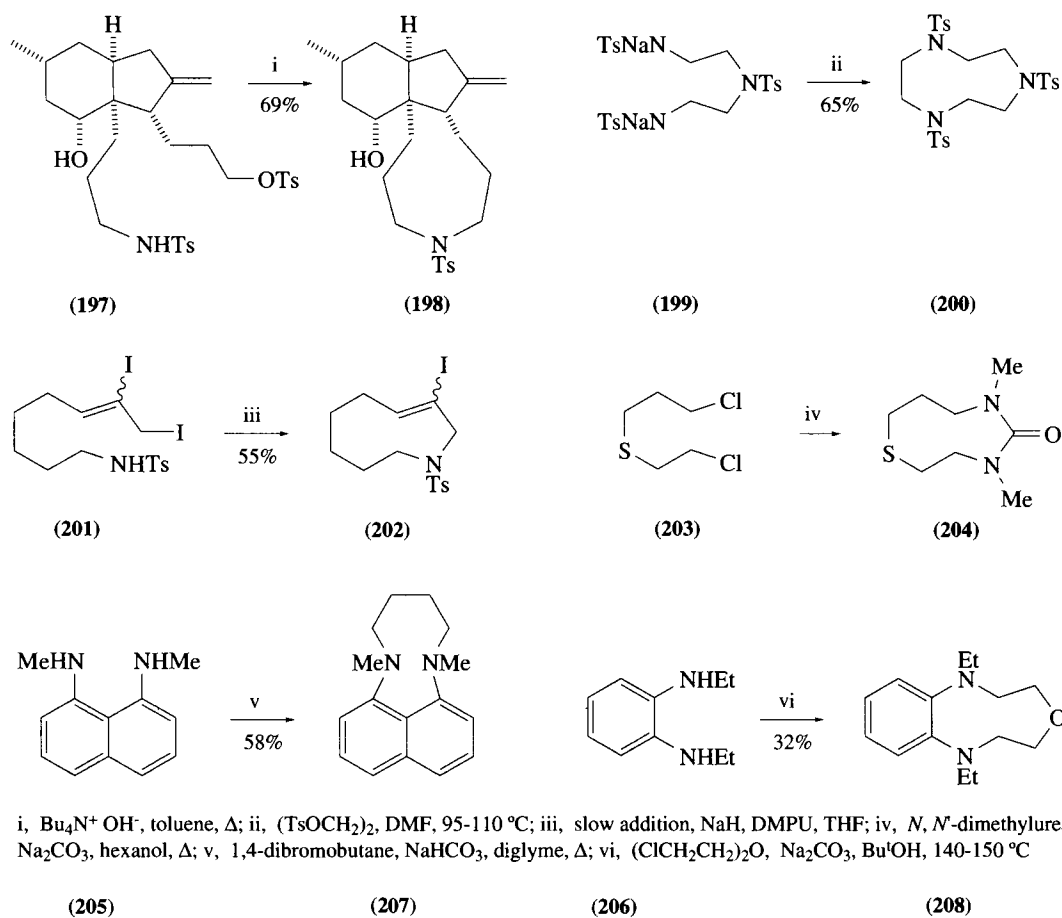


9.27.7.2.2 N-Alkylations

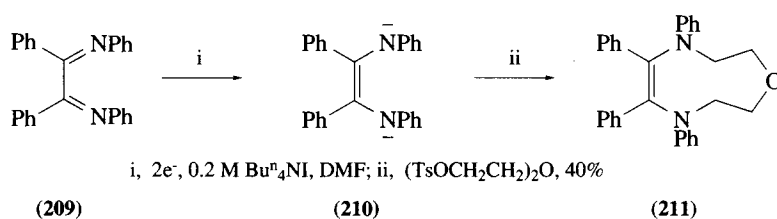
As with cyclization of nine-membered rings by lactamization, ring closure by *N*-alkylation proceeds best when the precursor amine possesses several conformational constraints. Synthetically useful yields have been achieved even when only a single ring fusion, or one or two *sp*²-hybridized nitrogens were present in the precursor. Examples are the ring closure of *N*-tosylamide (197) to form (198), a key intermediate in the synthesis of fawcettimine by Heathcock *et al.* <89JOC1548> (see also <91TL6219>), the conversion of (199) to tris(tosylamide) (200) <79JA4921> (see also <76LA916, 83PJC597, 84PJC251>), the cyclization of the diiodide (201), derived from the corresponding allene, to (202) <90SL584>, and the reaction of the bischloride (203) with dimethylurea to form (204) <87MI 927-02> (see also <73CC427, 77CI(L)373>). Naphthalene-1,8-diamines (205) <81JCS(P1)2840> and phenylenediamines (206) <77RZC351> have also been used as substrates in the formation of nine-membered rings (207) and (208) (Scheme 18).

The bisalkylation of cyclic hydrazines, and treatment of diazacycloalkanes with ω -chloroaldehydes, have been used to form bridgehead nine-membered ammonium salts (see Section 9.27.8.2).

Boujlel and Simonet have reported the novel preparation of nine, and larger, ring systems by the electrolysis of the diimine (209) to the dianion (210). The reaction of (210) with bifunctional electrophiles then gave heterocycles of type (211) (Scheme 19) <79TL1497>.



Scheme 18



Scheme 19

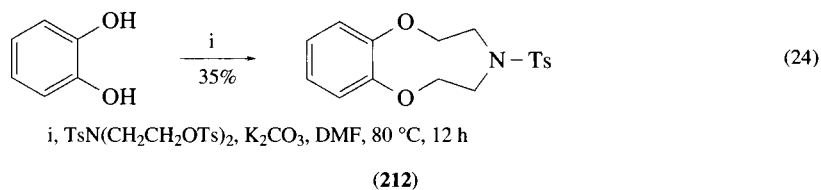
9.27.7.3 C—O Bond Formations

9.27.7.3.1 Lactonizations

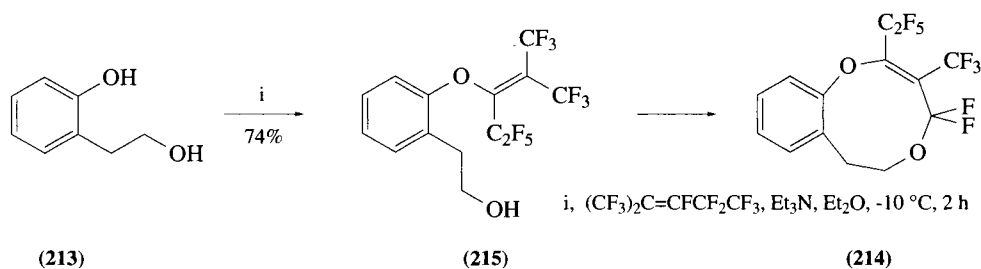
The preparation, reactivity and applications of medium-ring lactones have been comprehensively reviewed by Rousseau ^{<95T2777>}. This section will therefore concentrate on the chemistry of other nine-membered oxacycles.

9.27.7.3.2 O-Alkylations

Most of the literature regarding the formation of nine-membered rings by *O*-alkylation relates to the preparation of 1,4,7-trioxonanes (9-crown-3 ethers) and related compounds. The preparation of 1,4,7-trioxonane itself proceeds in only 1% yield, by the trimerization of ethylene oxide with BF_3/HF <74ACS(B)378>, but higher yields of substituted 9-crown-3 ethers have been achieved when a substrate possessing a ring fusion or a *cis* double bond has been employed <77AG(E)467>. Högberg and Cram reported the synthesis of the benzo crown amino ether (**212**), in moderate yield, by bis-*O*-alkylation of catechol (Equation (24)) <75JOC151>. Boujlel and Simonet have prepared phenanthrene- and acenaphthene-fused 9-crown-3 ethers, in good yields, by electrolytic reduction of phenanthrenequinone and acenaphthequinone (cf. Scheme 19) <79TL1497>.

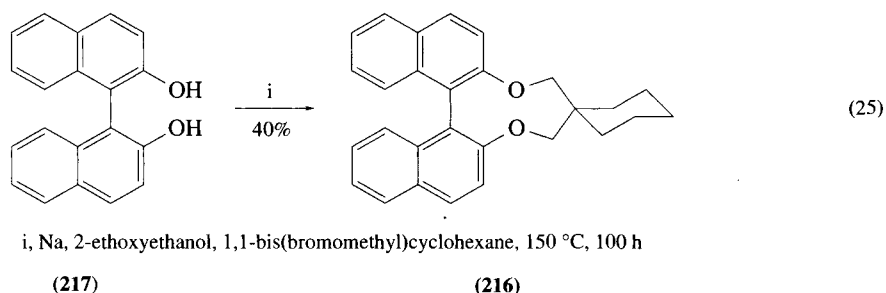


Ishikawa *et al.* have shown that the treatment of the diol (**213**) with perfluoro-2-methyl-2-pentene gives a good yield of the benzodioxonin (**214**), presumably via the intermediate (**215**) (Scheme 20). Phthalyl alcohol similarly gave the corresponding 1,5-benzodioxonin <81JFC(18)447>.



Scheme 20

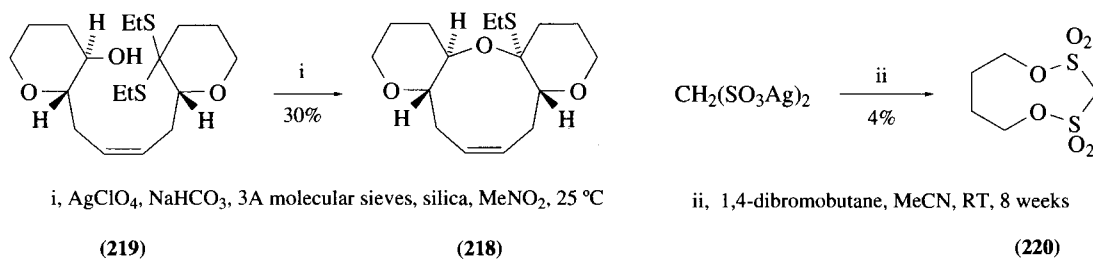
Smolinski and co-workers have prepared several nine-membered benzo- and naphthaleno-fused spirans (**216**) by the bisalkylation of phenolate salts (**217**) with alkyl dihalides (Equation (25)) <77MI 927-01, 77T1219>.



Nicolaou and co-workers have reported the synthesis of the bis fused oxonin (**218**), albeit in low yield, by the silver-promoted ring closure of the hydroxy dithioketal (**219**) (Scheme 21) <89JA5321>.

The use of acyclic precursors lacking a ring fusion or other conformational constraint generally leads to cyclic products in poor yields. An example is the preparation of the bis-sulfonic ester (**220**) by the route shown in Scheme 21 <85MIP8503075>.

The nine-membered carboxylic acid anhydride 4,4,7,7-tetramethyloxan-2,9-dione (**75**) has been prepared in 4% yield by the cyclization of 3,3,6,6-tetramethylsuberic acid with acetic anhydride <74CC243>.



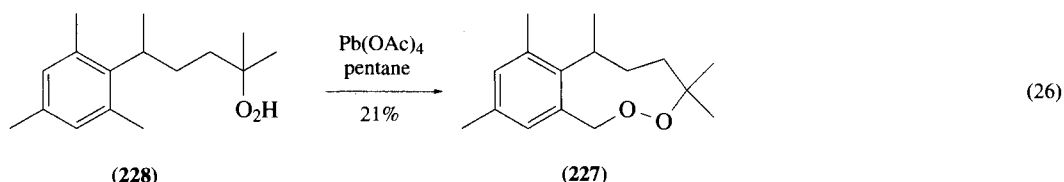
Scheme 21

9.27.7.3.3 Acetal formations

Fanton *et al.* have shown that nine-membered acetals (**221**) can be formed readily, although in poor yield, by the treatment of lactose (**222**) with 2-methoxypropene in *N,N*-dimethylformamide <80CC21>. Paul and co-workers have demonstrated that acetals of dihydroperoxides (**223**) can be prepared in high yield, even when no ring fusions or *cis* double bonds are present in the precursor (**224**) <76JOC1283> (see also <49LA(564)7, 70S181>). In a similar vein, dihydroperoxide (**225**) was found to form nine-membered peroxyketals (**226**) when treated with ketones in the presence of acid (Scheme 22) <77GEP2600656>.

9.27.7.3.4 Radical couplings

A methodology for the preparation of 1,2-dioxonins (**227**), in poor yield, by lead tetraacetate-mediated peroxide radical insertion into the benzylic bonds of (**228**) has been demonstrated by Kropf and co-workers (Equation (26)) <83LA624>.

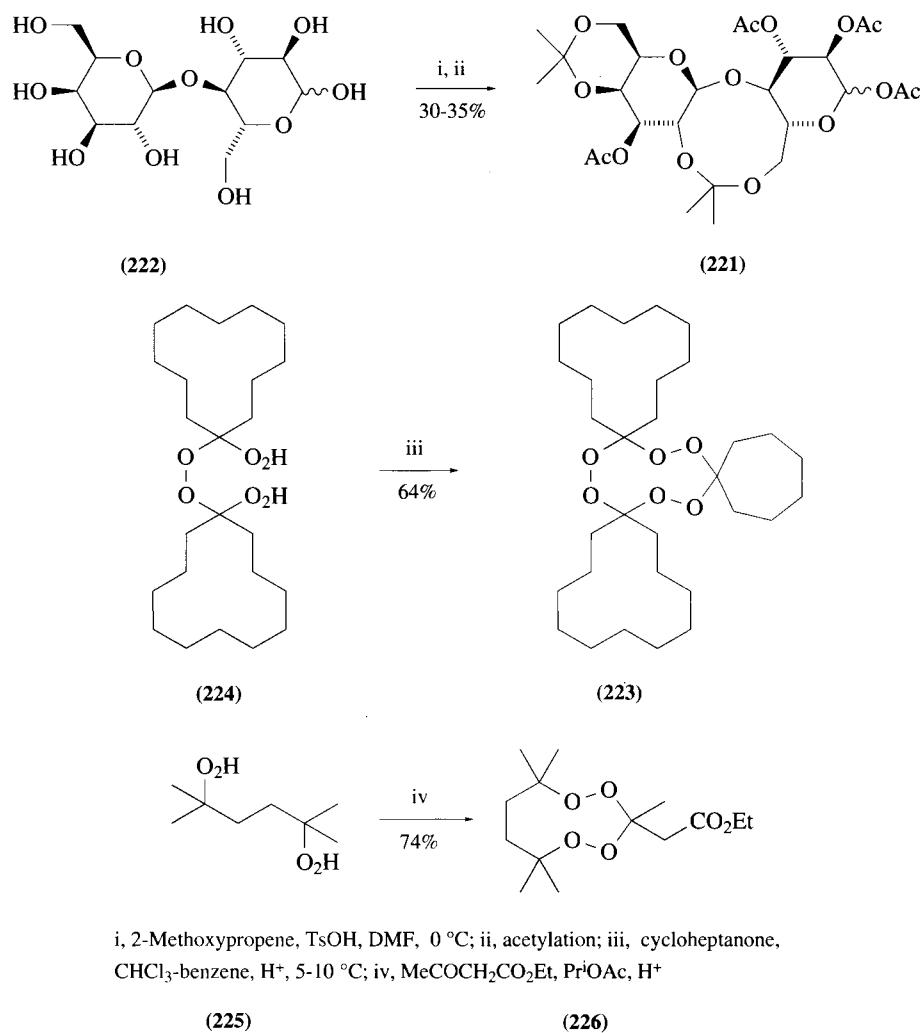


Kerr and McCullough have reported the novel formation of the lactone (**229**), in fair yield, by the thermolysis of the trioxane (**230**). The reaction presumably proceeds via the diradical intermediate (**231**) (Scheme 23) <85CC590>.

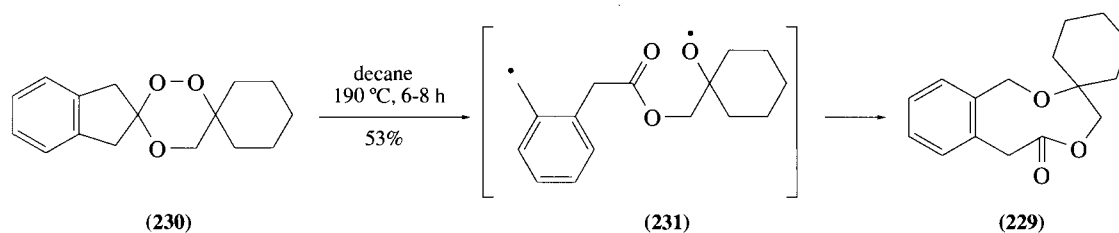
9.27.7.4 C—S Bond Formations

Müller *et al.* first reported the preparation of thionane (**15**), in 7% yield, by the high-dilution bisalkylation of sodium sulfide with 1,8-dibromooctane in ethanol <53M1206>. The same product has been obtained by the reaction of 1,8-dibromooctane with sodium sulfide, either in methanol–hexamethylphosphorous triamide solution (28% yield) <79SC857>, with sodium sulfide supported on activated alumina (38% yield) <92TL7709>, or with an active form of Li_2S in THF (22% yield) <85JOC4969>. However, Regen and co-workers have shown that medium-sized cyclic sulfides, including thionane (**15**) are formed in remarkably good yield by the reaction of sodium sulfide with dibromoalkanes under concentrated and heterogeneous conditions (Scheme 24). No cyclic dimer contaminants were detected by MS <81SC409>. As with many previous examples, restricted rotation of a single bond, or the presence of *cis* double bonds in the acyclic precursor, greatly aids the cyclization step. Harpp *et al.* prepared the dithionane (**232**) in excellent yield by simple alkylation of the potassium dithiolate (**233**) with diiodomethane (Scheme 24) <81JOC2072> (see also <72AG(E)727, 73CC427, 77CI(L)373>).

Meier and Dai reported the synthesis of medium-ring alkynes, including the strained dithiaalkyne



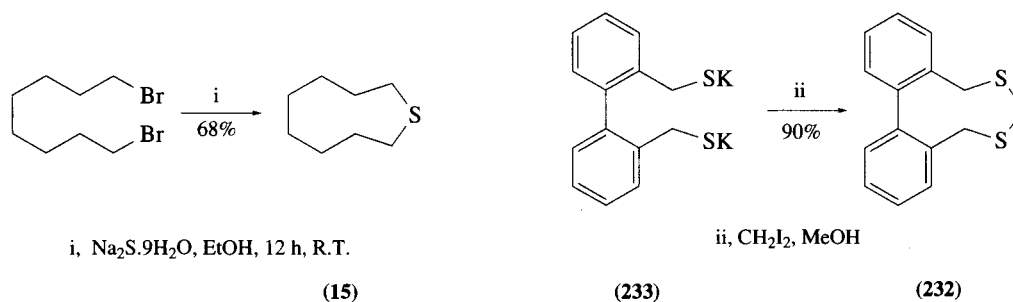
Scheme 22



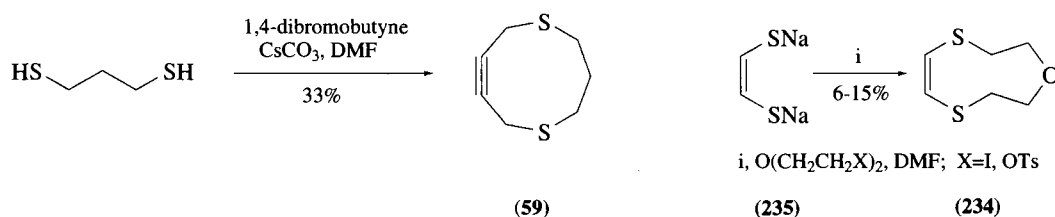
Scheme 23

(59) in 33% yield by alkylation of 1,3-propanedithiol with 1,4-dibromobutyne. The “caesium effect” was suggested as a significant factor in the ease with which the cyclization proceeded (Scheme 25) <93TL5277, 94CB2035>. The unsaturated dithia-9-crown-3 ether **(234)** was prepared in poor yield, along with the dimeric tetrathia-18-crown-6 ether, by the bisalkylation of the disodium salt **(235)** (Scheme 25) <85ZC138>. Improved yields have been reported for the syntheses of 1,3-dithiole-fused di- and trithia-9-crown-3 ethers <94JPR177>.

The inorganic complexes derived from tridentate ligands such as **(236)**, **(237)** and **(28)** (thio-9-crown-3 ethers) are of considerable interest; however, the poor yields associated with the preparation

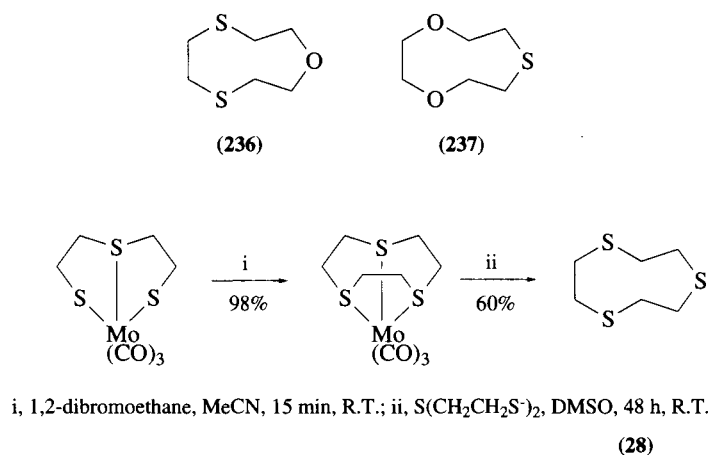


Scheme 24



Scheme 25

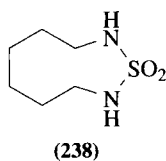
of these ligands have discouraged extensive investigations into their chemistry $\langle 87\text{MI } 927\text{-}01 \rangle$. For example, the reaction of ethanedithiol with bis(2-chloroethyl)ether, under highly dilute conditions, gave only a 6% yield of (236). Similarly, the reaction of 1,2-bis(2-chloroethoxy)ethane with sodium sulfide gave only a 5% yield of (237) $\langle 73\text{JHC1} \rangle$. Sellmann and Zapf have, however, described a high-yielding template synthesis of (28) (previously only obtainable in very poor yields), employing a molybdenum catalyst (Scheme 26) $\langle 84\text{AG(E)807} \rangle$.



Scheme 26

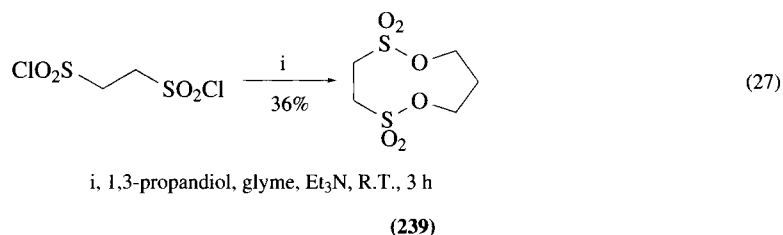
9.27.7.5 N—S Bond Formations

Arya and Shenoy have prepared the nine-membered sulfamide (238), in 55% yield, by heating a mixture of 1,6-diaminohexane and sulfamide at 170°C $\langle 74\text{M114, } 76\text{JC(B)766} \rangle$.



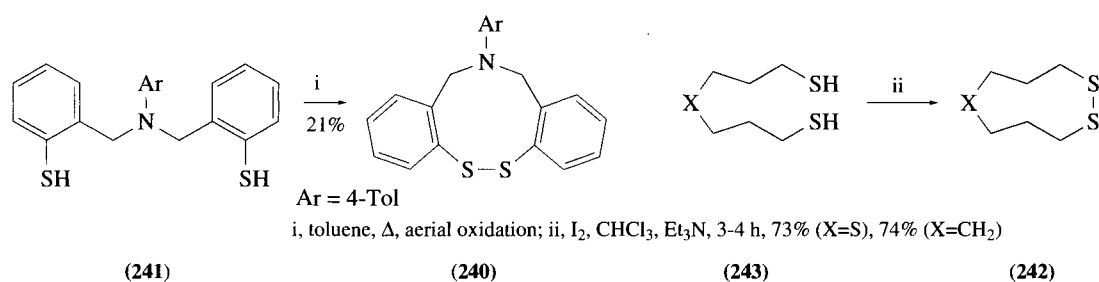
9.27.7.6 S—O Bond Formations

Cronyn reported the preparation of the cyclic bissulfonate (**239**), in poor yield, by the reaction of ethane-1,2-bissulfonyl chloride with propan-1,3-diol (Equation (27)) <85MIP8503075>.



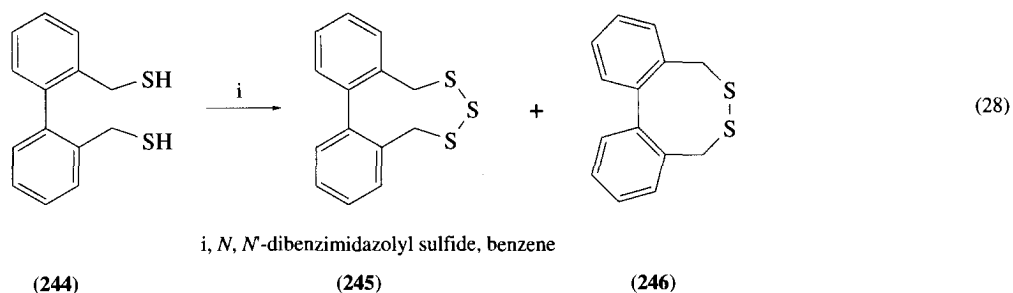
9.27.7.7 S—S Bond Formations

Few examples of the preparation of nine-membered rings by S—S bond formation exist. In general, oxidative cyclizations of dithiols generally appear to be unfavorable, probably because of the predominance of polymerization reactions. With benzo-fused systems, low yields of cyclic products (**240**) have been obtained from (**241**) <84AG(E)244>. Goodrow and Musker have described an effective high-dilution method for the synthesis of nine-membered, and smaller, disulfides (**242**). Slow addition of iodine and the dithiol (**243**) to triethylamine, at such a rate that only a very pale iodine color remains visible, allows these rings to be formed in good yield (Scheme 27) <81S457>.



Scheme 27

Attempts to prepare nine-membered trisulfides by the reaction of *N,N'*-dibenzimidazolyl sulfide with dithiols have been frustrated by a preponderance of oligomeric and polymeric products. In one case the dithiol (**244**) gave the trisulfide (**245**), which spontaneously extruded sulfur to yield the eight-membered disulfide (**246**) (Equation (28)) <81JOC2072>. A report describing the preparation of 1,2,3-trithionane by the base treatment of bis(sulfonyl)thiocarbonates <76TL3001> has been found to form instead the corresponding dimeric 18-membered ring <81JOC2072>.

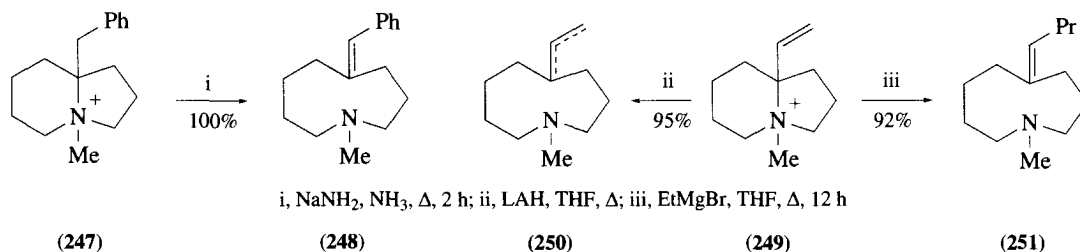


9.27.8 RING SYNTHESSES BY RING EXPANSION AND RING CONTRACTIONS

9.27.8.1 Ionic Ring Openings

The synthesis of medium-sized carbocyclic and heterocyclic rings by ring expansion reactions has been reviewed by Roxburgh <93T10749>. In general, this section covers work not discussed by Roxburgh, except where particularly important or illustrative reactions are featured.

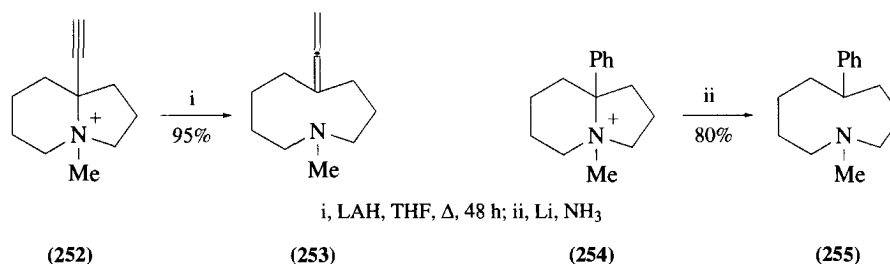
One of the most successful strategies for the synthesis of medium-sized rings involves the cleavage of the bond fusing two smaller rings. For the preparation of nine-membered rings, the usual precursor then is a 5,6-fused system. In the synthesis of nitrogen rings, the heteroatom is often located at one of the bridgehead positions, and this strategy is commonly applied whereby the bridgehead nitrogen of the precursor is alkylated or acylated, thus activating the other bridgehead atom to nucleophilic attack. This approach is illustrated by the reactions described below. The treatment of the indolizidine methiodide (247) with a base effected its quantitative conversion to the octahydro-1*H*-azonine (248) bearing an exocyclic alkenyl function <72JOC3489>. Similarly, the ring fusion bond of (249) was cleaved by treatment with LAH to give (250), or by conjugate Grignard addition to form the elaborated alkene (251) (Scheme 28) <72JOC3494>.



Scheme 28

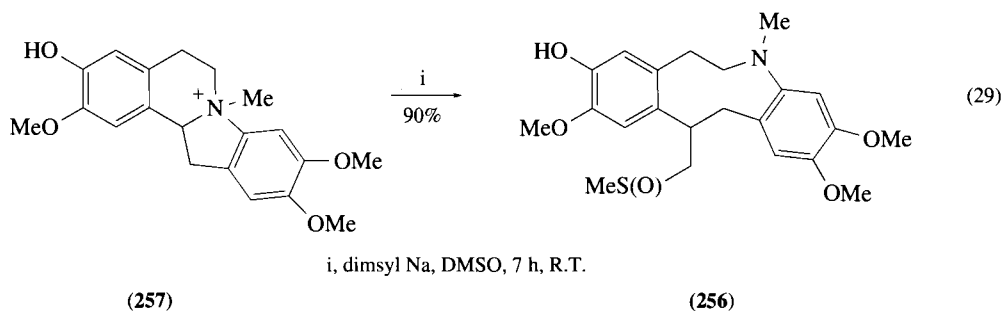
The treatment of the alkyne (252) with LAH yielded the unusual allene (253), and reductive cleavage of (254) gave (255) (Scheme 29) <72JOC3494> (cf. Section 9.27.8.2).

This strategy has also been applied by Kano *et al.* in the synthesis of the dibenzoazonine (256)

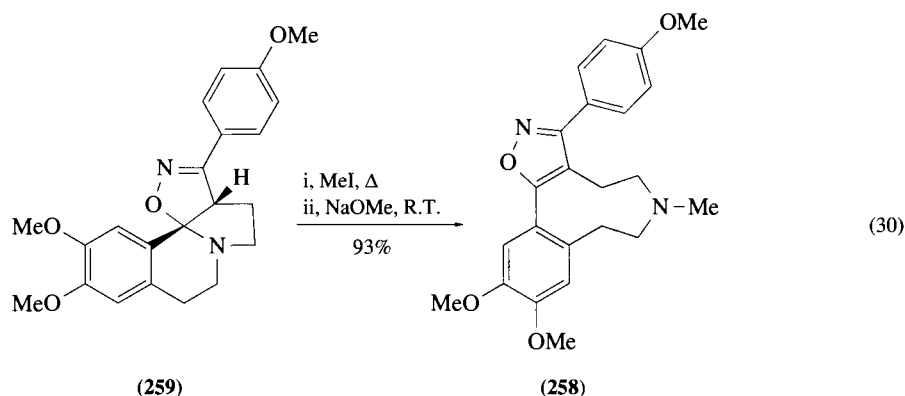


Scheme 29

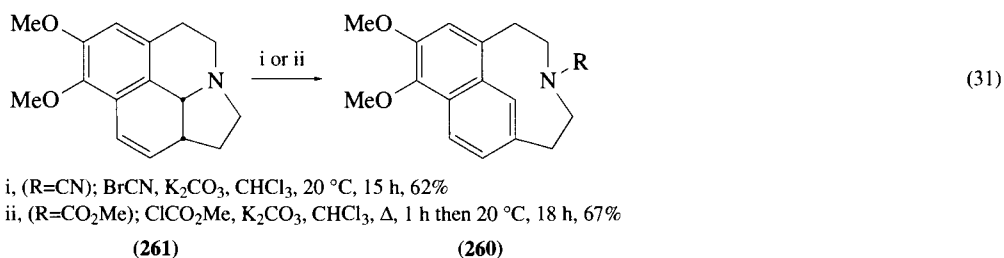
by cleavage of **(257)** (Equation (29)) <75CPB2058>. Hofmann eliminations of bridgehead quaternary ammonium salts have yielded nine-membered rings <80HCA1785> (see also <72CPB1445>).



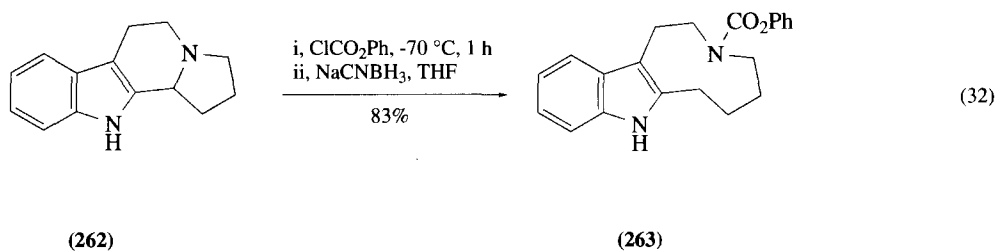
Wentland has communicated the synthesis of the isoxazolobenzazonine **(258)** <89TL1477>. Compound **(259)**, prepared by nitrile oxide cycloaddition with the corresponding enamine, was first quaternized at the sp^3 nitrogen, then this salt was allowed to react with sodium methoxide to give **(258)** in excellent yield (Equation (30)).



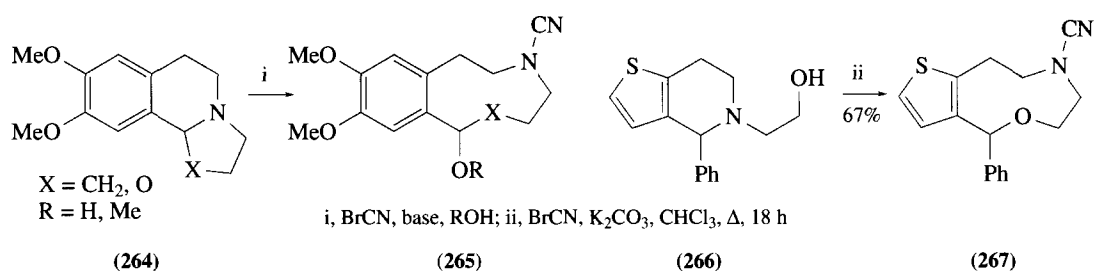
A variation on this theme is the cyanogen bromide or chloroformate ester-mediated rupture of the fusion bond, accompanied by elimination. An example is the synthesis of the strained naphthaleno-fused azonine **(260)** from the tetracycle **(261)** reported by Bremner *et al.* (Equation (31)) <85JA3910> (see also <85H(23)1451, 86JOC3295>). A similar approach has been used by Danishefsky and co-workers in their total synthesis of indolizomycin <90JA2003>.



Calverley has shown that the chloroformate ester cleavage can be performed in the presence of a reducing agent, giving a product arising from hydride attack at the carbon bridgehead. Thus, the tetracycle **(262)**, upon treatment with phenyl chloroformate followed by cyanoborohydride, gave the indolo-fused azonine **(263)** in good yield (Equation (32)) <81CC1209>. In this instance, the reaction probably proceeds via an intermediate iminium ion, as Magnus *et al.* have shown in a related example that such an intermediate can be trapped with electron-rich aromatic rings <89CC518>. Potier and co-workers have utilized the TFAA-mediated ring opening of an amine *N*-oxide in their synthesis of the alkaloid vinblastine <79JA2243>.

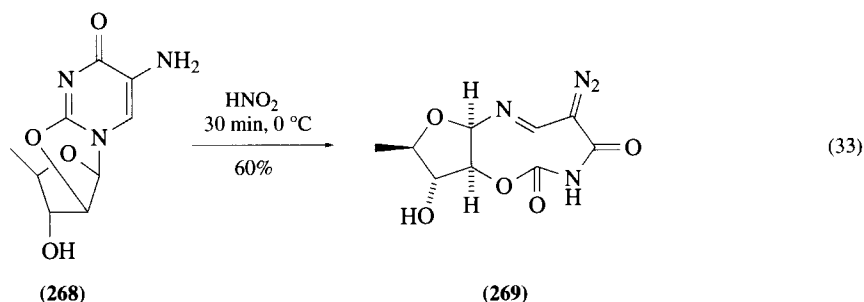


The intermediate *N*-cyanoammonium salts derived from cyanogen bromide reaction with (264) may be attacked by a hydroxylic solvent to give (265) <79CI(L)319, 81CC1209, 84AJC367>. An intramolecular version of this reaction has been described by Bremner *et al.* The treatment of (266) with cyanogen bromide resulted in the formation of the thieno-fused oxazonine (267) in moderate yield (Scheme 30) <84AJC1043>.



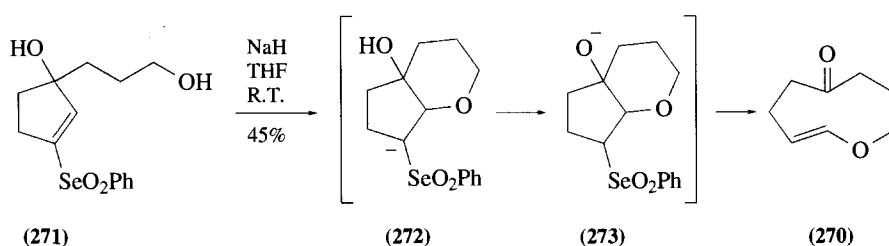
Scheme 30

A novel synthesis of a fused nine-membered ring is that presented by Thurber and Townsend, who treated the cyclodeoxyaminouridine (268) with nitrous acid and obtained the diazo compound (269) (Equation (33)) <76JOC1041>.



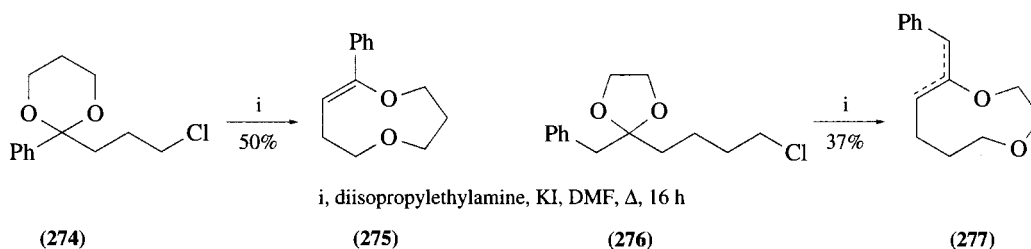
Shimizu *et al.* prepared the cyclic (*E*)-vinyl ether (270) in moderate yield by an addition–fragmentation reaction of the diol (271) by treatment with sodium hydride in THF overnight. The conjugate addition of the alkoxide to the vinyl selenone generates (272), then (273), leading to bond rupture and the expulsion of phenylselenone to form (270) (Scheme 31) <84JOC1230>.

Nine-membered oxacycles have been prepared by the base-induced bond rupture of oxonium



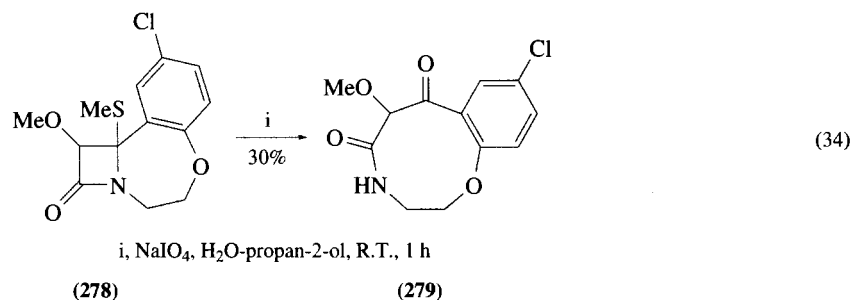
Scheme 31

salts, albeit under rather harsh conditions. Heating acetal (**274**) with a base and a catalytic amount of potassium iodide in refluxing DMF gave the dioxonin (**275**). The treatment of (**276**) under the same conditions gave (**277**) as a mixture of isomers (Scheme 32) <94TL49>.

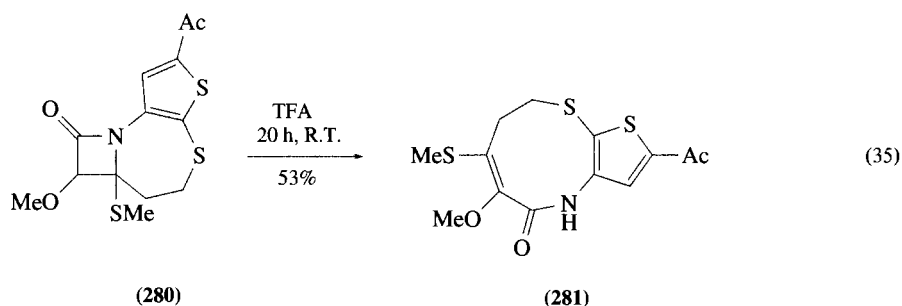


Scheme 32

A method for the preparation of both keto-azonines and nine-membered lactams relies on the formation of an intermediate cyclic hemiaminal which then undergoes ring expansion. For example, treatment of the β -lactam (**278**) with aqueous periodate gave the corresponding sulfoxide, which was hydrolyzed to the nine-membered oxazonine (**279**) (Equation (34)) <76JCS(P1)2343> (see also <72RZC857, 81JA6990, 83TL4253, 89JCS(P1)2431, 94T9167>).



A related ring expansion reaction was observed for the β -lactam (**280**), which reacted in TFA to give the thienothiazonine (**281**) (Equation (35)) <94H(38)1627>.

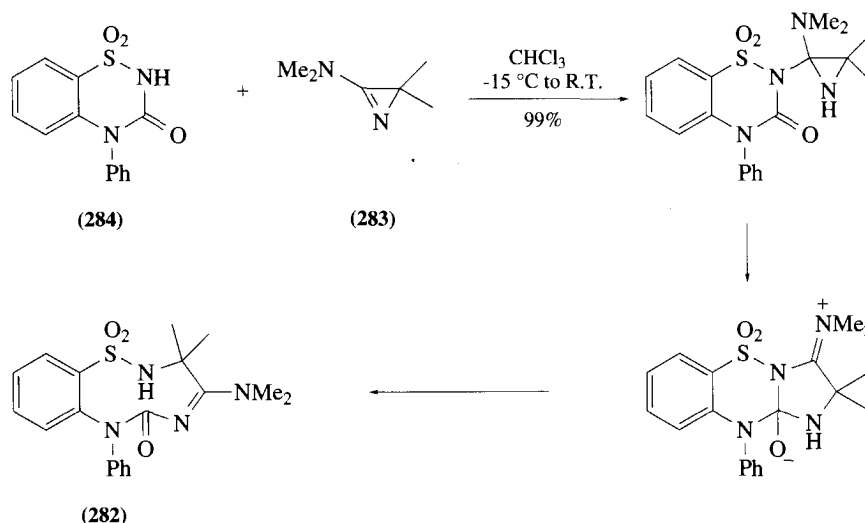


The formation of the novel benzothiaziazonin (**282**) which resulted from the addition of azirine (**283**) to (**284**) is also believed to proceed via an intermediate hemiaminal, by the mechanism outlined in Scheme 33 <84H(22)1667>.

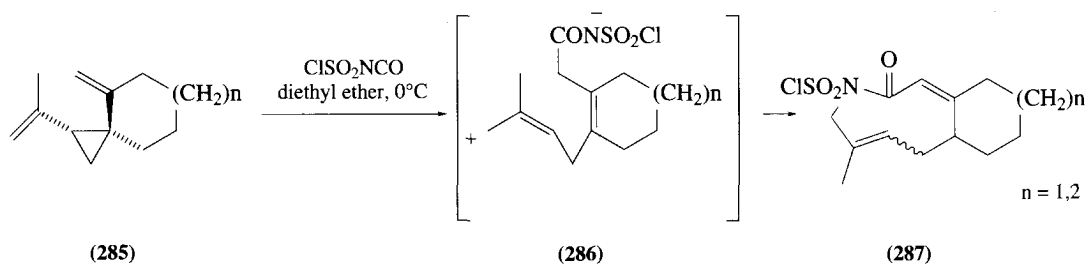
The reaction of *N*-chlorosulfonyl isocyanate with alkenes has been used as a method of constructing nine-membered lactams. Thus, the spirocyclopropane (**285**) reacted exclusively at the methylene rather than at the isoprenyl alkene to generate a zwitterionic intermediate (**286**), which cyclized to give the nine-membered lactam (**287**) as the major product (Scheme 34) <78TL2613>.

9.27.8.2 Reductive Ring Openings

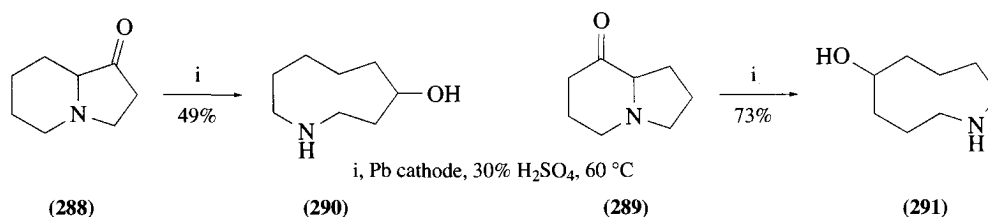
The reductive ring opening of 5,6-fused ring systems has proved to be a valuable means of entry to nine-membered heterocycles. Leonard showed that bicyclic α -aminoketones (**288**) and (**289**) could be electrolyzed at a lead cathode to give octahydroazoninols (**290**) and (**291**) (Scheme 35) <52JA4620>.



Scheme 33



Scheme 34

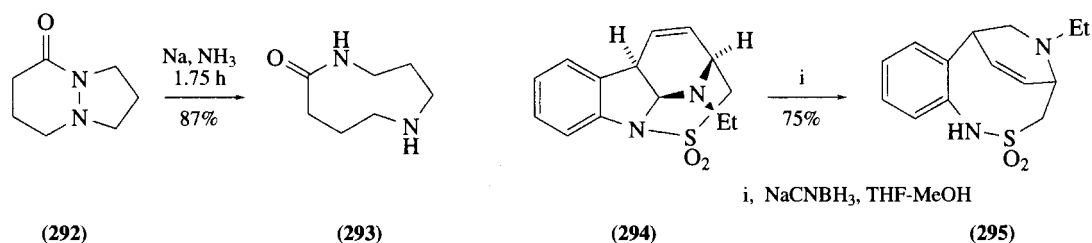


Scheme 35

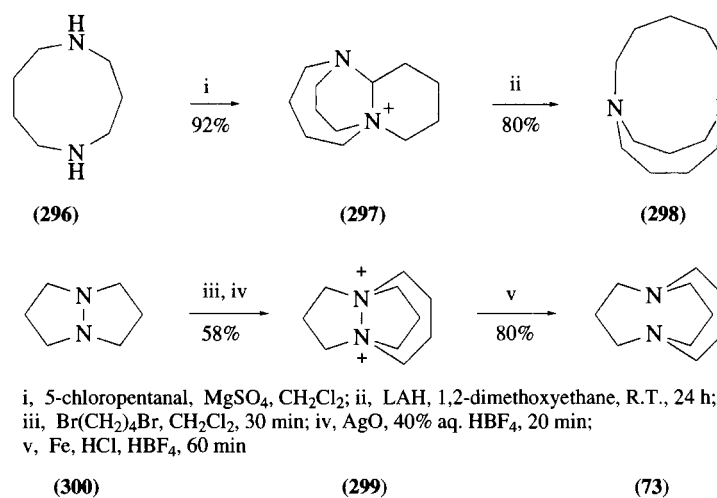
This strategy has been extended to the reduction of 7-oxo-1,6-diazabicyclo[4.3.0]nonanes. Wasserman and Matsuyama reported that the bicycle (292) underwent conversion to (293) with sodium in liquid ammonia (80TL3493, 81JA461) (cf. Scheme 29 in Section 9.27.8.1; see also 70MI 927-01, 86JOC3295). Alkaline Raney nickel has also been used to cleave the N—N bond in these systems when sodium in ammonia proved troublesome (92T3775). The hydrogenation of (294) resulted only in the reduction of the double bond, but with sodium cyanoborohydride ring opening was effected, leading to the nine-membered sultam (295) (Scheme 36) (86JOC4739) (see also 80TL3493, 91JOC1535).

Alder and co-workers have developed general and high-yielding routes to bicyclic diamines with bridgehead nitrogens. One method involves the treatment of a diazacycloalkane (296) with ω -chloroaldehydes, followed by reductive cleavage of the intermediate ammonium salt (297) to give the bridged diamine (298) (82TL1121, 82TL4181). Another method utilizes the reductive cleavage of a hydrazinium dication (299), itself formed by the bisalkylation of the diamine (300), to give the bridged diamine (73) (Scheme 37) (77CC747, 82JCS(P)603).

Reductive ring opening reactions have also been used to synthesize sulfur- and oxygen-containing

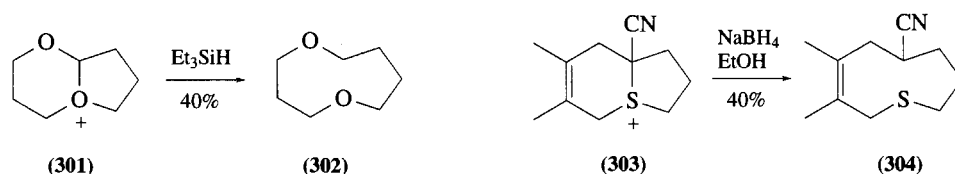


Scheme 36



Scheme 37

nine-membered rings. The triethylsilane trapping of an intermediate oxonium cation (301) gave (302) <89CC277>, and the borohydride reduction of sulfonium (303) yielded cyanothionin (304) (Scheme 38) <90TL3027, 92JCR(S)393> (see also <92PS(67)169>).

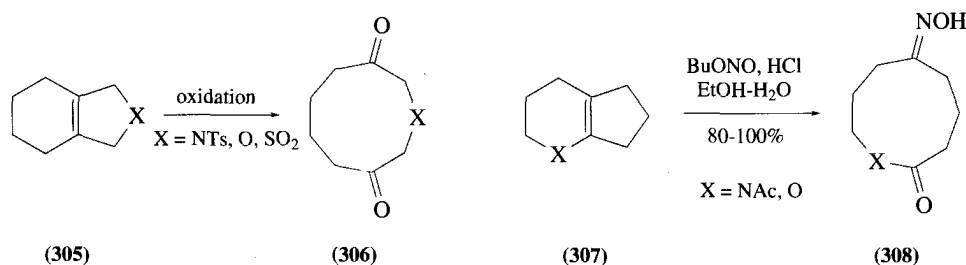


Scheme 38

9.27.8.3 Oxidative Ring Openings

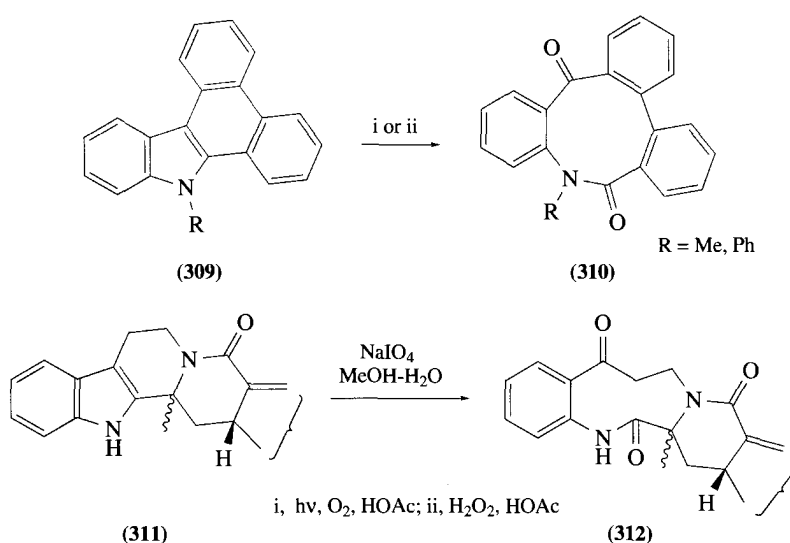
Where the fusion bond of a 5,6-bicycle is alkenyl, the opportunity exists of oxidatively cleaving this bond to form a nine-membered heterocycle containing a 1,5-diketone function. This approach has been successfully applied to systems (305) where $\text{X} = \text{NTs}$ (RuCl_3 , NaIO_4 , 66% yield) and $\text{X} = \text{O}$ (RuCl_3 , NaIO_4 , 58% yield) <93SL909>, and where $\text{X} = \text{SO}_2$ (O_3 , -78°C , 91% yield) <79JOC3496> (see also <63CB919, 79LA473>) to give diketones (306). Mahajan and co-workers have extended this reaction to the cleavage of fused enol ethers and enamines (307) to give lactams and lactones (308) (Scheme

39) <72CC1078, 73S313, 75S54> (see also <79BSF350, 87CL1175, 92JCR(S)290>). Bicyclic bridgehead diols may be cleaved to give nine-membered diketones <77TL2751>.



Scheme 39

Indole derivatives may be oxidatively cleaved to give benzo-fused nine-membered rings, although care must be taken as there is a tendency for the initially formed keto amides to undergo ring closure by intramolecular condensation (Camps reaction) <50JA1428, 51JA2196, 53JA3371, 78USP4100277>. Thus, photolytic or peroxide oxidation of (309) led to the lactam (310) <74T2983>, and periodate cleavage of (311) gave (312) (Scheme 40) <74CC928>. Tetrahydroindoles can also be oxidatively opened using sodium periodate to give nine-membered unsaturated keto lactams <83S390>.

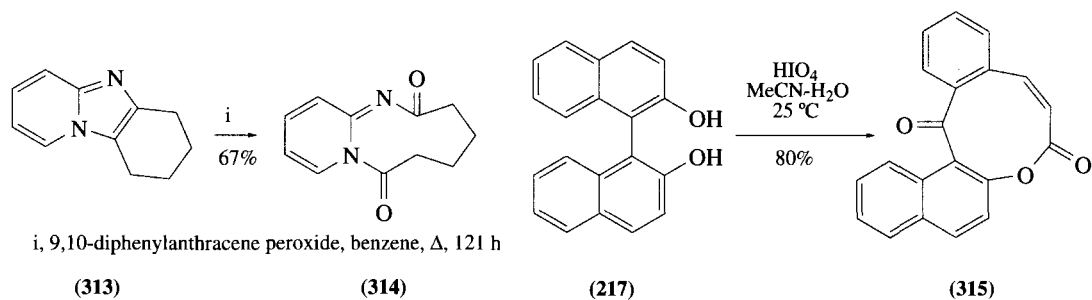


Scheme 40

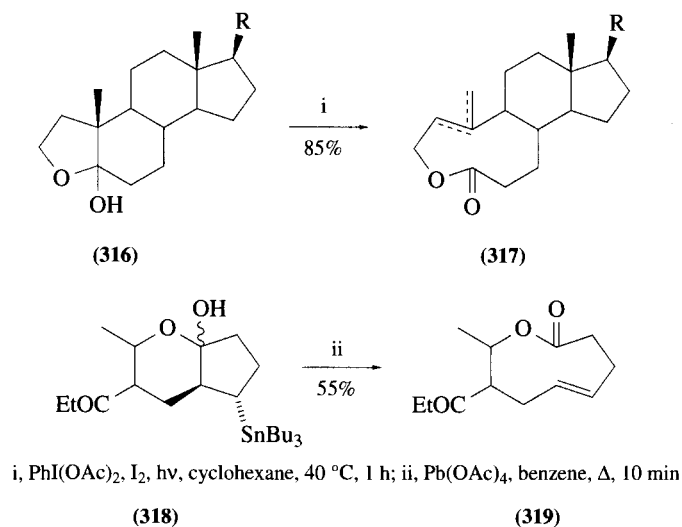
Wasserman and co-workers have studied 9,10-diphenylanthracene peroxide as a source of singlet oxygen. They found that prolonged heating of this peroxide with the imidazopyridine (313) gave a moderate yield of the dione (314) <85JOC2799>. Periodate oxidation of binaphthol (217) gave a good yield of the nine-membered keto lactone (315) (Scheme 41) <72JA4991>.

9.27.8.4 Radical Fragmentations

Alkoxy radicals, generated from lactols, can undergo β -fragmentation to yield ring-expanded lactones in good yields. Thus, the lactol (316) gave the unsaturated nine-membered lactone (317), as a mixture of regioisomers <86TL383>, and treatment of the lactol (318) with lead tetraacetate gave the (*E*)-lactone (319) (Scheme 42) <88JA4754>.

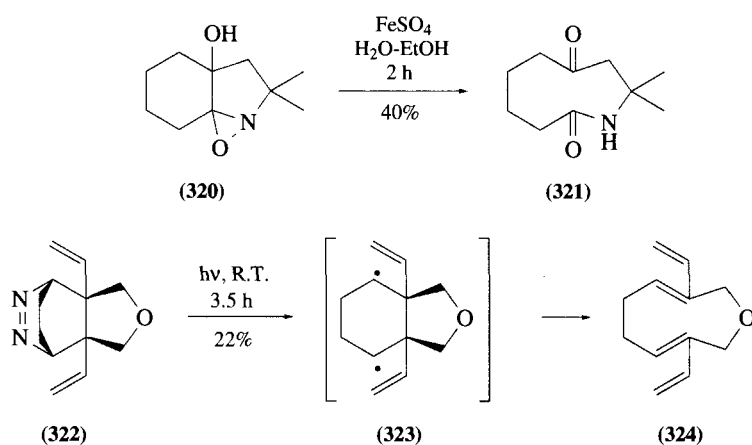


Scheme 41



Scheme 42

The initial step of the ferrous ion-mediated ring opening of oxaziridine (320) to the keto lactam (321) is cleavage of the N—O bond with the formation of an alkoxy radical $\langle 81\text{AG(E)}670, 84\text{AJC}599 \rangle$. The photolysis of the diazo tricycle (322) led, via the diradical (323), to the nine-membered ether (324) (Scheme 43) $\langle 73\text{T}2373 \rangle$.

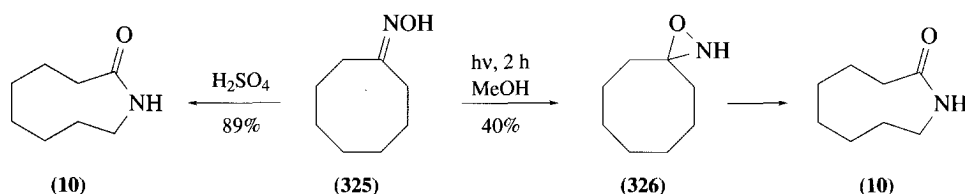


Scheme 43

9.27.8.5 Beckmann and Related Rearrangements

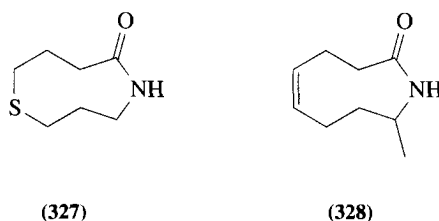
This section includes, as well as a survey of Beckmann rearrangements in the synthesis of nine-membered rings, miscellaneous ring enlargement reactions involving a 1,2-shift in the ring expansion step.

The Beckmann rearrangement of cyclooctanone oxime (**325**) to caprylactam (**10**) in sulfuric acid is well documented, particularly in the patent literature, because of the importance of (**10**) in the manufacture of polymers <48MI 927-01, 58GEP1046623, 62BRP911806, 63GEP1144729>. The rearrangement can also be effected using hydroxylamine-*O*-sulfonic acid in formic acid (61% yield) <79S537>. The action of nitrosylpyrosulfuric on cyclooctylacetic acid yields caprylactam (81% yield) <67CI(M)701>. Cyclooctanone oxime (**325**) undergoes a photochemical Beckmann rearrangement to afford (**10**) via the oxazirane intermediate (**326**) (Scheme 44) <71CJC2891>.

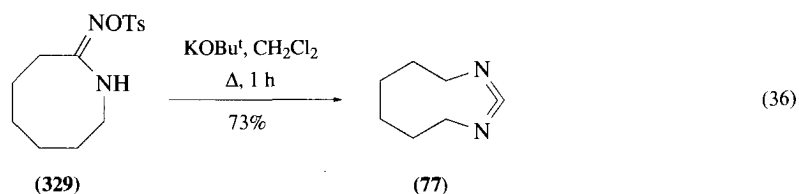


Scheme 44

For more sensitive substrates, the Beckmann rearrangement is usually performed on the tosylate derived from the eight-membered oxime. Thus, the oxime derived from thiacyclooctan-5-one gave (**327**) when treated with tosyl chloride in pyridine (24% yield) <74JMC1232>; (**328**) was formed by the reaction of its oxime tosylate precursor with K_2CO_3 in aqueous THF (59% yield) <79JOC330>, as was (**38**) (30% yield) <90JA323> (see also <86TL4841, 87H(25)29>). The action of triphenylphosphine on 1-chloro-1-nitrosocyclooctane also brought about a Beckmann-type rearrangement to give caprylactam in moderate yield <79BCJ3381>. The ring expansion of the oxime tosylate derived from cyclooct-2-enone has been reported <71T5381>. The reaction of methyl lithium with the tosylate derived from (**325**) gave 2,2-dimethyloctahydroazone in 71% yield <64JOC3129>.

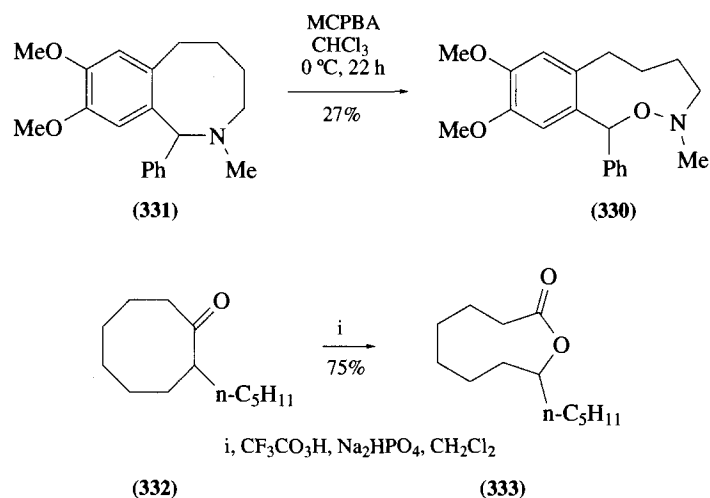


Damrauer and co-workers have shown that the nine-membered carbodiimide (**77**) can be formed in good yield by the treatment of the tosylate (**329**) with a strong base (Equation (36)) <80JOC1315> (see also <83JOC1694>). The mesylate derived from cyclooctanone oxime gives the nine-membered imino nitrile in 48% yield when treated with TMS-CN and Et_2AlCl <83JA2831>.



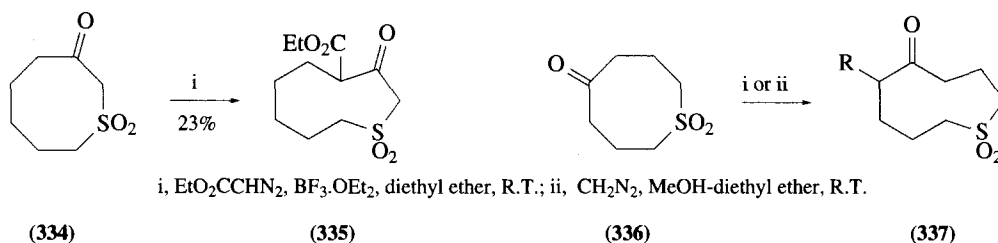
Bremner and co-workers have reported the formation of the hexahydrobenzoxazonine (**330**) by Meisenheimer rearrangement of the *N*-oxide derived from (**331**) <80AJC1323>. Yamamoto and co-workers have demonstrated that the ethyl carbonate derived from (*N*-benzyl,*N*-cyclooctyl) hydroxylamine undergoes ring expansion upon exposure to trimethylaluminum to give *N*-benzyl-2-methyloctahydro-1*H*-azonine in 62% yield <84TL2367>. The Baeyer-Villiger oxidation of cyclooctanone derivatives provides a reliable, high-yielding entry into nine-membered lactones. For

example, the reaction of (332) with buffered trifluoroperacetic acid gave the nine-membered lactone (333) (Scheme 45) <89TL6081> (see also <77JA7359>).



Scheme 45

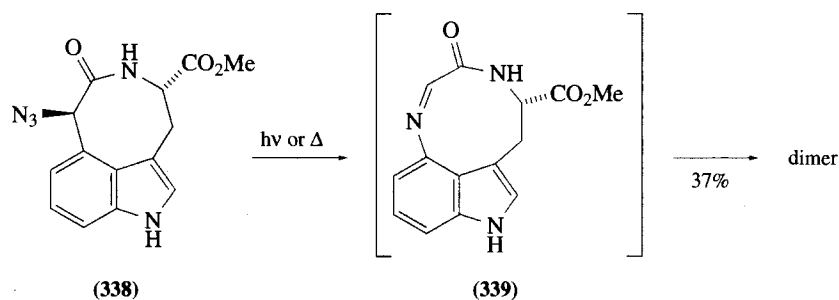
Arackal and co-workers have investigated the ring expansion reactions of eight-membered keto sulfones when treated with diazo compounds. Thus, with ethyl diazoacetate, the keto sulfone (334) gave a low yield of the nine-membered ring (335), while the isomeric precursor (336) gave a 37% yield of (337; R = H) when treated with diazomethane, and a 60% yield of (337; R = CO₂Et) upon treatment with ethyl diazoacetate (Scheme 46) <77CB1069>.



Scheme 46

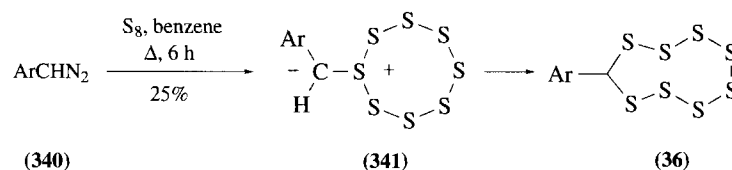
The decomposition of the azide (338) is believed to involve the nine-membered acyl imine (339) as a reactive intermediate which ultimately forms an 18-membered product by dimerization and metathesis (Scheme 47) <93JA813>.

Tokito *et al.* have shown that the carbene derived from (340; Ar = 2,4,6-tris[bis(trimethyl-



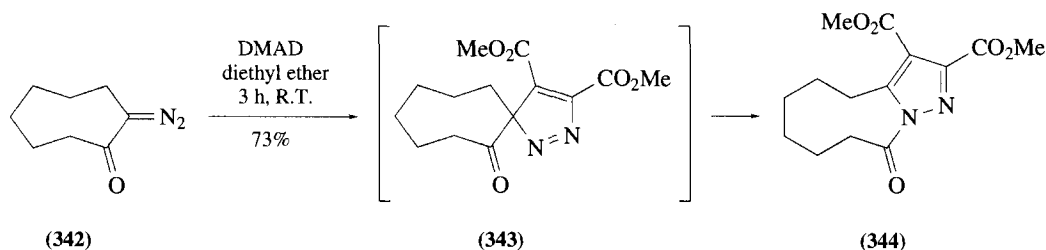
Scheme 47

silyl)methyl]phenyl) can insert into the S_8 molecule to give the nine-membered ring (**36**) via the ylide (**341**) (Scheme 48) <92CL1599>.



Scheme 48

Martin and Regitz have prepared a series of pyrazolo fused lactams by the reaction of α -diazoketones with DMAD. Thus, diazocyclooctanone (**342**) gave the intermediate spiro pyrazole (**343**) by a 1,3-dipolar cycloaddition, and this adduct then underwent a 1,5-acyl shift to give the ring-expanded fused lactam (**344**) in good yield (Scheme 49) <74LA1702>. A similar approach has been used to prepare nine-membered imidazolo fused systems <75JOC2562>.

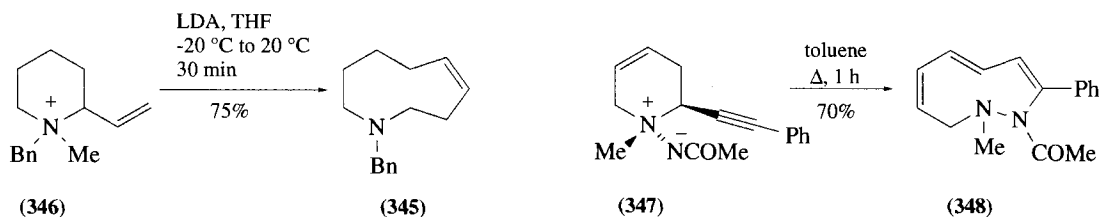


Scheme 49

9.27.8.6 Electrocyclic Ring Expansions

A powerful strategy for the construction of nine-membered rings involves the sigmatropic ring opening of a smaller ring. Since these pericyclic reactions are usually concerted and proceed via highly ordered transition states, they are often highly stereoselective and give rise to unsaturated rings with well-defined double bond geometries.

Vedejs and co-workers have described the preparation of the *cis* unsaturated amine (**345**) by a [2,3]-sigmatropic ring expansion of the ylide derived from (**346**) <78JOC4831, 78TL523>. In a related reaction, the ylide (**347**) underwent ring expansion to afford the dihydrodiazonine (**348**) as a single geometric isomer (Scheme 50) <84CPB4600>.

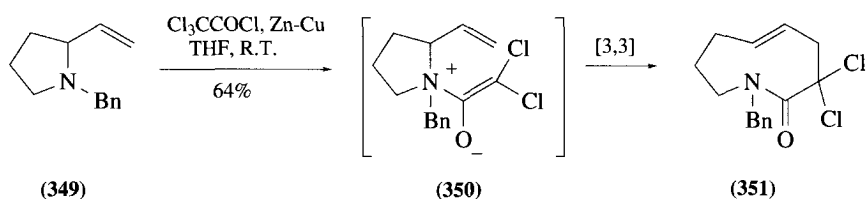


Scheme 50

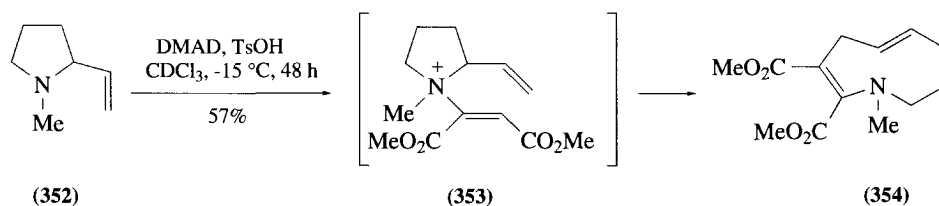
The reaction of *N*-benzyl-2-vinylpyrrolidine (**349**) with dichloroketene gave the zwitterionic intermediate (**350**), which underwent a [3,3] ring expansion to give the lactam (**351**) as a single geometric isomer (Scheme 51) <91JA6690>.

A similar approach has been described by Vedejs and Gingras for the preparation of nine-membered azacycles. The reaction of the 2-vinylpyrrolidine (**352**) with DMAD under acid catalysis led to the cationic intermediate (**353**), which underwent a [3,3] aza-Cope rearrangement under mild conditions to afford the tetrahydroazonine (**354**) (Scheme 52) <94JA579>.

Cook and Stille investigated the aza-Cope rearrangement of the *N*-allyl enamine (**355**). The Lewis acid-mediated rearrangement of (**355**) resulted in the formation of the corresponding imine, which

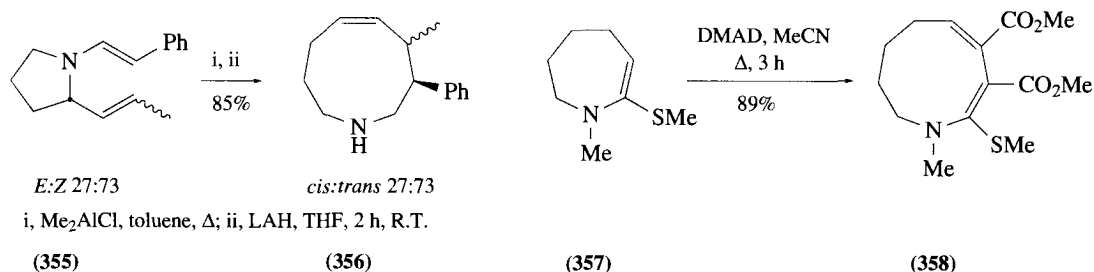


Scheme 51



Scheme 52

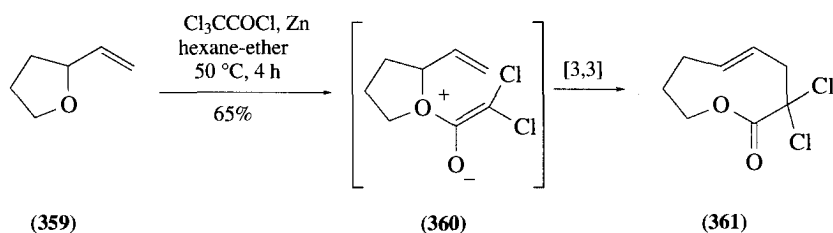
was not isolated but immediately reduced to give (356) as a mixture of isomers. The reaction was stereospecific: the isomer ratio of the starting enamine was exactly reproduced in the product. A boat-like transition state was invoked to explain the product distribution $\langle 94\text{T4105} \rangle$. The reaction of the *S,N*-ketene acetal (357) with DMAD resulted in the formation of a cyclobutene ring which underwent ring expansion to yield the tetrahydroazonine (358) (Scheme 53) $\langle 82\text{CPB3959} \rangle$ (see also $\langle 82\text{ACS(B)435} \rangle$).



Scheme 53

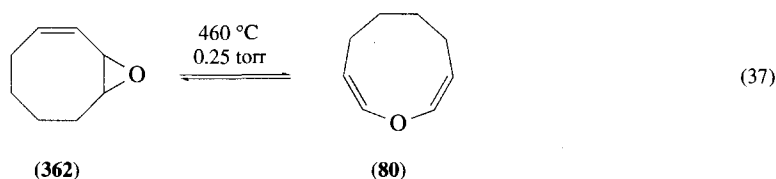
The reaction of vinylpiperidines with dichloroketenes (Scheme 51) has been extended by Taylor and co-workers to the synthesis of nine-membered oxacycles. Thus, 2-vinyltetrahydrofuran (359) reacted with dichloroketene via the zwitterion (360) to give the dichlorolactone (361) (Scheme 54) $\langle 93\text{CC1593} \rangle$. The geometry of the double bond in (361) was the same as for the analogous nitrogen compound (351).

The flash vacuum pyrolysis of the monoepoxide of 1,3-cyclooctadiene (362) gave, in a clean and

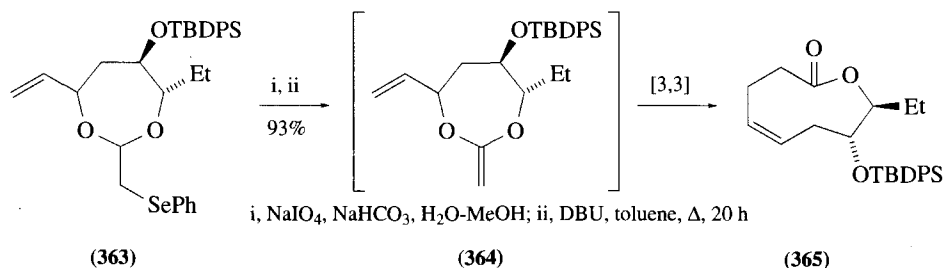


Scheme 54

reversible reaction, the *cis,cis*-tetrahydrooxonin (**80**). The reaction proceeds by a 1,5-hydrogen shift (Equation (37)) <67TL1717>.

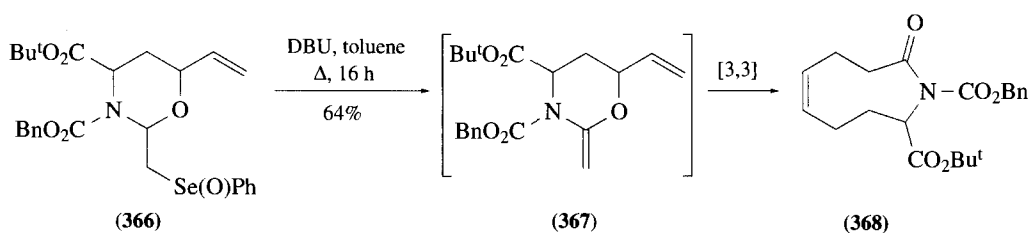


The Claisen rearrangement of cyclic ketene acetals has proved to be a reliable method for the synthesis of medium-sized unsaturated lactones <95T2777>. Holmes and co-workers have exploited the Claisen rearrangement in the synthesis of a wide range of functionalized nine-membered lactones. For example, the oxidation of the selenide (**363**) followed by thermal elimination of the selenoxide generated the unsaturated ketene acetal (**364**), which underwent a Claisen rearrangement to give the lactone (**365**) in excellent yield (Scheme 55). The geometry of the double bond, predicted to be *cis* by the consideration of plausible chair-like transition states, was confirmed by NMR experiments <91T7171>. A similar strategy was employed in the synthesis of the marine ascidian ascidiatrienolide A <93JA5815>.



Scheme 55

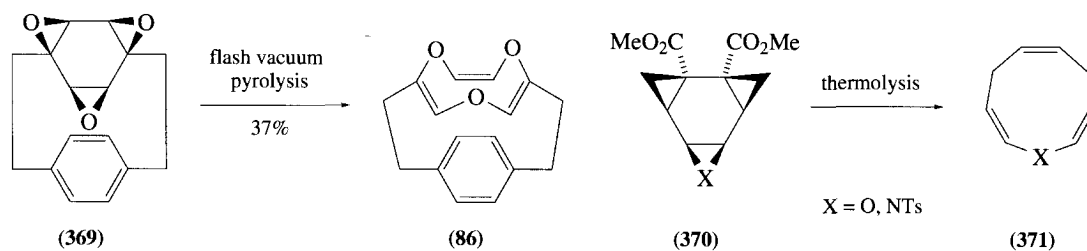
Holmes and co-workers have also applied the Claisen rearrangement to the synthesis of medium-sized lactams. The thermal elimination of phenylselenenic acid from the selenoxide (**366**) gave the unsaturated ketene aminal (**367**), which rearranged to the unsaturated nine-membered lactam (**368**) (Scheme 56) <92TL6857, 96JCS(P1)123>.



Scheme 56

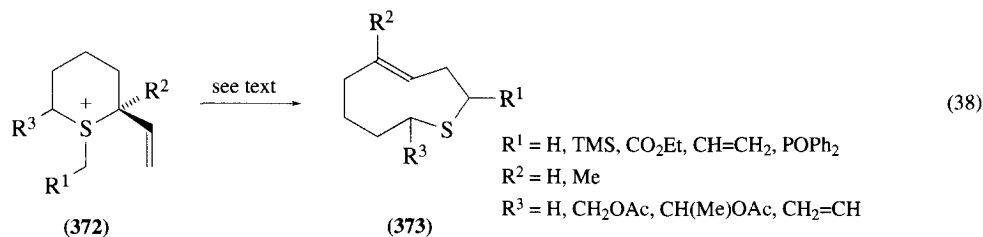
The novel phane-bridged 1,4,7-trioxonin (**86**) has been prepared by a thermal $3\sigma \rightarrow 3\pi$ valence isomerism of the *cis* benzene trioxide (**369**) <83AG(E)867> (see also <72AG(E)942>). In a related reaction, the all-*cis*-oxa- and azatrishomobenzenes (**370**) were reported to undergo clean $3\sigma \rightarrow 3\pi$ isomerism, in unspecified yields, to the dihydrooxonin (**371**; X = O) and the dihydroazonin (**371**; X = NTs) (Scheme 57) <71HCA755>.

Numerous examples are reported in the literature of the [2,3]-sigmatropic rearrangements of sulfonium ylides derived from (**372**) to nine-membered hexahydrothionins (**373**) (Equation (38)). Both stabilized and nonstabilized ylides are reactive, and in all these instances, a marked preference for the formation of the (*E*)-alkene is apparent. The ylides are typically formed by the treatment of (**372**) with a strong base at low temperature, and the sigmatropic rearrangement then occurs at or below room temperature to give good yields of the nine-membered product: R¹ = R² = R³ = H, 85% yield, (*E*):(*Z*) = 24:1 <78JOC4826, 91JOC4513>; R¹ = TMS, R² = R³ = H, 73% yield <92JOC1457>;

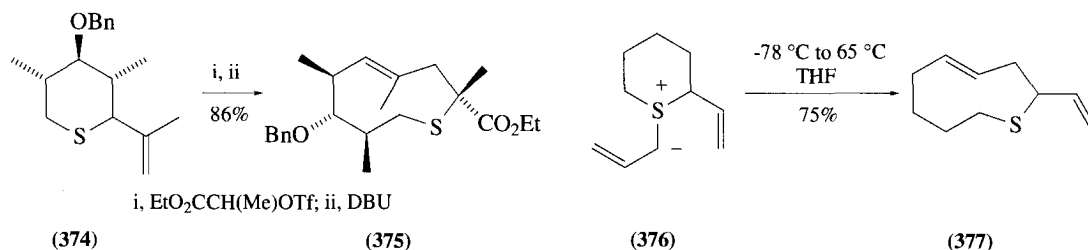


Scheme 57

$R^1 = R^2 = \text{Me}$, $R^3 = \text{H}$, 89% yield <79JOC4128>; $R^1 = \text{CO}_2\text{Et}$, $R^2 = R^3 = \text{H}$, 99% yield <78JOC4831, 78TL523>; $R^1 = \text{CO}_2\text{Et}$, $R^2 = \text{H}$, $R^3 = \text{CH}_2\text{OAc}$, 91% yield <81JOC5451>; $R^1 = \text{CO}_2\text{Et}$, $R^2 = \text{H}$, $R^3 = (\text{CH}=\text{CH}_2)$, 85% yield <84JA1840>; $R^1 = \text{POPh}_2$, $R^2 = \text{H}$, $R^3 = \text{CH}(\text{Me})\text{OAc}$, 83% yield <82JA2046>.



Vedejs and co-workers have also shown that this reaction occurs very well even with more complex substrates. *S*-Alkylation of (374) proceeded with equatorial selectivity, then deprotonation of the sulfonium salt intermediate resulted in rearrangement to the (*E*)-hexahydrothionin (375) in good yield <83JA127>. If the starting thiane possesses an allyl group, rearrangement of the resulting ylide (376) then gives a nine-membered ring (377) bearing an α -vinyl group, and this can then be utilized in a repeating series of three carbon expansions (Scheme 58) <78TL519>.



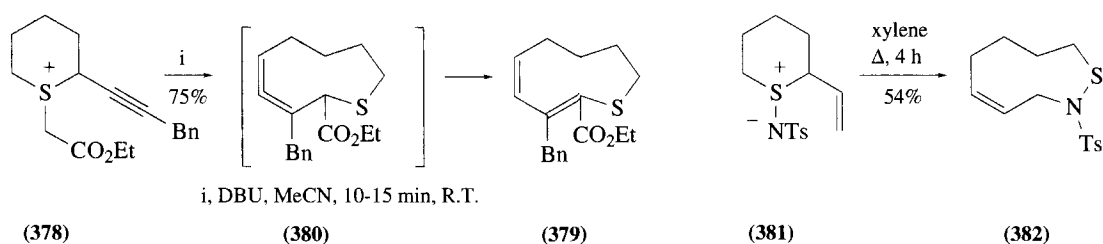
Scheme 58

Sashida and Tsuchida have shown that this rearrangement also occurs with thianes bearing an alkynyl side chain. The treatment of the sulfonium salt (378) with a base led to the tetrahydrothionin (379), presumably via the allenic intermediate (380) <82H(19)2147>. The same authors have reported the thermal rearrangement of the ylide (381), but in this case the product (382) had the (*Z*)-alkene geometry (Scheme 59) <84H(22)1303, 86CPB3682>.

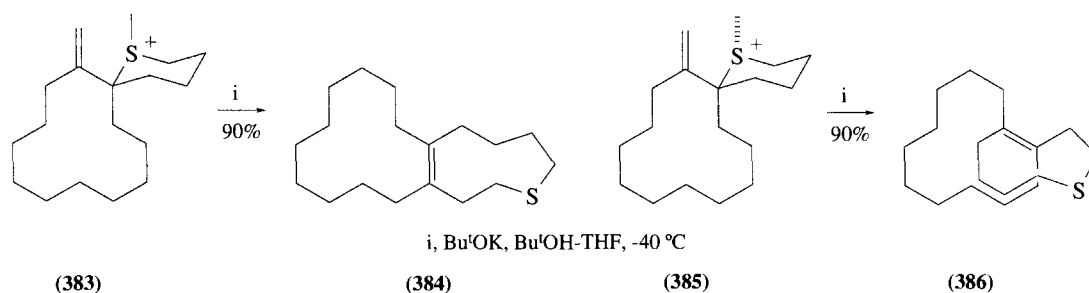
When the alkene component of the precursor sulfonium ylide is itself part of a ring, the product then is a fused nine-membered hexahydrothionin. Céré *et al.* have shown that this reaction is stereospecific. The spiro ylide (383) reacted at low temperature to give exclusively the fused bicycle (384), whereas the other diastereoisomer (385) yielded the novel betweenanene (386) (Scheme 60) <81JOC486>.

Sulfonium ylides have also been generated by reactions involving carbenoids. Copper-mediated decomposition of ethyl diazoacetate in the presence of the dithiane (387) led to the intermediate ylide (388), which then rearranged to yield a mixture of the betweenanene (389) and the (*Z*)-alkene (390) in a 3 : 1 ratio (Scheme 61) <84TL3555>.

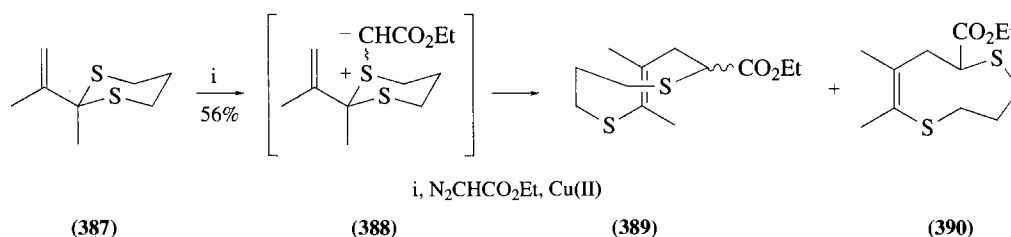
In analogy to the reactions shown in Schemes 51 and 54, the dithioketal (391) reacted with dichloroketene to afford the nine-membered product (392) <87JOC3693> (see also <81JOC2228>). Kato



Scheme 59

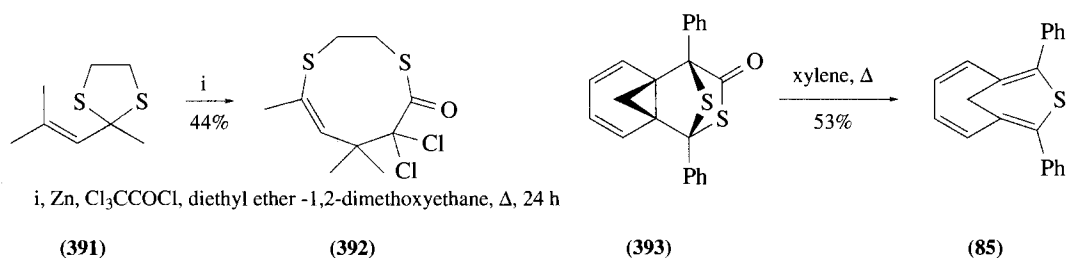


Scheme 60



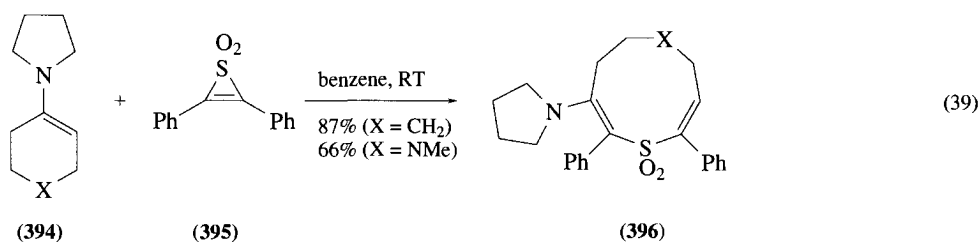
Scheme 61

and Toda prepared the bridged thionin (**85**) by the thermolysis of (**393**) (Scheme 62). Also prepared by similar means was 9-phenyl-3,8-methano-1,2-thiazonine (**84**) ^{<82CC510>}. The rearrangement of the sulfoxide (**81**) to thionin oxide (**83**) has already been discussed (Scheme 1), as has the photolytic ring opening of (**89**) (Scheme 2).

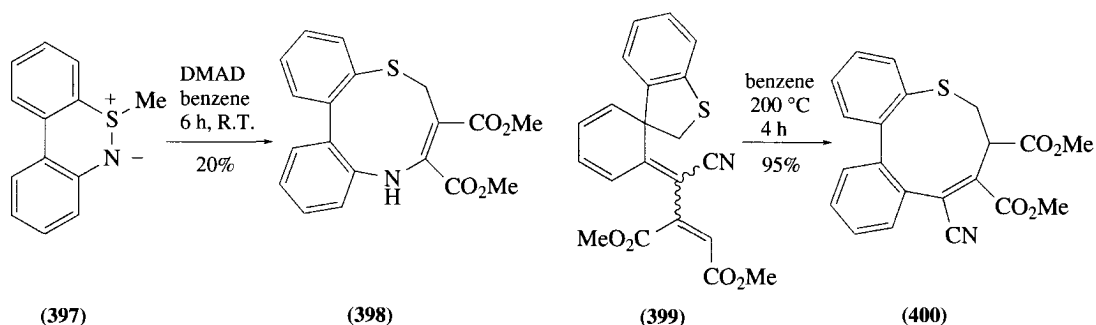


Scheme 62

A number of miscellaneous methods have been described for the preparation of nine-membered sulfur-containing compounds. The enamine (**394**) reacted with the thiirene dioxide (**395**) to give the nine-membered product (**396**), presumably via a cyclobutane intermediate (Equation (39)) ^{<74JOC3805>}.

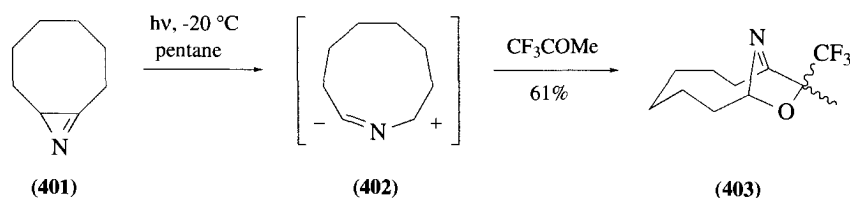


Hori and co-workers have described the reaction of the ylide (397) with DMAD to give the dihydrothiazonine (398) <84CPB4360> (see also <82TL2597>), and the spiro compound (399) underwent a [1,5]-sigmatropic shift to afford the dihydrothionin (400) in excellent yield (Scheme 63) <85CC883>.



Scheme 63

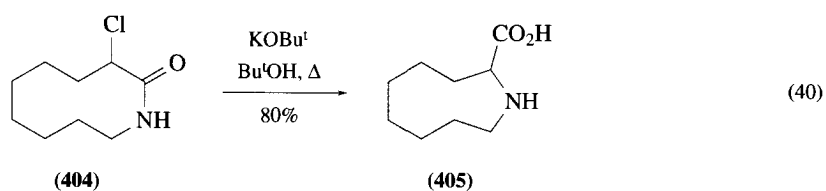
The photo-induced electrocyclic ring opening of 9-azabicyclo[6.1.0]non-1(9)-ene (401) formed the nine-membered nitrile ylide (402), which reacted with dipolarophiles to form bridged oxazolines (403) (Scheme 64) <74HCA2626>. The photochemical ring opening of cycloheptane-fused pyrimid-4-ones to give nine-membered ketolactams has been reported <80TL3067>.



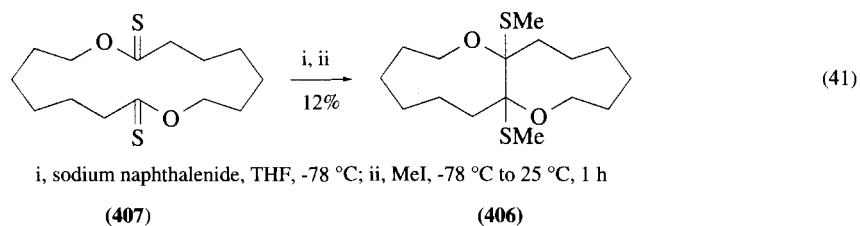
Scheme 64

9.27.8.7 Ring Contractions

Nagasawa and co-workers have demonstrated the Favorskii rearrangement of bromo- and chloro-lactams (404) to form the nine-membered proline analogue (405) (Equation (40)) <66TL5393, 71JMC501>.



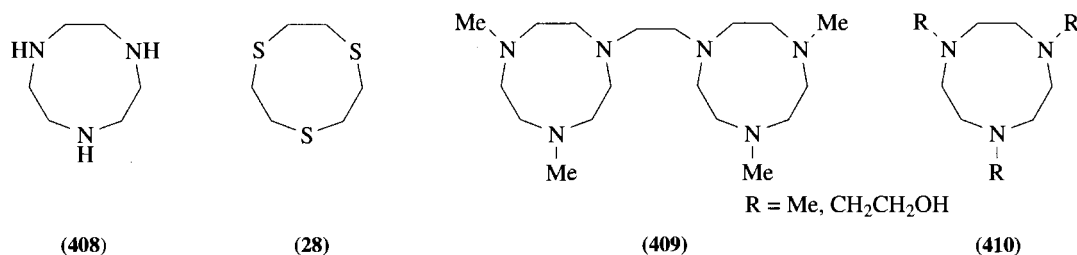
Nicolaou *et al.* reported the synthesis of the fused bicyclic ether (**406**), albeit in poor yield, by the transannular radical ring closure of the macrodithionolactone (**407**) (Equation (41)) <90JA3040>.



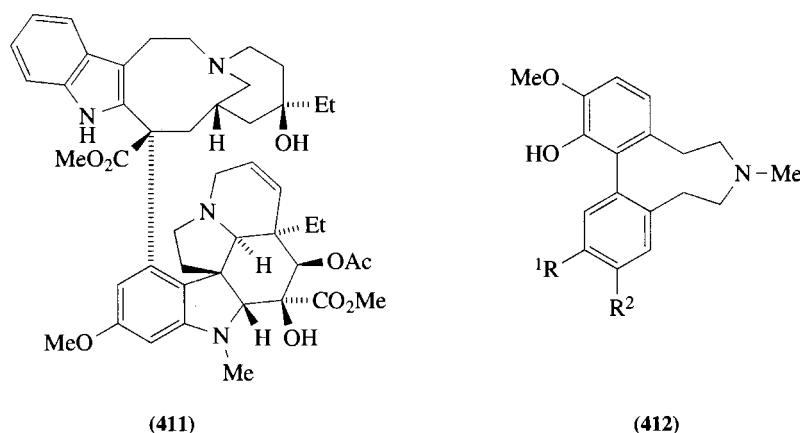
9.27.9 USEFUL AND NATURALLY OCCURRING NINE-MEMBERED HETEROCYCLES

Caprylolactam readily polymerizes, and there exists a large amount of journal and patent literature on the subject <58JA6404, 83MI 927-01>. The kinetics and mechanism of the polymerization of several *N*-alkylcaprylolactams have been examined <75CCC93>, as has the polymerization of 2-thiono-octahydroazonine <58JA6404>.

Octahydro-1,4,7-triazonine (**408**) and 1,4,7-trithianane (**28**) are important ligands in inorganic chemistry. Their synthesis and chemistry have been reviewed <87MI 927-01>. Manganese complexes of the triamine ligands (**409**) and (**410**) have been shown to act as very effective catalysts for the bleaching of stains by hydrogen peroxide, particularly at low temperatures <94NAT637>.

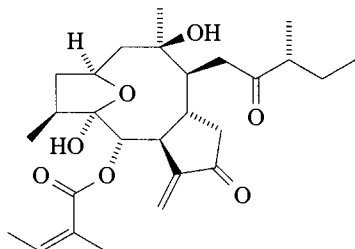


The antibiotic griseoviridin (**60**) has been mentioned (see Section 9.27.3.3). The antitumor alkaloid vinblastine (**411**) (from *Vinca rosea*) is used widely in the treatment of Hodgkin's disease <89CC518>. The dibenz[*d,f*]azonine alkaloids neodihydrothebaine (**412**; R¹ = OMe, R² = H) and bractazonine (**412**; R¹ = H, R² = OMe) have been isolated from *Papaver bracteatum* <84H(22)2007> (see also <75TL1201>).

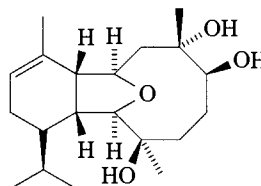


The nine-membered ether ineupatolide (**413**) was isolated from *Inula eupatoriodes* <80JOC4838>. The eunicellins are metabolites of the *Cladiella* genus of soft coral. Many examples have been reported <94MI 927-02>, and (**414**) is a typical member <92TL1317>. The marine natural product

neohalicholactone (**51**) has been mentioned (see Section 9.27.3.1), and other naturally occurring nine-membered lactones have been reviewed by Rousseau <95T2777>.

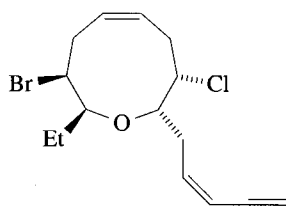


(413)

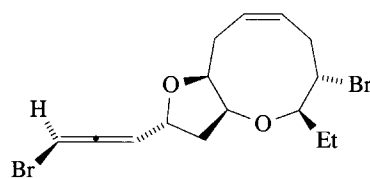


(414)

Numerous acetylenic cyclic ethers have been isolated from algae of the *Laurencia* genus. Obtusenyne (**415**), isolated from *Laurencia obtusa*, is a nine-membered example of this class whose structure has been determined by x-ray crystallography <79TL1453>. Epimers of obtusenyne have also been found in the gastropod mollusc *Aplysia dactylomela* <81JOC5192>. The dehydrobromo derivative, brasilenyne, was isolated from *Aplysia brasiliiana* <79PNA(76)3576>. Isolaurallene (**416**) possesses a novel bicyclic structure and an allene side chain. It was isolated from *Laurencia nipponica* <82CL1031>. A stereoisomer, neolaurallene, was isolated from *Laurencia okamurai* <84CL1033>. The polycyclic polyether brevetoxins and ciguatoxins possess central nine-membered cyclic ethers.

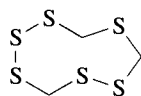


(415)

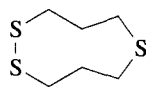


(416)

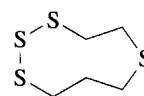
Several sulfur-containing nine-membered rings have been isolated from natural sources. The hexasulfide (**417**) was tentatively identified as a component of the Shiitake mushroom on the basis of GC-MS <86MI 927-02>. A mixture of cyclic tri- and tetrasulfides, typified by structures (**418**) and (**419**), and isolated from *Azadirachta indica* leaves, were identified by GC-MS <85MI 927-01>.



(417)



(418)



(419)

9.28

Ten-membered Rings or Larger with One or More Nitrogen Atoms

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9.28.1 INTRODUCTION

Compared to the number of compounds noted in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I), the field of rings larger than ten with one or more nitrogen heteroatoms has steadily developed and increased in importance. Most of these compounds were prepared in view of their use as complexing agents for metal ions, anions, or neutral organic molecules (host–guest complexes).

Template reactions, first described in the 1960s by Curtis <60JCS4409> and Busch <64RCPI07>, have found many applications for the preparation of polyazacycloalkanes and have clearly shown their synthetic potential <68CCR3, 75MI 928-01>. The role of metal ions in these reactions is not only found in their ability either to stabilize by coordination the macrocyclic product (thermodynamic template effect) or to activate the reactants, so that the cyclization is preferred over the polymerization (kinetic template effect), but also in more subtle ways, in determining for example whether 1:1 or 2:2 cyclization occurs. In general, larger metal ions or metal ions with no specific preference for a

coordination geometry tend to give 2:2 cyclization products <80PAC2461>. Such large rings with many donor atoms are ideal ligands to form binuclear metal complexes.

Large cavity macrocycles with many amino functions in their protonated form are also able to bind inorganic (SO_4^{2-} , $\text{Fe}(\text{CN})_6^{4-}$) or organic (carboxylate, nucleotide) anions <85ICAL9, 87IC3902>. Selectivity in these systems depends on electrostatic and geometric effects, so that the greater the extent of protonation, the more stable the complex.

Azacyclophane-type macrocycles, which possess a large hydrophobic cavity, form host–guest inclusion complexes with charged or uncharged organic molecules in aqueous solution by hydrophobic and/or coulombic interactions. For optimum stability of the host–guest complex, perfect matching of the cavity and the shape of the included species is necessary <89MI 928-01>.

Whereas for anion binding, the charge and shape of the macrocycle are of paramount importance; the stability and selectivity in metal complexation are governed by several other factors, which have been summarized into the term “macrocyclic effect” <88MI 928-01>. The higher stability of metal complexes with cyclic polyamines compared to that with open-chain polyamines is, however, only found for smaller rings such as 1,4,7-triazacyclononane and 1,4,8,11-tetraazacyclotetradecane, for which a favorable enthalpic contribution to the stability has been observed.

Another group of interesting derivatives of this class of compounds is that of functionalized polyazamacrocycles, which carry side chains with donor groups able to coordinate the metal ion and thus have given some of the most stable known complexes <84TCC157>. Because of their high thermodynamic and kinetic stability, several complexes with such ligands have found medical applications as contrast agents in magnetic resonance imaging (MRI) or to label monoclonal antibodies used for diagnosis or therapy against tumors (see Section 9.28.7).

This chapter covers the synthesis and reactivity of nitrogen-containing rings larger than ten, but also includes their reactivity in regard to metal complexation and the properties of such complexes.

9.28.2 THEORETICAL STUDIES

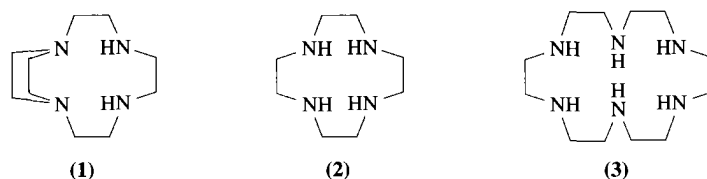
9.28.2.1 Metal Complexes

Molecular mechanics have become more and more important in the study of the correlation between cavity size and ionic radius of the coordinated metal ion <84CCR1, 93CCR177>. The different aspects of metal ion reactivity and ligand design for specific and selective binding can be modeled and understood in detail.

The idea of a good match between macrocyclic cavity size and size of the complexed metal ion is supported by several lines of evidence <78ACR49>. The high selectivity of crown ethers or cryptands towards alkali metal ions has been shown to stem from such correlations and has resulted in the so-called “peak selectivity,” typical for cyclic compounds. However, work on tetraazamacrocycles <85IC3378> has shown that for these ligands, the actual factors inducing complexation selectivity for transition-metal ions are the sizes of the chelate rings formed by coordination of the metal ions. Thus, when chelate ring size is varied in the process of varying the macrocyclic ring size, it is found that the higher the number of six-membered chelate rings, the lower the stability of the complexes with larger metal ions <89MI 928-02>. Exactly the same effect is observed in open-chain ligands indicating that the chelate ring and bite size and not the cyclic structure are important.

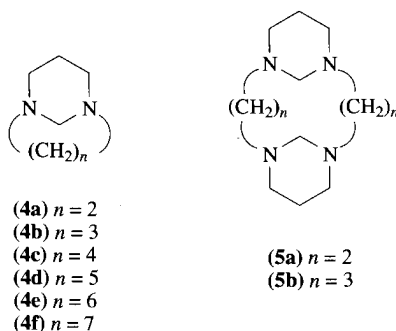
If a more rigid structure is built into the macrocycle as for (1), the ring cannot fold and adapt to the geometrical requirements of the metal ion. A highly stable low spin species is formed with Ni^{2+} with a large value of $D_q = 2180 \text{ cm}^{-1}$ <82CC277> (compare $D_q = 2115 \text{ cm}^{-1}$ for (2)). Molecular mechanics calculations reproduce the structure of the complex remarkably well and confirm that the Ni^{2+} has been compressed. The Ni—N bonds are $0.05 \text{ \AA}$ shorter than its strain-free bond length of $1.91 \text{ \AA}$ <89JA2788>.

Only a few molecular mechanics studies of complexes with macrocyclic ligands containing more than four nitrogens have been performed. In one case, calculations were run on the metal complexes of the hexaazamacrocycle (3) taking into account several conformations and geometrical environments, namely chiral octahedral, *meso* octahedral, trigonal prismatic, and hexagonal bipyramidal <93MI 928-01>. It was shown that for smaller metal ions, the preferred structure is the *meso* octahedral one. For metal ions with slightly larger M—N bonds, the trigonal prismatic structure is possible, whereas for metal ions with even larger M—N bonds, the hexagonal bipyramidal structure is most ideal. The fit between molecular mechanics calculation and the available crystal structure is excellent.



9.28.2.2 Azacycloalkanes

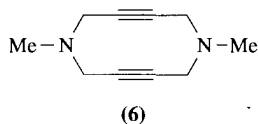
A completely different study on aminals of diaza- (**4a–f**) and tetraazacycloalkanes (**5a,b**) about the *out,out* to *out,in* transition as a function of the ring size, combines experimental results and force-field calculations <93JA6580>. The calculations were run using the Monte Carlo multiple minimum internal coordinate search method so to obtain the energy of the different isomers. The problems and difficulties in finding the low-energy isomers can be seen from the fact that 113 conformations were found to be within 19 kcal mol⁻¹ of the global minimum. The borderline for the change over from the *out,out* to *out,in* isomer for the series of molecules studied was found for compound (**4d**) in the gas phase, but for compound (**4e**) in CDCl₃; the solvent effect was due to the better solvation of *out* lone pairs.



9.28.3 STRUCTURAL ASPECTS

The x-ray structure of *N,N'*-dimethyl-1,6-diazacyclodeca-3,8-diyne (**6**) shows, that both methyl groups are in axial position of the chair conformation so that the interaction between the lone pairs of the nitrogen atoms and the triple bond is minimal. The linearity of the ethyne groups deviates somewhat, probably because of its cyclic structure <91TL2887>.

The x-ray structure of the monoprotonated form of (**6**) as iodide salt resembles that of *cis*-decalin, with the central C—C bond replaced by a symmetrical hydrogen bond, with a N—N distance of 2.600 Å and a N—H—N angle of 169° <88CC1528>.

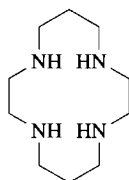


Several structures of tetraazamacrocycles in different protonated forms and with functional side chains are known. So for the diprotonated form of (**7**), the structure of which was already known as a diperchlorate <74JCS(D)2351>, has been measured now as a triflate <93MI 928-02> and the result is, that the two cations are practically superimposable.

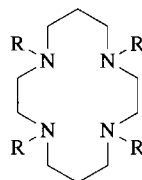
The tetraprotonated form of (**7**), as the CuCl₄²⁻ salt, shows the typical quadrangular conformation [3434] with a methylene group in each corner <89HCA1253>. This conformation belongs to the diamond lattice type and is the most stable conformation of cyclotetradecane itself <76ACS(A)155>. Whereas in its metal complexes and as a diprotonated cation (**7**) is endodentate, in its tetraprotonated form it is exodentate, so that the charges are as far apart as possible.

The same rectangular conformation of the 14-membered macrocycle is also found for the dipro-

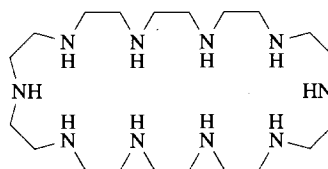
tonated form of (8a) as diiodide. Two of the side chains extend laterally from the ring, whereas the other two point up and down from the mean plane of the macrocycle <93ICA7>. The tetraacetate (8b) also shows the typical rectangular conformation with two protonated nitrogens *trans* to each other. Each of these carry a side chain with a carboxylate group, whereas the two nitrogens, which are not protonated, carry each a CH_2COOH group <91JCS(D)2477>. With this arrangement, the electrostatic repulsion is reduced to a minimum. No intramolecular hydrogen bonds are observed, whereas intermolecular hydrogen bonds between NH^+ groups and water molecules are present.



(7)

(8a) $\text{R} = (\text{CH}_2)_2\text{CO}_2\text{Me}$ (8b) $\text{R} = \text{CH}_2\text{CO}_2\text{H}$

The molecular structure of the octaprotonated form of (9) consists of macrocyclic units with an elongated elliptic shape and its conformation appears essentially dictated by the coulombic repulsion between the positively charged ammonium groups <87IC3902>. The counter ions $[\text{Co}(\text{CN})_6]^{4-}$ are not incorporated into the ring and form hydrogen bonds with the NH^+ groups.



(9)

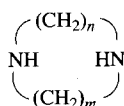
9.28.4 THERMODYNAMIC ASPECTS

Thermodynamic properties of polyazacycloalkanes have been carefully studied in regard of their protonation and complexation reactions. Since a review from 1991 is available <91CRV1721>, only a few points are discussed here.

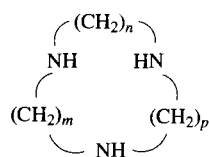
9.28.4.1 Protonation and Basicity

Medium-ring monocyclic diamines (10a-e) have $\text{p}K_{\text{H},1}$ values ≥ 12 in aqueous solution, so they cannot be measured by potentiometric methods <88CC1528>. Studies in DMSO with the "proton sponge," 2,7-dimethoxy-1,8-bis(dimethylamino)naphthalene, indicate that (10e) has the highest $\text{p}K_{\text{H}}$ value in this series. This results from internal hydrogen bonding as indicated by NMR measurements and effective force-field calculations.

For the series of the triazacycloalkanes (11a-g), the values of $\text{p}K_{\text{H},1}$ are given in Table 1. For the

(10a) $n = m = 3$ (10b) $n = 4, m = 3$ (10c) $n = 5, m = 3$ (10d) $n = 5, m = 4$ (10e) $n = m = 4$

10–12-membered rings, the $pK_{H,1}$ values are much higher than those of open chain secondary amines, whereas the 13-membered ligand (**11g**) has a normal value.



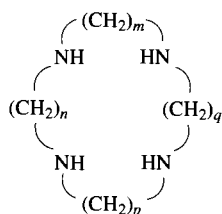
- (**11a**) $n = m = p = 2$
 (**11b**) $n = m = 2, p = 3$
 (**11c**) $n = m = 2, p = 4$
 (**11d**) $n = 2, m = p = 3$
 (**11e**) $n = m = 2, p = 5$
 (**11f**) $n = m = p = 3$
 (**11g**) $n = m = 2, p = 6$

Table 1 $pK_{H,1}$ Values of the cyclic triamines (**11a–g**) at 25 °C.

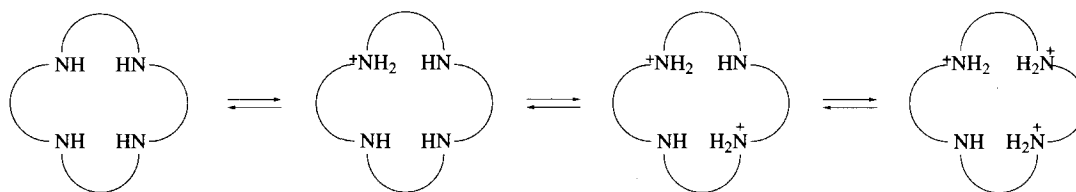
Compound	$pK_{H,1}$	Medium	Ref.
(11a)	10.59	0.2 M NaClO ₄	77JCS(D)1473, 78JCS(D)1081
	12.6	0.5 M KNO ₃	79HCA1089
	10.68	0.1 M KNO ₃	73NKK1119
	10.94	0.5 M KNO ₃	89HCA307
	10.42	0.1 M KNO ₃	76IC1499
	11.03	0.2 M Na ₂ SO ₄	87HCA680
(11b)	10.85	0.2 M NaClO ₄	78JCS(D)1081
	12.75	0.5 M KNO ₃	77C320
	12.02	0.1 M KNO ₃	78IC2531
	13.2	0.2 M Na ₂ SO ₄	87HCA680
(11c)	13.4	0.2 M Na ₂ SO ₄	87HCA680
(11d)	12.8	0.2 M Na ₂ SO ₄	87HCA680
	11.96	0.1 M KNO ₃	78IC2531
(11e)	11.5	0.2 M Na ₂ SO ₄	87HCA680
(11f)	12.6	0.1 M KNO ₃	78IC2531
(11g)	10.36	0.1 M NaNO ₃	86IC2992

Tetraazamacrocycles (**12a–i**) generally show the typical trend, that two of the pK_H values are high, whereas the other ones are distinctly lower <91CRV1721>. This is clearly due to electrostatic effects, since the second proton can bind to a nitrogen atom *trans* to the first one, whereas the third and forth must bind *cis* to an ammonium group and thus feel the neighboring positive charge in a much stronger way (Scheme 1). However, as the size of the macrocycle ring increases from 12 to 16 this interaction becomes less and less unfavorable and the values of $pK_{H,3}$ and $pK_{H,4}$ become larger (Table 2).

Similar observations have been made for larger macrocycles containing five or more nitrogen atoms. These compounds behave as strong bases in their first protonation steps and as weaker bases in the last protonation steps <87IC1243>.



- (**12a**) $n = m = p = q = 2$
 (**12b**) $n = m = p = 2, q = 3$
 (**12c**) $n = p = 2, m = q = 3$
 (**12d**) $n = m = 2, p = q = 3$
 (**12e**) $n = m = p = 2, q = 4$
 (**12f**) $n = m = p = 3, q = 2$
 (**12g**) $n = p = 2, m = 3, q = 4$
 (**12h**) $n = m = p = 2, q = 5$
 (**12i**) $n = m = p = q = 3$



Scheme 1

Table 2 pK_H Values of tetraazacycloalkanes.

Compound	$pK_{H,1}$	$pK_{H,2}$	$pK_{H,3}$	$pK_{H,4}$	Temperature ($^{\circ}\text{C}$)/ Medium	Ref.
(12a)	10.6	9.6			25; 0.1 M NaNO_3	88ICA229
	10.51	9.49	1.6	0.8	35; 0.2 M NaClO_4	80JCS(D)327
(12b)	10.91	9.91	~ 1.6	~ 0.9	35; 0.2 M NaClO_4	80JCS(D)327
(12c)	11.54	10.53	2.43	1.97	20; 0.1 M KNO_3	86TAL721, 84HCA441
	11.59	10.63	1.64	2.41	25; 0.5 M KNO_3	78JCS(P2)945
	11.50	10.30			25; 0.2 M NaClO_4	84IC4181
	11.78	10.55	< 2	< 1	25; 0.1 M NaClO_4	78IC362, 90JA9237
	10.80	10.2	3.7	2.5	25; 0.1 M KNO_3	78IC362
	11.23	10.30	1.5	~ 0.8	35; 0.2 M NaClO_4	80JCS(D)327
(12d)	11.29	10.19	4.52	2.2	25; 0.5 M KNO_3	90HCA716
	11.05	9.98	3.5	1.0	25; 0.2 M NaClO_4	80JCS(D)327
(12e)	10.57	9.56	4.13	~ 2	25; 0.2 M NaClO_4	83IC2055
	10.92	9.40	4.62	1.6	25; 0.1 M NaNO_3	87JCS(D)2911
(12f)	11.09	10.39	5.28	3.6	25; 0.5 M KNO_3	78JCS(P2)945
	11.4	10.3			15; 0.2 M NaClO_4	76JCS(D)2341
	11.2	10.1	~ 2	~ 2	25; 0.2 M NaClO_4	76JCS(D)2341
	10.7	9.92	5.23	3.54	25; 0.1 M KNO_3	86M1 928-01
(12g)	11.04	10.47	3.98	3.41	25; 0.5 M KNO_3	82JCS(P2)1345
	10.76	9.94	3.6	1.5	25; 0.2 M NaClO_4	83IC2055
(12h)	10.33	9.48	5.71	1.28	25; 0.5 M KNO_3	84IC1201
	9.83	8.95	4.50	1.6	25; 0.1 M NaNO_3	87JCS(D)2911
	10.37	9.35	5.29	~ 2	35; 0.2 M NaClO_4	83IC2055
(12i)	10.77	9.63	6.90	5.38	20; 0.1 M KNO_3	78JCS(D)945, 84HCA441, 84TL645
	10.85	9.80	7.21	5.69	25; 0.5 M KNO_3	80JCS(D)1722, 78HCA2296

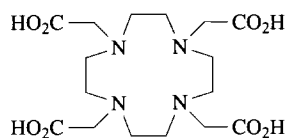
9.28.4.2 Metal Complexation

A large number of stability constants for metal complexes with triaza-, tetraaza-, and polyazamacrocycles has been measured and their values are tabulated (91CRV1721). Whereas smaller rings with three and four nitrogen atoms generally form 1:1 species ML (but sometimes also ML_2), larger rings with more nitrogen donors can give protonated species MLH_n and/or binuclear complexes M_2L .

Many of these complexes are more stable than those formed with the corresponding open-chain ligands. This has been called the "macrocyclic effect." It has been shown that it is determined by enthalpic as well as by entropic contributions (74IC2941, 83JCS(D)1189). Even higher stability constants are obtained when side chains with additional donor groups are attached to the macrocycle; thus tetraacetate (13) (DOTA) forms complexes with most metal ions, such as earth-alkali ions, transition-metal ions and lanthanides; these complexes possess the highest known stabilities (82TAL815, 84IC359). Beside high stability, specificity, and selectivity are two additional aspects of the coordination of polyazamacrocycles. By changing the number of ligating atoms in the ring, the size of the macrocycle, and the nature of the side chain donor groups, the chemist has a good possibility for obtaining ligands, which can be designed for a specific purpose.

9.28.4.3 Anion Coordination

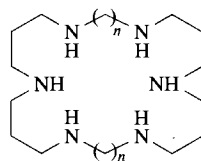
Macrocyclic polyamines, which can be highly protonated at neutral pH, appear to be good ligands for both inorganic and organic anions (91CRV1721). Since selectivity in these systems depends on



(13)

coulombic interactions and geometrical effects, the size of the macrocyclic cavity and the number of ammonium groups are of paramount importance. A study of the interaction of tetraprotonated macrocyclic hexamines with inorganic anions revealed, that desolvation of the macrocycle and of the anion is the driving force for the complexation process $\langle 85JA909, 86IC1527 \rangle$. In the complexation of large polyazacycloalkanes with large polyanions, such as $\text{Fe}(\text{CN})_6^{4-}$ and $\text{Co}(\text{CN})_6^{4-}$, it was found that there is no selectivity towards the anions $\langle 87IC3902 \rangle$.

Macrocycles containing two triamine units, such as in (14), can be used as ditopic receptors for dianions such as dicarboxylates $^{-}\text{OOC}-(\text{CH}_2)_n-\text{COO}^{-}$ $\langle 86HCA587 \rangle$. The most stable complexes are formed when the length of the dianion chain exactly fits into the cavity of the ditopic receptor $\langle 86HCA587 \rangle$.



(14)

9.28.5 REACTIVITY

9.28.5.1 Reactivity of the Ring

Cyclic monoamines (15) can be electrochemically oxidized to bicyclic compounds (16) (Equation (1)). The authors found that specific conditions have to be used to produce the bicyclic products in good yields $\langle 85CJC1170 \rangle$. These are 20% H_2O in acetonitrile, 0.1 M LiBr, carbon anode, and a current of 100–150 mA corresponding to a voltage of about 2.3 V. To obtain the maximal yield the reaction must be monitored, since high voltage and high current of the anode cause destruction of the compounds. The results are summarized in Table 3. Since the experimental conditions necessary to obtain the best yields are similar to those of the Kolbe oxidation or more specifically to the Hofer–Most reaction, the authors suggest a similar mechanism.

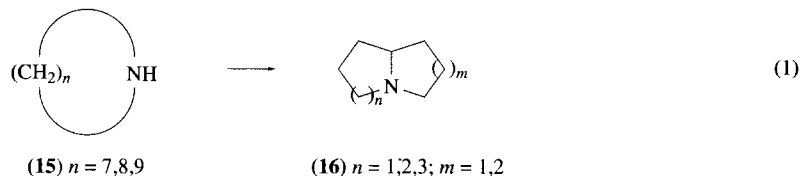
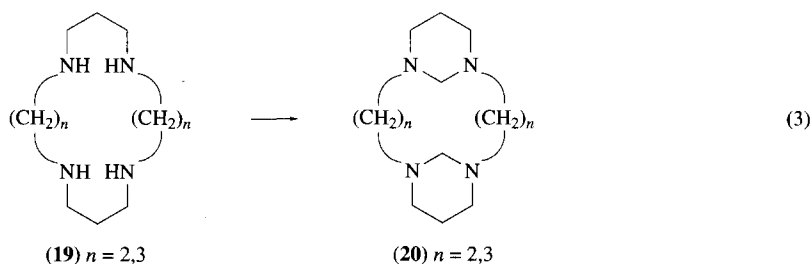
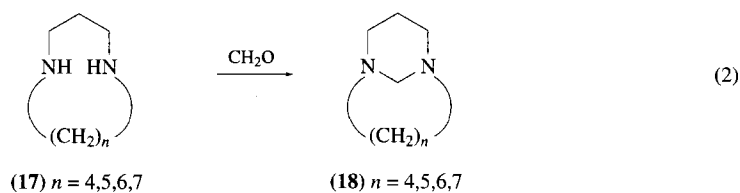


Table 3 Bicyclization of monocyclic amines by electrochemical means.

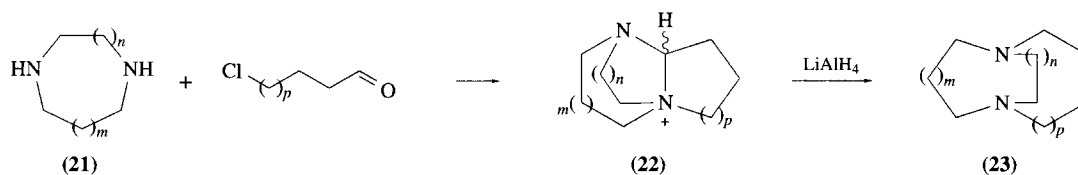
Compound (15)	Product (16)	Yield (%)	Time (h)
$n = 7$	$n = m = 1$	52	2.5
$n = 8$	$n = 2, m = 1$	71	2.5
$n = 9$	$n = m = 2$	10	3.0
$n = 9$	$n = 3, m = 1$	3.5	3.0

In a study of the synthesis of thymidine-3-phosphoramidites of various amines and their use in the synthesis of fully protected thymidine dimers, a series of monoazacycloalkanes was tested as the amine component <84TL5513>. It was shown that the condensations in solution work especially well with yields exceeding 90% when *p*-nitrophenylethyl phosphoramidites of hexahydroazepine, octahydroazonine, and azacyclotridecane were used. These compounds can easily be purified and stored at room temperature, so that they might be useful synthons for large-scale synthesis of oligodeoxyribonucleotides, where a low excess of phosphoramidites is desirable.

1,5-Diazacycloalkanes of the type (17) easily react with CH_2O to give aminals (18) with yields ranging from 73 to 90% (Equation (2)) <93JA6580>. Compounds (17) with $n = 6$ and $n = 7$ are liquids, but form solid oligomers on standing, from which they can be recovered by distillation. The two tetraazacycloalkanes (19) give a similar reaction to afford the tricyclic bisaminals (20), which are in this case solids, of which x-ray structures have been determined (Equation (3)) <82AX(B)2752, 83AX(C)275>.



Mixing medium-ring monocyclic diamines (21) with 4-chlorobutanal or 5-chloropentanal in CH_2Cl_2 solution containing suspended MgSO_4 produces α -aminoammonium salts (22), which can efficiently be cleaved with LiAlH_4 in 1,2-dimethoxyethane to bicyclic diamines (23) (Scheme 2) <82TL4181>. The formation of the tricyclic α -aminoammonium salts proceeds via a bicyclic amina followed by a slower cycloalkylation step. The tricyclic salts derived from unsymmetrical diamines may exist in two diastereoisomeric forms differing in their stereochemistry at the methine group. Amines (21) with $n = 2, m = 3$, (21) with $n = 2, m = 5$, and (21) with $n = 3, m = 6$ give a single isomer as detected by ^{13}C NMR, while amines (21) with $n = 3, m = 4$ and (21) with $n = 3, m = 5$ give mixtures. Table 4 summarizes the result of this investigation.



Scheme 2

9.28.5.2 Reactivity of Side Chain Functional Groups

A few reactions, in which side chain functional groups have been modified in the presence of a coordinated metal ion have been described. The nitrile group in the Cu^{2+} complex of (24a) rapidly hydrolyzes to the amide (24b), when the pH is made alkaline <88PAC1117>.

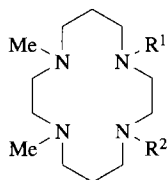
The reaction mechanism involves an intramolecular attack of a coordinated OH^- onto the nitrile. The role of the metal ion is to organize the two reactants, to fix them sterically so that an ideal geometry for the transition-state results.

Table 4 The reaction of 1,X-diazacycloalkanes to give bicyclic derivatives.

Compound (21)	α -Aminoammonium salt (22)	Bicyclic product (23)
$n = 2, m = 3$	with (A) 86% $\rightarrow$ [4.3.2.0 ^{1,5}] with (B) 74% $\rightarrow$ [5.3.2.0 ^{1,6}]	78% $\rightarrow$ [4.3.2] 70% $\rightarrow$ [5.3.2]
$n = m = 3$	with (A) 74% $\rightarrow$ [4.3.2.0 ^{1,5}] with (B) 82% $\rightarrow$ [5.3.3.0 ^{1,6}]	62% $\rightarrow$ [4.3.3] 73% $\rightarrow$ [5.3.3]
$n = 2, m = 5$	with (A) 89% $\rightarrow$ [5.4.2.0 ^{1,8}] with (B) 85% $\rightarrow$ [5.5.2.0 ^{1,6}]	65% $\rightarrow$ [5.4.2] 71% $\rightarrow$ [5.5.2]
$n = 3, m = 4$	with (A) 82% $\rightarrow$ [4.4.3.0 ^{1,5}] with (B) 92% $\rightarrow$ [5.4.3.0 ^{1,6}]	72% $\rightarrow$ [4.4.3] 80% $\rightarrow$ [5.4.3]
$n = 3, m = 5$	with (A) 73% $\rightarrow$ [5.4.3.0 ^{1,8}] with (B) 65% $\rightarrow$ [5.5.3.0 ^{1,6}]	60% $\rightarrow$ [5.4.3] 67% $\rightarrow$ [5.5.3]
$n = 3, m = 6$	with (A) 94% $\rightarrow$ [6.4.3.0 ^{1,9}] with (B) 85% $\rightarrow$ [6.5.3.0 ^{1,9}]	70% $\rightarrow$ [6.4.3] 70% $\rightarrow$ [6.5.3]

^a A = 4-Chlorobutanal; B = 5-Chloropentanal.

Similarly, the hydrolysis of the bis(cyanomethyl) derivative (24c) also rapidly takes place in the presence of coordinated Cu^{2+} , but surprisingly the monoamide mononitrile (24d) is the final product. The large difference in hydrolysis rate between the two nitrile groups can be explained by the same mechanism proposed for the mononitrile hydrolysis. First a hydroxo species is formed, then through an intramolecular attack of the OH^- onto the nitrile, the amide is produced. At alkaline pH, the amide group deprotonates and coordinates axially to the metal ion. This blocks the coordination site for a second OH^- , which would be necessary for the hydrolysis of the second nitrile. Thus internal inhibition of the second hydrolysis step makes it possible to selectively react only one of the two nitrile groups.



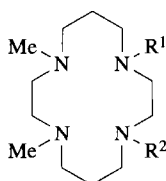
(24a) $\text{R}^1 = \text{Me}, \text{R}^2 = \text{CH}_2\text{CN}$

(24b) $\text{R}^1 = \text{Me}, \text{R}^2 = \text{CH}_2\text{CONH}_2$

(24c) $\text{R}^1 = \text{R}^2 = \text{CH}_2\text{CN}$

(24d) $\text{R}^1 = \text{CH}_2\text{CN}, \text{R}^2 = \text{CH}_2\text{CONH}_2$

A further interesting reaction, in which selectivity through the metal ion has been achieved, is the acylation of (25a) (88PAC1117). If the free ligand is reacted with benzoyl chloride, both primary amino groups are benzoylated, as expected, to give (25b). However, if the same reaction is performed with the Cu^{2+} complex of (25a), only one amino group is benzoylated (25c), since the two side chains are not equivalent. One is free and can react with benzoyl chloride, the other being coordinated to the metal ion is protected.



(25a) $\text{R}^1 = \text{R}^2 = (\text{CH}_2)_2\text{NH}_2$

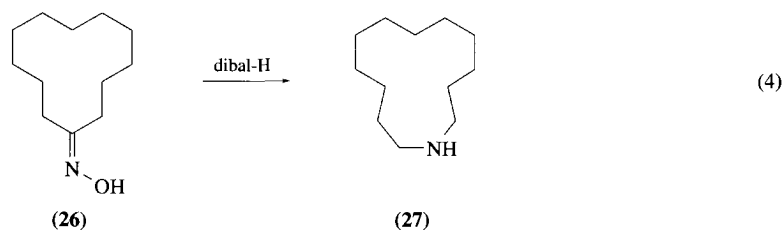
(25b) $\text{R}^1 = \text{R}^2 = (\text{CH}_2)_2\text{NHCOC}_6\text{H}_5$

(25c) $\text{R}^1 = (\text{CH}_2)_2\text{NH}_2, \text{R}^2 = (\text{CH}_2)_2\text{NHCOC}_6\text{H}_5$

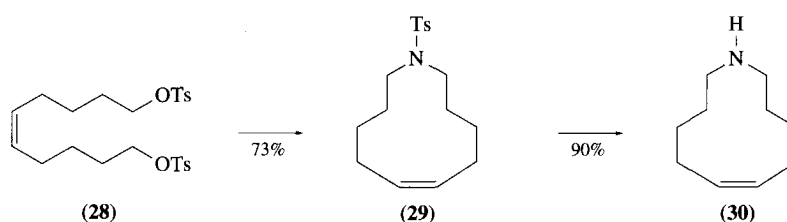
9.28.6 SYNTHESSES

9.28.6.1 Monoaza- and Diazacycloalkanes

Whereas monoazacycloalkanes are generally prepared by reduction of the corresponding lactams with LiAlH_4 , somewhat different reactions for their synthesis have also been described. The reduction of the cyclic oxime (**26**) with diisobutylaluminum hydride (dibal-H) gives the cyclic amine (**27**) in 70% yield (Equation (4)) $\langle 83\text{TL}4711 \rangle$.



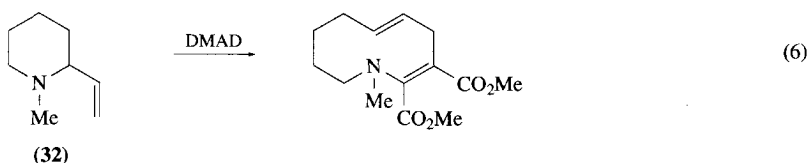
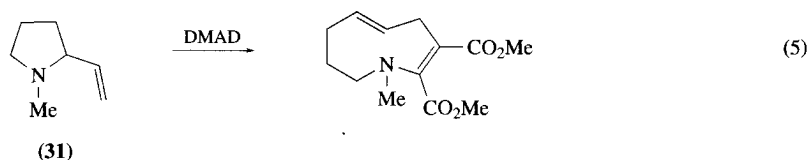
For the total synthesis of manzamine C, the simplest member of oncolytic alkaloids isolated from *Okinawa* marine sponges, it was necessary to prepare the 6-(*Z*)-azaundecene ring $\langle 89\text{TL}6549 \rangle$. This was done by cyclization of the *cis*-ditosylate (**28**) under phase-transfer conditions (TsNH_2 , NaOH , Bu_4NI , benzene, reflux, 4 h) to afford the desired product (**29**) (Scheme 3). Deprotection of (**29**) using Red-Al gave the unsubstituted aza-derivative (**30**), which was coupled with the β -carbolineester to give, after reduction of the amide bond, manzamine C.



Scheme 3

With a variety of catalyzed and uncatalyzed reaction conditions for the Michael addition and aza-Claisen rearrangement, ring expansion was explored by reacting the five- and six-membered amines (**31**) and (**32**) with dimethyl acetylenedicarboxylate (DMAD), as the Michael acceptor $\langle 94\text{JA}579 \rangle$ (Equations (5) and (6)). The cyclic enamines are rather sensitive to hydrolysis during isolation and are easily destroyed by acid.

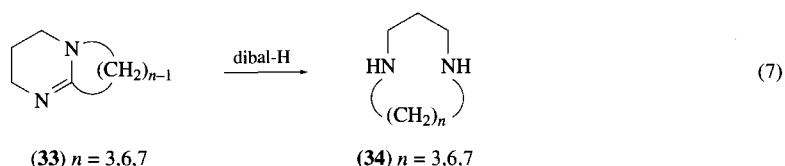
The six-membered amine (**32**), however, gave rearrangement products which were more stable. The best yield was obtained by adding toluenesulfonic acid. All products have the (*E*)-disubstituted double bonds, as shown by the characteristic coupling constants in their ^1H NMR spectra.



Papers from the 1990s describing the synthesis of diazacycloalkanes use with small variations the method of Yamamoto and Maruoka $\langle 81\text{JA}4186 \rangle$. So the preparation of 1,5-diazacycloalkanes (**34**) with ring sizes of 8, 11, and 12 starts from the parent 1,5-diazabicycloalkenes (**33**), which are then

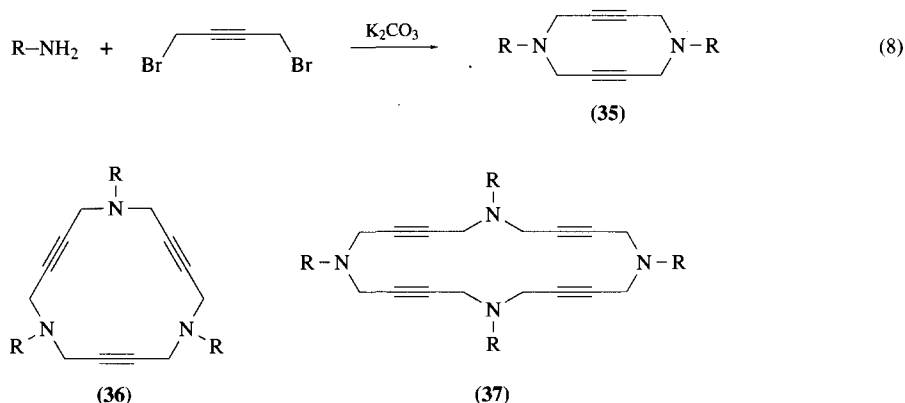
reduced with dibal-H obtaining yields between 59% and 94% (Equation (7)) <93JA6580>. The corresponding 1,5-diazacyclodecane (**34**) with $n = 5$ was obtained by reduction of 1,5-diazabicyclo[4.4.0]decane, itself prepared by the condensation of 5-chloropentanal with 1,3-diaminopropane <93JA6580>.

Similarly 1,6-diazacyclodecane was prepared by condensation of 4-chlorobutanal with 1,4-diaminobutane to give 1,6-diazabicyclo[5.3.0]decane, followed by reductive cleavage using one equivalent of BuLi and an excess of dibal-H <88CC1528>.



A series of N,N' -disubstituted diazacyclodecadiynes (**35**) was synthesized by a one-pot reaction between the amine component ($R = \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_3\text{H}_7, \text{cyclohexyl}$) and 1,4-dibromo-2-butyne in the presence of K_2CO_3 in THF giving low (5%) yields (Equation (8)) <91TL2887>.

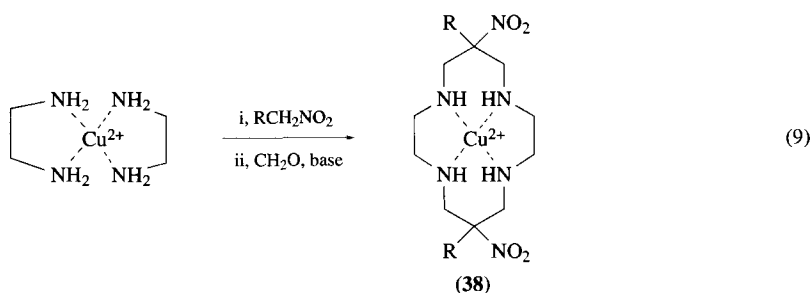
Additional isolated products of this reaction are the 15-membered triynes (**36**) and the 20-membered tetraynes (**37**).

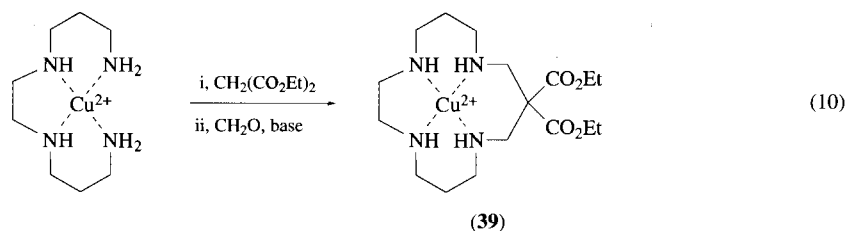


9.28.6.2 Polyazacycloalkanes

The fundamental step in the preparation of polyazamacrocycles is the cyclization reaction. The classical synthesis, using metal ions as templates <75MI 928-01>, cyclizations at high dilution <61CB1410>, or the tosylate method of Richman and Atkins <74JA2268>, have been reviewed extensively. Several newer approaches have been developed in the 1980s and 1990s.

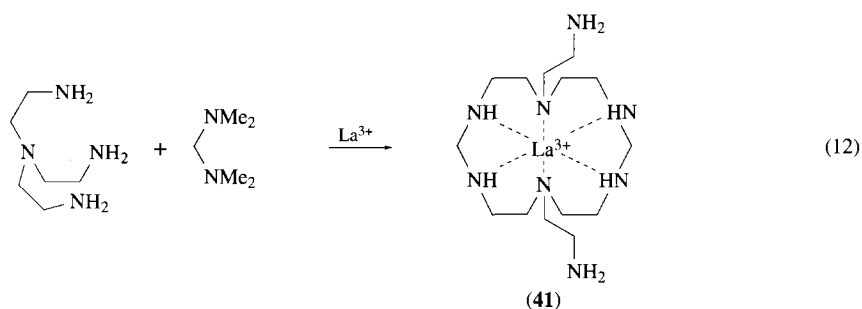
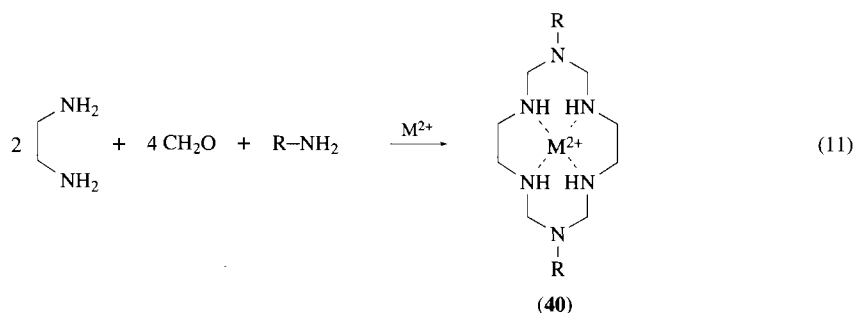
The condensation procedure between metal complexes of multidentate polyamines with formaldehyde and a variety of compounds with an activated methylene group yields monocyclic polyamines, for example (**38**) <86IC4260, 88AJC1533> or (**39**) <87AJC1441>. When nitroalkanes or diethyl malonate were used as activated carbon compounds, C -substituted derivatives were isolated (Equations (9) and (10)).





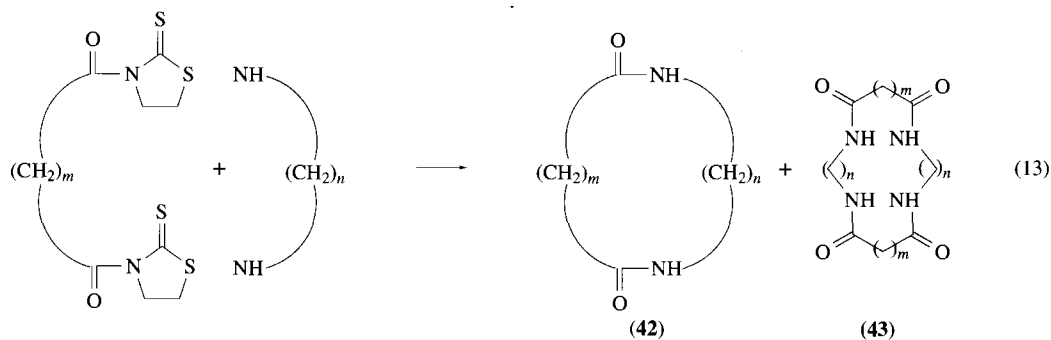
A similar procedure using ethylenediamine, formaldehyde, and a primary amine allows the synthesis of Ni^{2+} and Cu^{2+} complexes of the hexaazamacrocyclic (40) (Equation (11)) <84IJC(A)541>.

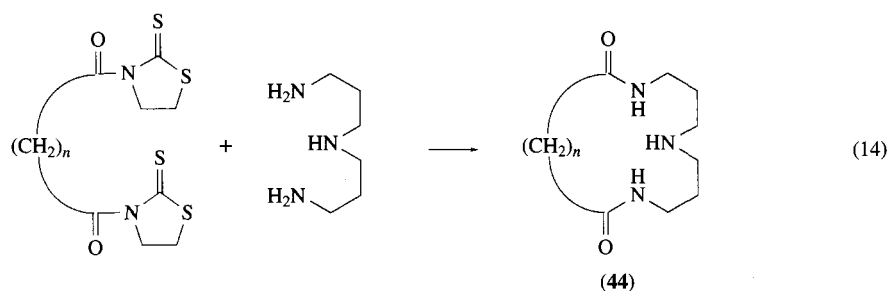
Instead of formaldehyde, bis(dimethylamino)methane can also be used for the synthesis of larger rings such as (41), in which La^{3+} is coordinated (Equation (12)) <85IC3469>.



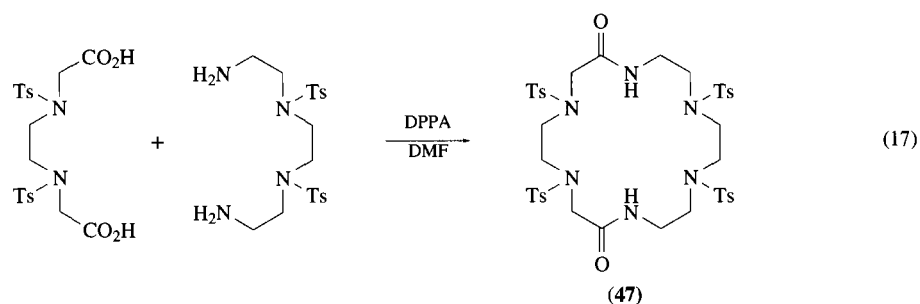
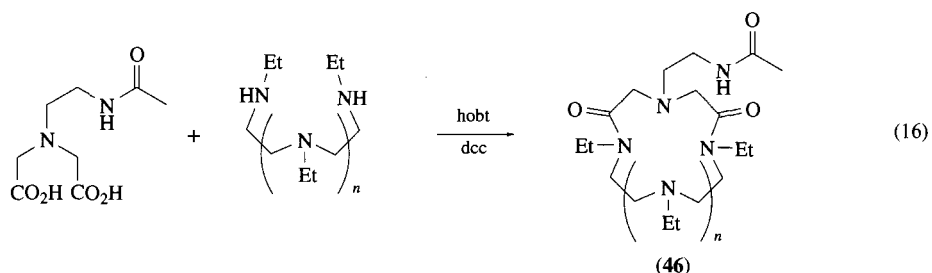
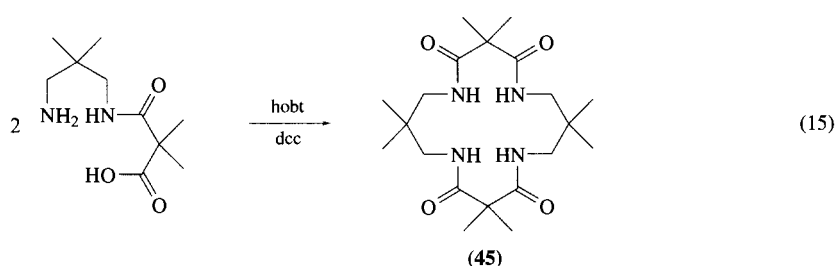
In the field of high-dilution condensations, the substitution of the more commonly used acid chlorides, by thiazolidine-2-thione derivatives of dicarboxylic acids gave new interesting results <81H(15)1037>. The cyclization yielded 1:1 (42) as well as 2:2 (43) products depending on the ring size.

Also when the bis(thiazolidine-2-thione) derivatives of dicarboxylic acids were reacted with a polyamine only the primary, not the secondary, amino groups are attacked to give (44) (Equation (14)) <81H(15)1037>.





Other activating groups for carboxylic acids, such as 1-hydroxybenzotriazole (hobt) <89TL2897> or diphenylphosphorylazide (DPPA) <90TL6469>, have also been used with good success to give (45), (46) or (47) (Equations (15), (16), and (17), respectively).

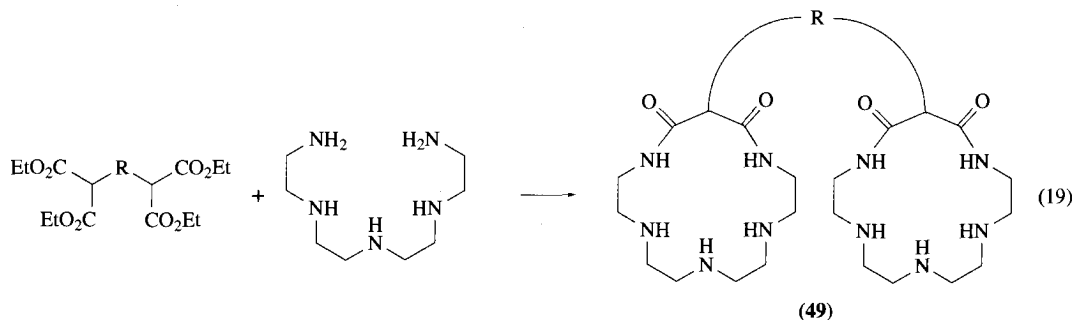
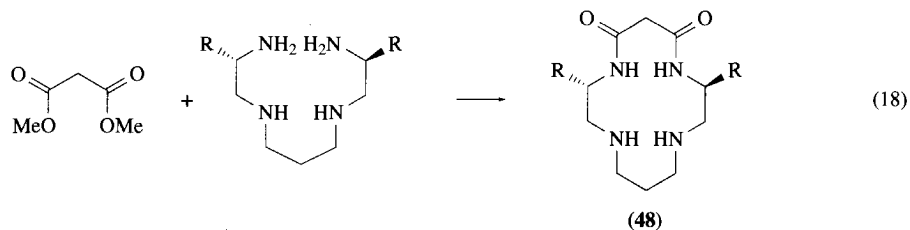


New developments in the Richman and Atkins tosylamide cyclization procedure have shown, that coupling the electrophile containing the shortest chain length with the nucleophile containing the longest chain length gave the best yields <89SC1009>. This rule seems to apply for larger rings, whereas no such difference was noted for smaller ones. Interesting also is the observation that the cyclization needs not to be carried out at high temperatures ($\approx 100^\circ\text{C}$), but is best run between room temperature and 50°C <89JOC2990, 89SC1009>.

Careful studies of this reaction indicate, that besides 1 : 1 cyclization products, 2 : 2 compounds and linear tosylated amines are often produced <87HCA680>. Sometimes purification can be achieved by fractional crystallization, but in several cases column chromatography was needed. Separation of the 1 : 1 and 2 : 2 cyclization products from each other can also be done by complexation with an appropriate metal ion. For example, the binuclear Cu^{2+} complex of $[\text{24}]N_6$ was isolated and purified from the 1 : 1 cyclization product $[\text{12}]N_3$ <88IC1641>.

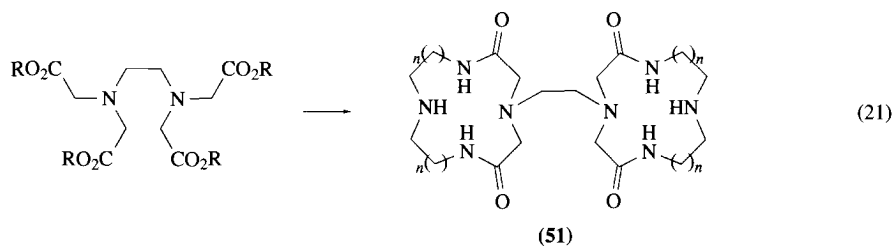
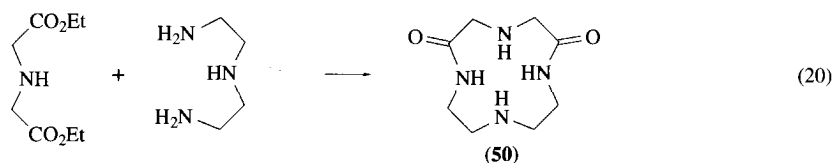
The diester-diamine condensation reaction to give cyclic diamides was first reported by Tabushi *et al.* <77TL1049> and has been applied with some variations. For example, chiral diamides (**48**) were obtained from chiral tetraamines (Equation (18)) <89JOC1584>.

Even larger bismacrocycles (**49**) can be prepared by this method (Equation (19)) <90JOC42>.

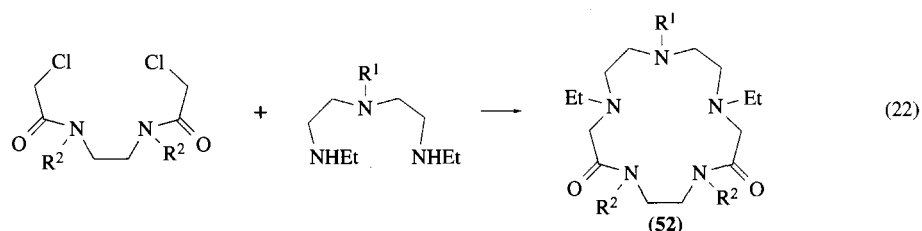


Two other starting materials for the ester condensation are diethyliminodiacetate and the tetra-ester of edta, which give the monocycle (**50**) (Equation (20)) <86IC321> and the bismacrocycles (**51**) derivatives (Equation (21)).

Most of these products containing amide functions have been reduced using $\text{BH}_3 \cdot \text{THF}$ or LiAlH_4 to give the corresponding polyazamacrocycles.



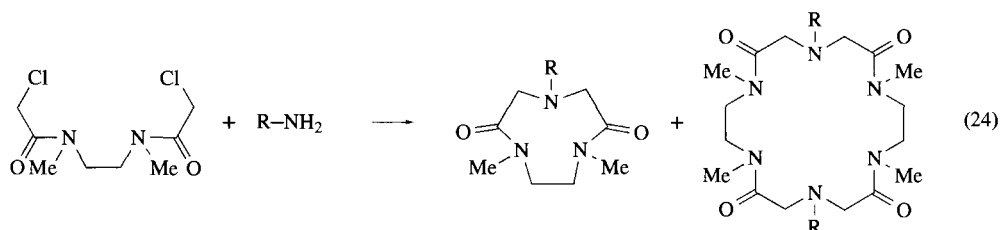
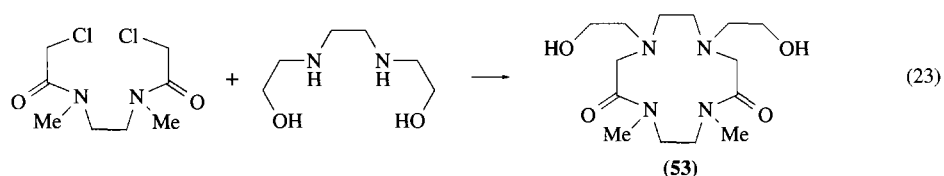
In the so-called "crab-like" cyclization procedure, bischloroacetamide derivatives are reacted with amines or diamines to form macrocycles <89PAC1619, 90JOC3364>. The reaction offers several advantages over the other syntheses since the starting bischloroacetamides can easily be prepared in yields of 70–100% by the acylation of appropriate diamines with chloroacetyl chloride in water/chloroform mixtures in the presence of K_2CO_3 . The cyclization is then carried out by reacting the bischloroacetamide with the amine component in acetonitrile using an alkali carbonate, as base. Examples of this reaction show that it is possible to include side chains with functional groups on the amino component without major problems, for example to give (**52**) (Equation (22)) <89TL2897>.



Azamacrocycles with two hydroxyethyl side chains attached at the nitrogen atoms (**53**) have also been prepared by the same method (Equation (23)) <90TL1077>. An analog synthesis produces the 14-membered macrocycle, which can be reduced to the amine, thus giving the possibility to obtain cyclam derivatives in high yield <90TL1077>.

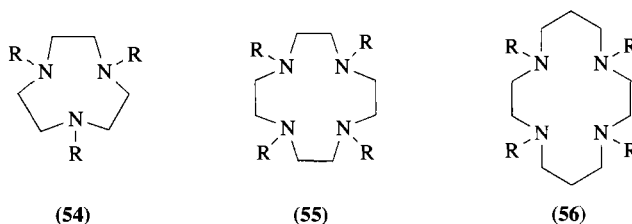
For smaller rings <90JHC1585> or for rigid starting compounds <91JOC2675>, 2:2 and 3:3 cyclization products were observed (Equation (24)).

In contrast to the high yields obtained with α -chloroamides, β -chloroamides were not reactive, even when KI was added, the yields were relatively low <90JHC1585, 90TL1077>.

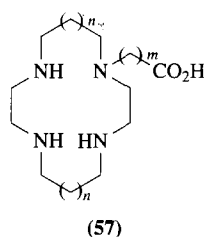


9.28.6.3 N-Functionalized Derivatives

N-Functionalization is generally simpler than C-functionalization. When the nitrogen atom is nucleophilic, it can be either alkylated or acylated. The substitution of all nitrogens in such polyazamacrocycles is easy and does not need special techniques, whereas the selective substitution of a single nitrogen atom is more demanding, since selective protection of the nitrogen atoms, which should not react, must be achieved. Here again, the main interest is the macrocyclic complexation of metal ions, by the introduction of side chains, which carry additional donor groups and are able to bind to the metal ion. Thus, a large number of persubstituted azamacrocycles of the type (**54**), (**55**), and (**56**) have been reported, via this technique, where R can be, for example, —CH₂—COOH, —(CH₂)₂—NH₂, —(CH₂)₃—NH₂, —CH₂—CN, —(CH₂)₂—CN, —(CH₂)₂—OH, or —CH₂—PO₃H₂. In general, these side chains are introduced into the preformed macrocycle by alkylation with halogeno derivatives, or by condensations of formaldehyde and CN[−] or H₃PO₃, or by reaction with an α,β -unsaturated compound such as acrylonitrile, or by reaction with ethylene oxide. Two reviews on these compounds have appeared <84TCC157, 90CCR297>.

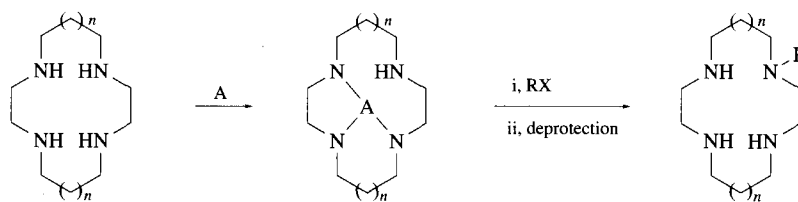


The preparation of mono-*N*-substituted polyazacycloalkanes is generally more difficult and involves several steps, since protection and deprotection are often necessary in order to substitute selectively a single nitrogen atom. Many of the older procedures have used this approach, however, there are now some simpler methods. One possibility is to employ the statistical effect by using a large excess of polyazamacrocyclic over the alkylating agent and to separate the unreacted and the monosubstituted macrocycle $\langle 86\text{HCA}2081 \rangle$. This is easy, when a carboxylate side chain is incorporated, since the extraction of the polyamine excess is then relatively trivial. Macrocycles of the type (57) were synthesized by this technique.



The other possibility is to incorporate a hydrophobic side chain, which also allows separation of product and educt $\langle 91\text{MI} 928-01 \rangle$.

A second method uses protecting groups, which are able to block three amino nitrogens at once, so that in tetraazacycloalkanes only one nitrogen remains available for further alkylation. Protecting groups (A) of this type are trisdimethylaminoborane, hexamethylphosphorotriamide, dimethylformamidediacetal, and certain metal carbonyls, as shown in Scheme 4 $\langle 91\text{AG}(\text{E})561, 91\text{TL}639 \rangle$.



Scheme 4

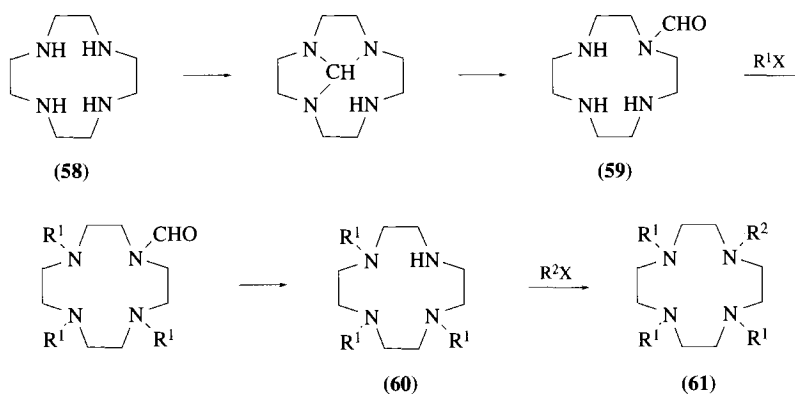
Of course, the side chain can also be introduced in one of the fragments of the cyclization procedure, as already discussed for the "crab-like" cyclization (see Section 9.28.6.2).

Other *N*-substituted derivatives have also been described. There are only a few examples of disubstituted triazacycloalkanes, and of di- and trisubstituted tetraazacycloalkanes $\langle 84\text{TCC}157 \rangle$. Especially well studied is the $[12]\text{N}_4$ system because of its potential applications as MRI contrast agents (see Section 9.28.7.1); one example illustrates the procedure $\langle 88\text{EUP}0292689 \rangle$. The tetraazamacrocyclic (58) is reacted with dimethylaminoformamidediacetal and carefully hydrolyzed to the monoformyl derivative (59). This can be subsequently alkylated three times, to give for example the triacetate. Deprotection affords a trisubstituted tetraazacyclododecane, which still has a secondary nitrogen (60). This can be further substituted to form mixed substituted ligands (61) (Scheme 5).

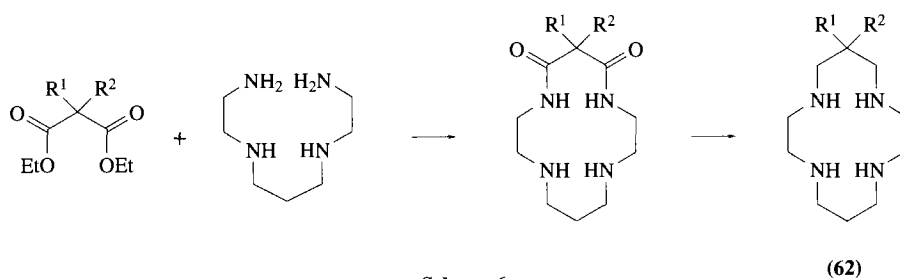
9.28.6.4 C-Functionalized Derivatives

The synthesis of *C*-substituted polyazamacrocyclics generally needs a precursor, which already has the side chain incorporated, prior to cyclization. Using the Tabushi *et al.* approach $\langle 77\text{TL}1049 \rangle$ for the condensation of polyamines with substituted malonate diesters, several *C*-substituted tetraazamacrocyclics (62) have been prepared, in which R^1 and/or R^2 are alkyl groups $\langle 83\text{IC}2055 \rangle$ or one or two fluorine atoms (Scheme 6) $\langle 88\text{JA}3679 \rangle$.

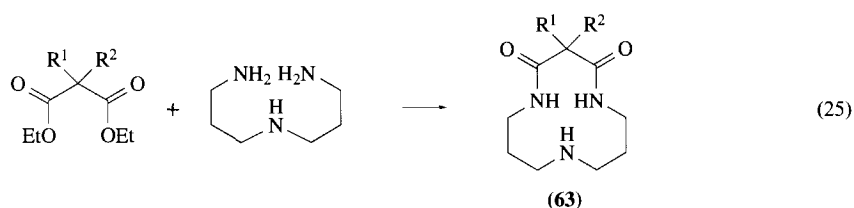
Similarly, this condensation also affords *C*-substituted triazacyclononanes (63) (Equation (25)) $\langle 89\text{JHC}1431 \rangle$.



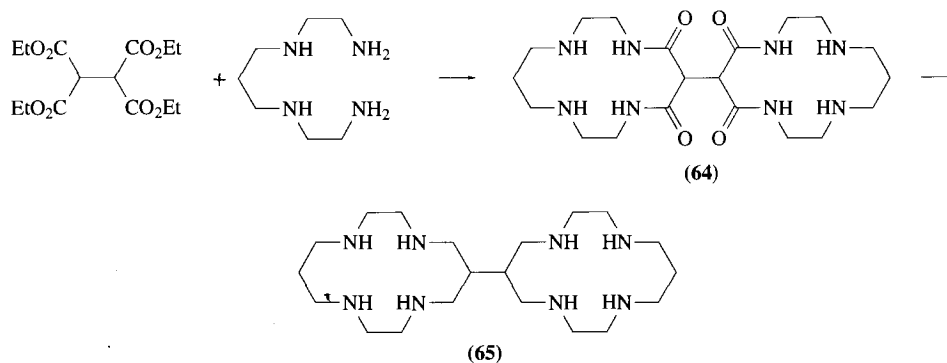
Scheme 5



Scheme 6



A further variant of this method using bismalonate tetraester allows the preparation of bis-macrocyclic amides (64) (84IC3917), which can be then reduced with B_2H_6 in diglyme to the corresponding bismacrocyclic amine (65) (86IC2671, 87JCS(D)2631).

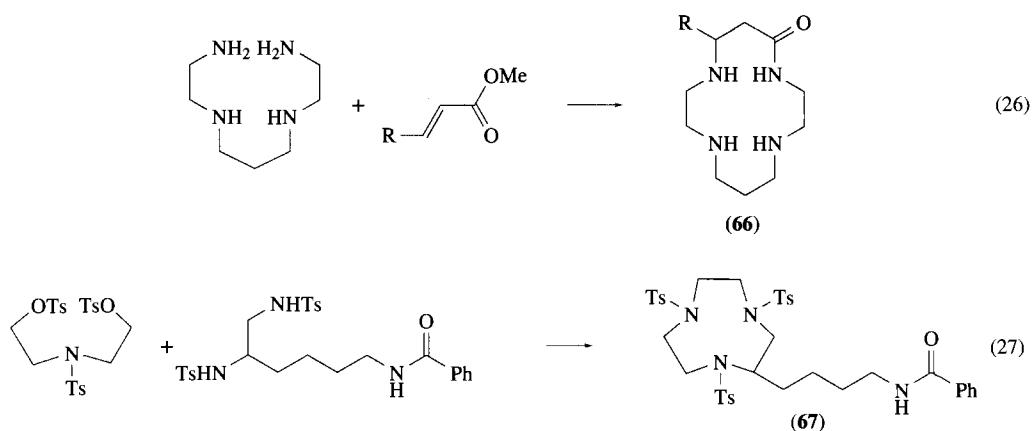


Scheme 7

A different approach has been the use of methyl acrylates to prepare macrocyclic monoamides (66) (Equation (26)) (85CC385, 86CC1322, 86IC3883, 86PAC1461, 87CC1712, 87IC2975).

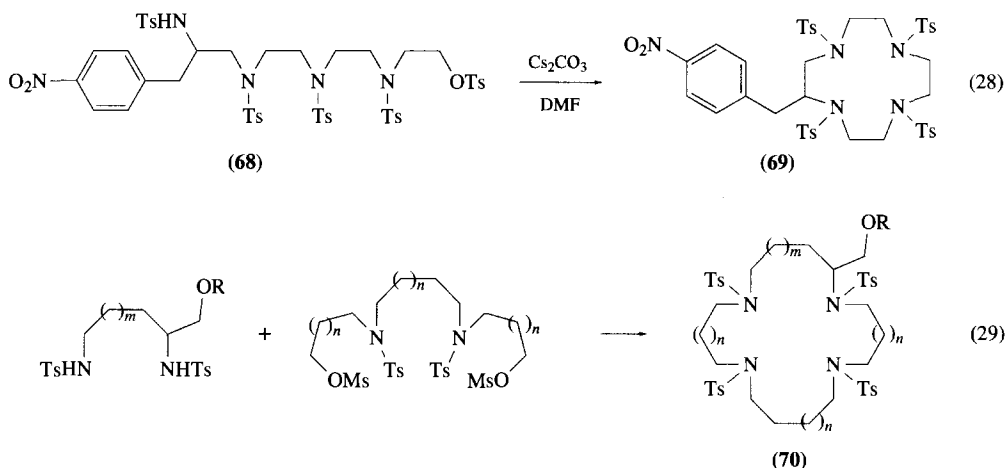
The β -substituent R on the acrylate was varied from phenyl to pyridyl and imidazolyl.

A further interesting polyazamacrocycle (**67**) carrying a functional group in the side chain attached to a ring carbon atom has been synthesized using the tosylate method (Equation (27)) <88HCA602>.



The intramolecular ring formation of a sulfonamide with a tosyloxy group allows formation of the C-substituted compound (**69**) <88JA6266>. The precursor (**68**) was synthesized by peptide formation and subsequent reduction of the amide groups (Equation (28)).

Burrows *et al.* have synthesized tetraazamacrocycles (**70**) containing a free as well as protected hydroxy functional group (Equation (29)) <86TL5943, 87CC277>.



9.28.7 APPLICATIONS

Several polyazamacrocycles have found applications in the field of medicine. The high thermodynamic and kinetic stability of their metal complexes, as well as the flexible coordination of these compounds towards very different metal ions, make them ideal candidates for *in vivo* applications. The complexes formed by such polyazamacrocycles remain intact, are not decomposed by transmetallation with ligands present of biological fluids, and show a relatively good selectivity for metal ion binding.

9.28.7.1 Macrocyclic Gd³⁺ Complexes as NMR Contrast Agents

Developments in NMR technology have opened a new diagnostic technique of NMR tomography. Differentiation between healthy and pathological tissues becomes possible, since the relaxation time of the water protons in the two kind of tissues is dissimilar <57JCP(27)572>. The differences in relaxation time may be enhanced through the use of paramagnetic compounds, such as Mn²⁺ and Gd³⁺ complexes. Beside the open-chain ligand diethylenetriamine pentaacetic acid (DTPA), cyclic

compounds derived from [12]N₄ such as DOTA (**13**), DO3A (**60**; R = CH₂COOH), and other derivatives seem to be ideal chelators for Gd³⁺ <86MI 928-02, 88MI 928-02>. They are not toxic, have high stability constants, and are highly inert towards dissociation.

The interest for such compounds is well documented also by the large number of patents, which have appeared <84FRP2539996, 88EUP0287465, EUP0292689, EUP0305320>.

9.28.7.2 Antibody Labeling with Functionalized Macrocyclic Metal Complexes

The idea to label monoclonal antibodies with macrocyclic metal complexes takes advantage from the fact that several isotopes can be used. So ^{99m}Tc, ¹¹¹In, ⁶⁷Ga, ⁵⁵Co, and ⁵²Fe are ideal for diagnostic applications whereas ⁹⁰Y, ⁶⁷Cu, ¹⁸⁶Re, and ¹⁸⁹Re can be used for therapy <90CBR942, 90MI 928-01>.

The process of antibody labeling consists of three steps: (i) a functionalized azamacrocycle must be developed to coordinate the specific isotope; (ii) the macrocycle or its metal complex must be covalently attached to the antibody; and (iii), the medical application must be tested. Hereby several points must be fulfilled. As for NMR contrast agents, the macrocyclic metal complex must be thermodynamically and kinetically stable so that no dissociation or transmetallation occurs in the body of the patient. The covalent bond between the macrocycle and the antibody must be stable against enzymes which can break it. Finally, the modification of the antibody should not be to drastic as to deactivate it.

Several attempts have been made with triaza- as well as tetraazamacrocycles, which are either *N*- or *C*-functionalized for the attachment to the antibody <90CRV271>.

9.29

Ten-membered Rings or Larger with One or More Oxygen Atoms

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9.29.1 INTRODUCTION

The standard arrangement in 12 sections could not be applied in this chapter. The large number of described compounds (over a hundred), their large diversity, and the limited amount of published information likely to be introduced in the various sections prevented presentation in the prescribed order. All the mentioned compounds have been “designed” for a specific purpose (recognition in most of the cases), therefore the authors efforts were mainly concentrated on this aspect. This chapter will reflect this orientation.

The discovery of crown ethers by Pedersen in 1967 opened one of the largest field of research in chemistry up to 1995 <67JA7017, 88AG(E)1021>. This discovery was the spark for the emergence of the concept of “molecular design” introduced by Lehn <73MI 929-01> which, by the virtue of chemist’s

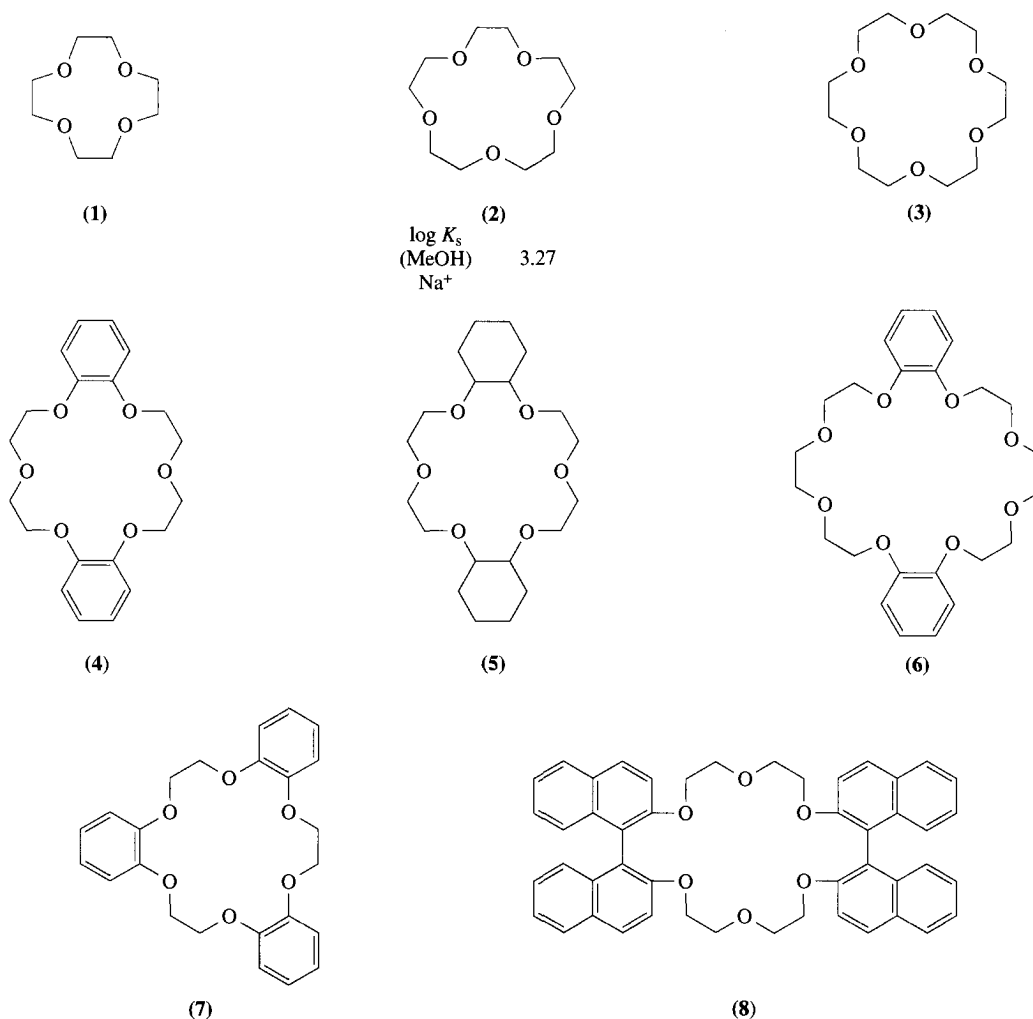
imagination, led to the foundation of a large variety of new classes of compounds all of macro(hetero)cyclic or macropoly(hetero)cyclic type: cryptands, spherands, cavitands, speleands, calixarenes, cyclidenes, cryptophanes, sepulchrates, etc.

The aim of the design was to obtain systems (receptors) able to recognize defined species (substrates) which may be cations, anions, or neutral molecules. A further step in sophistication was the design of systems able to achieve self-assembly, self-organization, or self-recognition <88AG(E)89, 90AG(E)1304, 91NJC153>.

All the above described processes being based on weak interactions, the whole area was designed as "supramolecular chemistry" <B-95MI 929-01>, in other words a coordination chemistry not limited to metal-ion coordination but extended to all types of intermolecular associations <B-92MI 929-01, 93CRV847, B-94MI 929-01, 94PAC1961>.

According to its title, this chapter should contain: (i) an updated treatment of the compounds described by Anastassiou in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(7)709>; (ii) a description of the numerous natural (and synthetic) macrocyclic lactones like the macrolides antibiotics <B-87MI 929-01, 91TCC107, 95CRV2021>, the bioactive marine macrolides <95CRV2041>, the bolaamphiphiles <86ACR130>, etc.; and (iii) the crown ethers. However, even restricted to the crown ethers (roughly 10000 references and several hundred reviews), space imposes drastic limitations.

The fundamental aspects of crown ethers (and cryptands) have been pertinently reported by Hamilton in CHEC-I <84CHEC-I(7)731>; some of the compounds which were discussed in this chapter are the crown ethers (1)–(8).



The preamble to this chapter is absolutely necessary for a reader not familiar with the field, since there is no room here to repeat its basics. Many books and reviews have appeared on crown ethers <74CRV351, B-78MI 929-01, B-78MI 929-02, B-79MI 929-01, B-79MI 929-02, B-81MI 929-01, B-82MI 929-01, 85CRV271,

B-87MI 929-02, B-87MI 929-03, B-89MI 929-01, B-89MI 929-02, B-90MI 929-01, 91CRV1721, B-91MI 929-01, 92CRV543, 92CRV1261, 94CRV467). The 11-volume series entitled *Comprehensive Supramolecular Chemistry* constitutes the largest survey of the field, in particular the numerous aspects of crown ethers are treated thoroughly (B-96MI 929-01).

This chapter focuses on the aspects which could not be described in CHEC-I and depicts the new trends which have been developed since the mid-1980s. Mention is also made of applications of this class of compounds. Other chapters of this volume are devoted to: ten-membered rings or larger with one or more sulfur atom (Chapter 9.30), ten-membered rings or larger with one or more nitrogen and oxygen and/or sulfur atoms (Chapter 9.31), ten-membered rings or larger with one or more oxygen and sulfur atoms (Chapter 9.32); this contribution will treat only the oxygen-containing macrocycles. This separation may not be totally satisfactory for both the author and the reader, but the abundance of publications imposes this choice.

9.29.2 CROWN-RELATED MACROCYCLES

Since the beginning of crown ether chemistry it has been realized that the nature of the organic framework has an influence on the binding properties of the ligand. The macrocycles (4), (5), and (7) may all be considered as derivatives of (3), but they exhibit different cation binding capabilities and various solubility properties and therefore different cation extraction capacities. Many derivatives of this type have been described. Solubility enhancement in organic solvents has also been obtained with macrocycles bearing hydrocarbon side chains. The introduction of chiral units leading to chiral crown ethers has been actively studied.

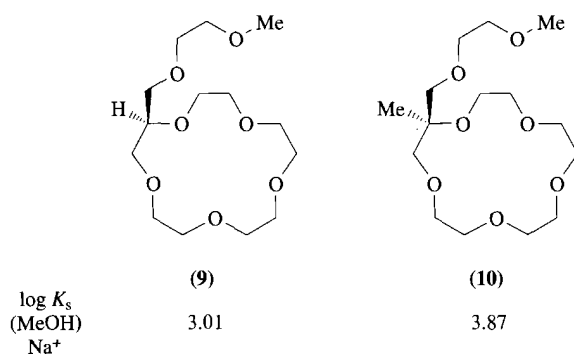
Binding properties have been improved by the introduction of side-chain containing binding sites; this class of compounds was named "lariat ethers". Crown ethers may also contain arms bearing photosensitive groups, switchable units, or functionalized groups which allow coupling with other entities like polymers or biological materials. A close look at most of the described crown ethers reveals that most of them belong to the "armed" crown ethers class of compounds, i.e. they combine complexation properties provided by the central core and additional characteristics given by the appendage.

9.29.2.1 Armed Crown Ethers

The definition of "armed crown ether" is self-evident and covers all of the crowns containing arms. This definition includes the lariat ethers which are characterized by the presence of binding sites in the arms (96CCR1).

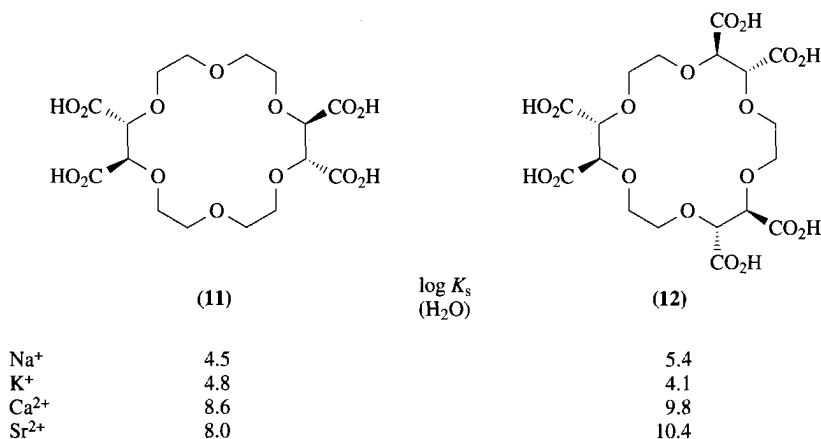
9.29.2.1.1 Lariat ethers containing ethyleneoxy units

The name "lariat ether" was proposed in 1980 by Gokel *et al.* for macrocycles bearing a side chain containing donor atoms (80CC1053). Compared with the parent macrocycle containing no extra donor sites, enhancement of the cation binding properties was generally observed with this new type of ligand. These original compounds were nitrogen-pivot lariat ethers. In order to avoid protonation problems on the nitrogen atom, carbon-pivot analogues, such as (9) and (10), were synthesized and studied. They usually do not present the same attractive improvement of binding strength (compare (9) and (2)) as shown by nitrogen-pivot lariat ethers. But it was discovered that this unfavorable feature can be corrected by the presence of a geminal group, as in (10) (B-90MI 929-02).

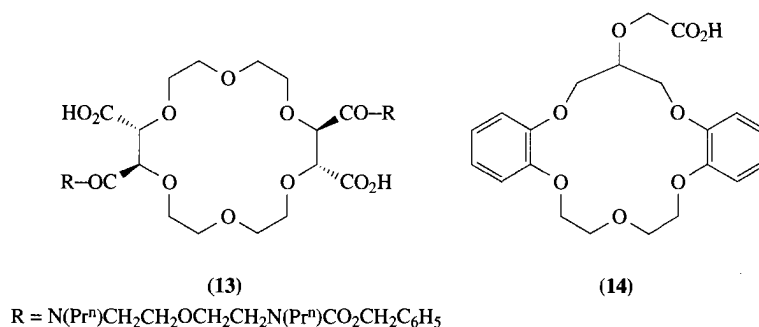


9.29.2.1.2 Lariat ethers containing charged groups

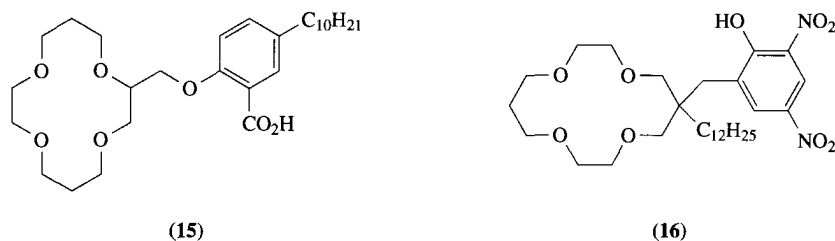
Lariat ethers containing charged sites in the side arms have been described. Two typical examples, (11) and (12), display high complexation abilities toward Na^+ , K^+ , Ca^{2+} , and Sr^{2+} cations as seen in the reported $\log K_s$ values <B-90MI 929-03>.



Regulation by the pH of the $\text{Ca}^{2+}/\text{K}^+$ transport selectivity has been achieved with the dicarboxylic ligand (13); at high pH the dicarboxylate transports Ca^{2+} , whereas at low pH only the monocarboxylate is formed, i.e. the transport of K^+ is dominant in these conditions <83PNA(80)6426>. pH-dependent metal ion selectivity has also been observed with compound (14) <86IC396>.



For several reasons selective complexation of lithium is an important target and many investigations have been performed in this field <91CRV137>. Several charged lariat ethers achieve high extraction or transport selectivity: the Li^+/Na^+ selectivity observed with ligands (15) and (16) is in both cases around 20 <85CC669, 85JA4997>.

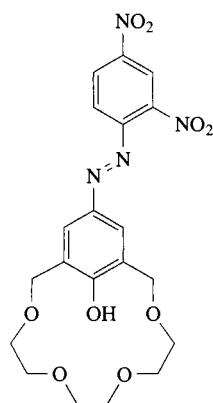


9.29.2.1.3 Chromo- and fluoroionophores

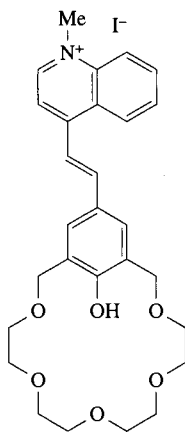
These compounds which combine a crown ether and a chromophoric unit have been largely studied since the late 1970s; the practical possibilities of these systems have been the major stimulus for their development <84TCC67, 85ACR65>. The large majority of these compounds are monoaza

crown ethers, the chromophoric unit being anchored on the nitrogen pivot; but carbon pivots have also been described and a few examples are given here.

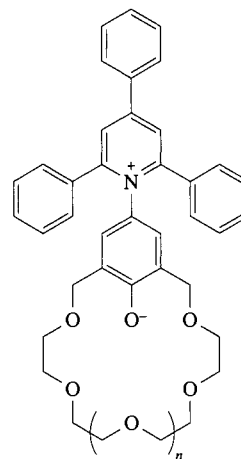
The phenol-containing macrocycle (**17**) gives a yellow solution in chloroform, but in the presence of a lithium salt the color changes to violet; this compound has a high selectivity for this cation <81TL4407, 82CL1781, 85JA4802>. Compound (**18**) strongly binds Ca^{2+} and Ba^{2+} in methanol and gives valuable color changes in the presence of these cations <88CC893>. Other phenol-containing systems have been described; the series of compounds (**19**) show the largest color changes for Na^+ ($n = 0$), K^+ ($n = 1$), and Cs^+ ($n = 2$) <91AG(E)558>. The systems (**17**)–(**19**) are well adapted for the detection of cations in organic media.



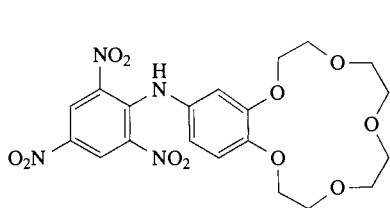
(17)



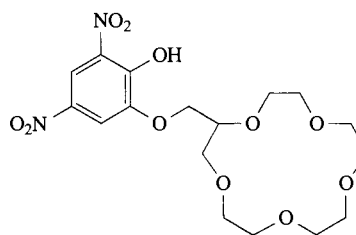
(18)

(19) $n = 0, 1, 2$

Ligands for extraction photometry have also been designed. One of the first examples of this type was (**20**). This picrylamino chromophore is able to extract K^+ (or Rb^+) from water into chloroform, and the color of the chloroform solution changes from orange to blood red. By this method the concentration of salt in the aqueous solution can be measured; other chromoionophores of this type have been described <84TCC39>. Many chromoionophores containing phenol in the side arm have been synthesized and studied. Compound (**21**) is a typical example of this class: this chromoionophore allows efficient photometric determination of Na^+ <84TCC39>. It may be noted that compound (**16**) also belongs to the chromoionophores. A detailed analysis of the way the various types of chromoionophores operate can be found in a review article by Takagi <B-90MI 929-04>.



(20)



(21)

Fluorometry is a very sensitive method and is therefore well adapted for trace analyses. Several types of crown ethers containing fluorescent moieties have been described <B-93MI 929-01>. The fluorescence of compound (**22**) (which is not an armed crown ether but is mentioned here for the sake of consistency) is completely quenched by the Cs^+ cation. By stepwise addition of K^+ (which is not a quencher), the complexed Cs^+ is displaced and a gradual increase of fluorescence is observed leading to a calibration curve for the measurement of K^+ concentration. This type of fluorescent crown ether opens interesting perspectives in analytical chemistry <B-93MI 929-02>. The sodium cation enhances the fluorescence quantum yield of the anthracene-containing system (**23**) by a factor of 15; in addition this compound shows a good selectivity for Na^+ versus the other alkali cations <92CSR187, 93TCC223>. Fluorescent chemosensors containing coumarin, a fluorescent group as in (**24**), have also been studied <B-93MI 929-03, 93PAC447>.

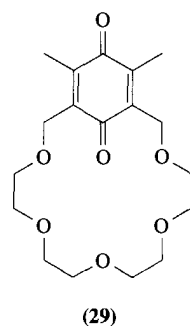
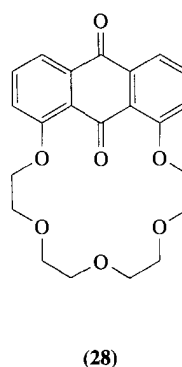
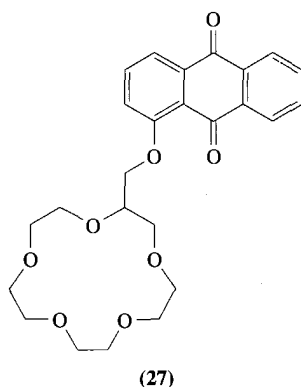


This class of compounds combines a crown ether and a redox-active group. Of special interest are redox units like nitrobenzene and quinone which afford radical anions by reduction. The radical anions may, if located in an appropriate position, contribute to the binding of the crown complexed cation.

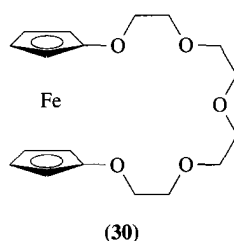


Several quinone-containing macrocycles like **(29)** have been synthesized; electrochemical and in some cases ESR studies have been performed on these compounds (<81TL1619, B-90MI 929-05, 92JA8983>).

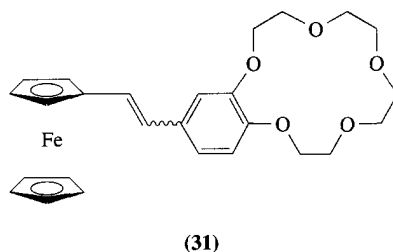
A large variety of ferrocene-containing crown ethers have been described ^{⟨89CSR409⟩}. The ferrocene unit can be easily oxidized to the ferrocenium cation; therefore, if incorporated at an appropriate position in a crown ether, it will result in a decrease of the cation-binding strength as demonstrated in the following example. The ligand **(30)** has been used for the transport of Na⁺ and the concept described above has been applied, but in this case the neutral ligand binds the Na⁺ cation in the source phase and the oxidized form, which has less affinity for the cation, favors the cation decomplexation at the receiving phase ^{⟨86CC716⟩}. In this type of complex the decrease of



affinity of the oxidized form is explained by a through-space electrostatic repulsion between the two positively charged metal centers.



In compound (31) there is a larger distance between the ferrocene redox center and the metal binding site, but the binding of a metal cation is electrochemically recognized via the conjugated alkenic linkage between the benzo crown ether and the ferrocenyl redox center: in the presence of cations (Na^+ , K^+ , Mg^{2+}) shifts of the ferrocene oxidation wave are observed $\langle 89\text{CSR}409, 90\text{IC}378 \rangle$.

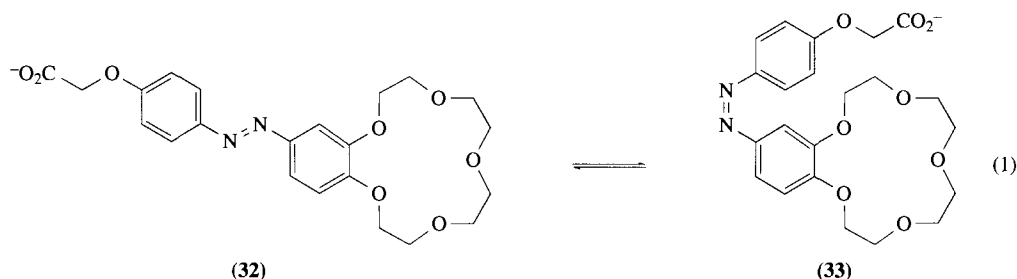


9.29.2.1.5 Photo-switched crown ethers

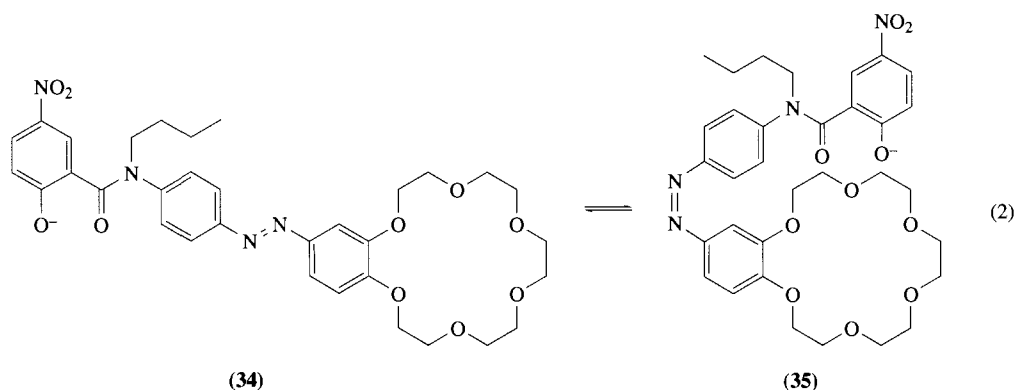
The aim of the design of a photoresponsive crown ether is to control the cation binding capacity of the ligand via a photochemical reaction. Expressed in another way, the photoresponsive crown ether exists in two forms: a basic (stable) one, and a second one which is obtained by light irradiation

of the parent compound. To be of some utility the two forms should present large structural differences leading to significant disparity of their cation binding properties. A further requirement is the reversibility of the system, i.e. the photomodified compound should return easily to the initial form; ideally this back reaction should proceed spontaneously with the switch-off of the irradiation. The *trans*–*cis* (or (*E*)–(*Z*)) photoisomerization of azobenzene fulfills these criteria and has been widely used by Shinkai *et al.* <84TCC67, B-90MI 929-06>.

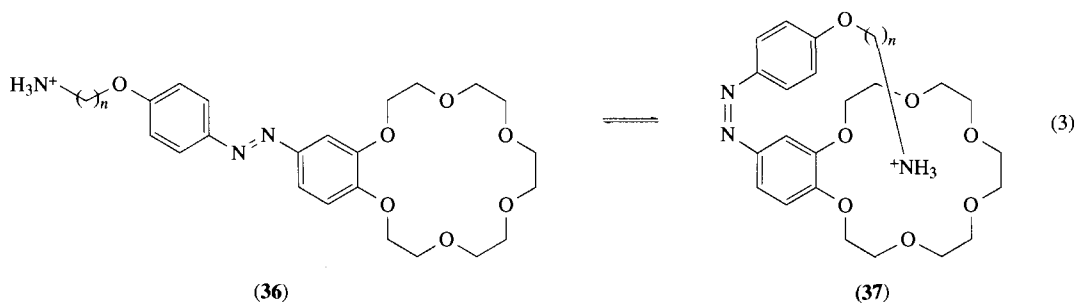
The photoisomerization of (32) gives (33) which extracts K^+ more selectively than (32) (Equation (1)). It was postulated that in (33) the carboxylate anion is located above the crown ether ring and therefore contributes to the binding of the ring-complexed cation; this contribution is supported by a decrease of the rate of the thermal *cis*–*trans* isomerization of the complexes formed with (33) <80TL4463>.



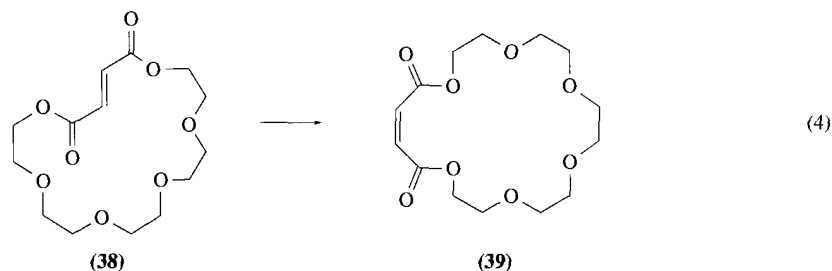
The same lariat behavior was observed with the phenolate-containing ligand (35) obtained by irradiation of (34). The lipophilicity of the ligand (34) allows, under light irradiation, efficient extraction of K^+ , Rb^+ , Cs^+ , and Ca^{2+} . The transport by the ligand (34) of cations between two aqueous phases through an organic phase was also studied. The rates of Na^+ , K^+ , and Ca^{2+} transport were accelerated by UV irradiation. It was also established that the presence of a proton source in the out phase accelerates to a large extent the rate of Ca^{2+} transport (the neutralization of the phenoxide group in (35) favors the release of Ca^{2+} from the complex) <82JA1967>.



Compound (36) and its photoisomer (37) present several interesting features. Solvent extraction experiments have shown that the K^+ extraction capacity of (37) is strongly reduced for $n = 6$ and $n = 10$; this was explained by the intramolecular complexation of the ammonium cation in (37). No such competitive complexation was observed when the chain is too short ($n = 4$). Potassium transport with compounds (36)–(37) was also investigated: the K^+ release at the out phase is favored by the intramolecular ammonium complexation <85JCS(P2)511>.



Enhancement of cation binding by *trans*–*cis* isomerization of a double bond itself contained in the macrocycle has also been considered. The *trans* macrocycle (**38**) very poorly extracts cations, the oxygen atoms being unable to occupy appropriate positions for an efficient binding. By contrast in the *cis* isomer (**39**), obtained by photosensitized isomerization of the double bond of (**38**), it is apparent that the shape of the molecule is similar to the classical crown ethers; therefore this compound exhibits a larger binding ability than (**38**). The *cis*–*trans* reversibility observed with the azobenzene derivatives is not present in this case, both *cis* and *trans* forms being stable <86CL1785>.



9.29.2.1.6 Miscellaneous armed crown ethers

Each of the various classes of armed crown ethers described above contains a large number of representatives and all of them are permanently enriched by new related derivatives. Several less abundant types of arm-containing crown ethers have been described.

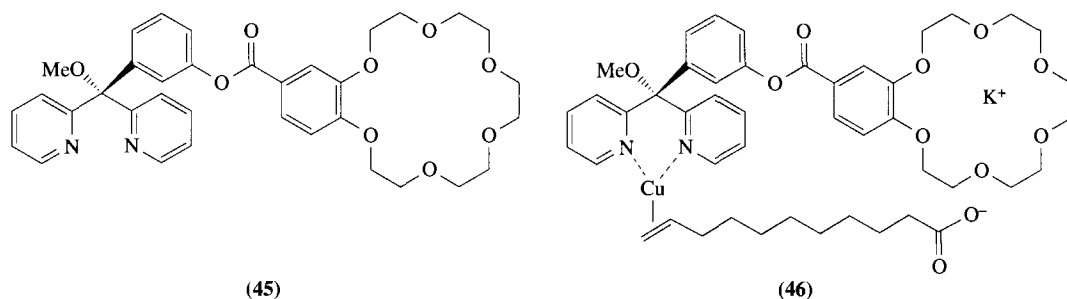
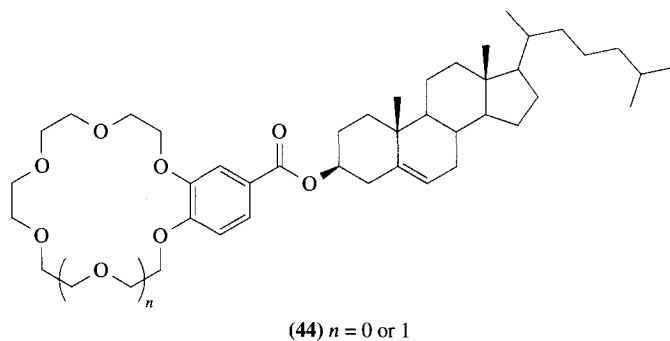
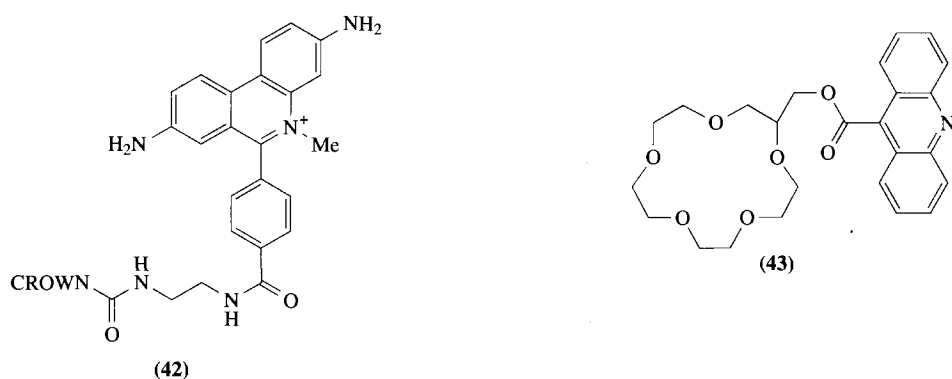
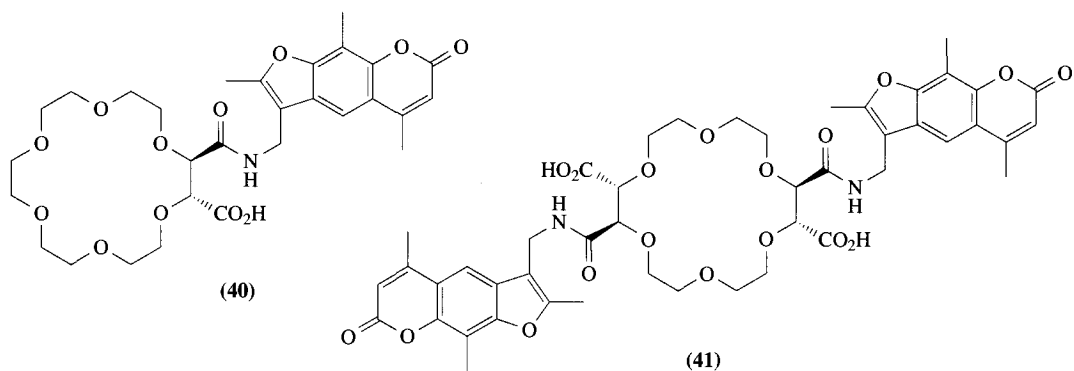
Design of DNA intercalating agents is a field of high interest. Some studies oriented toward this goal have shown that in bis-intercalant molecules the rigidity of the chain linking the two intercalating units has a positive effect on the binding efficiency of the bis-intercalant to DNA. Based on these observations, compounds (**40**) and (**41**) containing psoralen units have been designed by Basak and Dugas; the linking unit in (**41**) is the semi-rigid crown ether backbone. It has been found that good binding properties are obtained with the mono-substituted crown (**40**), but the bis-*syn*-psoralen derivative (**41**) does not exhibit the expected binding ability. This nonperformance was explained by an efficient stacking between the two psoralen rings. Mono- and bis-methidium crown ethers have also been synthesized (compound (**42**)); the same behavior as in the psoralen series was observed <86TL3>. The acridine-containing macrocycle (**43**) has also been designed as a DNA intercalator. It has been shown that the DNA-binding properties of this compound is controlled by the nature of the metal ions: the DNA-binding affinity of (**43**) increases in the order $K^+ > Na^+ > NH_4^+ > Li^+$ which is the order of metal complex stability of 15-crown-5 in methanol. The increase of the binding affinity can be rationalized by the interaction of the cationic crown ether complex with the anionic sites located on DNA <90CC1028>.

The steroidal crown (**44**) has been incorporated in cholesteric liquid crystals. In the presence of alkali metal cations changes (reflected by a color modification) of the helical pitch of the cholesteric liquid crystals are observed. The largest changes are observed with K^+ (**44**; $n = 0$) and Cs^+ (**44**; $n = 1$) <90CC303>. Owing to the presence of the optically active steroidal skeleton this procedure has been extended to the detection of optically active ammonium ions. In this instance the helical pitch of the cholesteric liquid crystals changes in an enantioselective mode; color changes are observed in some cases allowing a visual detection of chirality <91CC339>.

Dinuclear complexes present many interesting features. Compound (**45**) is an example of a heteroditopic ligand containing both hard and soft binding sites. Heterodimetallic complexes of this ligand can be easily prepared, for example a complex containing a K^+ ion in the crown-ring and $PdCl_2$ bound by the dipyridylmethane unit. Binding of difunctional organic substrates to dimetallic complexes of (**45**) has also been investigated. For instance, the formation of the cascade complex (**46**) has been established <94TL5473>.

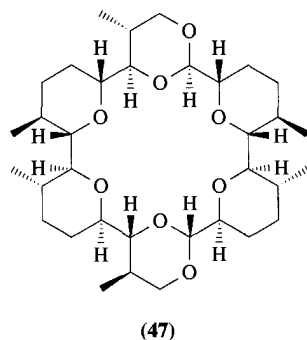
9.29.2.2 Exotic Crown Ethers

In this section some singular crown ethers will be presented. These less-common compounds are the results of the creative faculty of their authors.

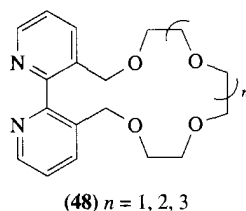


The macrocycle 18-crown-6, structure (3), is a very flexible molecule and its preorganization for binding is relatively poor ^[86AG(E)1039]; as a result a significant energy penalty arises during the complexation process because the ligand has to modify its conformation in order to reach the D_{3d} symmetry observed in most of the cation complexes. Based on a conformational locking mechanism

the rigid 18-crown-6 derivative (**47**) has been synthesized by Li and Still; the rigid structure of (**47**) appears as being frozen in the binding-favorable D_{3d} conformation. As a result, valuable cation-binding enhancements are observed: the ligand (**47**) binds K^+ twice as well as does (**3**), whereas, a 10^3 -fold increase of Na^+ binding was found. The very large increase observed with Na^+ has been explained by: (i) a slightly smaller cavity size in (**47**) compared with the cavity of (**3**); and (ii) the capping of Na^+ by a water molecule as revealed by the x-ray structure of the $NaSCN$ -(**47**) complex <93JA3804>.

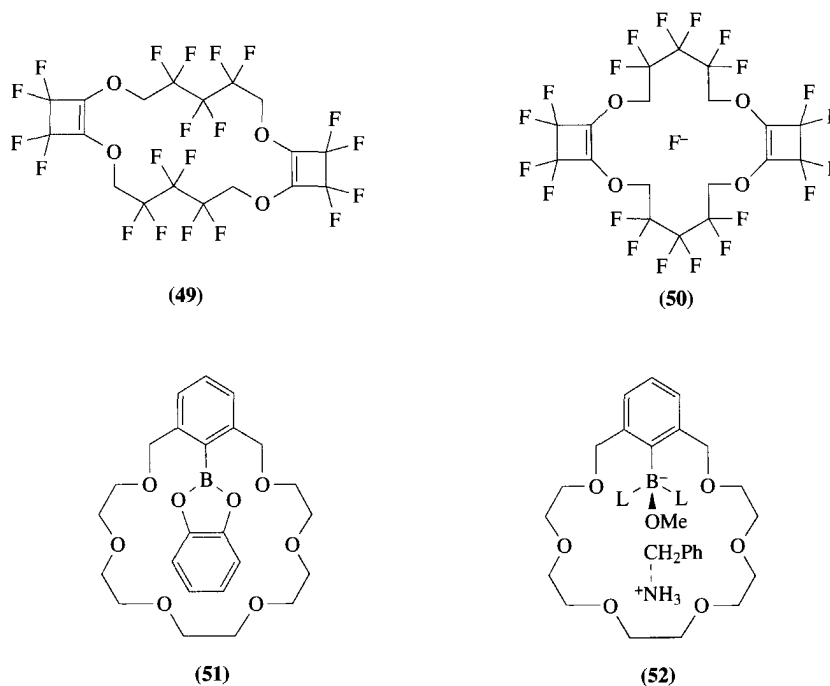


The ligands (**48**) described by Rebek *et al.* possess two binding sites: a crown ether macrocycle for binding of the hard cations, and a 2,2'-bipyridyl unit for the binding of soft cations. The binding at the latter site forces the aromatic nuclei toward coplanarity leading to a restricted conformational mobility of the macrocycle. Allosteric effects were therefore expected for the compounds (**48**) <79JA4333>. This behavior was indeed observed: without metal binding at the bipyridyl unit (**48**; $n = 2$) transports K^+ in preference to Na^+ ; on the other hand in the presence of tungsten tetracarbonyl, which is bound at the bipyridyl moiety, the transport selectivities are reversed <84ACR258>. Platinum complexes of bipyridyl-crown ethers (**48**) present interesting antineoplastic properties analogous to *cis*-platin <94AG(E)186>.



Despite their ubiquitous roles, perhaps due to intrinsic complications associated with them, i.e. hydration energy, large size, numerous geometry (and absence in the periodical table of easy-to-handle electron-acceptor atoms), the recognition of anions by synthetic receptor molecules has not received the same attention as cation complexation <85TCC113, B-91MI 929-02, 93PAC1457, 95TCC101>; in particular neutral hosts for anions are rather rare. Several fluorinated macrocyclic (and macrobicyclic) ethers have been synthesized by Lagow *et al.* <B-94MI 929-02>. The partially fluorinated crown ether (**49**) presents interesting fluoride-binding properties: treated with tris(dimethylamino) sulfonium trimethyldifluorosilicate, (**49**) provides the fluoride complex (**50**). By comparing the molecular shape of (**49**) and (**50**) it is clear that in order to accommodate F^- the ligand has to undergo important conformational changes. The x-ray crystal structure of (**50**) revealed that the anion is held in the cavity by interactions with the four CH_2 groups located in close proximity <90JA7707>.

Ligand (**51**) has been designed by Reetz *et al.* to recognize cations and anions simultaneously: the binding site for the former is the macrocyclic crown ether, the binding unit for the latter being a boron (Lewis acid) center <91AG(E)1472>. The compound (**51**), treated by a 1 : 1 mixture of benzylamine and methanol, affords (**52**); the formation of this anion-cation complex was supported by ^1H , ^{13}C , and ^{11}B NMR investigations and confirmed by the x-ray crystal structure of (**52**). This structure shows: (i) the binding of the methoxide anion by the boron center; and (ii) that the ammonium ion, located inside the cavity, interacts on one side with the ether oxygen atoms, and on the other side forms a hydrogen bond with the complexed methoxide <91AG(E)1474>.



9.29.2.3 Bis- and Oligo Crown Ethers

Interest in this type of complex started in the mid-1970s. The design, by Smid and co-workers, of the first bis(crown ether) <75JA3462> proceeds from the observations that many crown ethers form complexes with two crown moieties per cation: “sandwich complexes”; it was postulated that the connection of the two crown units should improve the stability of the complex. The schematic representation in Figure 1 illustrates the bis(crown ether) complexation process: the two macrocycles connected by a bridge surround the cation. It should be mentioned that the best sandwich complexes are obtained when the cation is too large to fit the cavity; therefore to fulfill this requirement the best macrocycles are: the 12-crown-4 for Na^+ , the 15-crown-5 for K^+ , and the 18-crown-6 for Cs^+ . This active field of research has been extensively reviewed by Izatt and co-workers <94CRV939>.

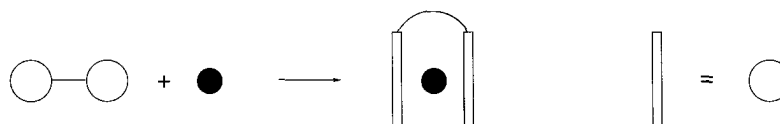


Figure 1 Schematic representation of the cation complexation by a bis(crown ether).

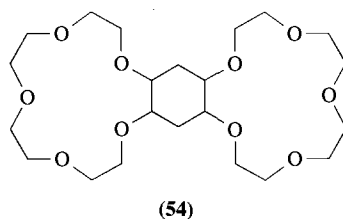
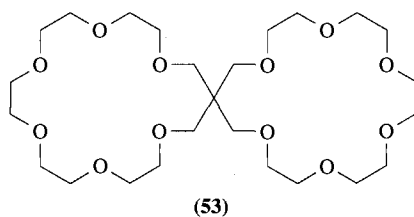
9.29.2.3.1 Bis(crown ethers)

The spiro-bis(19-crown-6) (**53**) binds two Ba^{2+} cations, the crown ether having the appropriate size for this cation <79AG(E)219>. Surprisingly the ligand can also accommodate two Li^+ cations together with water molecules: the x-ray structure shows that in each ring the Li^+ cation is pentacoordinate interacting with three ring oxygens, one internal water molecule (which is hydrogen bonded to two ring oxygens) and one external water molecule. The internal solvation ensures partial filling of the cavity, i.e. a cavity size better adapted to the size of Li^+ <81CC472>.

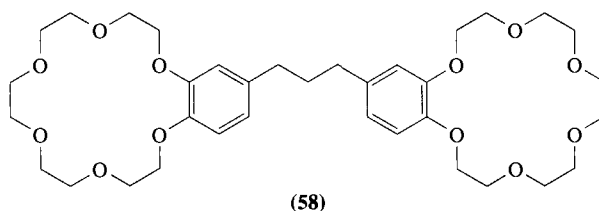
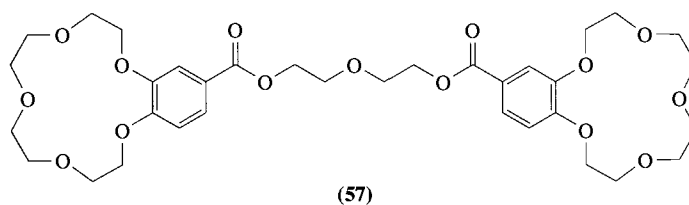
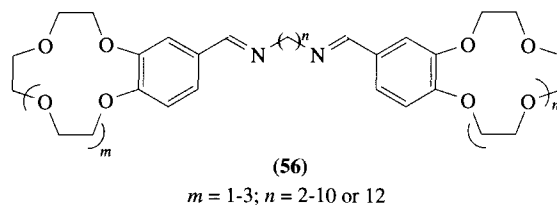
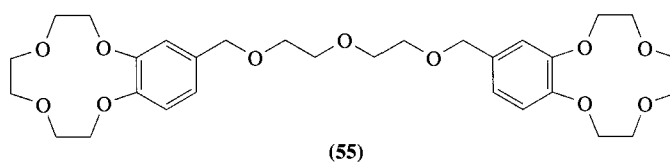
The cyclohexane-containing system (**54**) forms a sandwich complex with K^+ but of 2:2/ metal : ligand stoichiometry, i.e. two molecules of (**54**) coordinate simultaneously the two K^+ cations <83JCS(P2)407>.

Due to their limited flexibility, ligands (**53**) and (**54**) do not form complexes of the type described in Figure 1.

Several hundred bis(crown ether)s of the type (**55**)–(**64**) have been described. The most widely



used macrocycles are the crowns: 12-crown-4, 15-crown-5, and 18-crown-6. The abundance of these compounds originates from the innumerable variety of linkages connecting the two crown moieties. Only a few selected examples are given here.



Ligand (55) containing two 12-crown-4 macrocycles forms sandwich complexes with Na^+ and K^+ ; compared with the monomeric crown ether, (55) exhibits much higher extraction ability $\langle 81\text{JCC}49 \rangle$.

The Schiff-base containing bis(crown ethers) (56) have been synthesized. The interaction of these

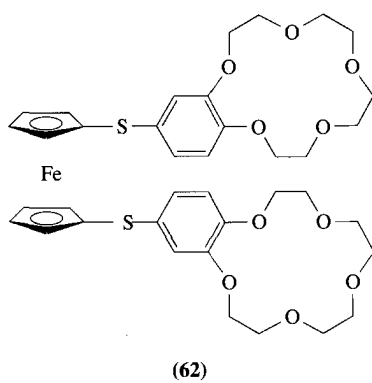
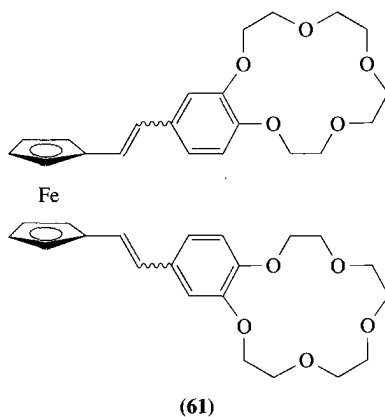
Compound (**57**) was the first described bis(crown ether); compared with the monocyclic analogue, (**57**) is considerably more effective in binding K^+ and NH_4^+ cations. The presence of oxygen atoms in the linkage increases the chain flexibility: replacing the central oxygen by a CH_2 group leads to a five-fold decrease in the formation constant $\langle 75JA3462 \rangle$.

Compound (**59**) is an example of a photoresponsive bis(crown ether) (Equation (5)) (see Section 9.29.2.1.5 on the photoisomerization of the azobenzene moiety). No sandwich complex can be formed with the (*E*)-form (**59**); therefore the two crowns will operate independently and Na⁺, which fits the cavity size, will be complexed by both crown ethers. By contrast in the (*Z*)-form (**60**) the cooperative action of the two crown units can take place and the formation of a sandwich-type complex can be expected with the larger cation K⁺. Results of extraction experiments are in agreement with these expectations: (**59**) extracts Na⁺ 5.6 times more efficiently than (**60**), whereas (**60**) extracts K⁺ 42.5 times more efficiently than (**59**) $\langle 81JA111 \rangle$. Light-driven transport of K⁺ between two aqueous phases through an organic phase has also been studied with (**59**) and (**60**). The highest rate of transport was observed by alternate irradiation with UV and visible light: (i) the UV irradiation isomerizes the (*E*)- to (*Z*)-form, the latter ensures a good K⁺ extraction from the in phase; (ii) the irradiation by visible light isomerizes the (*Z*)- to (*E*)-form, the low affinity of this latter for K⁺ accelerates the K⁺ release from the organic phase to the out phase. In practice the alternate irradiation was achieved in the following way: the half-volume of the membrane in contact with the in phase was irradiated by UV light and the half-volume of the membrane in contact with the out phase was irradiated by visible light $\langle 82JCS(P1)2735 \rangle$.

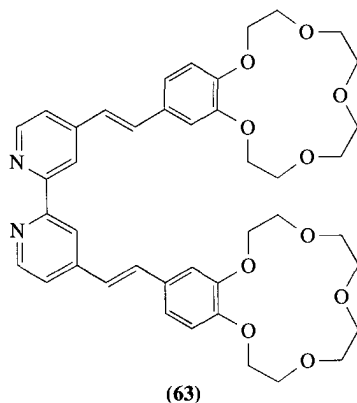


The sulfide-linked ferrocene (**62**) binds Na^+ and K^+ with the same stoichiometry as observed above with ligand (**61**). The electrochemical investigations revealed unexpected and unprecedented results. With Na^+ a positive shift of the redox potential of the ferrocenyl redox couple of (**62**) was observed (binding of Na^+ to the crown ether withdraws electron density from the ferrocene group, resulting in an increase of the oxidation potential); this anodic shift is expected and has been often observed with this type of system. By contrast, in the presence of K^+ a cathodic shift of 60 mV of the ferrocenyl redox couple was observed. This astonishing result was ascribed to the presence of the sulfur atoms: in the sandwich complex formed with K^+ , the two sulfur atoms are constrained to be in close proximity inducing a repulsion of their lone pairs which are compelled to adopt a conformation which forces electron density towards the ferrocene redox center; the oxidation of the ferrocenyl moiety is therefore easier $\langle 93\text{CC1735 \rangle}$.

Ligand (**63**) contains an additional binding site in the connecting bridge, the bipyridyl unit which



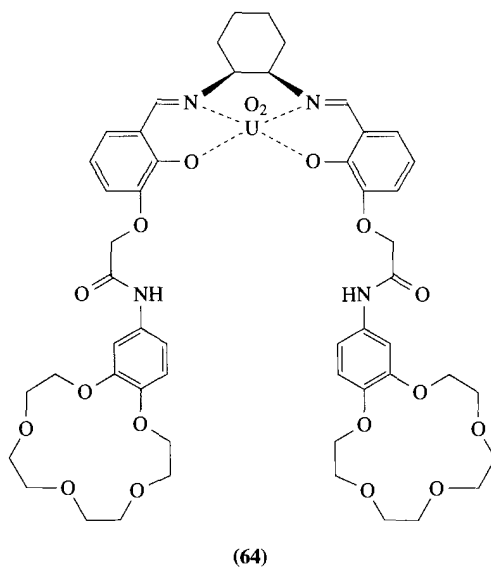
allows the complexation of ruthenium(II). Cyclic voltammetry of (63) and its ruthenium(II) complex was studied <93JCS(F1)333>. (Other features of compound (63) are discussed in Section 9.29.2.3.4).



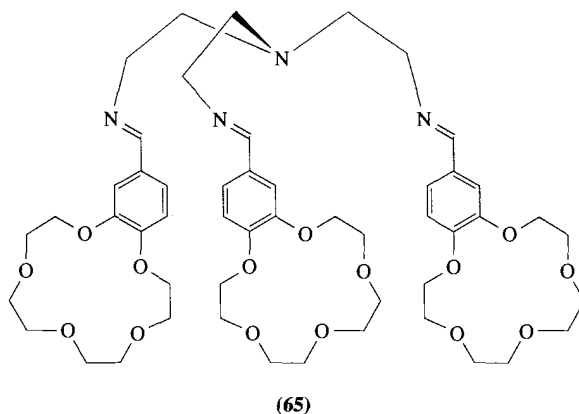
Compound (64) has been designed by Reinhoudt and co-workers for the simultaneous binding of anions and cations. This ligand combines: (i) for the anions, an immobilized Lewis acid binding site (UO_2^+) and additional hydrogen-binding sites provided by the amido units; (ii) for the cations, two crown ether binding moieties. It has been established by several techniques (in particular FAB-MS measurements) that (64) binds the K^+ , H_2PO_4^- salt. Compound (64) is also able to transport this salt through a supported liquid membrane <94AG(E)467>.

9.29.2.3.2 Tris(crown ethers)

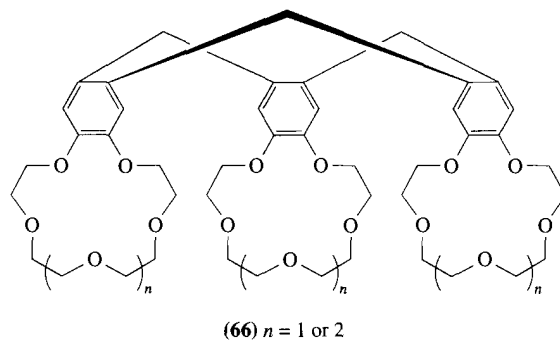
In compound (65) three benzo-15-crown-5 are attached via three imine functions to a tripod unit. A trinuclear sodium complex (3Na^+ , (65)) has been obtained, each crown moiety binding one



cation. A tetranuclear complex (3Na^+ , Cu^+ , (65)) has also been isolated, the copper being complexed by the four nitrogen atoms <88POL2649>.

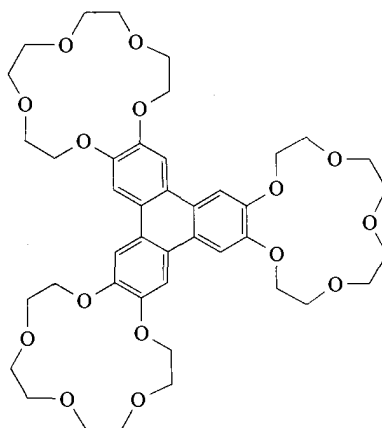


Compounds (66), described by Frensch and Vögtle, contain three crowns attached to the cyclo-triveratrylene unit. Both ligands gave 1 : 3 crystalline complexes: with NaSCN (66; $n = 1$) and KSCN (66; $n = 2$) <79LA2121>.



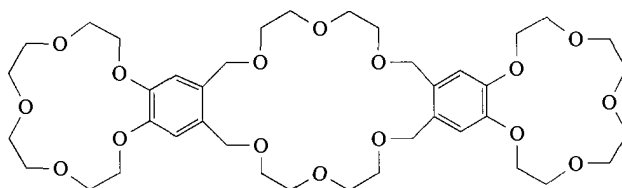
The tris(15-crown-5) triphenylene (67), reported by Simonet and co-workers, has been obtained by an anodic trimerization of benzo 15-crown-5 <87CC984, 89NJC131>. Films of polydibenzo-18-crown-6 were also prepared by electrochemical oxidation of dibenzo-18-crown-6 <85NJC419>. These

films treated with alkali-metal solutions in methylamine afforded polyelectride-like compounds <93NJC201>.



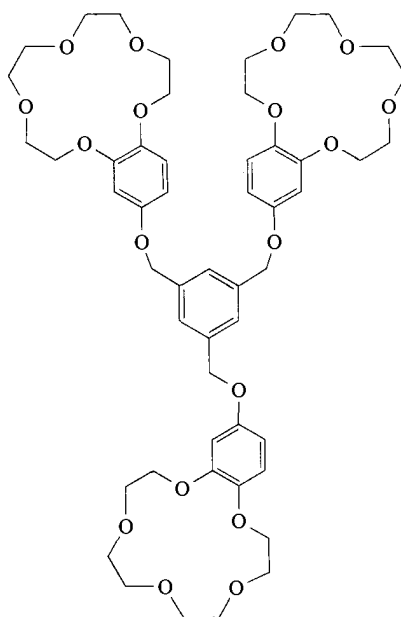
(67)

The triloop (68) forms a trinuclear complex with NaSCN and a more complicated structure with Ba(SCN)_2 : $[(68)]_2[\text{Ba(SCN)}_2]_5$. This ligand displays high extraction ability ($\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$) for the picrate salts of K^+ , Rb^+ , Tl^+ , and Ba^{2+} <90BCJ3670>.



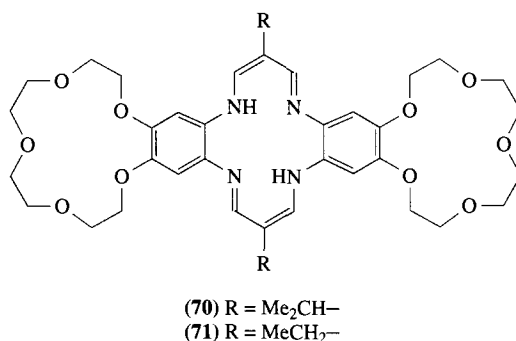
(68)

The tris(benzocrown ether) (69) belongs to a range of related compounds in which the benzocrown units are bonded onto various positions of the benzene ring. Compound (69), as well as other members of this family, exhibits surfactant properties <83AG(E)616>.



(69)

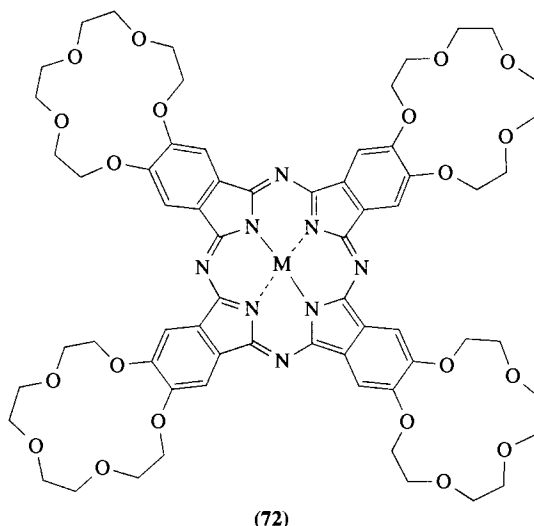
In compounds (70) and (71) two crown ethers are attached to a tetraazamacrocyclic. A simultaneous binding of soft and hard cations was observed with these ligands. Thus (70) forms complexes with Ni(II) and Co(II) and a mixed nickel-potassium complex, [Ni(II), K⁺, (70)], was also isolated; one may notice that surprisingly only one potassium cation is complexed <81CB832>. The structure of this complex was elucidated later with the closely related ligand (71) which complexes Ni(II) and Cu(II) and also forms mixed complexes with several alkali-metal cations. The UV-visible measurements and in particular ESR spectroscopy on the complex [Cu(II), K⁺, (71)] suggest the formation of an axial dimer containing two Cu(II), two K⁺, and two ligands (71) with a structure similar to the 2:2 complex observed with ligand (54) (see Section 9.29.2.3.1) <90ICA123>.



9.29.2.3.3 Tetrakis(crown ethers)

Crown ether-substituted phthalocyanines of the type (72) have been studied by several research groups. These compounds exhibit very interesting complexation properties.

The copper phthalocyanine [Cu-(72)], described by Kobayashi and Nishiyama, has a high tendency to aggregate (this process is favored by some solvents and by several cations). In the presence of K⁺ this process leads to large changes in the absorption spectrum of (72), in particular on the absorbance at 676 nm (corresponding to the monomeric species). This K⁺-induced aggregation can be maintained at concentration of [Cu-(72)] down to 10⁻⁸ M; this means that [Cu-(72)] can be used as a colorimetric reagent for the detection of K⁺ at concentrations as low as 10⁻⁸ M <86CC1462>.



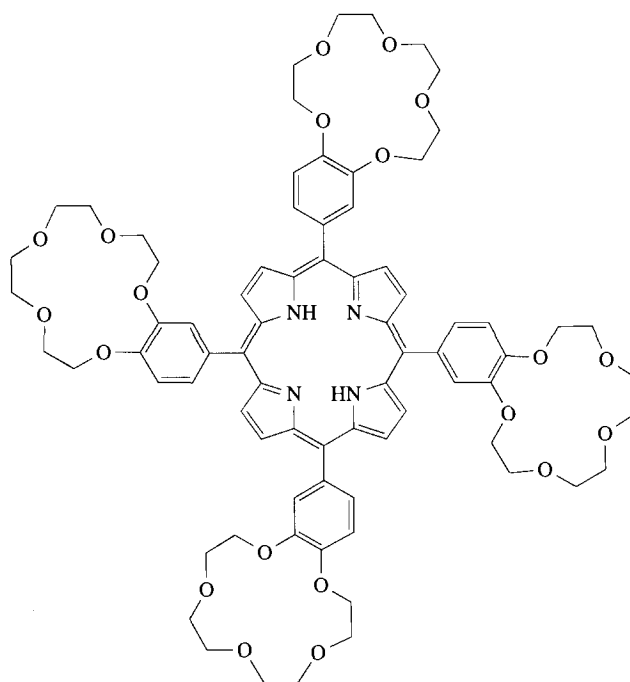
Other studies performed in a different laboratory suggested a K⁺-induced dimerization of [Cu-(72)]. Free energies of complexation for a number of cations by this ligand have also been investigated by the picrate extraction method <86CC1464>.

Metal-free ligand (72) and metal (Cu, Co, Ni, or Fe) derivatives have been subjected to detailed studies. The stoichiometries (established by elemental analysis) of alkali-metal ions binding by the

latter indicate that all four [M-(72)] form complexes of the type [M-(72)-4Na⁺] with the sodium ion and of the type [M-(72)-2K⁺] with the potassium or ammonium ions. By solvent extraction experiments, it was established that the cobalt derivative has the highest affinity for K⁺ among the alkali-metal cations <88JCS(D)401>.

Finally, x-ray determinations at small angles of (72) and [Cu-(72)], by Simon and co-workers showed that the phthalocyanine moieties are superposed in an eclipsed conformation and that the crown ether macrocycles form channels <87CPL(139)362>.

The meso-[tetrakis(benzo-15-crown-5)] porphyrin (73) and its metal (Mg(II), Ni(II), Cu(II), Zn(II), and Mn(III)) derivatives also dimerize in the presence of K⁺, NH₄⁺, and Ba²⁺. It has been established that the photophysical and redox properties of these dimers are different from those of the monomeric porphyrin units <85IC3253>.

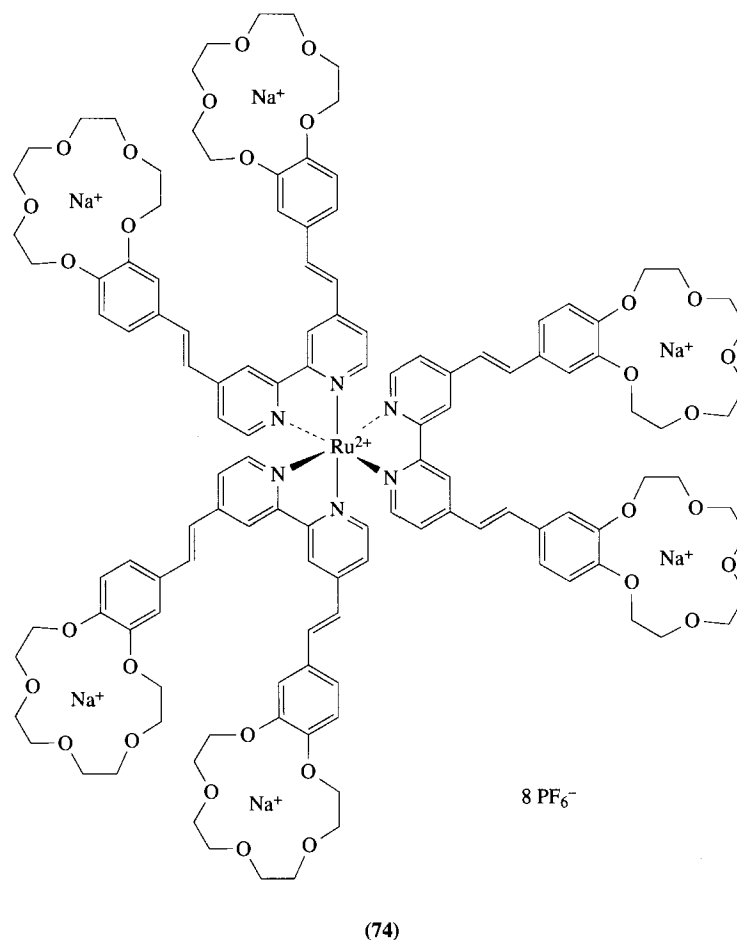


(73)

9.29.2.3.4 Hexa-, octakis-, and higher-(crown ethers)

The spectroscopic, photophysical, and redox properties of the Ru(bipy)₃²⁺ complex (bipy = bipyridyl) as well as its numerous applications have been extensively studied. It was therefore of interest to employ the bipy unit in the building of elaborated systems. The bipyridyl-containing ligand (63) mentioned earlier in this chapter (see Section 9.29.2.3.1), when treated with the appropriate ruthenium salt, affords the complex Ru(63)₃²⁺, which, when treated with excess amounts of NaPF₆ yields the heteropolymetallic complex (74) <91CC1460>. The Ru(63)₃²⁺ complex has been electropolymerized leading to a poly[Ru(63)₃]²⁺ film (for steric reasons better electropolymerizations were obtained with a bipyridyl unit containing only one benzo-15-crown-5 ether substituent). It was expected to use these films to produce surface-modified electrodes for electrochemical recognition of alkali and alkaline-earth cations. Unfortunately, despite the fact that the polymeric film maintains its cation-binding ability as well as the Ru(III)/Ru(II) redox response, this latter is insensitive to changes in the supporting electrolyte. To explain this disappointing observation it has been postulated that in the polymeric film the bound metal cations are too distant from the redox sites <93JCS(F1)333>.

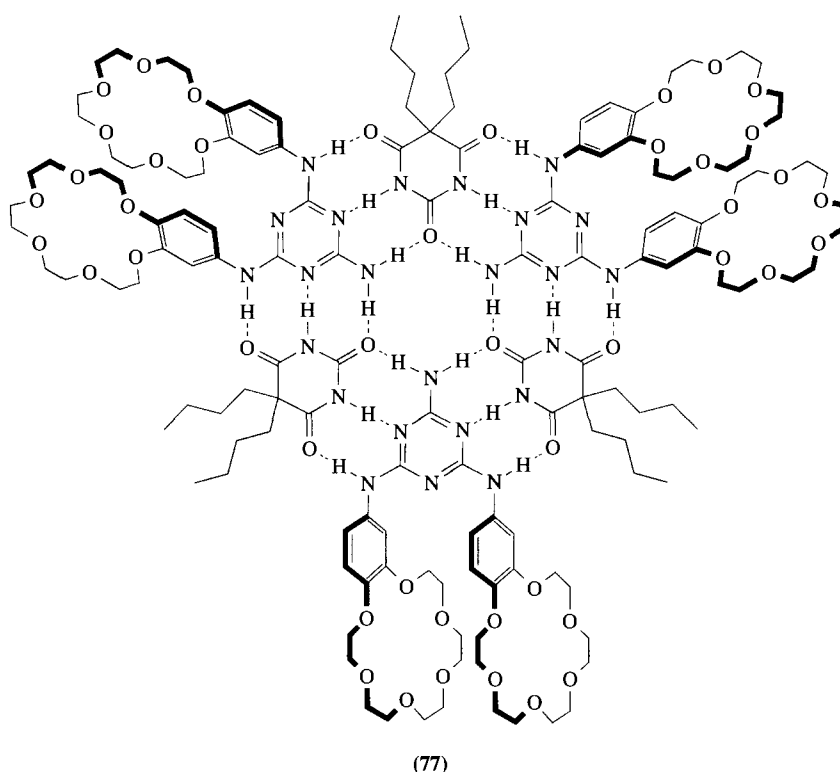
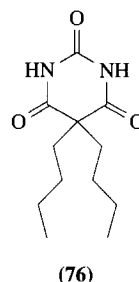
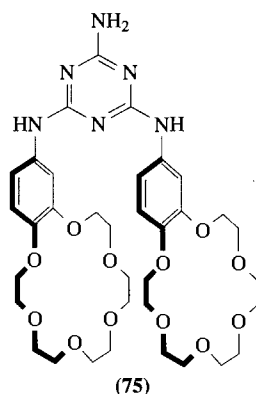
The system (77) containing six benzo-18-crown-6 units was not designed with the aim of obtaining peculiar properties; the purpose was to observe in solution the existence of the hydrogen-bonded supramolecular species formed by self-assembly of the complementary compounds (75) and (76). It



has been established by x-ray crystallography that some triaminotriazine derivatives can form with diethylbarbituric acid macrocyclic assembly of the type shown in the central core of (77) (the name "rosette" was proposed for this class of assembly) <92JA5473>. It was of interest to know if this type of assembly is maintained in solvents of low polarity. Electrospray mass spectrometry (ESMS) is a powerful tool for the characterization of a large range of molecules like proteins, oligonucleotides, polynuclear complexes, etc. But the application of this technique to supramolecular assemblies based on hydrogen bonds is not possible since these architectures are not charged and protonation will disrupt them. By indirect means it was nevertheless possible to fully characterize this self-assembled species. The presence of the benzo-18-crown-6 units, which do not participate in the assembly process, allows the complexation of potassium cations, thus charged species can be formed and detected, demonstrating the existence of the self-assembled species (77) in solution. This new technique, called ion-labeling electrospray mass spectrometry (IL-ESMS), reported by Van Dorsselaer and co-workers, has a promising future <95AG(E)209>.

The octakis(crown-ether) (78) does not present the same changes in absorption spectrum as described above with the tetrakis(crown-ether) (72): in the presence of metal ions (Li^+ , Na^+ , K^+) there was no observable change in the spectrum. It was concluded that K^+ forms an intramolecular sandwich-type complex and not an intermolecular dimer as does (72) <89CB291>.

A poly(isocyanide crown ether) (79) in which R is benzo-18-crown-6 has been synthesized by Nolte *et al.* Its molecular weight was about 15000 which corresponds to 40 repeating crown units. The polymer forms a helix, and this structure leads to stacking of the crown ethers thus forming four channels as schematically represented in Figure 2. The channel compound complexes alkali-metal ions <84IJ297, 94CSR11>. The polymer (79) was incorporated in dihexadecyl phosphate vesicles and transmembranous transport of Co^{2+} was observed. Determination of the ion transport rate as a function of temperature yields the activation energy; its value supports a pore mechanism <85CC1275>.

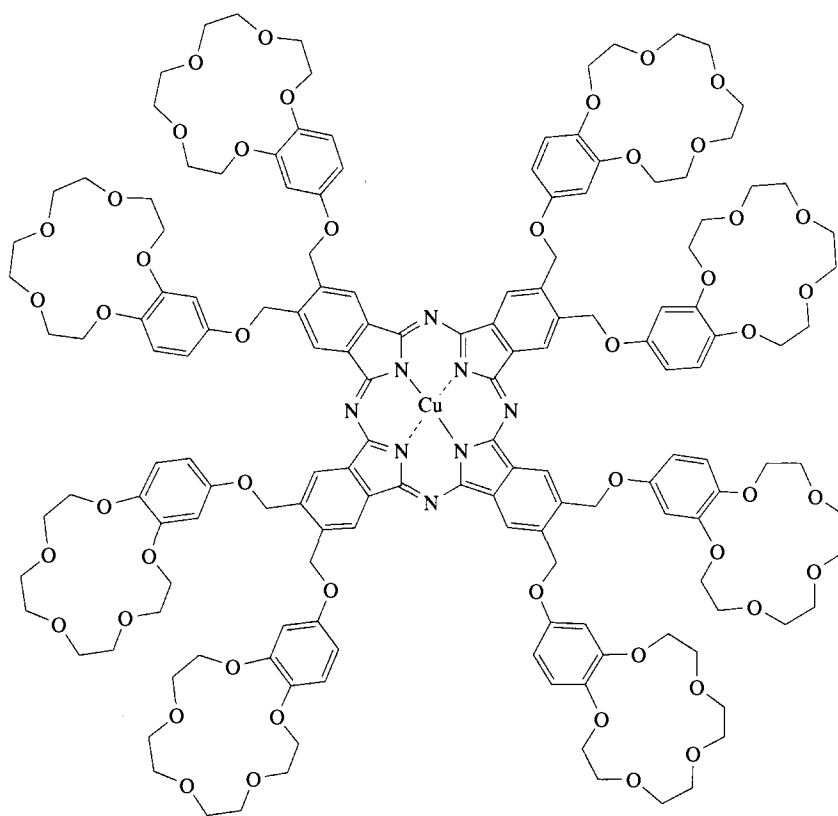


9.29.2.4 Chiral Crown Ethers

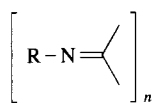
Macrocyclic polyethers of the 18-crown-6 type form complexes with NH_4^+ and primary ammonium salts RNH_3^+ . In the latter case, the charged end is attached to the ligand through a tripod arrangement of $\text{NH}^+ \cdots \text{O}$ hydrogen bonds as represented in (80), the R group being located above the macrocycle <B-84MI 929-01>. It has been realized since the earliest time of molecular recognition that enantiomer selectivity (chiral recognition) may be achieved by the use of chiral macrocycles; to obtain efficient chiral discrimination only one of the two enantiomers in the racemic mixture should be complexed strongly by the macrocycle.

The macrocycle (81), synthesized by Cram and Cram in the early 1970s, contains the appropriate features to achieve this goal: (i) a complexation site ensured by the ether functions; and (ii) chiral barriers conferred by the chiral binaphthyl units. Enantioselective recognition of 1-phenyl-ethylammonium salts was performed with (81) <73JA2692, B-94MI 929-03>.

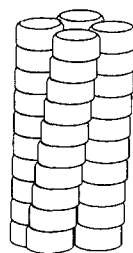
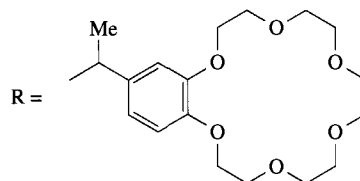
Ligand (82) exhibits improved chiral recognition in complexing amino-acid salts. The two enantiomers (*R,R*)-(82) and (*S,S*)-(82) have found use in the design of an amino-acid resolving machine. Chiral ligand (82) has also been attached to a polymer support, allowing chromatographic resolution of racemic amino-acid salts <B-94MI 929-03>.

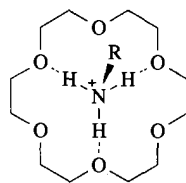


(78)

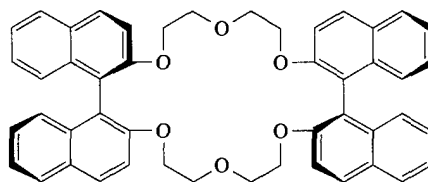


(79)

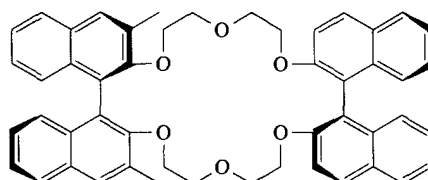
**Figure 2** Schematic illustration of the four channels formed by the superposed crown ethers.



(80)

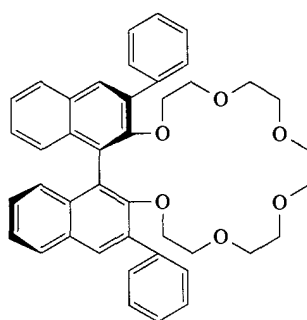


(81)



(82)

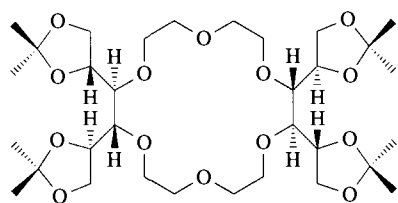
Enantioselective transport of several amino-acids through a polymer-supported liquid membrane containing the chiral crown ether (**83**) has been reported. The best result was observed with the racemic mixture of phenylglycine: the *D*-enantiomer was transported 22.7 times faster than the *L*-enantiomer <85CL1549>.



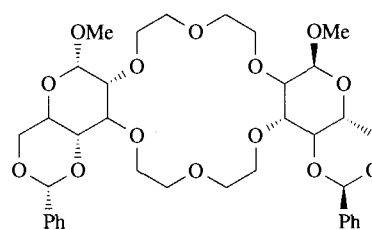
(83)

Compounds (**84**) and (**85**) are examples of a large variety of macrocycles incorporating optically active carbohydrate residues which have been synthesized and studied by Stoddart. Strong binding of ammonium salts has been often observed and chiral recognition was established in some cases <79CSR85, B-87MI 929-04>.

The chiral macrocycle (**86**) (a derivative of the tetracarboxylic acid (**11**), see Section 9.29.2.1.2) incorporated in solvent polymeric membranes, exhibits a preference for the (*R*) over the (*S*)-1-phenylethylammonium ion by a factor of 2.6 <81HCA657>. Based on these results, a cell assembly with two membranes each containing an enantiomer of (**86**) (*RRRR* or *SSSS*) has been devised.

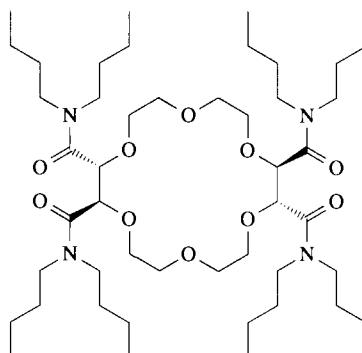


(84)



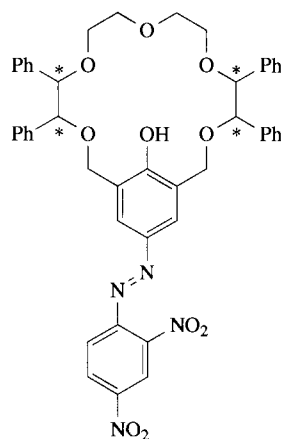
(85)

The direct potentiometric determination of the enantiomeric excess of 1-phenylethylammonium ions in aqueous solutions was achieved with this equipment <84HCA1439>.

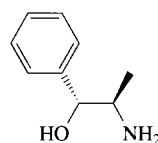


(86)

The two enantiomers (*RRRR* and *SSSS*) of the chiral azophenol crown ether (**87**) have been designed to achieve enantiomeric selective coloration with chiral amines. Studies of complexation of the (*RR*)-norpseudoephedrine (**88**) by the two enantiomers revealed that the binding of the substrate was more efficient with (*SSSS*)-(**87**) than with (*RRRR*)-(**87**). In addition, over a certain range of concentration of (**88**), a color change from yellow to reddish violet was observed with (*SSSS*)-(**87**); whereas no such color change was detected under the same conditions with the (*RRRR*)-(**87**) enantiomer, i.e. the expected enantiomer selective coloration was achieved <93TCC163>.



(87)



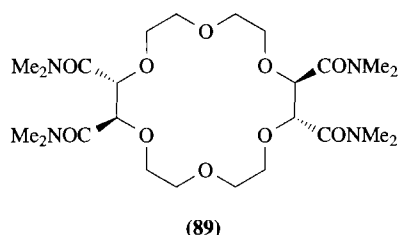
(88)

9.29.2.5 Synthetic Ion Channels

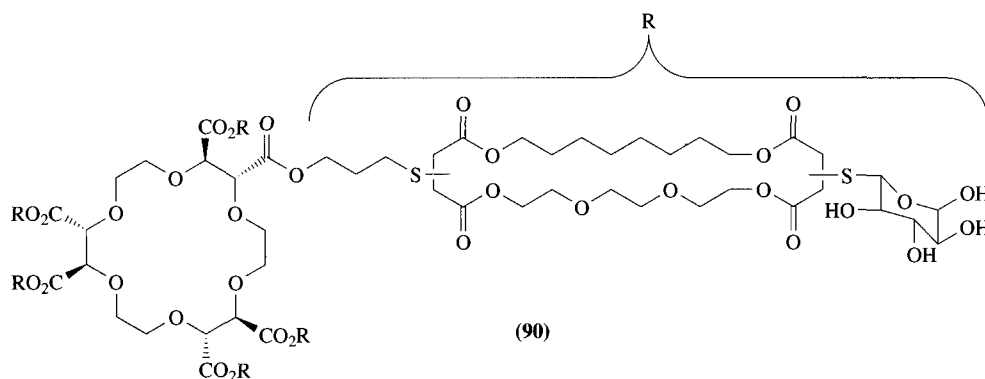
Cell membranes, consisting of lipid bilayers of low dielectric constant, present a high barrier to ion penetration. In natural systems, two processes lead to the lowering of this barrier to ion

penetration. The first one involves a "carrier" which: (i) forms a complex with the ion to be transported; then (ii) diffuses across the membrane; and (iii) ultimately releases the ion into the receiving aqueous phase. The second one occurs via formation of a transmembrane "channel". Natural antibiotics provide representative compounds of the two classes: (i) valinomycin, nonactin, enniatin, etc. are typical examples of ion carriers; (ii) gramicidin, alamethicin, and suzukacillin are specimens of channel forming antibiotics. Among the various differences between carrier molecules and channel forming species the most important one (in biomimetic or abiotic synthetic perspectives) concerns the "size" of the systems: while the molecular weight of carriers are in a medium range (a few hundred to slightly above a thousand), the molecular weights of the "active channels" are rather high (several thousand). These high molecular weights are easy to explain: the overall length of the channel has to be large enough to span the membrane which has a thickness in the range 40–50 Å. Many artificial carriers have been synthesized and studied; several examples have been provided in some of the previous sections. By contrast, the field of artificial channels has been only poorly explored because of the molecular weight problem mentioned above. Indeed, it has been estimated that a channel consisting of face-to-face connected crown ethers would have a molecular weight slightly above 4000 g mol⁻¹ <93SL449>. The synthetic problems (number of steps, purification, and characterization of the compounds) have apparently discouraged people from entering the field of artificial channel-type molecules.

An early approach by Lehn and co-workers was suggested by the x-ray structure of the potassium complex formed with the 18-crown-6 tetracarboxamide (**89**) which revealed: (i) a channel-like packing of the macrocycles; and (ii) that half of the complexed potassium ions are bound in the plane of the macrocycles, while the other half are located between two successive macrocycles. This structure was considered as a solid-state model of a channel <82NAT526>. Based on these observations, the synthesis of a channel formed by several face-to-face connected crown ethers was attempted <85TL215, 88CJC195>.



Fyles and co-workers designed and synthesized the artificial channel (**90**) as well as many other related structures. This channel (see the schematic representation in Figure 3) is formed by the following parts: (i) a central core containing two sets of three carboxy groups pointing in directions perpendicular to the mean plane of the macrocycle (three on the left side from the macrocycle, three on its right side); (ii) six wall units fixed on the central core; these units contain polar and apolar functionalities in order to provide oxygen sites for the binding of the cation and polymethylene chains for favorable interactions with the lipidic membrane, respectively; and (iii) hydrophilic head groups giving an amphiphilic character to the molecule <93SL449>. An impressive total of 35 structures containing a large variety of central cores, walls and head groups have been synthesized. Efficient transport of cations was observed with some of these compounds, in particular (**90**). By comparison with a known channel (gramicidin) and carrier (valinomycin), a channel-like mechanism has been established for some of these compounds <93SL449>.



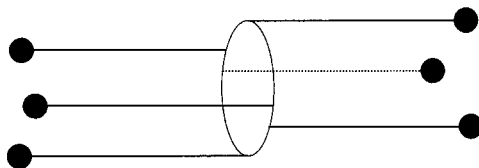
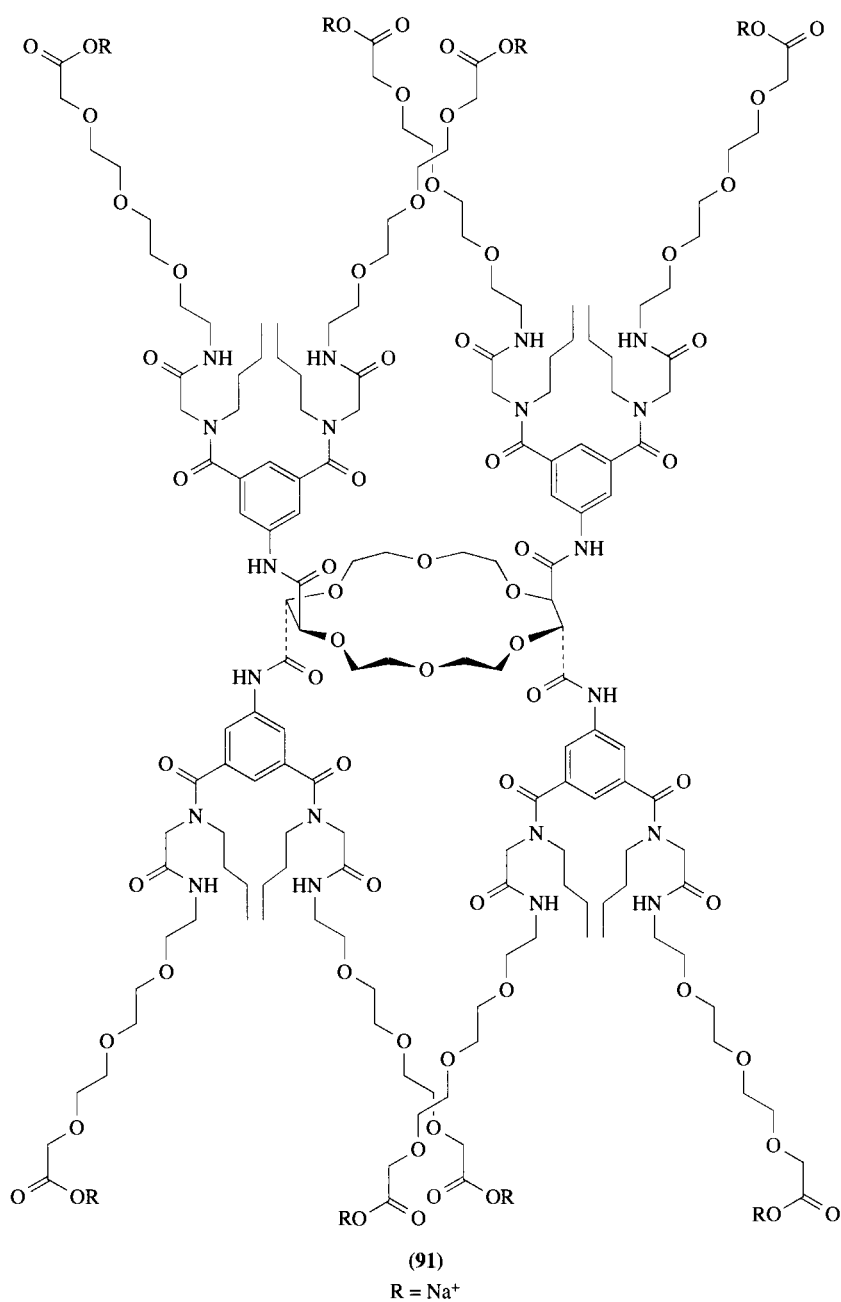


Figure 3 Schematic representation of the channel formed by compound (90).

The compound (**91**) (nicknamed “bouquet”) described by Jullien and Lehn constitutes a different approach to a molecular channel <92MI 929-02>. The molecule contains: (i) a tetrafunctionalized central core; (ii) long oxygen-containing chains, which provide binding sites for the metal cations; (iii) *n*-butyl groups, which ensure compatibility with the lipidic membrane; and (iv) terminal carboxylate groups, which will be located at the water-membrane interface and contribute to the transmembrane orientation of the molecule.

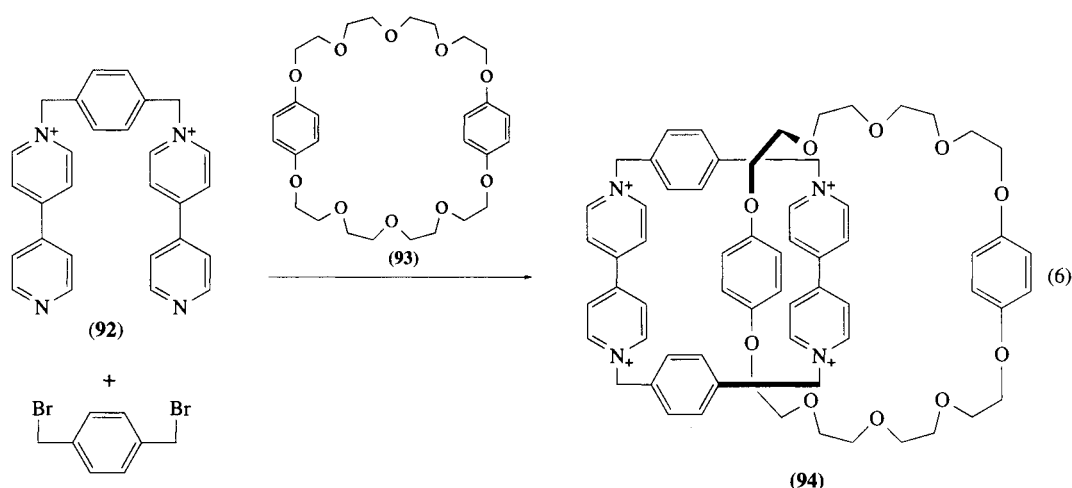


The bouquet (91), incorporated into a phospholipid membrane of liposomes, increases the permeability of the membrane to Na^+ and Li^+ . The ion transfer proceeds via a cation–cation antiport mechanism which has been established by ^{23}Na and ^7Li NMR spectroscopy (92AG(E)1637). The incorporation of the bouquet molecule into several vesicular systems has been monitored by numerous techniques (UV, NMR, and CD spectroscopies, differential scanning calorimetry). It was concluded that different modes of incorporation take place and that several orientations of the bouquet coexist in the membranes (93JCS(P2)1011).

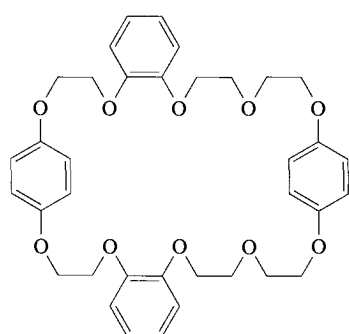
9.29.2.6 Catenanes and Rotaxanes

The possibility of forming interlocked rings, i.e. catenanes, was thought about in the early 1900s, but it was only in the 1960s that the first synthetic attempts were performed. Various synthetic routes were explored by several groups: (i) statistical threading; (ii) metathesis of cyclic dialkene; and (iii) directed step-by-step synthesis. Despite the creative imagination of chemists engaged in this quest and their efforts (in particular by Schill whose step-by-step approach is a masterpiece (B-71MI 929-01), the amount of obtained catenane was either very poor or in the best case rather minuscule (for a detailed history of the development of the catenane field see (B-91MI 929-03)). A major breakthrough was accomplished in 1983 by Dietrich-Buchecker *et al.*; their synthetic strategy was based on a 3D template effect induced by a transition metal cation. This self-assembly process (91NJC153) induces favorable positions of the reactants and therefore significant yields may be expected; indeed the first [2]-catenane was obtained in four steps with an overall yield of 14% (83TL5095). Because of the presence of a cation template, the compound formed is a complex of the catenane, i.e. a catenate, the free catenane (or catenand) may be subsequently obtained by a demetalation reaction. Since the macrocycles of the latter catenanes contain phenanthroline units, no further comments will be given in this chapter on this class of catenanes (for more information see (90ACR319, B-91MI 929-03)).

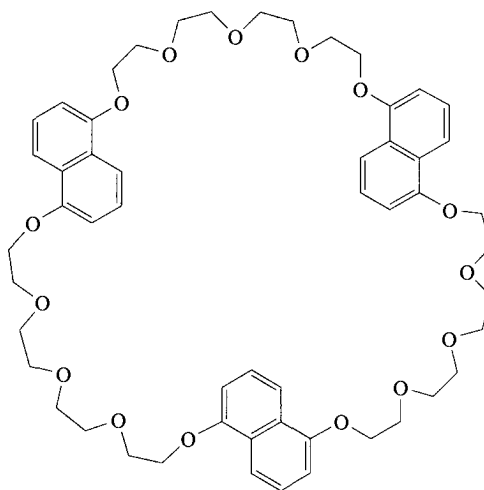
In 1992 Anelli *et al.* developed a template synthesis of catenane based on electron donor–acceptor interactions. The synthesis was accomplished by stirring 1 equiv. of bis(pyridinium) salt (92), 2PF_6^- , 1 equiv. of 1,4-bis(bromomethyl) benzene, and 2.5 equiv. of the bisparaphenylene-34-crown-10 (93) in acetonitrile at room temperature for 48 h; the catenane (94) was obtained with a remarkable 70% yield (Equation (6)) (92JA193). An analogous [2]-catenane was formed with macrocycle (95) (93RTC429). Polycatenanes were also synthesized (94AG(E)433). The macrocyclic polyether tris-1,5-naphtho-57-crown-15 (96) was used to form [3]-, [4]-, and [5]-catenanes (B-95MI 929-02).



The electron donor–acceptor induced self-assembly strategy was extended to the synthesis of rotaxanes. Two methods have been used by Anelli *et al.*: (i) the “threading” approach relies on the inclusion of (98) into the cavity of (97) leading to (99), followed by the attachment of bulky groups

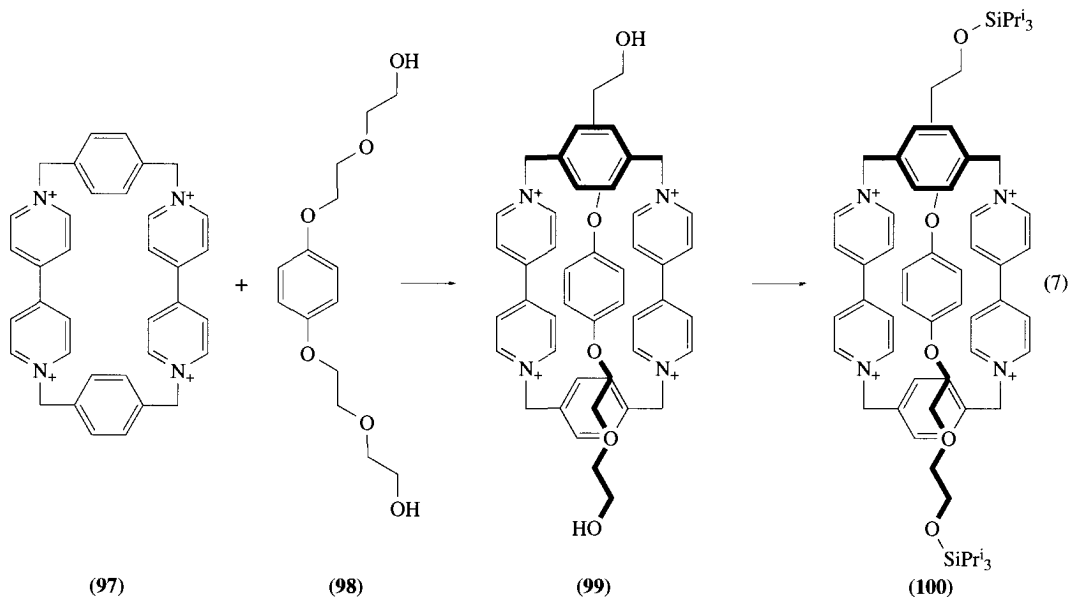


(95)



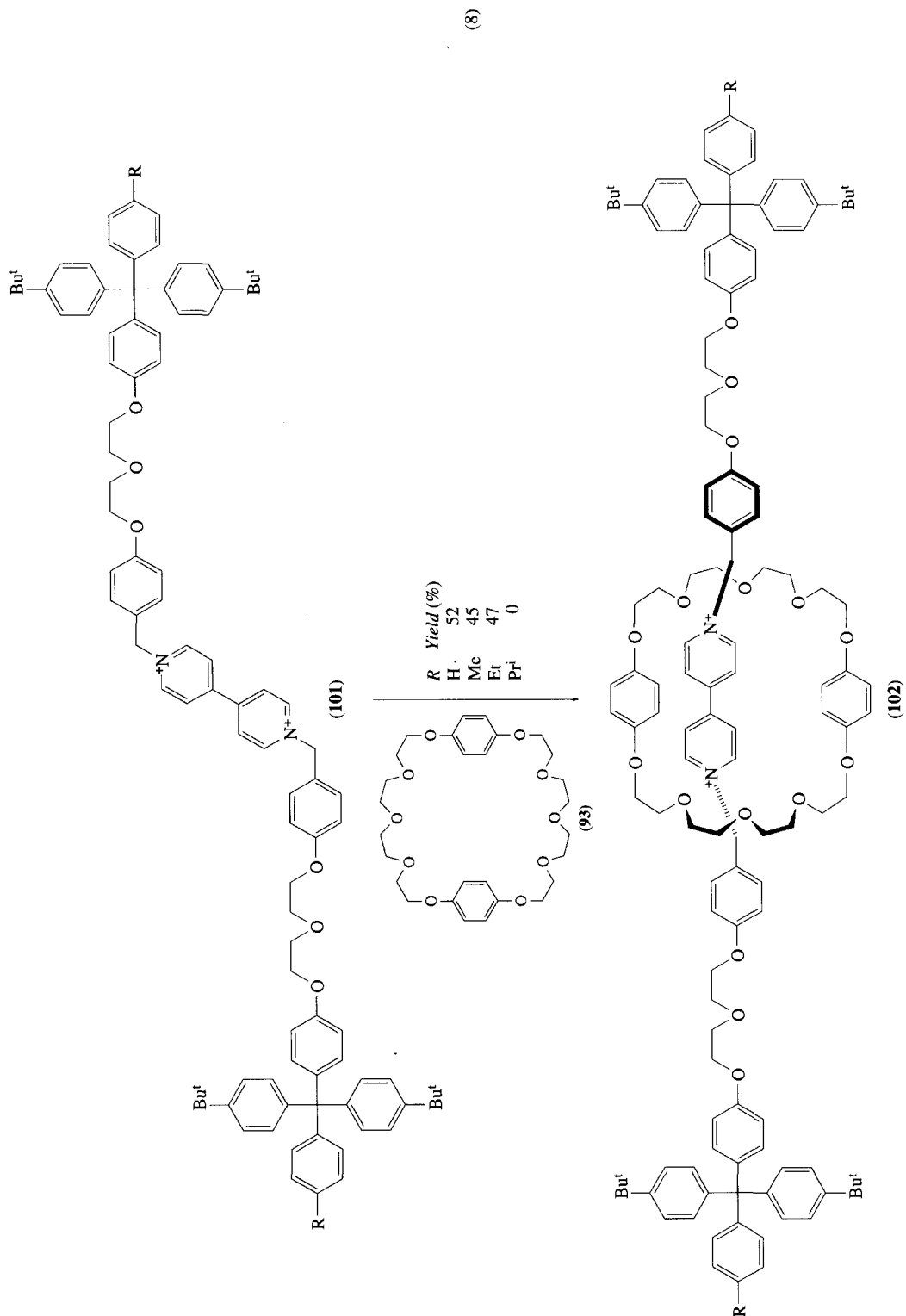
(96)

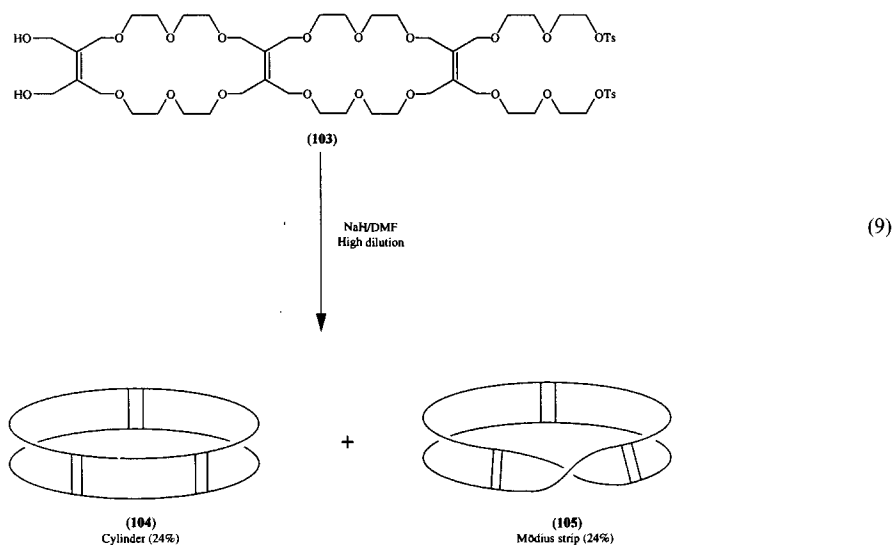
as shown in **(100)** (Equation (7)) <92JA193>; (ii) the second method rests on the “slippage” at elevated temperature (10 days in acetonitrile at 60 °C) of the rotaxane axis **(101)** into the cavity of macrocycle **(93)** (Equation (8)). The complexation of the 4,4'-bipyridinium dication within the macrocycle will raise the activation energy for the reverse process (extrusion) and therefore the rotaxane will be stable at room temperature. As seen in Equation (8), the blocking groups fixed on the rotaxane axis have to be of an appropriate size; if R in **(101)** is too large, this method cannot be used. Appreciable yields (about 50%) were obtained by this strategy <93CC1269>.



To conclude this part, mention has to be given to a Möbius-strip synthesis described by Walba *et al.*. The cyclization, under high-dilution conditions, of the diol-ditosylate **(103)** gave a mixture containing: (i) the cylindrical compound **(104)** and (ii) its topological isomer, the Möbius strip **(105)** (Equation (9)). The formation of **(105)** is explained by a half-twist along the axis of the precursor **(103)** prior to the double-ring closure <82JA3219>. In addition to several physical methods, the Möbius-strip formation was also clearly demonstrated by chemical means: the ozonolysis of **(104)** gave two 30-membered cyclic triketones; whereas due to its intrinsic characteristics (one edge), the Möbius strip **(105)** gave a 60-membered cyclic hexaketone <86T1883>.

An article by Amabilino and Stoddart gives a complete view of all types of interlocked and intertwined systems <95CRV2725>.



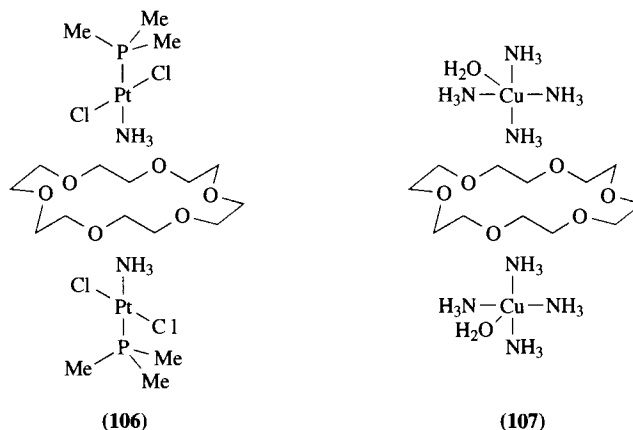


9.29.3 APPLICATIONS OF CROWN COMPOUNDS

In this section, a brief treatment of numerous applications of crown ethers will be provided.

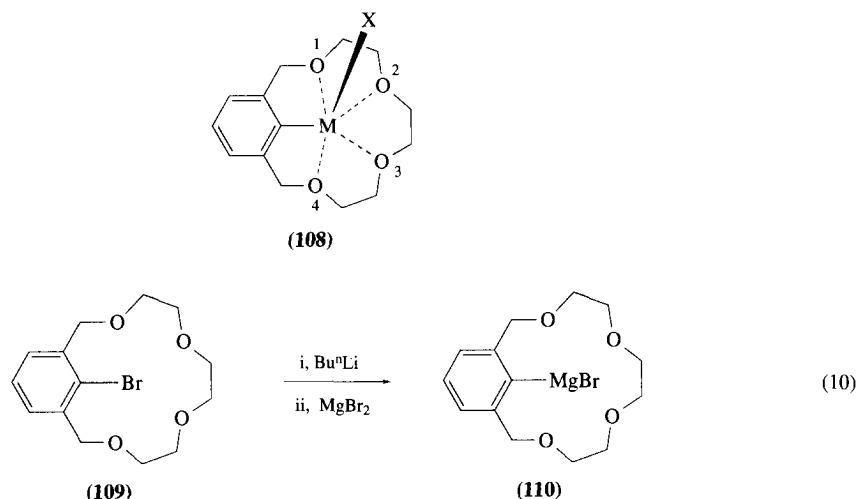
9.29.3.1 Second-sphere Coordination

The binding of a transition metal–amine complex of the type $[L_m, M(NH_3)_n]^{p+}$ by crown ethers has been initiated and largely studied by Stoddart and co-workers (86AG(E)487). It results in the formation of a “complex of complexes”, which contains two levels of complexation: (i) the metal–amine complex, in which the NH_3 is bound to the metal through its lone pair; and (ii) the binding of the complexed NH_3 by the crown ether via three $NH\cdots O$ hydrogen bonds in a similar manner to that described in Section 9.29.2.4 for $R-NH_3^+$ complexation by crown ethers. As a result the ammonia occupies the first coordination sphere of the metal and hence the macrocycle occupies the second one. Species like (106) and (107) are typical examples of second-sphere coordinated transition metal complexes. In (106) a stoichiometry 1 : 2 ligand/substrate was observed; whereas in (107) the presence of four NH_3 molecules in $[Cu(NH_3)_4(H_2O)]$ allows the formation of a linear polymeric structure. An interesting practical aspect was revealed by the treatment by 18-crown-6 of an equimolecular mixture of $[Cu(NH_3)_4(H_2O)] [PF_6]_2$ and $[Co(NH_3)_6] [PF_6]_3$: only the copper complex (107) precipitates leading to an efficient separation of copper from the mixture. Second-sphere coordination has been established with many other crown ether ligands as well as with a large number of transition metal complexes (B-90MI 929-07). In addition to the selective metal separation mentioned above, several other aspects have been explored: resolution of racemic transition metal complexes, and photochemistry of transition metal complexes as already shown with polyazamacrocycles (86CRV319, 92MI 929-03).



9.29.3.2 Intramolecular Coordination in Organometallic Compounds

The involvement of crown ethers in these types of complex has been explored mainly by Bickelhaupt and co-workers. Organometallic compounds are concerned in which the carbon-bound metal is coordinated by donor atoms belonging to the same macrocyclic molecule, as represented in (108). Compound (110) has been obtained in good yield from (109) (Equation (10)); x-ray crystallography revealed that the oxygen atoms O-2 and O-3 are strongly coordinated to the metal cation, whereas O-1 and O-4 interact only weakly. Complexes of the type (108) containing calcium and zinc have also been described <95CRV2405>.

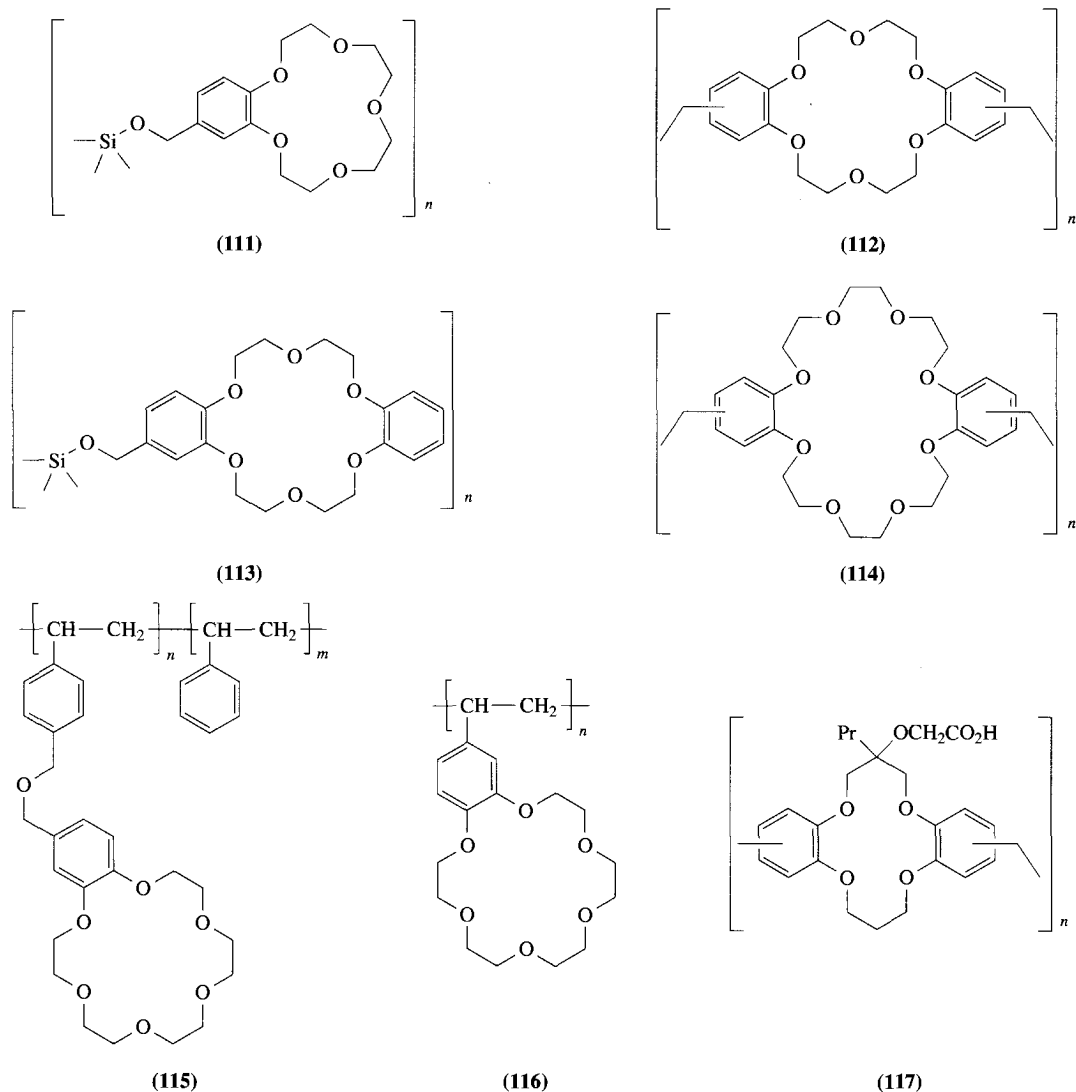


9.29.3.3 Immobilized Crown Ethers

For practical use, the attachment of crown ethers to a polymeric support is obviously of high interest. Numerous crown ethers, including chiral ones (see Section 9.29.2.4), have been anchored to a variety of polymers and to a silica gel matrix. Compounds (111)–(117) are examples of immobilized crown ethers; they allow efficient chromatographic separation of cations. Anions also may be separated: (112) is able to separate F[−], Cl[−], Br[−], and I[−] from each other; this polymer also separates with very high efficiency Na₂SO₄ from NaCl <82PAC2115>. The poly(vinylbenzo-18-crown-6), compound (116), has a polysoap-type behavior in water which allows it to bind optical and fluorescent species <82PAC2129>. Polyether carboxylic acid resins have also been prepared; resin (117) exhibits selective sorption properties toward Li⁺ and Na⁺ cations <92ANC815>. Applications of immobilized crown ethers are numerous: separation of ions, ion-sensitive electrodes, phase transfer catalysis, etc.

9.29.3.4 Lanthanides and Radioactive Nuclides Complexes: Isotopic Separation

Due to their interesting properties, macrocyclic complexes of lanthanides have attracted attention for a long time. All the lanthanides cations (La³⁺–Lu³⁺) have been isolated as crown ether complexes with ligands such as 12-crown-4, 15-crown-5, benzo-15-crown-5, 18-crown-6, dibenzo-18-crown-6, and dicyclohexyl-18-crown-6. Various metal: ligand ratios have been found (2:1, 3:2, 4:3, 1:1, 1:2) and high coordination numbers (CN = 8 to 12) are observed in these complexes; the high coordination numbers are obtained by the contribution, in addition to the ligand donor atoms, of solvent molecules and in many cases of the associated anions <84CCR191, B-90MI 929-08>. Because of the close M³⁺ ionic radii (0.2 Å difference between the largest ion, La³⁺, and the smallest one, Lu³⁺) and similarities in chemical properties, the separation of lanthanides is difficult. Crown ethers have been largely used in solvent extraction of the lanthanides from aqueous solution into organic phases and good separation factors have been observed in some cases. Separation on immobilized crown ethers of the type described above has also been investigated. Macrocyclic lanthanide complexes

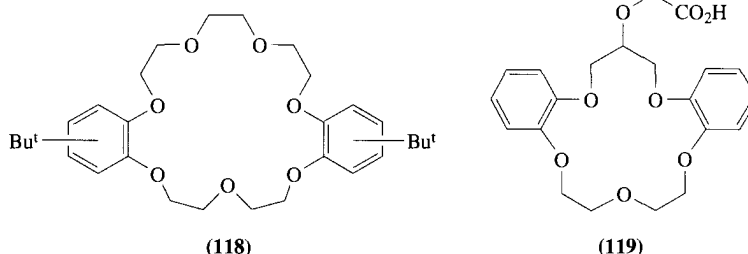


have beneficial impacts in many areas such as fluoroimmunoassays, biomedical diagnostics, NMR shift reagents, etc. <95CRV273>.

The increasing involvement of radioactive materials in today's life (energy production by nuclear reactors, medical applications, etc.) requires adapted chemical tools to handle these dangerous materials. The treatment of nuclear waste constitutes a major challenge for the researchers engaged in this field. The main goal is to separate the long-living radioactive elements (^{90}Sr , ^{135}Cs , ^{137}Cs , and various actinides) from the waste effluent in order to reduce to a minimum the volume of materials that need highly secure underground storage. Dicyclohexyl-18-crown-6 has been used for ^{90}Sr decontamination <92MI 929-04> and various 21-crown-7 derivatives for caesium extraction <84MI 929-02, 84MI 929-03>, for example, a selective extraction of caesium from acidic nitrate solutions (the usual effluent in nuclear technology) into toluene was obtained by (118) synergized with didodecyl-naphthalenesulfonic acid <92ANC3013>.

Technetium-99m is a widely used radionuclide in clinical diagnostics <95TCC123>. The design of new complexing or extracting agents for $^{99\text{m}}\text{Tc}$ may allow further developments in this field. Technetium, as pertechnetate TcO_4^- counteranion, has been extracted into organic phases by several crown ethers; the best extraction was obtained with dicyclohexyl-18-crown-6 in the presence of K^+ <86MI 929-01>. An interesting structure has been obtained by the treatment of $\text{Cs}_2(\text{TcNCl}_5)$ with 18-crown-6; it results in on one side an "infinite sandwich" $\text{M}^+/\text{crown ether}$ arrangement and on the other side a polymeric chain of $(\text{TcNCl}_4)^-$ anions located between the columns of the $[\text{Cs}(18\text{-crown-6})]^+$ cations <91CC954>.

Yttrium, ^{90}Y , is another radionuclide used in nuclear medicine; its handling requires special attention because of: (i) its short half-life (64 h); and (ii) its method of obtention. Indeed ^{90}Y is prepared from ^{90}Sr ; therefore, the obtained compound is always contaminated by its parent species ^{90}Sr , an unacceptable side product for medical applications. The ligand (119) is very selective for the extraction of $^{90}\text{Y}^{3+}$ over $^{90}\text{Sr}^{2+}$ from aqueous solutions into chloroform; by this method a highly pure (>99.9%) sample of ^{90}Y can be obtained <93ANC1350>.



The preparation of pure or enriched isotopes is of interest in various fields (medicine, pure, and applied sciences). Isotopic separation by chemical means can be reasonably considered in the particular cases of isotopes which exhibit high relative mass differences as, for example $^6\text{Li} / ^7\text{Li}$, $^{22}\text{Na} / ^{24}\text{Na}$, $^{40}\text{Ca} / ^{42}\text{Ca}$, $^{40}\text{Ca} / ^{44}\text{Ca}$, and $^{40}\text{Ca} / ^{48}\text{Ca}$. Isotopic separation of these systems by crown ethers has been studied using extraction procedures or immobilized ligands <85TCC77, 93PAC489>. Because of their higher binding capacities, the cryptands, which have also been studied, in general display better isotopic separation factors. The radical anion approach to $^6\text{Li} / ^7\text{Li}$ separation mentioned in Section 9.29.2.1.4 has also been applied, using a different system, to the $^{22}\text{Na} / ^{24}\text{Na}$ isotopic separation <92ANC607>.

9.29.3.5 Anion Activation

The vast majority of topics covered in this chapter concern the cation complexation. In this section attention is given to its inseparable companion the anion, and new properties resulting from the cation complexation will be reported. Anion activation by crown ethers was demonstrated in the very earliest paper by Pedersen in 1967 <67JA7017>. This aspect certainly constitutes the largest field of applications of crown ethers (and cryptands) and these compounds are by now of very common use in organic and inorganic laboratories. The large extent of applications may be explained very simply by saying that the course of all chemical reactions involving M^+ , X^- species will be affected (generally in a favorable way) by the presence of cation complexing agents.

The first effect of cation complexation by crown ethers (or cryptands) is a large solubility enhancement of M^+ , X^- in almost all the organic solvents, in particular in apolar aprotic ones. For the associated anion, the solubilizing process brings with it two major consequences: (i) very weak solvation by the organic solvent; and (ii) an increase in the size of the positive charge and therefore a decrease in the strength of the cation–anion interaction. As a consequence, the anion is somewhat “free” in solution; ideally a “naked anion” may be obtained. Not surrounded by solvent molecules, the anion becomes smaller and more “aggressive” and its normal properties, observed in protic solvents, are totally altered with regard to reactivity. The activation by crown ethers (or cryptands) can proceed in a homogenous medium or in heterogenous conditions (solid–liquid phase transfer catalysis). The reactions which use anion activation in organic chemistry are innumerable. Some examples are: hydrolysis of hindered esters; nucleophilic displacement; elimination; C-, O-, and N-alkylation; generation of carbanions and carbenes; aromatic substitution; esterification; etherification; oxidation; reduction; anion-assisted rearrangements; Michael addition; transesterification; and anionic polymerization. In inorganic chemistry crown ethers (or cryptands) have also found applications, such as in ligand exchange reactions. Valuable information on anion activation can be found in several reviews or books <B-77MI 929-01, B-78MI 929-03, 82TCC147, 83H(20)1379, 88MI 929-01, B-93MI 929-04, 94MI 929-04>.

9.29.3.6 More Applications

There are numerous other applications of macrocyclic complexing agents in the following fields: analytical chemistry <81TCC163, 84TCC1, 86JCC53>; ion transport <93RTC317, 94CSR75>; macrocyclic

liquid crystals <93PBI>; zeolite synthesis using crown ethers as templates <90MI 929-09, 92MI 929-05>; alkalides and electrides <79AG(E)587, 87ARP271, 89PAC1555, 93PAC435>; catalysis <79PAC979, 82TCC111, 84AG(E)782, 84BSF(2)5, 93CSR221>; and selective electrodes <B-90MI 929-10, 91MI 929-04>.

9.29.4 CONCLUDING REMARKS

Space limitation has prevented presentation of many other facets of crown ether compounds; on these omitted topics the reader can find detailed coverage in the following references: synthesis <B-82MI 929-01, 83TCC1, 91TCC1, B-93MI 929-05, 94TCC87>; complexation of neutral molecules <92CRV1261, 95CRV2529>; thermodynamic and kinetic studies <84AR(C)43, 85CRV271, 90PAC2259, 91CRV1721>; gas phase studies <93PAC409>; NMR <B-91MI 929-05>; mass spectrometry <83T1597, 89MI 929-03, 92TL3825>; and molecular mechanics and modeling <83JST(93)153, 85ACR105, 92JCC7, B-94MI 929-05>.

In this brief overview, the author has tried to illustrate some aspects of the enormous domain of crown ether compounds. The interdisciplinary nature of the field explains its tremendous development since its beginning in 1967. Its progressive growth may be compared with the iterative construction of dendrimers: the initiator core being the crown ethers described by Pedersen, the present peripheral surface still having functionalities for further expansion.

9.30

Ten-membered Rings or Larger with One or More Sulfur Atoms

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9.30.1 INTRODUCTION

This chapter discusses the chemistry of heterocyclic rings with ten or more sulfur and carbon atoms. Special emphasis is placed on thioether rings (rings containing CCSCC units) because of their importance in transition-metal chemistry and their prevalence in the scientific literature. Several comprehensive reviews have been published on transition-metal complexes of crown thioethers; the reader is directed to those for an in-depth discussion ($\langle 74\text{JHC}649, 75\text{MI } 930\text{-}01, 80\text{MI } 930\text{-}01, 81\text{CRV}365, 85\text{CRV}271, \text{B-}87\text{MI } 930\text{-}01, 87\text{MI } 930\text{-}02, \text{B-}88\text{MI } 930\text{-}01, 88\text{ACR}141, 88\text{CCR}89, 88\text{PAC}517, 90\text{MI } 930\text{-}01, 90\text{MI } 930\text{-}02, \text{B-}92\text{MI } 930\text{-}01, \text{B-}92\text{MI } 930\text{-}02 \rangle$). Rings containing sulfur atoms in other oxidation states such as sulfones and sulfoxides are discussed only briefly. Cyclophanes, thiophenophanes, annulenes, and compounds containing sulfur atoms in subheterocyclic rings (e.g. thiophenes) have been omitted.

The crown thioethers are named nonsystematically by an extension of the nomenclature for crown ethers ($\text{B-}78\text{MI } 930\text{-}01$). According to this nomenclature, for example, 1,4,7-trithiacyclodecane is abbreviated to 10S3 (**3**), indicating there are ten members in the ring, three of which are sulfur atoms. The highest possible symmetry is assumed (Figure 1), otherwise the positions of the sulfur atoms are stated expressly. Numbering of the ring always begins from a sulfur atom, and takes in the shortest linking groups first. Further clarification or systematic names are used for heterocycles with functional groups or nonthioether rings.

9.30.2 THEORETICAL METHODS

A number of theoretical and experimental approaches toward conformational analysis of crown thioethers have been developed. A molecular mechanics force field for thiols and thioethers, developed from crystal structures and experimental data ($\langle 87\text{JST}(159)137 \rangle$) reproduces molecular structures and provides reasonable fits for both the energy differences between conformers and barriers to internal rotation. Thioethers with *gauche* placement at carbon–sulfur bonds were calculated to be 0.69 kJ mol^{-1} more stable than those with *anti* placement, in agreement with earlier SCF-MO calculations ($\langle 85\text{MP}331 \rangle$).

^1H NMR spectroscopy ($\langle 92\text{JCS}(P2)533 \rangle$) on a series of crown thioethers (9S3, 10S3, 12S3, 12S4, and 18S6) showed the presence of a mixture of *gauche* and *anti* SCCS segments (from observation of averaged coupling constants in the spectrum of 10S3 and from analysis of the ^{13}C satellites for the symmetric crowns). Molecular dynamics calculations also showed a mixture of the two conformations, in contrast to the observation of solely *anti* SCCS units in the crystal structures.

Photoelectron spectroscopy (PES) confirmed the structures calculated by molecular orbital theory and molecular modeling for $n\text{S}2$ ($n = 7\text{--}10$) ($\langle 81\text{T}2743 \rangle$). In the solid and gas phases, 7S2 has a twisted chair conformation with C_2 symmetry, while 9S2 adopts the twist-boat-chair or [333] conformation. (The numbers in square brackets refer to the numbers of atoms between successive g^+g^- corners). 9S3 adopts a similar [333] conformation, although molecular mechanics predicts a [12222] conformation to be $2.7 \text{ kcal mol}^{-1}$ more stable. 10S2 adopts a quadrangular [2323] (boat-chair-boat) conformation, but the sulfur atoms occupy different sites in the gas and solid phases: in the crystal, the sulfur atoms occupy the middles of the two shorter sides. In the gas phase, PES indicates shorter transannular S—S distances (there is substantial overlap of the lone pairs), implying that the sulfur atoms move into the longer sides of the quadrangle, which is the more stable arrangement calculated by molecular mechanics ($\langle 81\text{T}2735 \rangle$). According to molecular mechanics calculations the lowest energy conformations for 10S3 and 9-keto-10S3 are [1333] and [2233], respectively ($\langle 90\text{HAC}425 \rangle$). Crystallography, however, shows that 9-keto-10S3 adopts a [2323] boat-chair-boat conformation with one exodentate and two endodentate sulfur atoms; molecular mechanics calculations indicate that the crystal structure lies $1.6 \text{ kcal mol}^{-1}$ higher in energy than the [2233] conformer.

Raman spectroscopy of cyclic disulfides indicates that S—S stretching frequency around 505 cm^{-1} is insensitive to CCSS torsion angles between 37 and 100° ($\langle 86\text{JA}1271 \rangle$). Above 100° , however, frequencies increased, approaching 525 cm^{-1} at 180° . Normal coordinate calculations with a Urey–Bradley force field confirmed this behavior.

Conformational analysis has also been applied to coordination compounds of crown thioethers and to the complexation process. Thus molecular dynamics has yielded some insight into the role of ligand pre-organization in the complexation of silver(I) by crown thioethers containing xylyl units ($\langle 92\text{JCS}(D)2889 \rangle$). Brubaker and Johnson ($\langle 84\text{IC}1591 \rangle$) calculated small intramolecular strain energies (ranging from 3.0 to $5.5 \text{ kcal mol}^{-1}$) in copper(II) complexes of S4 macrocycles, in contrast to the much higher strains calculated for nitrogen analogues ($\langle 77\text{JA}4977 \rangle$).

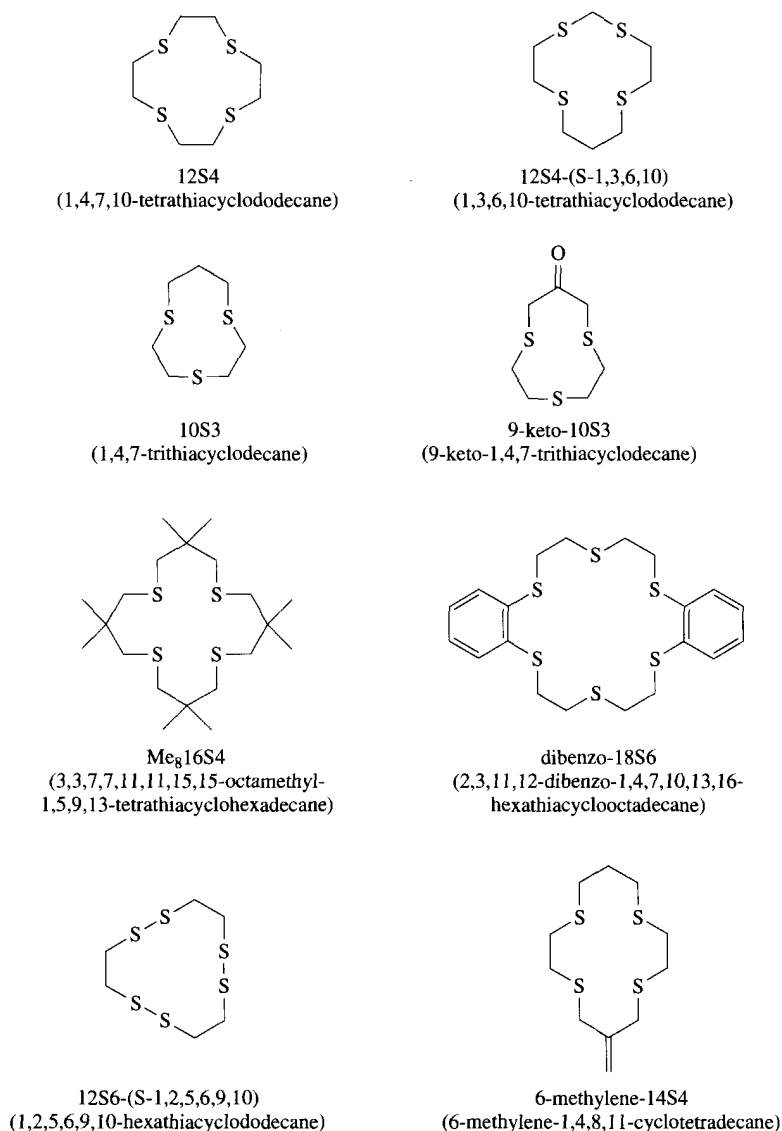


Figure 1 Nomenclature of sulfur-containing ring systems. Full IUPAC names are given in parentheses. Note that positions of sulfur atoms are not specified in the abbreviation for the highest symmetry molecule.

9.30.3 EXPERIMENTAL STRUCTURAL METHODS

9.30.3.1 X-ray Diffraction

X-ray crystal structures of free crown thioethers show that C—S bonds adopt *gauche* placement, in contrast to the *anti* preference of C—O bonds in crown ethers ^[87JA4328]. The large size of sulfur atoms and the differences in C—S vs. C—C bond lengths (1.82 Å vs. 1.53 Å, Table 1) create an attractive 1,4 effect in CSCC units and strong 1,4 repulsion of the sulfur atoms in SCCS units that leads to *anti* placement ^[87JA4328]. These preferences manifest themselves most clearly in the “bracket units” found for —SCCSCCS— linkages in crown thioethers.

Conformation and sulfur atom placement in crown thioethers are of paramount importance to the coordination of metals. For example, *endo* orientation (i.e. towards the central cavity) of all three sulfur atoms in 9S3 ideally suits facial coordination to octahedral metal centers; in contrast, *exo* placement of the sulfur atoms in 14S4 reduces the macrocyclic effect and often leads to bridging between metal ions.

Table 1 Typical bond lengths (Å) and angles (°) in unstrained sulfur-containing rings.

Bond	Length (Å)	Bonds	Angle (°)
CS—SC	2.04	S—C—C	115
SS—SS	2.06	S—C—S	110
CC—SC	1.84	C—S—C	102
SC—CS	1.53	C—S—S	105
CC—CS	1.52	S—S—S	107

X-ray diffraction is particularly important for characterizing coordination complexes of macrocycles where the paramagnetism of the metal core precludes use of NMR techniques. Numerous crystal structures containing metals have been published; the reader is referred to the review articles listed in Section 9.30.1 for a thorough discussion of these complexes. X-ray studies typically reveal an increase in S—C bond lengths on metal complexation by the thioether. An analogous effect for phosphine complexes is ascribed to the delocalization of metal electron density into P—C σ^* orbitals that are of π^* symmetry with respect to the M—P axis (and hence this delocalization leads to π -acceptor ability) (85CC1310). The effects of ring size on the redox, magnetic, and spectroscopic properties of metal ions have been discussed elsewhere (86JA1208, 87IC3769, 88IC1209, 91JA1600, 92JCS(D)2033).

9.30.3.2 NMR

Both ^1H and ^{13}C NMR spectroscopy have been used to probe the structure and solution dynamics of sulfur-containing rings. Chemical shifts of protons in —SCH₂CH₂S— linkages vary from 3.15 ppm in 9S3 and 10S3 to 2.6–2.8 ppm for the larger rings. Proton resonances β to thioether sulfur are more shielded and appear from 1.8 to 1.9 ppm. Functional groups affect proton shifts in the usual manner. For example, the proton resonances α to the carbonyl for 9-keto-10S3 shift 0.8 ppm downfield relative to the corresponding protons in 10S3 (to 3.7 ppm). Carbon resonances occur consistently between 25 and 35 ppm for unsubstituted crown thioethers. Analysis of ^{13}C satellites and proton coupling constants in ^1H NMR spectra shows that crown thioethers are fluxional, and the ratio of *gauche* and *anti* SCCS units can be calculated (92JCS(P2)533).

The formation of diamagnetic metal complexes of crown thioethers has also been studied using NMR techniques. ^1H NMR competition experiments elucidated the binding affinity of tetradentate crown thioethers for nickel(II) (91JA8663); addition of *gem*-dimethyl substituents to 14S4 increases the nickel(II) binding free energy by 1.1 kcal mol⁻¹ for each *gem*-dimethyl group. ^{13}C NMR studies of the Ag/Hg selectivity of crown thioethers (91JA6538) relied upon the distinct differences in T_1 and δ for the two metal complexes to determine the ratio of the bound metals. ^{199}Hg NMR was used to probe the complexation of methylmercury by 14S4 and 16S4 (86JOC1609); both crown thioethers yielded surprisingly low formation constants ($K_f < 1$) compared to acyclic analogues. The reactivity of complexes may also be investigated by NMR. Variable-temperature studies showed intramolecular ligand rotation fluxion for *fac*-[(12S4)PtMe₃]Cl (87CC978, 88JOM(341)559). The copper(II/I) self-exchange rates of a variety of copper crown thioether complexes have been measured by ^1H NMR line broadening (91IC5037, 94IC670).

9.30.3.3 Mass Spectroscopy

Mass spectroscopy has mainly been used to characterize metal complexes of crown thioethers and often only the parent ion is reported for the free ligand and metal complex. However, the paucity of data that does exist shows fragmentation patterns consistent with the loss of whole linkage groups (such as —CH₂CH₂— and —CH₂COCH₂—) between sulfur atoms, and of linkage groups plus sulfur atoms. Rings containing —SCH₂CH₂CH₂S— links give a peak at $m/z = 106$ due to the 1,2-dithiacyclopentane radical cation, whereas, —SSCH₂CH₂S— links give rise to the 1,2,3-trithiacyclopentane radical cation ($m/z = 124$) (82TL3231).

9.30.3.4 Electrochemistry

The electrochemistry of metal crown thioether complexes is rich and varied, as reflected by numerous reports in the literature <88ACR141, 90MI 930-01, 90MI 930-02>. Little, however, is known about the electrochemistry of the free macrocycles. Cyclic voltammetry of 9S3 in acetonitrile shows one irreversible oxidation peak at +0.99 V vs. Fc^+/Fc and a poorly defined reduction peak at -0.7 V. <85IC3067> Pulse radiolysis of 12S4 and 14S4 in hydrocarbon solvents yields, among other products, intermolecular radical cation complexes <78JPC2677>. The oxidized sulfur atom appears to be stabilized by attracting a lone pair from another sulfur atom to form a three-electron bond. Such species span a wide range of redox potentials, mimicking biological electron-transfer agents <B-92MI 930-01>. These short-lived cations may rearrange (in the absence of oxygen atom sources) to bicyclic sulfonium cations <90MI 930-01>. Strong chemical oxidants such as hydrogen peroxide readily oxidize thioethers to sulfoxides; a second equivalent yields the sulfones (Section 9.30.9.1). The sulfur atoms in thioether complexes are more resistant, and are converted only to sulfoxides. Ligand oxidation of $[\text{Fe}(\text{9S3})_2]^{2+}$ to $[(\text{9S3})\text{Fe}(\text{9S3}(\text{O}))]^{2+}$ by sodium persulfate can be effected without increasing the metal oxidation state <87IC3762>. (9S3(O) is the mono(sulfoxide) of 9S3, which binds iron(II) via the sulfur atoms only.)

9.30.3.5 UV/Vis Spectroscopy

The absorption maximum for gaseous diethylsulfide ($n \rightarrow \sigma^*$) occurs at 194 nm ($\epsilon = 4500 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$), with another weaker band at 225 nm ($\epsilon = 1800$) <B-89MI 930-01>. Crown thioethers should differ little from these values. Diethyldisulfide exhibits two $n \rightarrow \sigma^*$ transitions in hexane, one at 194 nm ($\epsilon = 5500$) and one at 250 nm ($\epsilon = 380$). UV/Vis spectroscopy has been more useful for characterizing metal complexes of thioethers and measuring the π acidity of the ligands; it shows that thioethers exceed amine and aquo ligands in ability to delocalize t_{2g} electrons.

9.30.3.6 Infrared/Raman Spectroscopy

Raman and infrared spectroscopy have been used extensively for studying metal binding to thioethers in biological systems but rarely for small molecules <78JA5939>. The most useful information is gathered from the fingerprint region; the weak, broad C—S stretch typically occurs at $710\text{--}570 \text{ cm}^{-1}$ and S—S stretching bands arise at ca. 500 cm^{-1} <B-89MI 930-02>. Sharp, strong, characteristic bands for sulfones occur between 1225 and 980 cm^{-1} and for sulfoxides between 1420 and 1000 cm^{-1} , all shifting according to the organic substituents bound to the sulfur atom.

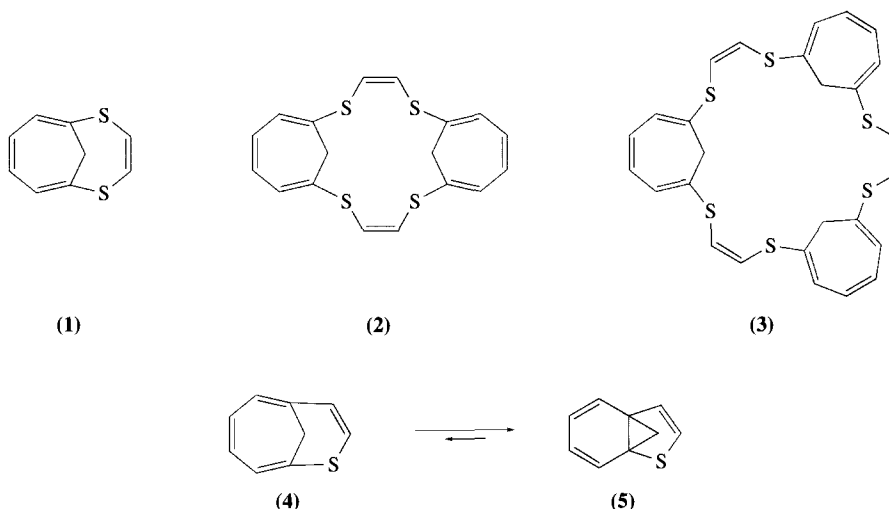
9.30.4 THERMODYNAMICS

The melting points of crown thioethers reflect the rigidity of the ring (i.e. the stability of the crystal conformation relative to the conformations available in the liquid phase) and the crystal packing forces <63JCS93>. In general, the melting points can be qualitatively estimated from the following generalizations: (i) replacement of a methylene group by a sulfur atom in a ring increases the melting point, presumably because the larger sulfur atom reduces ring flexibility; (ii) for systems containing the same number of sulfur atoms, the melting point decreases with increasing ring size; (iii) macrocycles with ethylene bridges exhibit a distinct conformational preference (see Section 9.30.3.1), which raises their melting points with respect to those of their isomers <87JA4328>; (iv) unsymmetric macrocycles have lower melting points than symmetric ones, presumably because they pack less efficiently <74JHC45>.

Crown thioethers dissolve readily in polar aprotic solvents such as acetone, DMF, DMSO, ethyl acetate, dichloromethane, chloroform, and THF, but only sparingly in hydrocarbons, alcohols, and water. The lower-melting crowns tend to be most soluble. Chromatographic purification is usually performed on silica gel, through use of moderately polar mobile phases; elution generally follows ring size (with the smallest being eluted first). Reverse-phase HPLC has also been used to purify the molecules <84MI 930-01>. However, owing to the lack of a chromophore in most of the macrocycles, the expense of doing preparative-scale HPLC, and the ease of separation on silica gel columns, its use has not been extensive.

9.30.5 REACTIVITY OF FULLY CONJUGATED RINGS

Few fully conjugated crown thioethers containing more than nine members have been described, and even for these only synthesis and characterization are reported (65AJC70, 72JOC504, 82AG(E)618, 82TL4973, 84JA5271, 89JA6846). Reaction of cycloheptatriene-2,7-dithiolate with 1,2-dichloroethene yields the ten-membered ring (1) in 11% yield, the 20-membered ring (2) in 13% yield and the 30-membered ring (3) in 11% yield (82TL4973). The extent of antiaromaticity in these 12, 24 and 36 π electron compounds has not been addressed, nor has any electrocyclic tautomerization been reported. The nine-membered ring monosulfur analogue (4), with 10 π electrons exists predominantly as the cyclohexadiene isomer (5) (84JA5271).

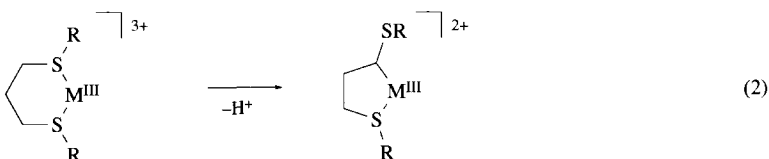
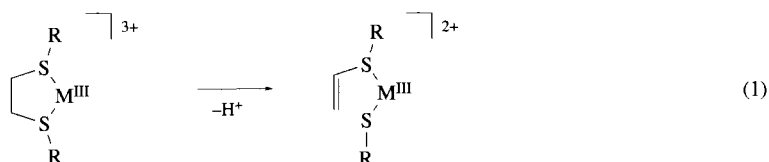


9.30.6 REACTIVITY OF NONCONJUGATED RINGS

9.30.6.1 Attack at Ring Carbon Atoms

Rings containing dithioacetal units, $R^1SCH_2SR^2$, are readily deprotonated at the methylene positions and subsequently undergo electrophilic attack (93JOC5282, 93RTC370). Treatment of 1,3,5-trithiane with butyllithium, followed by an alkyl halide, gives the mono-, di- and trisubstituted products in reasonable yield (93RTC370). Several larger rings incorporating dithioacetal units have been synthesized and alkylated further.

Numerous examples of carbon-sulfur cleavage occur in metal complexes containing thioether rings (85POL1371, 88IC3960, 89CC1600, 91ZN(B)303, 92CC1180, 92POL3165, 93IC1860). Highly charged metal ions increase the acidity of protons on the α -carbon, enabling abstraction of a proton by base. For five-membered chelate rings subsequent cleavage of the adjacent C—S bond forms a vinyl thioether and a thiolate, both coordinated to the metal center (Equations (1) and (2)). Six-membered chelate rings can undergo ring contraction via cyclometallation, although this has not yet been observed in a macrocyclic complex (94IC816, 94IC4959).



9.30.6.2 Attack at Ring Sulfur Atoms

Reactions of the ring sulfur atoms in crown thioethers are limited to oxidation/reduction and coordination to transition metals or main group elements. Thioethers oxidize readily to sulfoxides, $R^1S(O)R^2$, or sulfones, $R^1S(O)_2R^2$, while disulfides undergo reduction with ring opening. A rare example of a coordinated sulfonium ion (R_3S^+) was reported for $[Mo(CO)_2(Me_916S4)]^+$ in which the sulfonium group acts as an extremely strong π -acceptor ($Me_916S4^+ = 1,3,3,7,7,11,11,15,15$ -nonamethyl-1,5,9,13-tetrathiacyclohexadecane cation, the *S*-methyl derivative of Me_816S4). This is borne out by the crystal structure which shows a shortened R_3S-Mo bond distance; all the other $Mo-S$ bonds are longer than in the parent compound $[Mo(CO)_2(Me_816S4)]$. Infrared spectroscopy shows a greatly reduced carbonyl stretching frequency, also indicating increased $Mo-sulfonium \pi$ -interaction <93CC1511>.

Strong oxidizing agents such as MCPBA <90CC1066>, aqueous iodine <81JA1159, 82JA725, 90JOC2580>, sodium periodate <78JOC4295>, permanganate <23JCS2174>, and hydrogen peroxide in acetic acid <78JOC4295, 81H(16)1701, 86JCS(P1)465> oxidize the sulfur atoms in crown thioethers to sulfoxides or sulfones. Oxidation rates depend heavily on the type of macrocycle, the pH and the oxidizing agent. For instance, oxidation of transannular dithioethers (e.g. 1,5-dithiacyclooctane, 8S2) is accelerated up to 10^6 times by intramolecular catalysis through formation of $S-S$ bonds (see also Section 9.30.3.4).

9.30.7 REACTIVITY OF SUBSTITUENTS ON RING CARBON ATOMS

Because of their unique complexation properties, crown thioethers have been studied extensively for use in sequestering agents, membrane transport, metal extraction, and drug delivery. Desirable properties such as hydro- or lipophilicity, size and charge can be further exploited by modifying the periphery of the macrocycle and the most common substituents are discussed below.

9.30.7.1 Alkanes

Addition of successive *gem*-dimethyl pairs to the 6 and 13 positions of 14S4 improves the nickel <91JA8663> and copper <92IC3990> binding successively by $1.1 \text{ kcal mol}^{-1}$. The increased metal affinity is attributed to conformational changes induced by the *gem*-dimethyl pairs, which force the sulfur atoms to adopt *endo* orientations <91JA8663>. Similar effects were seen with 6-hydroxy- and 6,13-dihydroxy groups <88IC2164, 94IC670> and for fusing the ethyl linkage into a cyclohexyl ring <93IC381>. Molybdenum, rhodium, and ruthenium complexes of Me_816S4 and Me_414S4 have also been structurally characterized; methylation of the propyl backbone promotes *syn* ligand conformations in these *trans* complexes <88JA4872, 90CC342, 90PAC1127, 91CL1067, 92CL2447, 92JOM(428)C12, 93AG(E)1621, 93CC1511>. The *syn* conformer stereochemically differentiates the two axial sites, engendering pronounced differences in their reactivity. The methyl groups were incorporated by use of 3,3-dimethyl-1,5-dithiaheptane in the cyclization process (Section 9.30.9.2.1).

9.30.7.2 Alcohols

Primary and secondary alcohols are introduced into crown thioethers by cyclization of α,ω -dihaloalcohols with the appropriate dithiol under standard conditions (Section 9.30.9.2.1). One useful property of hydroxy derivatives of crown thioethers is their moderate solubility in water ($5 \times 10^{-2} \text{ mol dm}^{-3}$), which contrasts the extremely low solubility of the parent rings. 3-Hydroxymethyl-9S3 could be made using Sellman's molybdenum tricarbonyl template synthesis (Section 9.30.9.2.1) <91CC475>. Further treatment of 3-hydroxymethyl-9S3 with benzyl bromides in the presence of sodium hydride gave the corresponding ethers in 43–87% yield <91CC475>. Coordination compounds of 9-hydroxy-10S3 have been synthesized, but no further functionalization of the secondary alcohol group has been reported <90IC2672>. 6-Hydroxy-11S3 and 3-hydroxy-12S3 have also been synthesized in 11% and 20% yield, respectively, but again no further reactions have been reported <90HAC375>. Commercially available 3,11-dihydroxy-16S4 was functionalized with 4-(*n*-hexyloxy)benzoyl chloride to form 3,11-bis[4-(*n*-hexyloxy)benzoyloxy]-16S4 in 20% yield <94ICA1>. 3-Hydroxymethyl-16S4 was made by hydroboration and subsequent oxidation of the corresponding alkene <90CC282>; the alcohol group was successfully acetylated with acetyl chloride.

9.30.7.3 Alkenes

3-Methylene-16S4 was made by addition of 3-chloro-2-chloromethyl-1-propene to the appropriate dithiol in the presence of cesium carbonate. The macrocycle was further treated with borane and oxidized with hydrogen peroxide to yield the corresponding alcohol in high yield. Kellogg and co-workers correctly speculated that complexation of BH_3 would protect the sensitive thioethers from oxidation during this process <90CC282, B-92MI 930-01>.

Bis(alkene) derivatives of crown thioethers may also be prepared; [2 + 2] reaction of 1,4,7-trithiaheptane with 3-chloro-2-chloromethyl-1-propene in the presence of $\text{B(OPr)}_3/\text{Al(OPr)}_3$ gave 9,19-dimethylene-20S6 in 67% yield <93AG(E)436>.

9.30.7.4 Carbonyl

A number of rings have been synthesized with carbonyl groups incorporated into the structure. 9-Keto-10S3 and 6-keto-14S4 react with hydrazine and a catalytic amount of TsOH to form the symmetric azine bis-crown thioethers in 57% and 38% yields, respectively. Interestingly, reaction of 9,19-diketo-20S6 with hydrazine results in an intramolecular transannular condensation <92CC1558>. The low yield (15%) suggests that a competing reaction forms polymeric azines as well. Although many other carbonyl containing crown thioethers have been synthesized, further reactions remain to be explored.

9.30.8 REACTIVITY OF SUBSTITUENTS ON RING SULFUR ATOMS

As discussed in Section 9.30.6.2, the sulfur atoms of crown thioethers can undergo oxidation to sulfoxides or sulfones, which can subsequently be reduced back to their original forms. Crown sulfoxides have attracted interest as ionophores and ion-transport agents. Kellogg proposed that sulfonium cations (R_3S^+) could be used as second-sphere hosts for encapsulating tetrahedral ions such as PO_4^{3-} <B-92MI 930-01> but this intriguing possibility has not been investigated.

9.30.9 SYNTHETIC METHODS

9.30.9.1 Synthesis by Transformation of Another Ring

9.30.9.1.1 Thioethers

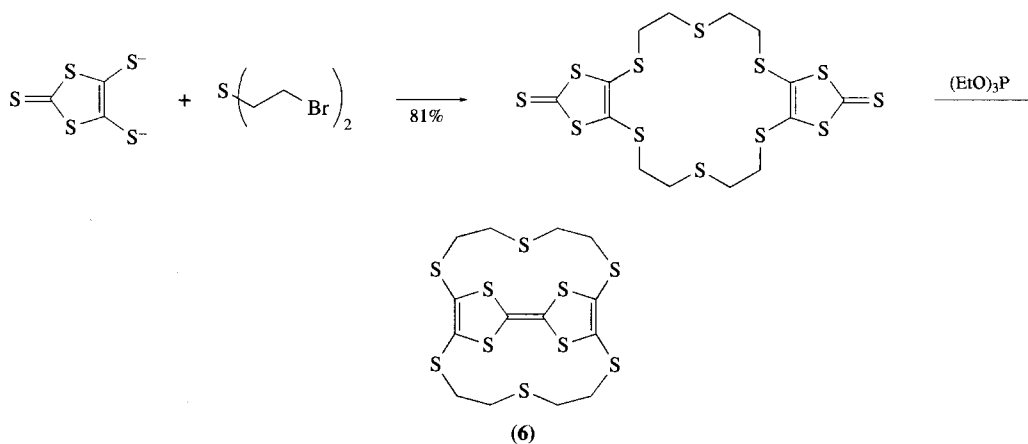
Crown thioethers are rarely synthesized from other rings. In older syntheses of crown thioethers from poly(thioether)dithiols and α,ω -dihalides, ring-contracted products (particularly *p*-dithiane) were occasionally obtained <77JOC2644>. These arise from internal attack ("intrachain cyclization") of a thioether group (rather than the terminal thiolate) on the halide terminus of the intermediate α -halo- ω -thiolate, yielding a cyclic sulfonium salt which subsequently cleaves to give two smaller rings. This problem rarely arises with modern methodology (Section 9.30.9.2). An example of intrachain cyclization, which occurs on a ruthenium template, provides a benzo-9S3 complex <88AG(E)691>.

Refluxing thietane (thiacyclobutane) polymerizes to 12S3, 16S4, and 24S6 in the presence of $\text{Re}_3\text{H}_3(\text{CO})_{10}$ (thietane). The trirhenium cluster acts as an electrophilic catalyst, and an intermediate zwitterion has been isolated, in which a 12S3 ring is *S*-alkylated by a $\text{Re}_3\text{H}_3(\text{CO})_{10}\text{SCH}_2\text{CH}_2\text{CH}_2$ group <93JOM(463)C5, 94JA10540>.

9.30.9.1.2 Cyclic disulfides

Cyclic disulfides can undergo ring contraction to their thioether analogues on treatment with sulfur-extrusion agents such as trimethyl phosphite or hexaethylphosphorus triamide <93HAC487>.

Triethyl phosphite induces intramolecular coupling of two 2-thioxo-3,5-dithiole units to give the tetrathiafulvalene (6) (Scheme 1) <92JCS(P1)2907>. Treatment of α,ω -di(episulfides) with Lewis acids, such as SnCl_4 , yields macrocycle-containing polymers, but with little regiocontrol <84MI 930-02>.



Scheme 1

9.30.9.1.3 Sulfoxides and sulfones

Macrocyclic sulfoxides and sulfones have begun to attract interest as phase transfer catalysts <81H(16)1701, 86JCS(P1)465>; they are best obtained by oxidation of the parent crown thioether. By way of illustration, mono(sulfoxide) of 9S3 has been isolated as an iron(II) complex (Section 9.30.3.4), while the tris(sulfone) can be prepared from 9S3 with excess permanganate <87IC3762>. Cyclic sulfones extrude SO_2 at 500°C (60–80 Pa) to give cyclophanes <89JOC2632, 90CC1066>.

9.30.9.2 Synthesis via Cyclization Reactions

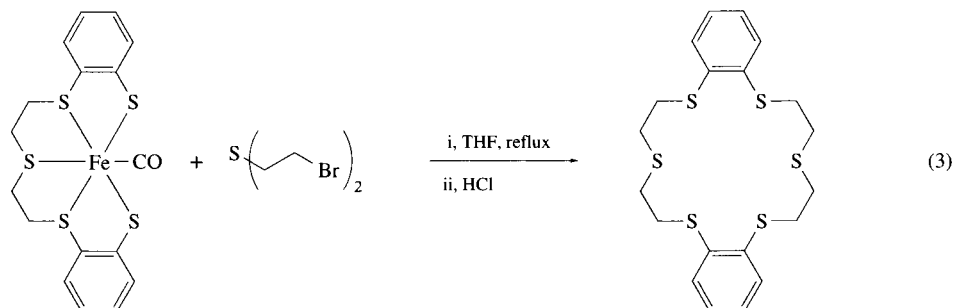
Syntheses of sulfur-containing rings by cyclization reactions, classified by ring size, are presented in Table 2 at the end of this section. The various approaches adopted are discussed in more detail below.

9.30.9.2.1 Crown thioethers

(i) Template syntheses

Few template syntheses seem efficacious for crown thioethers (although the potential of these methods has probably not been fully explored). Alkali and alkaline earth cations, successful templates for polyether macrocycles, have no utility here as they do not bind the α,ω -dithiolate precursors. Occasionally, transition-metal fragments are used as templates, but in most cases the potential starting dithiolate complexes are bridged polynuclear species that tend to be neither soluble nor particularly nucleophilic <52JCS146, 78IC1296, 86JCS(D)1747, 91IC3700, 91ZN(B)209>. In the most noteworthy exceptions, 9S3 has been synthesized efficiently around a $\text{Mo}(\text{CO})_3$ template <84AG(E)807, 85JOM(289)57> and a template method for some S4 crowns has been described <70JA1935>. Reaction of $[(\text{dpttd})\text{Fe}(\text{CO})]$ ($\text{dpttdH}_2 = 2,3,11,12$ -dibenzo-1,4,7,10,13-pentathiatriadecane) with 1,5-dibromo-3-thiapentane (Equation (3)) gives dibenzo-18S6 in 55–75% yield <86AG(E)1107>; preparation of the tetra(*t*-butyl) analogue proceeds in 62% yield <90ICA231>. 2,3,8,9-Dibenzo-15S5 can be prepared

either from [(dpttd)Fe(CO)] and dibromoethane or (better) from [(dtttd)Fe(CO)₂] and 1,5-dibromo-3-thiapentane (dtttdH₂ = 2,3,8,9-dibenzo-1,4,7,10-tetrathiadecane).

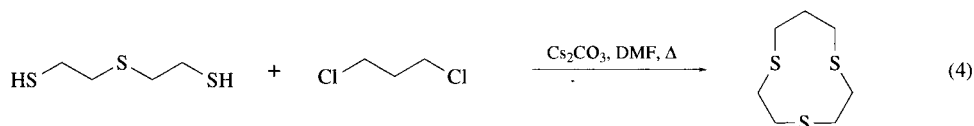


(ii) Direct (non-template) syntheses

Rings containing two or more S atoms can usually be synthesized directly from α,ω -dithiols and α,ω -dihalides by the procedures outlined below. Disconnection to a polythioether dithiol and 1,2-dibromoethane or 1,3-dibromopropane usually obviates the need for preparing or handling mustards. Two-component [1 + 1] cyclizations are generally preferred, but four-component [2 + 2] cyclizations have been used where the intermediates required for a two-component procedure are difficult to synthesize or handle (e.g. a volatile dithiol or a mustard). Indeed, this is the only effective approach to large rings such as 20S6, 24S6, 24S8, and 28S8.

Older cyclization techniques relied on the slow, simultaneous addition of separate ethanolic solutions of the α,ω -dithiolate (preformed from the dithiol by treatment with base) and the α,ω -dihalide to a heated reaction vessel (Table 2). Maintaining constant, matched addition rates and protecting the dithiolate from oxidation during the long addition times are difficult, but such procedures are still used occasionally. In some cases the vigorous conditions promote unselective ring closure (intrachain cyclization, see Section 9.30.9.1), producing unusual ring products <77JOC2644>.

Synthesis of crown thioethers has been revolutionized by the advent of efficient high dilution techniques, particularly the use of Cs₂CO₃/DMF and the Ziegler influxion technique: the dithiol and dihalide (which do not react in the absence of base) are mixed in solution and then slowly added to a reaction vessel containing a stirred suspension of Cs₂CO₃ (Equation (4)) <80CC466, 81JOC4481, 89IS122>. This procedure generates the reactive dithiolate *in situ* in the presence of a low concentration of dihalide. Rapid reaction between the dithiolate and the dihalide maintains high-dilution conditions during the course of the reaction, which obviates the use of matched constant addition funnels <87OS(65)150>. Small rings can be separated from higher macrocycles and polymeric by-products by sublimation (for sufficiently volatile products) or chromatography <87IC2009>. The influence of effective molarities on the yields of such cyclization reactions has been discussed <82CC251, 93CC538>. Use of the cheaper and more readily available carbonates of the lower alkali metals causes yields of cyclic products to decrease progressively from Cs to Li <80CC466, 81JOC4481>. B(OPr)₃/Al(OPr)₃ in MeOH/THF solutions has also been effectively used as a base <93AG(E)436>.



In addition to simple alkyl dihalides, other bis(electrophilic) compounds have been cyclized with α,ω -dithiols, thereby introducing functionality into the macrocyclic backbone. 1,3-Dichloropropan-2-one provides a keto group (—CH₂COCH₂— unit) <89MI 930-03, 90HAC425, 90IC2672, 91CC910> while 3-chloro-2-chloromethyl-1-propene can be used to introduce an *exo* methylene group <90CC282>. 2,5-Bis(chloromethyl)thiophene provides for introduction of a thiophene group <88CJC1506, 89CJC639, 90CJC644>.

Use of 1,3-dibromopropan-2-ol, 1,3-dichloropropan-2-ol <90HAC375> or α,ω -bis(chlorohydrins) allows introduction of hydroxy groups into crown thioethers. Thus 6-hydroxy-14S4 was synthesized in 55% yield from the disodium salt of 1,4,8,11-tetrathiaundecane and 1,3-dichloropropan-2-ol in

ethanol. The *cis* and *trans* isomers of 6,13-dihydroxy-14S4, which are separable (the *cis* isomer is more soluble), were obtained from ethanedithiol and 1,10-dichloro-2,9-dihydroxy-4,7-dithiadecane. Interestingly, with these hydroxy-substituted systems, use of Cs_2CO_3 instead of K_2CO_3 as base in the cyclization reaction affords only a 25% increase in yield (a 100% increase is more usual), so the latter affords a significant cost advantage for large-scale syntheses <88IC2164>.

Backbone functionalization can also be introduced via α,ω -dithiol components such as 1,3-dithiolpropan-2-one <93JOC5624> and 1,3-dithiolpropan-2-ol <76JOC134>. Fujihara and co-workers have outlined the use of 2,6-dithiaspiro[3.3]heptane as a masked $(\text{MeSCH}_2)_2\text{C}(\text{CH}_2\text{SH})_2$ equivalent <81H(16)1701, 86JCS(P1)465>.

(iii) Others

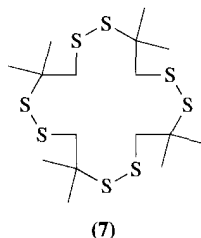
Synthesis of sulfur-containing macrocycles from a single organic component is rarely attempted, although this is the only viable strategy for rings containing one sulfur atom. Cyclic thioethers have been synthesized from α -chloro- ω -thiouronium salts; base hydrolysis generates an α -chloro- ω -thiolate which cyclizes <79AJC2777>. Reaction of S^{2-} with dihalides comprises another 1-component approach to crown thioethers: commercial polymers obtained by reaction of S^{2-} with $p\text{-C}_6\text{H}_4\text{Cl}_2$ (nucleophilic aromatic substitution) contain small quantities of cyclic S4 (0.02%) and S5 (0.12%) rings <82CL287>. Reaction of 1,3-dibromopropane in dichlorobenzene with $\text{S}^{2-}(\text{aq.})$ in the presence of a phase transfer catalyst yields almost 80% cyclic material <90MAC71>. Reaction of NaSH with α,ω -di(epoxides) yields dihydroxy crown thioethers <86JOC1128> while electrophilic addition of SCl_2 to α,ω -dialkenes provides chloromethyl derivatives. The methodology of group 14-metal assisted C—S bond formation <84S140, 85JOC4969, 87TL5981> has also found use in macrocycle synthesis.

Alkynes can cyclize with α,ω -dithiols in the presence of $\text{Pr}_3\text{B}/\text{O}_2$ or a radical initiator to yield crown thioethers <92MC48, 92SL233>. Reaction of $[\text{Co}_2(\text{CO})_9(2\text{-butyne-1,4-diol})]$ with 1,4,7-trithiaheptane in the presence of HBF_4 gives good yields of crown thioethers incorporating a triple bond (i.e. the $-\text{SCH}_2\text{CCCH}_2\text{S}-$ unit) in the backbone <91CC350>.

9.30.9.2.2 Cyclic disulfides

Cyclic disulfides result from oxidation of α,ω -dithiols at high dilution. 10S3-(S-1,2,6) was synthesized by simultaneous addition of 1,5,10-trithiadecane and iodine solutions to triethylamine in chloroform <86JA1271>. Two- or even three-component cyclizations can occur under these conditions; thus addition of ethanedithiol and iodine to $\text{Et}_3\text{N}/\text{CHCl}_3$ yields material from which 8S4-(S-1,2,5,6) <82TL3231> and 12S6-(S-1,2,5,6,9,10) <86JA1271> can be sublimed. 10S4-(S-1,2,6,7) (the cyclic disulfide dimer of propanedithiol) <83PS(16)299> and 18S6-(S-1,2,6,10,11,15) (the dimer of 1,5,9-trithianonane) have also been prepared in low yields by this procedure.

The intriguing compound $(\text{SSCMe}_2\text{CH}_2)_4$ (7) can be prepared by reaction of NaSH with either $\text{Me}_2\text{C}:\text{CH}_2/\text{S}_2\text{Cl}_2$, $(\text{Me}_2\text{C}:\text{CHS})_2$ or $(\text{Me}_2\text{C}(\text{Cl})\text{CH}_2\text{S})_2$. Each C—C bond adopts *anti* placement, but the remaining C—S and S—S bonds are all *gauche* to give an overall centrosymmetric structure <78JA6160>. The CH_2 groups are endodentate while the sulfur atoms and CMe_2 groups are exodentate.



No template syntheses of macrocyclic disulfides have been reported, nor any syntheses from α,ω -dihalides and S_2^{2-} . Macrocyclic trisulfides can be formed from the parent dithiol via reaction of the Bunte salts with Na_2S <61JCS4850, 63JCS3608, 65JCS2901> or using SCl_2 or other sulfur-transfer agents <78JA1222> but no rings greater than nine members have been synthesized.

9.30.9.2.3 Cyclic dithioacetals

Cyclic dithioacetals are usually made from α,ω -dithiolates and dibromomethane; $\text{ClCH}_2\text{SCH}_2\text{Cl}$ can be used to introduce two neighboring dithioacetal groups (i.e. the $-\text{SCH}_2\text{SCH}_2\text{S}-$ moiety) $\langle 92\text{T8065} \rangle$. There are no examples of syntheses from α,ω -dithiols and aldehydes. Thus 16S6-(S-1,3,6,9,11,14) was obtained in 8% yield as the [2 + 2] product from simultaneous addition of the disodium salt of 1,4,7-trithiaheptane and dibromomethane to ethanol. This compound could also be obtained in 62% yield as the [1 + 1] product from 1,7-dichloro-3,5-dithiaheptane and 1,4,6,9-tetrathianonane (disconnecting the thioether rather than the dithioacetal) using $\text{Cs}_2\text{CO}_3/\text{DMF}$ $\langle 89\text{IC3573} \rangle$. Similarly, 12S4-(S-1,3,6,10) was synthesized from 1,4,6,9-tetrathianonane and 1,3-dibromopropane rather than from 1,4,8,11-tetrathiaundecane and dibromomethane $\langle 93\text{JOC5282} \rangle$.

9.30.10 IMPORTANT COMPOUNDS AND APPLICATIONS

Crown thioethers have found a number of uses as ligands, related particularly to their affinity for late- and post-transition elements. Attention has focused on the coordination chemistry of silver, with relevance to photography, silver-selective electrodes, and ligands for chromogenic analysis and recovery of silver. Biomedical applications include the removal of toxic heavy metals such as Cd, Hg, Pb, and Tl and delivery of radioisotopes such as $^{99\text{m}}\text{Tc}$, ^{186}Re , and ^{188}Re to specific sites in the body. Finally, some crown thioethers have been found to promote novel reactivity in their transition metal complexes, including activation of small molecules such as N_2 , CO and C_2H_4 .

Crown thioethers afford several advantages for such applications: (i) metal selectivity and control of reactivity through ring size effects $\langle 89\text{CC781}, 91\text{IC3691} \rangle$; (ii) robustness; and (iii) insensitivity to pH—crown thioethers bind target metal ions even at low pH. Previously perceived disadvantages of crown thioethers, such as their low solubility in water, often weak binding, expense, and lack of ready functionalization are currently being addressed by several research groups.

9.30.10.1 Silver Complexes

It has long been known that inclusion of sulfur atoms imparts silver specificity to crown ligands $\langle 86\text{EUP166347}, 87\text{EUP216973}, 91\text{JA6538} \rangle$. Several silver complexes of 18S6 and 15S5 have been cataloged $\langle 89\text{IC4040}, 89\text{POL513}, 90\text{CC974}, 93\text{JCS(D)521} \rangle$ but 9S3 shows the highest affinity and $[\text{Ag}(\text{9S3})_2]^+$ undergoes a facile oxidation to the +2 oxidation state $\langle 87\text{AG(E)575}, 87\text{CC950} \rangle$.

Crown thioethers with xylol units and other lipophilic substituents have been studied as components of silver-selective electrodes $\langle 89\text{JCS(P1)1675}, 89\text{MI 930-04}, 91\text{JCS(D)1969}, 92\text{JCS(D)2889} \rangle$. Stripping voltammetry of Ag(I) has also been performed at electrodes modified with S4 crowns $\langle 89\text{TAL1044} \rangle$. Crown thioethers have also been incorporated in Ag(I)-selective $\langle 89\text{MI 930-05}, 93\text{MI 930-01} \rangle$ and Cu(II)-selective $\langle 82\text{CL287} \rangle$ PVC membrane electrodes. Several chromogenic derivatives of benzo-15S4 have been used for extractive separation and spectrophotometric determination of Ag(I) $\langle 85\text{TAL797}, 86\text{MI 930-01}, 86\text{NKK907}, 89\text{BCJ1797}, 93\text{MI 930-02} \rangle$.

14S4 is effective in liquid-liquid extraction of Hg(II), Cu(I), and Ag(I) $\langle 83\text{MI 930-01} \rangle$. Picrates of Ag(I) and Hg(II) are also extracted by 18S6 $\langle 77\text{JINC1409}, 80\text{JINC885} \rangle$ and extractive photometric determination of Cu(II) can be accomplished by 14S4 in the presence of a chromogenic counterion. Finally, an "armed" crown thioether derived from 3,11-dihydroxy-16S4 shows specific transport ability for Ag(I) $\langle 85\text{TL881} \rangle$.

9.30.10.2 Biomedical Applications

Crown thioether derivatives have potential in treatment of heavy metal poisoning. Complexes such as $[\text{Tl}(\text{18S6})]^+$, containing [2 + 4]-coordinate Tl(I) $\langle 92\text{JCS(D)2987} \rangle$ and $[(\text{9S3})_2\text{Pb}(\text{OClO}_3)_2]$, containing 8-coordinate square-antiprismatic Pb(II) $\langle 89\text{ZAAC(577)155} \rangle$ show the utility of crown thioethers in binding these ions. 14S4 forms a square-pyramidal complex with Hg(II) in which a water molecule occupies the apical binding site $\langle 78\text{JCS(D)394} \rangle$. 16S4 forms a more stable complex with Hg(II), the mercury lying in the S4 plane $\langle 79\text{CC140} \rangle$ but offers an "inverse macrocyclic effect" with methylmercury $\langle 86\text{JOC1609} \rangle$. The crystal structure of $[\text{Hg}(\text{15S5})]^{2+}$ shows all five sulfur atoms binding the metal ion to give distorted square-pyramidal geometry $\langle 91\text{POL1545} \rangle$.

In nuclear medicine the complexes $[\text{Tc}(\text{9S3})_2]^{n+}$ $\langle 92\text{IC5351} \rangle$, $[(\text{14S4})\text{TcNCl}]^+$ $\langle 93\text{POL2995} \rangle$,

Table 2 Synthetic strategies for macrocycles with ten or more members and at least one intrinsic sulfur atom. Macrocycles are listed by increasing number of sulfur atoms and further subdivided by increasing ring size.

Macrocycle	Reagents	Conditions	Technique ^a	Purification ^b	Yield (%)	m.p. (°C)	Crystal Structure	Note	Ref.
12S2 (S-1,6)	HS(CH ₂) ₅ SH + Br(CH ₂) ₅ Br	4 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 45–50 °C, 12–15 h	A 1 + 1	recryst. methanol	87.5	78.5–80		c	80CC466, 81JOC4481
17S2 (S-1,6)	HS(CH ₂) ₁₀ SH + Br(CH ₂) ₅ Br	4 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 45–50 °C, 12–15 h	A 1 + 1	chromatog., dichloromethane/ hexane	90	71.5–72		d,e	80CC466, 81JOC4481
22S2 (S-1,11)	HS(CH ₂) ₁₀ SH + Br(CH ₂) ₁₀ Br	4 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 45–50 °C, 12–15 h	A 1 + 1	chromatog., dichloromethane/ hexane	85	48–49		d	80CC466, 81JOC4481
28S2 (S-1,11)	HS(CH ₂) ₁₆ SH + Br(CH ₂) ₁₀ Br	5 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 45–50 °C, 12–15 h	A 1 + 1	MPLC, dichloromethane/ hexane	80–90	47–49		d	80CC466, 81JOC4481
34S2 (S-1,17)	HS(CH ₂) ₁₆ SH + Br(CH ₂) ₁₆ Br	5 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 45–50 °C, 12–15 h	A 1 + 1	MPLC dichloromethane/ hexane	50	75–77		d	80CC466, 81JOC4481
36S2 (S-1,17)	HS(CH ₂) ₁₆ SH + Br(CH ₂) ₁₈ Br	5 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 45–50 °C, 12–15 h	A 1 + 1	MPLC dichloromethane/ hexane	90			d,f	80CC466, 81JOC4481
3-methylene-10S2 (S-1,5)	HS(CH ₂) ₅ SH + H ₂ C=C(CH ₂ Cl) ₂	16 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 55–60 °C, 6–9 h	A 1 + 1		60				90CC282
3-methylene-15S2 (S-1,5)	HS(CH ₂) ₁₀ SH + H ₂ C=C(CH ₂ Cl) ₂	16 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 55–60 °C, 6–9 h	A 1 + 1		87				90CC282
3-methylene-17S2 (S-1,5)	HS(CH ₂) ₁₂ SH + H ₂ C=C(CH ₂ Cl) ₂	16 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 55–60 °C, 6–9 h	A 1 + 1		75				90CC282
3-methylene-21S2 (S-1,5)	HS(CH ₂) ₁₆ SH + H ₂ C=C(CH ₂ Cl) ₂	16 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 55–60 °C, 6–9 h	A 1 + 1		60				90CC282
10S3 (S-1,4,7)	S(CH ₂ CH ₂ SH) ₂ + Cl(CH ₂) ₃ Cl	Cs ₂ CO ₃ /DMF 100 °C, 48–72 h	A 1 + 1	chromatog., ethyl acetate/hexane	17.7	liquid at room temp.		f, g	89IC4128, 90HAC375
9-hydroxy-10S3 (S-1,4,7)	S(CH ₂ CH ₂ SH) ₂ + HOCH(CH ₂ Cl) ₂	Cs ₂ CO ₃ /DMF 65 °C, 48–72 h	B 1 + 1	recryst. ethanol	23	74–79			90IC2672, 90HAC375

Table 2 Continued.

Macrocycle	Reagents	Conditions	Technique ^a	Purification ^b	Yield (%)	m.p. (°C)	Crystal Structure	Note	Ref.
9-methylene-10S3 (S-1,4,7)	S(CH ₂ CH ₂ SH) ₂ + H ₂ C=C(CH ₂ Cl) ₂	Cs ₂ CO ₃ /DMF 70°C, 18 h	A 1 + 1	flash chromatog., dichloromethane/ hexane	16			h	94UP 930-01
9-keto-10S3 (S-1,4,7)	S(CH ₂ CH ₂ SH) ₂ + OC(CH ₂ Cl) ₂	Cs ₂ CO ₃ /DMF 52°C, 9 h	B 1 + 1	chromatog., ethyl acetate/hexane	2.5, 17.8	102–104		i	89MI 930-03, 90HAC375, 90IC2672
9-keto-10S3 (S-1,4,7)	S(CH ₂ CH ₂ SH) ₂ + OC(CH ₂ Cl) ₂	1.8 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 55°C, 10 h	A 1 + 1	chromatog., dichloromethane/ hexane	72		j	i	91CC910, 94IC2448
9-keto-10S3 (S-1,4,7)	S(CH ₂ CH ₂ Cl) ₂ + OC(CH ₂ SH) ₂	10 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 50–55°C	A 1 + 1	chromatog., dichloromethane/ hexane	78	106		k	93JOC5624
11S3 (S-1,4,8)	HS(CH ₂) ₂ S(CH ₂) ₃ SH + Cl(CH ₂) ₃ Cl	Cs ₂ CO ₃ /DMF 60°C, 34 h	B 1 + 1	chromatog., ethyl acetate/hexane	11.1	69–70		l	90HAC375
11S3 (S-1,4,7)	S(CH ₂ CH ₂ SH) ₂ + Cl(CH ₂) ₄ Cl	Cs ₂ CO ₃ /DMF 100°C, 34 h	A 1 + 1	chromatog., ethyl acetate/hexane	4.3	42–44			90HAC375
10-hydroxy-11S3 (S-1,4,8)	HS(CH ₂) ₂ S(CH ₂) ₃ SH + HOCH(CH ₂ Cl) ₂	Cs ₂ CO ₃ /DMF 70°C	B 1 + 1	chromatog., ethyl acetate/hexane	10.8	70			90HAC375
9-keto-11S3 (S-1,4,7)	S(CH ₂ CH ₂ SH) ₂ + ClCH ₂ COCH ₂ CH ₂ Cl	1.8 mmol dm ⁻³ Cs ₂ CO ₃ /10 : 1 THF : DMF, 55°C	A 1 + 1	chromatog., dichloromethane/ hexane	52		m		94IC2448
10-keto-11S3 (S-1,4,8)	S((CH ₂) ₃ SH) ₂ + OC(CH ₂ Cl) ₂	Cs ₂ CO ₃ /DMF 60°C	B 1 + 1	MPLC, ethyl acetate/hexane	6	112			90HAC375
12S3 (S-1,5,9)	S((CH ₂) ₃ SNa) ₂ + Br(CH ₂) ₃ Br	0.075 mol dm ⁻³ ethanol, reflux	D 1 + 1	codistillation with unidentified liquid	3	87–88			70IC262
12S3 (S-1,5,9)	S((CH ₂) ₃ SH) ₂ + Br(CH ₂) ₃ Br	Cs ₂ CO ₃ /DMF 70°C, 72 h	A 1 + 1	chromatog., dichloromethane; recryst. ethyl acetate/pentane	50	97–98	n		88JCS(D)93
3-hydroxy-12S3 (S-1,5,9)	S((CH ₂) ₃ SH) ₂ + HOCH(CH ₂ Cl) ₂	Cs ₂ CO ₃ /DMF 90°C	B 1 + 1	MPLC, ethyl acetate/hexane	19.9	95–97	o		90HAC375
3-keto-12S3 (S-1,5,9)	S((CH ₂) ₃ SH) ₂ + OC(CH ₂ Cl) ₂	Cs ₂ CO ₃ /DMF 90°C	B 1 + 1	MPLC, ethyl acetate/hexane	4.3	104			90HAC375

10-keto-12S3 (S-1,4,7)	$\text{S}(\text{CH}_2\text{CH}_2\text{SH})_2$ + $\text{OC}(\text{CH}_2\text{CH}_2\text{Cl})_2$	1.8 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 45 °C	A 1 + 1	chromatog., dichloromethane/ hexane	63		p	94IC2448
10S4 (S-1,3,5,8)	$\text{S}(\text{CH}_2\text{CH}_2\text{SH})_2$ + $\text{S}(\text{CH}_2\text{Cl})_2$	Cs ₂ CO ₃ /DMF 55–60 °C	A 1 + 1	chromatog., dichloromethane/ toluene	81			92T8065
10S4 (S-1,2,6,7)	$\text{HS}(\text{CH}_2)_3\text{SH}$	I ₂ /Et ₃ N chloroform	E oxidative dimerization	chromatog., dichloromethane/ hexane, or recryst. hexane		131–132	q	83PS(16)299
10S4 (S-1,2,6,7)	$(\text{S}(\text{CH}_2)_3\text{SH})_2$	I ₂ /Et ₃ N chloroform	E 1-component cyclization	chromatog., dichloromethane/ hexane, or recryst. hexane	1	131–132		83PS(16)299
12S4 (S-1,4,7,10)	$(\text{CH}_2\text{SCH}_2\text{CH}_2\text{SH})_2$ + BrCH ₂ CH ₂ Br	12 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 50 °C, 12 h	A 1 + 1	recryst. chloroform	83	216	s	87JA4328
12S4 (S-1,4,7,10)	$(\text{CH}_2\text{SCH}_2\text{CH}_2\text{SNa})_2$ + BrCH ₂ CH ₂ Br	ethanol, reflux	D 1 + 1	Soxhlet extract with ether; sublime	4	216		70IC262
12S4 (S-1,3,6,10)	$\text{CH}_2(\text{SCH}_2\text{CH}_2\text{SH})_2$ + Br(CH ₂) ₃ Br	Cs ₂ CO ₃ /DMF 50 °C	C 1 + 1	chromatog., dichloromethane/ hexane	72	92	t	93JOC5282
2,6-dioxo-12S4 (S-1,4,7,10)	$\text{S}(\text{CH}_2\text{CH}_2\text{SH})_2$ + $\text{S}(\text{CH}_2\text{COCl})_2$	simultaneous addition of separate solutions to benzene, 50 °C	1 + 1	recryst. ethanol	1.1	134–139		79JHC721
13S4 (S-1,4,7,10)	$\text{CH}_2(\text{CH}_2\text{SCH}_2\text{CH}_2\text{SNa})_2$ + BrCH ₂ CH ₂ Br	ethanol, reflux	D 1 + 1	recryst. ethanol/chloroform; sublime, 140 °C/700 Pa; recryst. again	16	134		70IC262
12-keto-13S4 (S-1,4,7,10)	$(\text{CH}_2\text{SCH}_2\text{CH}_2\text{SH})_2$ + $\text{OC}(\text{CH}_2\text{Cl})_2$	16 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 55–60 °C, 6–9 h	A 1 + 1	chromatog., dichloromethane/ hexane	70–80		u	91CC910
12-keto-13S4 (S-1,4,7,10)	$(\text{CH}_2\text{SCH}_2\text{CH}_2\text{Cl})_2$ + $\text{OC}(\text{CH}_2\text{SH})_2$	10 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 50–65 °C	A 1 + 1	chromatog., dichloromethane/ hexane	73	162–164	k	93JOC5624
14S4 (S-1,4,8,11)	$\text{CH}_2(\text{CH}_2\text{SCH}_2\text{CH}_2\text{SNa})_2$ + Br(CH ₂) ₃ Br	ethanol, reflux	D 1 + 1	ether extraction; sublime; recryst. ethanol	7.5	116	v	69JA4694, 76JA762
14S4 (S-1,4,8,11)	$\text{CH}_2(\text{CH}_2\text{SCH}_2\text{CH}_2\text{Cl})_2$ + NaS(CH ₂) ₃ SNa	butanol room temp., 6 h	C 1 + 1	chromatog., ethyl acetate/hexane; recryst. ether/hexane	22	121	w, k	74JOC2079

Table 2 Continued.

Macrocycle	Reagents	Conditions	Technique ^a	Purification ^b	Yield (%)	m.p. (°C)	Crystal Structure	Note	Ref.
14S4 (S-1,4,8,11)	CH ₂ (CH ₂ SCH ₂ CH ₂ SH) ₂ + Br(CH ₂) ₃ Br	Cs ₂ CO ₃ /DMF 55–60 °C, 9h	A 1 + 1	recryst. ethanol	58–62	119			87OS(65)150
14S4 (S-1,4,8,11)	NaSCH ₂ CH ₂ SNa + Br(CH ₂) ₃ Br	0.5 mol dm ⁻³ ethanol, reflux	D 2 + 2	ether extraction	1	122			33JA775
6-methylene-14S4 (S-1,4,8,11)	H ₂ C=C(CH ₂ Cl) ₂ + CH ₂ (CH ₂ SCH ₂ CH ₂ SH) ₂	16 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 55–60 °C	A 1 + 1			41–42	x		90CC282
Me ₂ 14S4 (S-1,4,8,11) (6,6-dimethyl)	CH ₂ (CH ₂ SCH ₂ CH ₂ Br) ₂ + Me ₂ C(CH ₂ SH) ₂	Cs ₂ CO ₃ /DMF 80 °C	A 1 + 1	chromatog., ethyl acetate/hexane	45	66	y	k	91JA8663
Me ₂ 14S4 (S-1,4,8,11) (6,6,13,13-tetramethyl)	Me ₂ C(CH ₂ SCH ₂ CH ₂ Cl) ₂ + Me ₂ C(CH ₂ SH) ₂	Cs ₂ CO ₃ /DMF 80 °C	A 1 + 1	chromatog., ethyl acetate/hexane	48	73	z	k	91JA8663
6-keto-14S4 (S-1,4,8,11)	CH ₂ (CH ₂ SCH ₂ CH ₂ SH) ₂ + OC(CH ₂ Cl) ₂	16 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 55–60 °C, 6–9 h	B 1 + 1	chromatog., dichloromethane/ hexane	70–80		aa		91CC910
6-keto-14S4 (S-1,4,8,11)	CH ₂ (CH ₂ SCH ₂ CH ₂ Cl) ₂ + OC(CH ₂ SH) ₂	10 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 50–65 °C	A 1 + 1	chromatog., dichloromethane/ hexane	67	124–125		k	93JOC5624
6-hydroxy-14S4 (S-1,4,8,11)	CH ₂ (CH ₂ SCH ₂ CH ₂ SH) ₂ + HOCH(CH ₂ Cl) ₂	K ₂ CO ₃ /DMF 100 °C, 28 h	A 1 + 1	chromatog., acetone/hexane; recryst. ether/hexane	34	112			88IC2164
6-keto-13-methylene-14S4 (S-1,4,8,11)	H ₂ C=C(CH ₂ SCH ₂ CH ₂ SH) ₂ + OC(CH ₂ Cl) ₂	16 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 55–60 °C, 6–9 h	B 1 + 1	chromatog., dichloromethane/ hexane	70–80				91CC910
2,3-benzo-15S4 (S-1,4,7,11)	CH ₂ (CH ₂ SCH ₂ CH ₂ SNa) ₂ + o-C ₆ H ₄ (CH ₂ Br) ₂	0.15 mol dm ⁻³ ethanol, reflux	D 1 + 1	multiple recryst. from chloroform/ethanol	38	85			67JCS(A)1852, 69JA4694, 74IC2591, 84JOM(260)91
16S4 (S-1,5,9,13)	CH ₂ (CH ₂ S(CH ₂) ₃ Cl) ₂ + NaS(CH ₂) ₃ SNa	butanol, room temp.	C 1 + 1	chromatog., ethyl acetate/hexane	19.5	57	cc	g, k	74JOC2079, 93AX(B)773
16S4 (S-1,5,9,13)	NaS(CH ₂) ₃ SNa + Br(CH ₂) ₃ Br	ethanol/butanol	D 2 + 2	chromatog., ethyl acetate/hexane	6.2			dd	34JA2177, 60JA4075
Me ₈ 16S4 (S-1,5,9,13) (3,3,7,7,11,11,15,15-octamethyl)	Me ₂ C(CH ₂ SNa) ₂ + Me ₂ C(CH ₂ Br) ₂	ethanol/butanol	D 2 + 2	chromatog., hexane	16	165–166			87AG(E)1171

3-keto-17S4 (S-1,5,9,14)	$(\text{CH}_2\text{CH}_2\text{S}(\text{CH}_2)_3\text{Cl})_2$ + $\text{OC}(\text{CH}_2\text{SH})_2$	10 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 50–65°C, 6–9 h	A 1 + 1	chromatog., dichloromethane/ hexane	68	96–99		k	93JOC5624
5,11,16,22- tetraoxo-20S4 (S-1,4,12,15)	$(\text{SCH}_2\text{CH}_2\text{S})\text{SnBu}_2$ + $\text{ClCO}(\text{CH}_2)_5\text{COCl}$	1–50 mmol dm ⁻³ chloroform reflux	2 + 2 template	HPLC	8–34	134–135		ee	84S140, 93CC538 94JA7081
15S5 (S-1,4,7,10,13)	$\text{S}(\text{CH}_2\text{CH}_2\text{SH})_2$ + $(\text{CH}_2\text{SCH}_2\text{CH}_2\text{OMs})_2$	Cs ₂ CO ₃ /DMF 85°C, 48 h	A 1 + 1	chromatog., ethyl acetate/hexane; recryst. ethanol	52	99–100		k, g ff	85JA2399
15S5 (S-1,4,7,10,13)	$(\text{CH}_2\text{SCH}_2\text{CH}_2\text{Cl})_2$ + $\text{S}(\text{CH}_2\text{CH}_2\text{SNa})_2$	butanol, 60°C	C 1 + 1	hexane extraction; chromatog., ethyl acetate/hexane; recryst. ethyl acetate/hexane	11	97.5–99		k	74JOC2079
2,3,8,9-dibenzo- 15S5 (S-1,4,7,10,13)	$\text{S}(\text{CH}_2\text{CH}_2\text{SC}_6\text{H}_4\text{S}^-)_2$ + $\text{BrCH}_2\text{CH}_2\text{Br}$	Fe(CO) template DMF, 100°C	1 + 1 template	recryst. dichloromethane	~ 10				88JOM(339)345
2,3,8,9-dibenzo- 15S5 (S-1,4,7,10,13)	$(\text{CH}_2\text{SC}_6\text{H}_4\text{S}^-)_2$ + $\text{S}(\text{CH}_2\text{CH}_2\text{Br})_2$	Fe(CO) ₂ template THF, reflux	1 + 1 template	recryst. dichloromethane	20			k	88JOM(339)345
15-keto-16S5 (S-1,4,7,10,13)	$\text{S}(\text{CH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{Cl})_2$ + $\text{OC}(\text{CH}_2\text{SH})_2$	10 mmol dm ⁻³ Cs ₂ CO ₃ /DMF 60–65°C	A 1 + 1	chromatog., dichloromethane/ hexane	25	110	gg	k	93JOC5624
12S6 (S-1,2,5,6,9,10)	$\text{HSCH}_2\text{CH}_2\text{SH}$	I ₂ /Et ₃ N/chloroform	E oxidative trimerization	sublime, 100°C/7 Pa torr		74	ii	hh	81S457, 86JA1271 89MI 930-06
16S6 (S-1,2,5,8,11,14)	$(\text{CH}_2\text{SCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{SH})_2$	I ₂ /Et ₃ N/chloroform	E 1-component oxidative cyclization						
16S6 (S-1,3,6,9,11,14)	$\text{S}(\text{CH}_2\text{CH}_2\text{SNa})_2$ + BrCH_2Br	ethanol, room temp.	C 2 + 2	recryst. from ethanol, then from chloroform	8.4		jj		89IC3573
16S6 (S-1,3,6,9,11,14)	$\text{CH}_2(\text{SCH}_2\text{CH}_2\text{SH})_2$ + $\text{CH}_2(\text{SCH}_2\text{CH}_2\text{Cl})_2$	Cs ₂ CO ₃ /DMF 50–55°C, 6h	A 1 + 1	recryst. from ethanol, then from chloroform	62			k	89IC3573
18S6 (S-1,4,7,10,13,16)	$\text{S}(\text{CH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{Cl})_2$ + $\text{S}(\text{CH}_2\text{CH}_2\text{SH})_2$	Cs ₂ CO ₃ /DMF 50–55°C	A 1 + 1	recryst. hexane/acetone	76–89	90–91	kk	k, g ll	87JA4328, 89IS122
18S6 (S-1,4,7,10,13,16)	$\text{S}(\text{CH}_2\text{CH}_2\text{SNa})_2$ + $\text{BrCH}_2\text{CH}_2\text{Br}$	butanol, 10°C	C 2 + 2	chromatog., ethyl acetate/hexane; recryst. ethyl acetate/hexane	8.1	92		mm, k	74JOC2079

Table 2 Continued.

Macrocycle	Reagents	Conditions	Technique ^a	Purification ^b	Yield (%)	m.p. (°C)	Crystal Structure	Note	Ref.
18S6 (S-1,4,7,10,13,16)	S(CH ₂ CH ₂ SCH ₂ CH ₂ Cl) ₂ + S(CH ₂ CH ₂ SNa) ₂	butanol, <25°C	D 1 + 1	chromatog., ethyl acetate/hexane; recryst. ethyl acetate/hexane	35	92			83JA131, 87JA4328
18S6 (S-1,2,6,10,11,15)	S((CH ₂) ₃ SH) ₂	I ₂ /Et ₃ N/chloroform	E oxidative dimerization	chromatog., dichloromethane/hexane	4	55–56		nn	81S457
2,3,11,12-dibenzo-18S6 (S-1,4,7,10,13,16)	(C ₆ H ₄ S ₂) ₂ Fe(CO) ₂ + 2 S(CH ₂ CH ₂ Br) ₂	THF, reflux	successive template additions		68	161	oo	k	88JOM(339)345
20S6 (S-1,4,7,11,14,17)	S(CH ₂ CH ₂ SH) ₂ + Br(CH ₂) ₃ Br	Cs ₂ CO ₃ /DMF 100°C, 48 h	A 2 + 2	Ni(II) complex	8	79		pp	90HAC375
20S6 (S-1,4,7,11,14,17)	S(CH ₂ CH ₂ SNa) ₂ + Br(CH ₂) ₃ Br	0.7 mol dm ⁻³ ethanol, reflux	D 2 + 2	chloroform extraction; recryst. ethanol	30	120–122			83IC3361
20S6 (S-1,4,7,11,14,17)	S(CH ₂ CH ₂ SH) ₂ + Br(CH ₂) ₃ Br	5 : 1 B(OPr) ₃ /Al(OPr) ₃ THF/MeOH, reflux 0.03 mol dm ⁻³	D 2 + 2	chromatog., dichloromethane/hexane	52		qq		93AG(E)436
9,19-diketo-20S6 (S-1,4,7,11,14,17)	S(CH ₂ CH ₂ SH) ₂ + OC(CH ₂ Cl) ₂	Cs ₂ CO ₃ /DMF 52°C, 9 h	B 2 + 2	MPLC, ethyl acetate/hexane	2.9–5.8	108	rr		89MI 930-03, 90HAC375
9,19-diketo-20S6 (S-1,4,7,11,14,17)	S(CH ₂ CH ₂ SH) ₂ + OC(CH ₂ Cl) ₂	5 : 1 B(OPr) ₃ /Al(OPr) ₃ THF/MeOH, reflux 0.03 mol dm ⁻³	D 2 + 2	chromatog., dichloromethane/hexane	42	107–108		ss	93AG(E)436
9,19-dimethylene-20S6 (S-1,4,7,11,14,17)	S(CH ₂ CH ₂ SH) ₂ + H ₂ C=C(CH ₂ Cl) ₂	5 : 1 B(OPr) ₃ /Al(OPr) ₃ THF/MeOH, reflux 0.03 mol dm ⁻³	D 2 + 2	chromatog., dichloromethane/hexane	67			ss	93AG(E)436
21S6 (S-1,4,8,11,14,18)	CH ₂ (CH ₂ SCH ₂ CH ₂ SNa) ₂ + (CH ₂ S(CH ₂) ₃ Cl) ₂	butanol	C 1 + 1	chromatog., ethyl acetate/hexane; recryst. ether/hexane	9.7	64–65		k	74JOC2079

21S6 (S-1,4,8,11,14,18)	NaSCH ₂ CH ₂ SNa + Cl(CH ₂) ₃ Cl	butanol, 15–40°C	D 3 + 3	chromatog., ethyl acetate/hexane; recryst. ether/hexane	0.5		tt	74JOC2079
22S6 (S-1,4,7,12,15,18)	S(CH ₂ CH ₂ SH) ₂ + Cl(CH ₂) ₄ Cl	Cs ₂ CO ₃ /DMF 100°C, 48 h	A 2 + 2	chromatog., ethyl acetate/hexane	4	62	uu	90HAC375
24S6 (S-1,5,9,13,17,21)	S((CH ₂) ₃ SH) ₂ + Br(CH ₂) ₃ Br	Cs ₂ CO ₃ /DMF 70°C, 48 h	A 2 + 2	chromatog., dichloromethane	9	43	dd	86CC1083
2,3,8,9,14,15- tetrabenzo-24S8 (S-1,4,7,10,13, 16,19,22)	(CH ₂ SC ₆ H ₄ S [−]) ₂ + BrCH ₂ CH ₂ Br	Fe template, DMF, 100°C	2 + 2 template	chromatog., pentane			vv	91ZN(B)209

^aMethod A: Solution containing both thiol and halide added to base. Method B: Separate solutions of thiol and halide simultaneously added to base (matched addition). Method C: Separate solutions of thiolate and halide simultaneously added to solvent. Method D: Addition of one component to the other. Method E: Simultaneous addition of separate solutions of dithiol and iodine to triethylamine in chloroform. ^bChromatography performed with silica gel as stationary phase. ^cCrude yield was 87.5%, but fell to 63% after recrystallization from methanol. ^dOxidized to the disulfone in high yield by excess MCPBA. ^e80% yield was obtained by method B. ^fViscous oil, solidifies slowly at room temperature. ^gCommercially available (from Aldrich). ^hYield not optimized. ⁱPremature polymerization of the reaction mixture can occur if method A is attempted with 1,3-dichloropropan-2-one. No thioketal formation or Favorskii-type chemistry is observed. ^jCrystal structure shows a distorted [3232] conformation. ^kCAUTION! VESICANT STARTING MATERIAL! ^lSynthesis of 11S3 from 1,5,9-trithianonane and 1,2-dibromoethane has not been reported, but would offer the advantage of yielding 22S6-(S-1,4,8,12,15,19) as the only 2 + 2 addition product. The present choice of reagents also yields 22S6-(S-1,4,8,11,15,19). ^mHigher yields were obtained by using potassium carbonate and THF. The crystal structure of keto-11S3 shows an irregular conformation. ⁿCrystal structure shows a square [3333] conformation with one sulfur atom in a corner position and two in side positions. ^oConformation similar to that of 12S3; the OH group is exodentate. ^pCrystal structure of 10-keto-12S3 is disordered, but clearly displays a SCCSCCS "bracket" unit. ^qCrystallography shows the quadrangular [3232] conformation typical of cyclodecanes. Sulfur atoms occur at corner positions and in the shorter sides, replacing the most crowded CH₂CH₂ segments of the parent cyclodecane molecule. ^rAttempted 2 + 2 synthesis of 12S4 from ethanedithiol and 1,2-dibromoethane yields predominantly *p*-dithiane. ^sCrystallography shows square [3333] conformation with sulfur atoms in all four corner positions. ^tOf two possible [3333] conformations, the one with two corner sulfur atoms is preferred over the one with none. ^uThe structure presented in this paper is actually that of keto-14S4 (note aa) (91CC910). ^vCrystal structure shows quadrangular [4343] conformation. ^w0.2% 7S2 also isolated. ^xCrystal conformation of 6-methylene-14S4 is analogous to that of 14S4. The methylene group is perpendicular to the S4 plane. ^yThe alternative disconnection to Me₂C(CH₂SCH₂CH₂SH)₂ + Br(CH₂)₃Br avoids the mustard intermediate. Structure of Me₂14S4 is intermediate between those of 14S4 and Me₄14S4. ^zThe 2 + 2 synthesis from Me₂C(CH₂SH)₂ + BrCH₂CH₂Br has not been reported. The *gem*-dimethyl groups adopt exodentate orientation (corner positions), forcing the sulfur atoms into side positions of the [4343] conformation. ^{aa}Crystal structure shows four sulfur atoms occupying the four corners of a rectangle. All sulfur atoms are exodentate, and the carbonyl bond is approximately perpendicular to the ring. See note x. ^{ab}25% enhancement of yield occurs using Cs₂CO₃. Separation of isomers by fractional crystallization is tedious. ^{ac}The quadrangular [3535] conformation occurs in both crystalline modifications of 16S4, putting two sulfur atoms in corner positions and two in the sides. The square [4444] conformation with S atoms at all four corner positions is predicted to be lower in energy by MM2 calculations, but is not observed in the solid state. ^{ad}This procedure yields 8S2, 16S4 and 24S6 in a 0.85:1.19:1 ratio. Reaction of propane-1,3-dithiolate and 1,3-dibromopropane in butanol is reported to yield 5.2% 8S2, 6.2% 16S4 and 7.3% 24S6 (74JOC2079). ^{ae}Yields mostly the 1 + 1 product (90%) at 1 mmol dm^{−3}, but the 2 + 2 product predominates (26%) at 50 mmol dm^{−3}. ^{af}The reagent mixture must be kept cool to prevent premature polymerization. ^{ag}Crystal structure of 15-keto-16S5 shows two SCCSCCS "bracket" units (fused at S7), whose termini are linked by an endodentate CH₂COCH₂ group. ^{ah}8S4 (S-1,2,5,6) (51%) sublimates first (60°C/7 Pa). ^{ai}Crystal structure of 12S6 shows no evidence for ring strain. ^{aj}Structure consists of two SCCSCCS "bracket" units linked by CH₂ groups. ^{ak}Crystal structure of 18S6 shows two SCCSCCS "bracket" units linked in such a way as to provide two endodentate sulfur atoms. ^{al}Previous methods had afforded 18S6 in 1.7% (34JA2177) and 4% (77JOC2644) yields. ^{am}Also yields 16% *p*-dithiane, 4.8% 12S4 and 0.04% 9S3, the former two products arising from intrachain cyclization. ^{an}1,2,6-9S3 (73%) is the major product. ^{ao}Crystal structure of dibenzo-18S6 shows benzo groups linked by all-*anti* SCCSCCS runs. ^{ap}Yields and melting points reported for 20S6 prepared by the 2 + 2 condensation of 1,4,7-trithiaheptane and dibromopropane in Cs₂CO₃/DMF vary widely. ^{aq}Crystal conformation of 20S6 is derived by inserting CH₂ units into the crystal conformation of 18S6. ^{ar}Crystal structure of 9,19-diketo-20S6 shows two "bracket" SCCSCCS units linked by endodentate CH₂COCH₂ groups. ^{as}Only minor amounts of 1 + 1 product reported. ^{at}This procedure yields 0.5% 21S6, 4.6% 14S4, 16.2% 7S2. ^{au}Crystal structure shows rectangular [8383] conformation from fusion of two "bracket" SCCSCCS units by linear CCCC runs. 4% 11S3 was isolated as well (note 1). ^{av}Crystallography reveals a quadrangular conformation in which corner *o*-C₆H₄S₂ units are linked by *anti* SCCS bonds.

$[(9S3)Re(CO)_3]^+$ <88ZN(B)299> and $[(9S3)ReO_3]^+$ <90CC979> suggest potential application of crown thioethers to tumor imaging and therapy. Technetium is the most used radioisotope in diagnostic nuclear medicine; its γ -emission is ideally suited for imaging tumors and organs. ^{186}Re and ^{188}Re emit β -radiation which destroys tissue in its immediate vicinity. The crux of nuclear medicine is to maximize the contrast of a particular area by delivering a radioisotope preferentially to the target sites. One possible mechanism of delivery is "tuning" the redox potential of the radionuclide complex so that it localizes in hypoxic tumors. By adjusting the ring size, crown thioethers offer the ability to dramatically change the redox potential while holding other factors such as lipophilicity constant <91JA1600>.

9.30.10.3 Catalysis and Novel Reactivity

In the d^6 species $[(15S5)Rh(Cl)]^{2+}$ and $[(15S5)Ru(PPh_3)_2]^{2+}$, the macrocyclic S5 ligands provide the electronic attractions of a thioether-dominated donor set, but allow substrate binding at the metal crucial to catalytic activity <92POL2501>. Coordination of small molecules is exemplified by the complexes $[(9S3)Rh(C_2H_4)_2]^+$ <91CC253> and $[(Me_816S4)Mo(N_2)_2]$ <88JA4872, 89CC1320, 92CC1464>, the latter containing an electron-rich dinitrogen group which can be alkylated to yield a formal Mo(IV) complex. Hydride complexes such as $[IrH(9S3)_2]^{2+}$ <90JCS(D)1759>, *trans*- $[(syn-Me_414S4)RuHCl]$ <92JOM(428)C12> and *trans*- $[(syn-Me_816S4)RuHCl]$ <90CC342> have been described. Crown thioethers are also starting to appear as coligands in organometallic chemistry <88CL525, 92MI 930-03> while thiacyclophanes containing the —SCCSCCCS— linkage form cyclometallated platinum <91CC893, 92OM3063> and lead <92IC3286> complexes. Thiacyclophanes also act as host molecules in supramolecular complexes <93JOC964>. For example, West *et al.* have described the synthesis of a large molecular bowl containing a 24S6-type ring with thioethers as the only heteroatoms <89JA6846>.

9.31

Ten-membered Rings or Larger with One or More Nitrogen and Oxygen and/or Sulfur Atoms

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9.31.1 INTRODUCTION

This chapter deals with “heteromacrocycles” rather than smaller-ring heterocycles. Traditionally, heterocycles are three- to eight- or nine-membered rings that contain one or more noncarbon “heteroatoms.” Many, if not most, of the known heterocycles are aromatic compounds in which the noncarbon atoms contribute electrons to meet Huckel rule requirements. The crown ether situation contrasts with that of traditional heterocycles. The bulk of crown ether compounds contain 12 or more members and are aliphatic rather than aromatic. Those heterocycles that have cation binding properties usually contribute one or at most two donors to a cation’s primary solvation

sphere. In contrast, crown ethers or heteromacrocycles generally complex cations internally using four or more donor groups to stabilize the Lewis acid. This is illustrated in Figure 1.

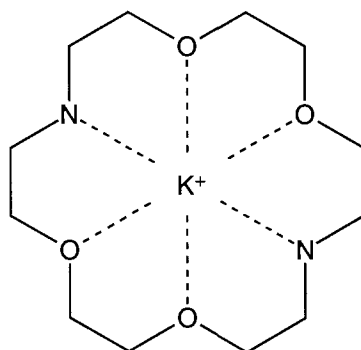
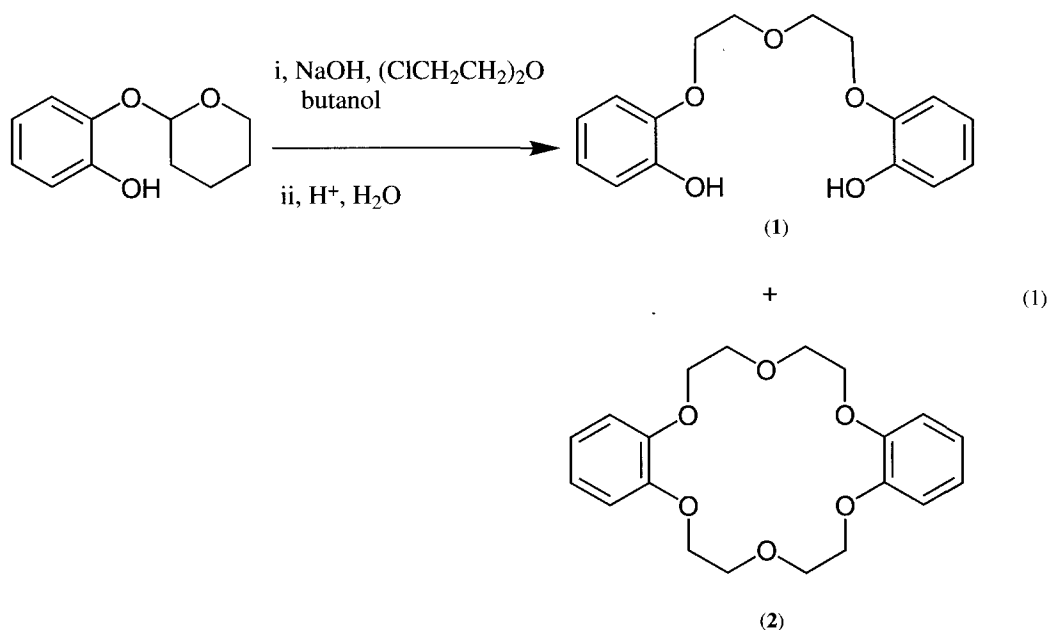


Figure 1

Heteromacrocycles were known before the commonly cited “beginning” of crown ether chemistry that occurred with Pedersen’s reports <67JA2495, 67JA7017, 88M1 931-01>. Lüttringhaus and Ziegler prepared a number of compounds that would now be called crown ethers in work reported in the 1930s <37LA(528)155>. A British patent was issued in 1957 for the synthesis of the compound now known as 12-crown-4 <55BRP785229>. Polyazamacrocycles were also well known before the advent of crown ether chemistry, having been prepared and studied by such pioneers as Goedken and Busch <71IC2679>, Curtis <68CCR3, 71JCS(A)2834>, and others.

9.31.1.1 Discovery of Crown Ethers

The crown ethers were discovered by Pedersen in the 1960s when he was searching for compounds that could bind calcium and had set as a goal the preparation of a bidentate bis(phenol). The target compound (1) is illustrated in Equation (1) along with the structure (2) that was isolated as an impurity. The latter resulted from the reaction between 2,2'-dichlorodiethyl ether and unprotected catechol. Pedersen was intrigued by the fact that this compound could complex cations even though it lacked a hydroxyl group as judged from the infrared spectrum. He correctly deduced the structure and set about a systematic exploration of variations in ring sizes, heteroatoms, fused groups, and the cations bound. It was the recognition that these compounds could bind alkali metal cations, which bind using *s*-orbitals rather than directed *d*- or *f*-orbitals, that made the discovery so important.



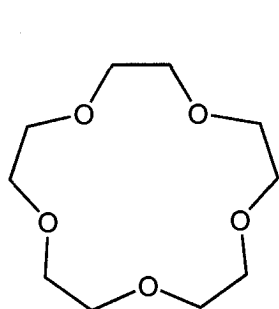
Pedersen prepared Corey–Pauling–Koltun molecular models of his new complexing agents and observed that they bound cations in a manner similar to the crowning of a regal head. He called the compounds crown ethers, inspired by the observation that they “crown” cations, and in part because their systematic names are impossibly cumbersome.

9.31.1.2 Nomenclature

The 18-membered ring compound containing oxygen as every third atom has the systematic name 1,4,7,10,13,16-hexaoxacyclooctadecane. Note that this is one of the simplest structures in the crown family. Pedersen devised a shorthand which presumed that crowns are cycles composed of ethyleneoxy ($\text{CH}_2\text{CH}_2\text{O}$) units. For the simple structures, it was necessary only to designate the overall ring size and the total number of heteroatoms. Thus, 1,4,7,10,13,16-hexaoxacyclooctadecane simplifies to 18-crown-6. Pedersen called the first crown (see above) “dibenzo-18-crown-6.” This name is not unequivocal since the benzo groups can be in other positions but the structure is the most readily accessible isomer.

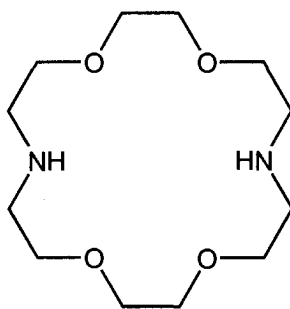
Some efforts have been made to improve the nomenclature system. Vögtle and Weber proposed to use the name “coronand” to describe a crown $\langle 73\text{ICA}65 \rangle$. A cation complex would thus be a coronate in analogy to the cryptand/cryptate nomenclature suggested originally by Lehn $\langle 69\text{TL}2885 \rangle$. In addition, these authors attempted to systematize the families further by referring to compounds possessing noncyclic polyethyleneoxy compounds $[\text{R}^1(\text{CH}_2\text{CH}_2\text{O})_n\text{R}^2]$ as “podands” and their complexes as “podates.” The latter term has, like the cryptand nomenclature, gained considerable acceptance. The coronand/coronate combination has been less widely used. It should be noted that an attempt to systematize crown nomenclature has been made by Fox $\langle 84\text{JCI}266 \rangle$. This method is based in part on the principles of nomenclature used in polymer chemistry.

For the time being, the nomenclature of crowns and other heteromacrocycles will likely remain imperfect due to the inherent complexity of the structures. Nevertheless, standard heterocycle naming practices should be applied but often have not been. For example, crowns containing O, S, and/or N should be numbered starting with O rather than one of the atoms differentiating the compound from a simple crown. The compound should likewise be named so the numbers are minimized and the numbering of heteroatoms is in the order O, S, N, if possible. Structures (3)–(5) illustrate this.



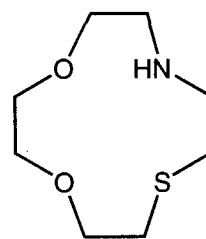
15-Crown-5

(3)



4,13-Diaza-18-crown-6

(4)



4-Thia-7-aza-12-crown-4

(5)

9.31.2 RING SIZES AND HETEROATOM PLACEMENT

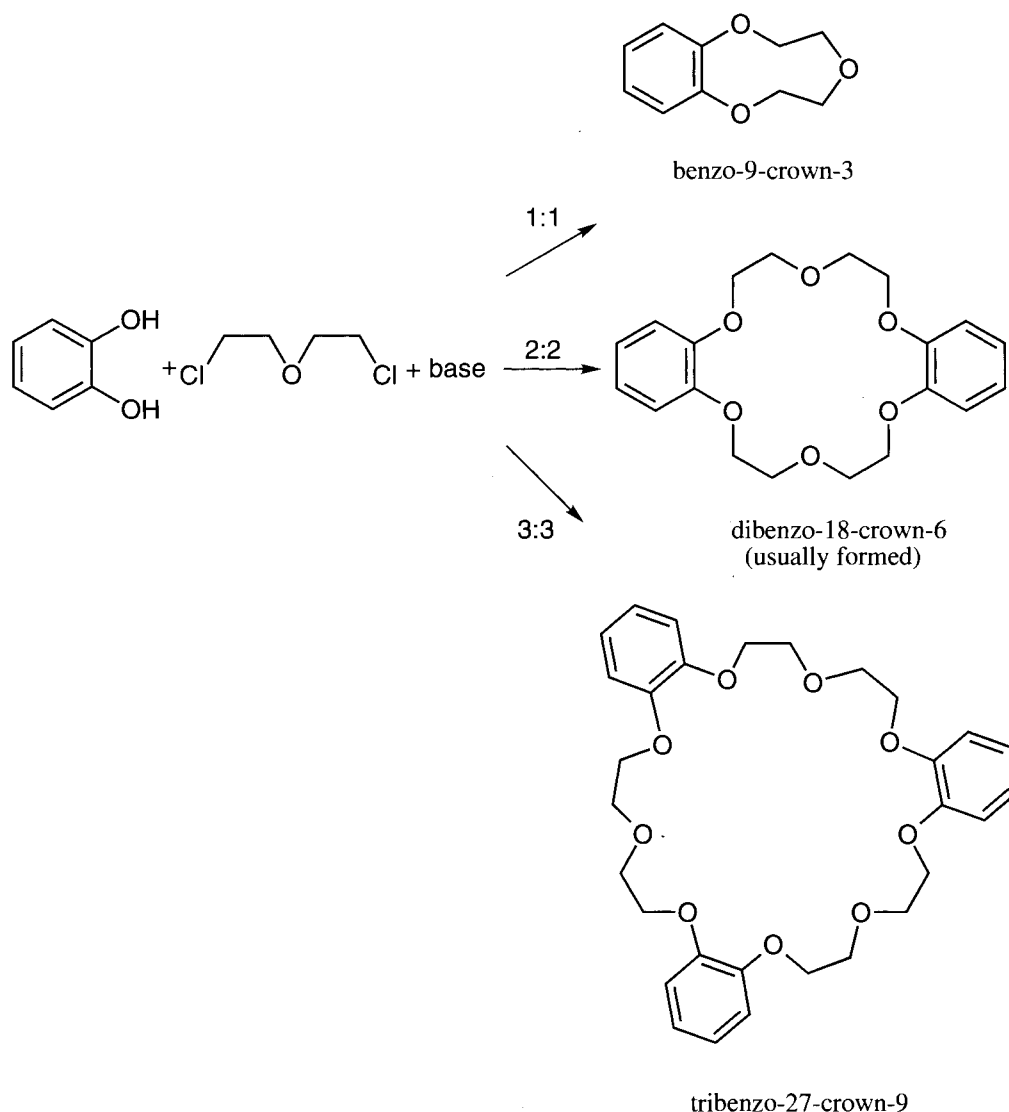
An important difference between the crown family and other heterocycles is that the latter have numerous representatives in all ring sizes but the crown ring sizes occur predominantly in increments of three atoms. This is because many crowns can trace their origins to the ethyleneoxy unit, $-\text{CH}_2\text{CH}_2\text{O}-$. There is no rule that requires the presence of this moiety but its nearly ubiquitous presence results from features that are both chemical and economic.

Ethylene oxide (EO, oxirane) is an inexpensive commodity chemical normally prepared by

oxidation of ethylene. Its strained, three-membered ring structure makes it susceptible to ring-opening reactions involving either nucleophiles or electrophiles. Reaction of ethylene oxide with simple alcohols leads to the family of commercially important solvents having the structure $\text{ROCH}_2\text{CH}_2\text{OH}$. Typical examples are methoxyethanol and butoxyethanol. Higher polymerization is possible which leads to the oligo(ethylene glycol)s or poly(ethylene glycol)s, "PEGs." The latter are available as half- or diethers but compounds of the type $\text{H}(\text{OCH}_2\text{CH}_2)_n\text{OH}$ are most common. These compounds are available under the name PEG-000 where "000" is the average molecular weight. Since the ethyleneoxy unit weighs 44 daltons, PEG-1000 contains an average of about 23 $(\text{CH}_2\text{CH}_2\text{O})$ units. The diols $\text{H}(\text{OCH}_2\text{CH}_2)_2\text{OH}$, $\text{H}(\text{OCH}_2\text{CH}_2)_3\text{OH}$, and $\text{H}(\text{OCH}_2\text{CH}_2)_4\text{OH}$ are particularly important as precursors to crown ethers and can be obtained in reasonably pure form.

Di- or triethylene glycol can be converted readily into the corresponding dichloride or ditosylate. Reaction of a diol with either the dihalide or the ditosylate under basic conditions can lead to crowns by the general reaction shown in Scheme 1. It should be noted that reaction of a diol $\text{HO}-\text{R}-\text{OH}$ with $\text{ClCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{Cl}$ in the presence of two equivalents of a suitable base can lead to more than one product. The stoichiometry for formation of the 1:1, 2:2, 3:3, etc. products is identical. Selective formation of a particular product will depend on the identity, size, and chemical properties of R and any templating ion present in the reaction mixture.

The synthesis illustrated in Scheme 1 is sometimes referred to as a "shotgun" approach because



Scheme 1

several possible products can be formed. The middle product, dibenzo-18-crown-6, is normally favored when the base is NaOH or KOH. This may be due to a complementarity of cation and hole sizes that is referred to as a "template effect." Ample evidence exists for the operation of a template effect but there are also many cases in which the efficacy of putative template ions is difficult to confirm. Dibenzo-18-crown-6 (the 2:2 product) is expected to form the most stable 1:1 (macrocycle:cation) complex with either Na^+ or K^+ and this, in turn, may drive the reaction by organization, precipitation, or crystallization.

An alternative synthetic approach that appears to demonstrate the importance of a template effect involves the formation of crowns directly from ethylene oxide in the presence of a Lewis acid such as BF_3 <81CC684>. Cyclic products of the type $(\text{CH}_2\text{CH}_2\text{O})_n$ are formed in which $n = 4, 5$, or 6 . The product composition is altered by addition of M^+BF_4^- salts where M is Li, Na, or K. In all cases, the bulk of the product appears to be dioxane, $(\text{CH}_2\text{CH}_2\text{O})_2$, but the proportion of 12-crown-4, 15-crown-5, and 18-crown-6 produced shifts to larger ring sizes when larger cations, rather than smaller ones, are added.

Virtually all crowns can also be prepared by sequential approaches. Indeed, these may afford higher yields of the desired product but much can be said for the simplicity of the shotgun approach wherever it is applicable. It should always be borne in mind, however, that while there is a great difference in the physical properties of $\text{HOCH}_2\text{CH}_2\text{OH}$ and $\text{HOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$, the differences are smaller for PEGs such as $\text{H}(\text{OCH}_2\text{CH}_2)_n\text{OH}$ or for crowns of the type $(\text{CH}_2\text{CH}_2\text{O})_n$ where $n = 5, 6$, or 7 . Thus, the preparation of a crown from tetraethylene glycol ditosylate contaminated by 10% of pentaethylene glycol ditosylate will produce a mixture of homologous crowns that differ very little in solubility properties, polarity, boiling point, etc. If the two homologues cannot be separated by crystallization, purification may be extremely difficult. Assessment of purity may also present problems as 15-crown-5 and 18-crown-6 both exhibit a single resonance in the ^1H NMR spectrum and each has exactly the same combustion analysis.

9.31.2.1 Heteroatom Position

It is relatively easy to ring-open ethylene oxide, more difficult to open oxetane, and tetrahydrofuran is relatively unreactive. The ease of ring opening oxirane favors its use in macrocycle synthesis. In addition, though, the placement of the heteroatoms that results from its use is particularly favorable.

Consider the situation of a ring containing several oxygen atoms in an otherwise aliphatic ring. When two oxygen atoms are adjacent, the linkage is called a peroxide and is relatively unstable. If two oxygen atoms are separated by a single carbon, the functional group is an acetal (of formaldehyde). Acetals are unstable to acid-catalyzed hydrolysis although they enjoy reasonable stability in neutral or basic solutions. Thus, the acetal function would not be generally appropriate for crown ether formation although it has been found that hydrolytic stability of certain macrocyclic acetals is enhanced by complexation with cations <78CC507>.

Separation of the oxygen atoms by three or four carbon atoms diminishes the "concentration" of donor groups within the macrocycle and also introduces potential conformational difficulties. The propylenedioxy residue, $-\text{OCH}_2\text{CH}_2\text{CH}_2\text{O}-$, can assume several different conformations. In order for the two oxygen atoms to be focused on a cation, the propylene unit must assume a "half-chair" arrangement (Figure 2). Likewise, when four methylenes are present, an unfavorable, eclipsed conformation is required to achieve the same heteroatom orientation.

9.31.2.2 Nitrogen and Sulfur Heteroatoms

Replacement of a macroring oxygen by either nitrogen or sulfur engenders several changes to the ring system as well as altering the binding properties of the heteromacrocycle. The observed changes, when sulfur is introduced, can be anticipated by the difference between this atom and oxygen. The C—Y bond lengths are longer and the C—Y—C bond angle is more acute when Y is S compared with O. The heterocycle's polarity is also reduced making it less soluble in water and more soluble in nonpolar solvents. Synthetic complications also attend this hypothetical exchange since the incorporation of sulfur must be planned from the outset of the synthesis.

Exchange of oxygen for nitrogen likewise decreases overall polarity. If the exchange is $-\text{NH}-$ for $-\text{O}-$, the possibility of protonation is dramatically increased. The pK_a observed for protonated

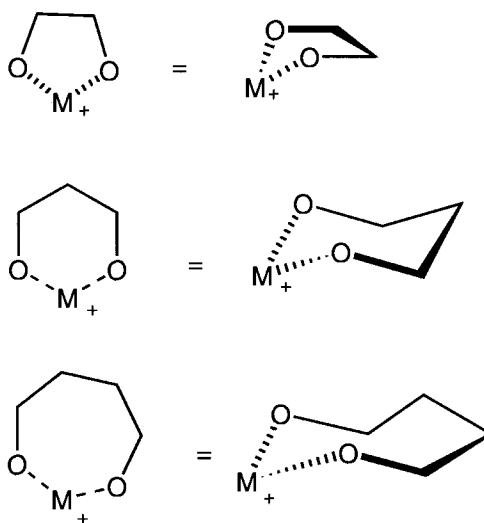


Figure 2

secondary amines is generally near 10, so some protonation is anticipated for simple azacrowns at neutral pH. Deprotonation of nitrogen ($>N-H \rightarrow >N^-$) is also possible although the pK_a of >30 requires that a very strong base be used.

The possibility of substituting nitrogen by numerous residues exists when nitrogen is present in the macroring, whereas this is not feasible for oxygen or sulfur. Substitution of an alkyl group on oxygen would lead to an unstable oxonium salt. Similar substitution on sulfur would lead to a sulfonium salt. The latter is expected to be far more stable than an oxonium salt but still reactive and generally quite rigid.

9.31.2.3 Subcyclic Units Containing Oxygen, Sulfur, or Nitrogen

Heteroatoms such as O, S, or N can be incorporated directly into the macroring to form derivatives of the simple crowns. For example, replacement of O by N in 18-crown-6 gives aza-18-crown-6. Similarly, a single sulfur in 15-crown-5 comprises the compound thia-15-crown-5. Combinations of O, S, and N are possible, as are macrocycles containing only nitrogen or only sulfur atoms. The latter have been explored by Ochrymowicz and Rorabacher and co-workers (77JOC2644, 79JA3511) and reviewed by Cooper (88ACR141). Macrocycles containing only nitrogen have been studied extensively for many years. The best known example of this group is “cyclam” which could also be called tetraaza-14-crown-4 or [14]aneN₄ (92T6175). This vast family of cation binders has been studied as complexing agents for transition metals and are reviewed separately in this volume. These “persulfur” and “pernitrogen” macrocycles are not discussed in this chapter except to note that replacement of any oxygen of a crown by one or more S or N moves the properties of that macrocycle in the direction of either extreme example.

A second means of incorporating S or N into a macroring is to incorporate a heterocycle within the macroheterocycle. The position of the subcyclic heteroatom is critical as it must be located within both the subunit and the larger ring. In addition, however, the smaller heterocycle may itself influence the macrocycle's chemistry. Consider, for example, the incorporation of furan or tetrahydrofuran into 18-crown-6, as illustrated in Figure 3. How does incorporation of furan into 18-crown-6 alter the structure and/or binding properties of the parent compound? There are actually several differences. Furan is aromatic as a result of the two double bonds and the oxygen lone pair. The latter must be contributed in the π sense meaning that hybridization of the oxygen is sp^2 rather than sp^3 . Because of the greater s -character in the former, it is less basic and therefore a poorer donor for a Lewis acid. The orientation of the furanyl oxygen's electrons is directly toward the “center” of the macrocyclic cavity. Although this might seem especially favorable, the other oxygen atoms each have two electron pairs directed above and below the mean plane of the ring. Normally,

when binding a suitably sized cation, 18-crown-6 will adopt a D_{3d} conformation in which alternate oxygens are above and below the mean plane. This arrangement tends to minimize the complex's overall dipole. This arrangement is not possible for furanyl-18-crown-6. If binding to an ammonium cation is the object, the lack of symmetry has another implication. Not only must the furan tilt upward to form a hydrogen bond to NH_4^+ , but also the two alternate (3 *H*-bond) binding modes are nonequivalent (Figure 4).

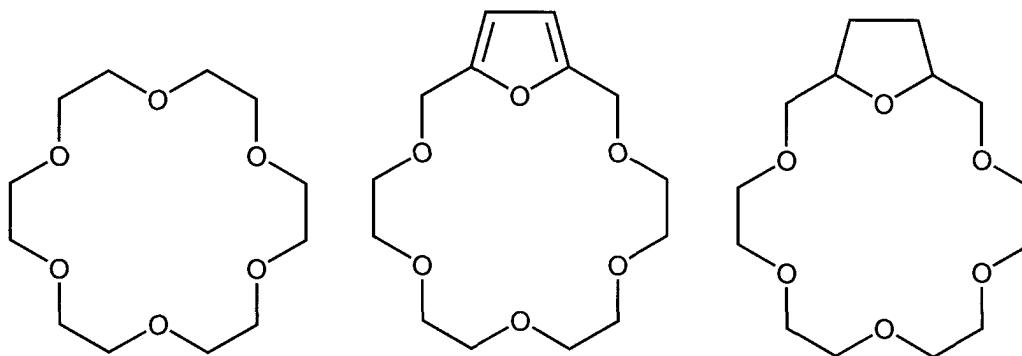
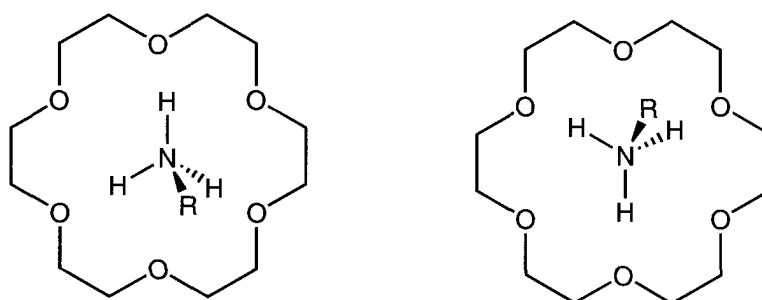
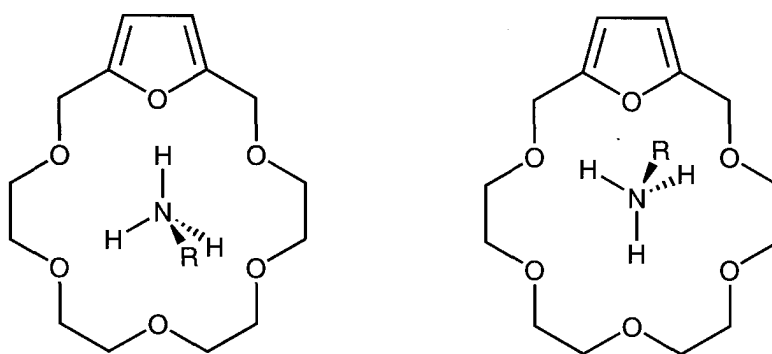


Figure 3



Equivalent

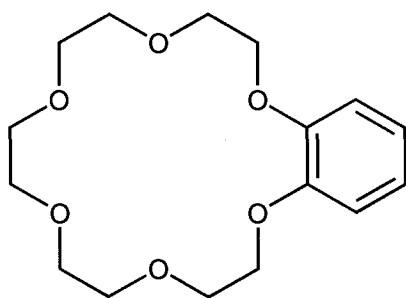


Nonequivalent

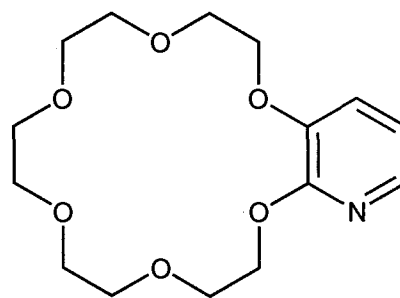
Figure 4

A second consideration is apparent for tetrahydrofuranyl-18-crown-6 (Figure 3). In this case, the oxygen is sp^3 -hybridized, so binding of an alkali metal cation by it or 18-crown-6 (see above) should not differ much on that account. The drawing of tetrahydrofuranyl-18-crown-6 does not, however, illustrate the isomer problem. The macroring is attached to tetrahydrofuran at the 2- and 5-positions but the stereochemistry could be *cis* or *trans*. These two possibilities are identical neither to each other nor to 18-crown-6. In many such cases, stereochemistry is not established and the details of differences, if any, in cation binding are uncertain.

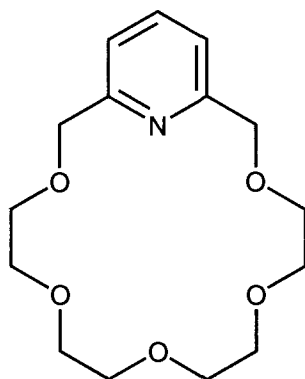
Structures (6)–(8) are three 18-crown-6 derivatives; (6) is benzo-18-crown-6; (7) is a pyrido-18-crown-6 derivative in which the nitrogen heteroatom is within the smaller (subcyclic) heterocycle but outside the crown macroring; in (8) the aromatic ring is substituted *meta* rather than *ortho* and nitrogen is within both rings.



(6)



(7)



(8)

Benzo-18-crown-6 is a poorer cation binder for appropriately-sized K^+ than is 18-crown-6, in part because it is inherently less flexible than the latter. A more significant consideration may be the hybridization of the *ortho* oxygen atoms attached to benzene. Resonance between the oxygen electron pairs and the aromatic ring means that these two oxygens are hybridized sp^2 rather than sp^3 . As noted above, sp^2 electron pairs on oxygen are less basic than are sp^3 electrons. In addition, the O—C—C—O sequence is planar reducing the macroring's overall flexibility.

When the benzene ring is replaced by pyridine, the same considerations apply. There is a new factor introduced, however. Pyridine nitrogen has an electron pair which is exocyclic (to the macroring). It may compete with internal complexation sites or it may be protonated. If nitrogen is protonated, the pyridine ring would be extremely electron withdrawing and the effect would be felt on the adjacent oxygen atoms. Even if not protonated, pyridine is electron poor compared to benzene so the endocyclic heteroatom donor array would be reduced in strength anyway.

Structure (8), pyrido-18-crown-6 in which nitrogen is within both heterocycles, can also be protonated. When this occurs, some attenuation of the adjacent oxygens' donicity no doubt occurs although these heteroatoms are not directly conjugated to pyridine. A more dramatic effect results

from the fact that a positive charge has been introduced directly into the binding cavity of the crown. The charge is expected to repel Lewis acidic cations that normally would be bound by the neutral structure. In contrast to furano-18-crown-6, pyrido-18-crown-6 is expected to bind ammonium cations strongly since pyridine nitrogen is an excellent donor.

9.31.3 AZACROWNS

Azacrowns are those heteromacrocycles that contain one or more nitrogen atoms. Macrocycles containing only nitrogen or only nitrogen and sulfur are considered elsewhere in this volume so the present discussion focuses on compounds in which nitrogen replaces an oxygen atom in an otherwise standard crown ether.

9.31.3.1 Azacrown Precursors

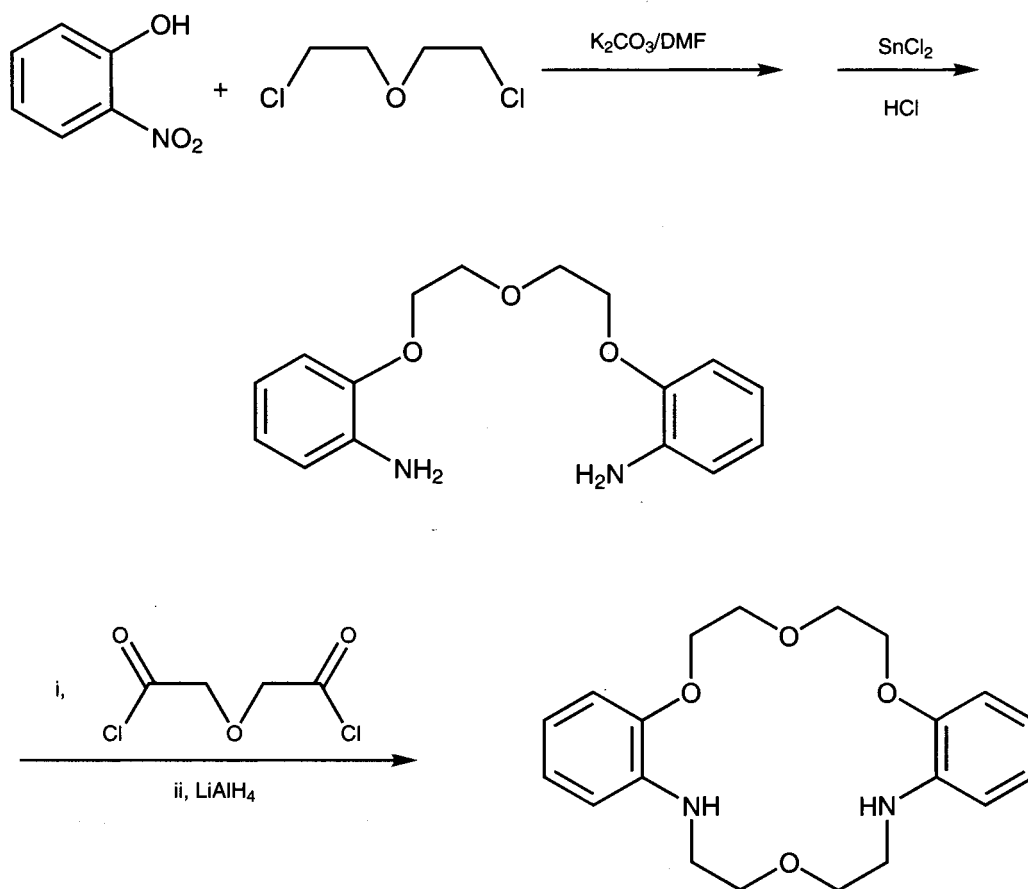
Many strategies can be adopted to prepare azacrown compounds. The macrocycles can be prepared from oligo(ethylene glycol) amines as are all-oxygen crowns. Of course, this requires the preparation of the appropriate precursors. Dietrich *et al.* used the Gabriel synthesis to prepare $\text{H}_2\text{N}(\text{CH}_2\text{CH}_2\text{O})_2\text{CH}_2\text{CH}_2\text{NH}_2$, an important cryptand precursor <69TL2885>. In this sequence, triethylene glycol was treated with PBr_3 in pyridine to form the dibromide. Reaction with potassium phthalimide in DMF gave the expected bis(phthalimide), which was cleaved using hydrazine and then acid. Reaction of the dibromide noted with *N*-tosylbenzylamine affords the *N*-tosyl-*N*-benzyl compound $\text{PhCH}_2(\text{Ts})\text{N}(\text{CH}_2\text{CH}_2\text{O})_2\text{CH}_2\text{CH}_2\text{N}(\text{Ts})\text{CH}_2\text{Ph}$. This can be detosylated to afford the bis(benzyl) derivative <80CCC1567>. A more straightforward approach to the diamine precursor was reported by King and Krespan who heated triethylene glycol dichloride with ethanolic ammonia <74JOC1315>. Several groups have prepared triethylene glycol diamine ($\text{H}_2\text{NCH}_2(\text{CH}_2\text{OCH}_2)_n\text{CH}_2\text{NH}_2$) by conversion of either its tosylate or chloride into the corresponding diazide, e.g. $\text{N}_3\text{CH}_2(\text{CH}_2\text{OCH}_2)_n\text{CH}_2\text{N}_3$. This substitution has been effected by a phase transfer catalytic method <76S823>. The azide was then reduced using either LiAlH_4 <77JINC1587> or ethanolic H_2S <80TL643>.

The nitro group has been used successfully by Lockhart and Thompson as a nitrogen precursor in the preparation of certain dibenzodiazacrowns <77JCS(P1)202>. Thus, 2-nitrophenol is treated with diethylene glycol dichloride and K_2CO_3 in DMF. The resulting dinitro derivative is reduced using stannous chloride and acid. Cyclization is then effected by using a diacid dichloride such as $\text{ClCOCH}_2\text{OCH}_2\text{COCl}$ which affords the diamide. Reduction with ($\text{LiAlH}_4/\text{THF}$) gives the diazacrown as shown in Scheme 2. Other uses of the nitro group as a masked amine have been reported by Högberg and Cram <75JOC151> and Pedersen and Bromels <74USP3847949>.

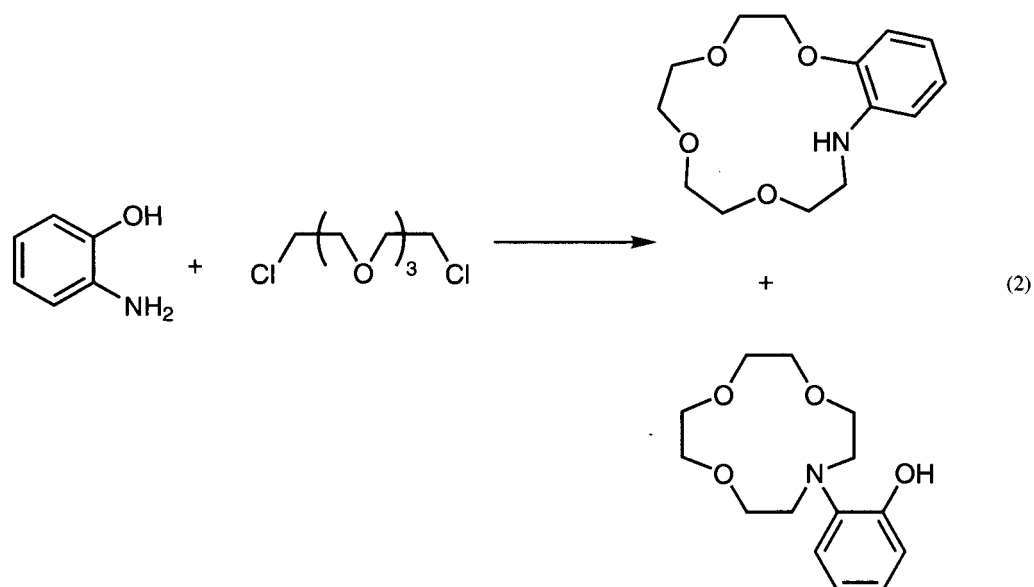
9.31.3.2 Monoazacrowns

The single nitrogen-containing derivative of 15-crown-5 is called aza-15-crown-5; the prefix "mono" is unnecessary. When two or more nitrogen atoms are present, the standard prefixes di-, tri-, etc. are applied. The term "monoazacrowns" is used here to designate the class of macrocycles containing a single nitrogen in combination with oxygen atoms as the macrocyclic donor array.

In an attempt to prepare a benzoaza-15-crown-5 derivative, Lockhart *et al.* used 2-aminophenol as a building block along with tetraethylene glycol dichloride <73JCS(P1)577>. The desired azacrown was formed along with one of the first lariat ethers (Equation (2)) <80CC1053>. This reaction nicely illustrates the challenge of preparing azacrown compounds. Unlike those containing oxygen or sulfur, the third valence of nitrogen must normally either be utilized or protected.

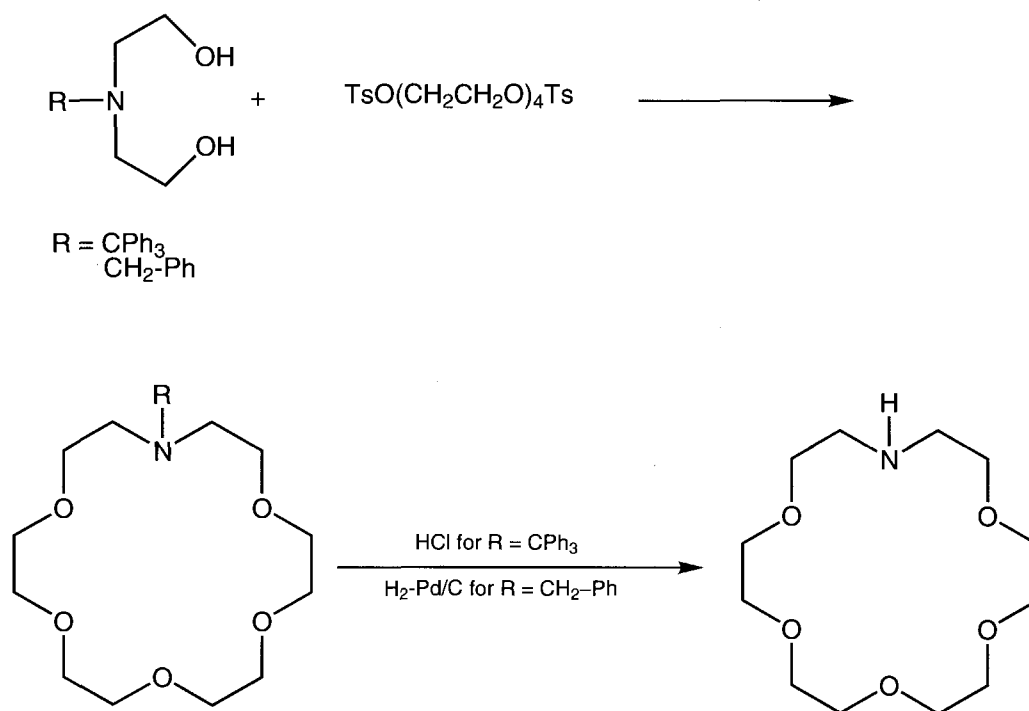


Scheme 2



A number of approaches have been used for nitrogen protection. The triphenylmethyl (trityl) group was used by Greene ^{<72TL1793>} and by Pedersen and Bromels ^{<74USP3847949>}. Greene's early synthesis of aza-18-crown-6 is shown in Scheme 3. In this approach, diethanolamine was converted into *N*-trityldiethanolamine which was then allowed to react with tetraethylene glycol ditosylate and potassium *t*-butoxide in THF. The *N*-tritylated crown was isolated in 43% yield and then

deprotected by treatment with HCl at room temperature (65% yield). An alternative protecting group for nitrogen in this context is benzyl which may be removed by acid but is more readily cleaved by hydrogenolysis. Thus *N*-benzyl diethanolamine, tetraethylene glycol ditosylate, and NaH react at room temperature in DMF to afford *N*-benzylaza-18-crown-6 (>25% yield). Hydrogenolysis afforded the parent compound in approximately 25% overall yield <77TL317>. This compares with ~28% using the trityl protecting group. These two approaches are summarized in Scheme 3.



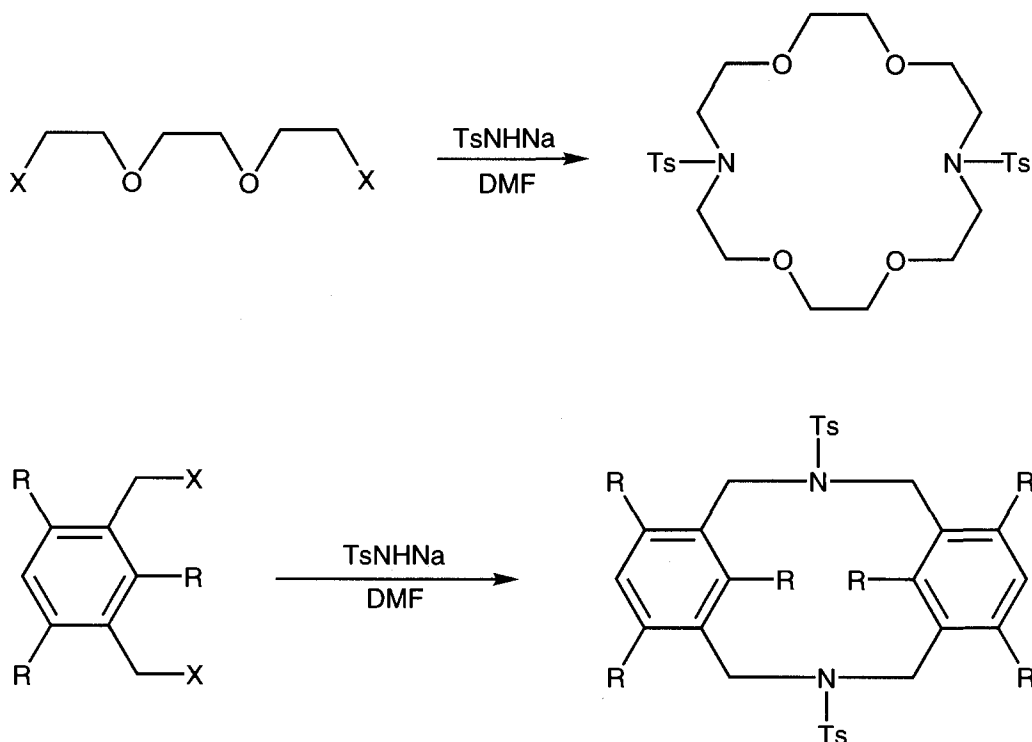
Scheme 3

Perhaps the most popular protecting group for secondary nitrogen has been toluenesulfonyl. The advantages of the *N*-tosyl group are ease of formation and crystallinity of products. In particular, the latter enhances the prospects for purification. Formation of the tosylamide from a primary amine acidifies the attached proton and reduces the base power required for deprotonation. The disadvantage is that removal of the sulfonamide is difficult in the best of cases and essentially impossible in the worst. The focus in macrocycle formation is normally successful cyclization; removal of the protecting group is therefore sometimes overlooked. Removal of the tosyl group from nitrogen is required, however, for cation binding since nitrogen in a tosylamide is partially positive. Many approaches have been reported for tosyl deprotection including electrochemical <79TL1059>, sodium naphthalenide <77JINC1587>, sodium in isopentyl alcohol <80CCCC1567>, HBr/phenol <77LA1344>, HBr/HOAc/phenol <91T8863>, and LiAlH_4 <75JA5022>. These methods require varying degrees of vigor and afford different levels of success.

Tosylamide (TsNH_2) may itself be deprotonated by base and serve as the nucleophile in a double ring closure with a dihalide. Azacrown (1 : 1) and diazacrown (2 : 2) products can be formed by this approach (Scheme 4) <85H(23)1881, 88JOC3521>.

The tosyl protecting group is still one of the most widely used protecting groups for the preparation of azacrowns because, despite numerous difficulties, it can usually be removed. In one case in particular, removal has proved effective even though the conditions seem at first to be drastic. Richman and Atkins used 97% sulfuric acid at 100°C to detosylate tetratosyltetraaza-12-crown-4 ([12]ane N_4). After a 48 h reaction time, the yield was >90% <74JA2268>. Despite the high yield in this case, cleavage of the *N*-tosyl group using LiAlH_4 is still the most often used approach.

The benzyloxycarbonyl protecting group, commonly used in peptide synthesis, has also been used in the preparation of azamacrocycles. Sutherland and co-workers <76CC639> prepared a benzodiazaz-15-crown-4 derivative from α,α' -dibromo-*m*-xylene <79JCS(P1)1089>. Although not specified in the report, deprotection was presumably accomplished using standard conditions (HBr/HOAc).



Scheme 4

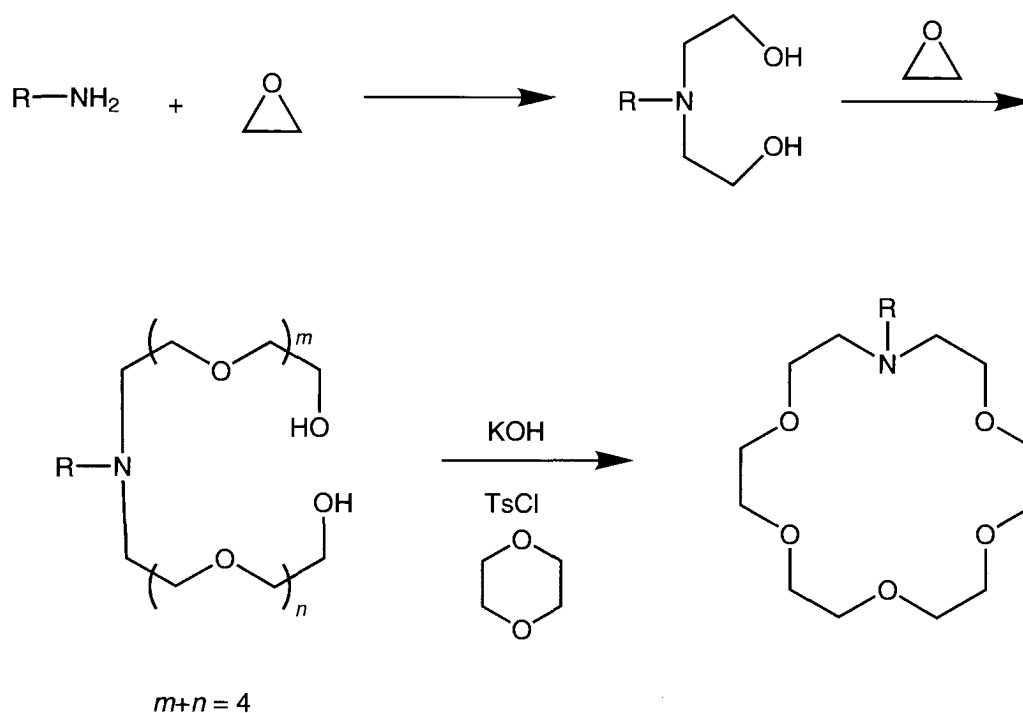
Okahara and co-workers developed a cyclization method for the preparation of azacrown compounds that has proved efficacious for a number of aliphatic azamacrocycles $\langle 78\text{TL}4273, 80\text{MI} 931\text{-}01, 83\text{BCJ}3073 \rangle$. In this sequence, a primary amine is treated with ethylene oxide to form the *N*-substituted diethanolamine. This is treated further with ethylene oxide to extend the ethyleneoxy chains. The mixture of precursors having the same total number of ethyleneoxy groups is then treated with toluenesulfonyl chloride and potassium hydroxide in dioxane (Scheme 5). Presumably, one of the available hydroxyl groups is tosylated and then displaced by the other as an alkoxide. Since the two ends of the chain react with each other, the individual lengths are immaterial so long as the final ring size is uniform.

A general alternative for the formation of azamacrocycles is lactam formation followed by reduction. Lactone formation is less satisfactory because reduction of the ester to the ether, while possible, normally results in ring cleavage. Diacyl chlorides have been used since Lehn and co-workers incorporated the sequence in the first cryptand synthesis $\langle 69\text{TL}2885 \rangle$. Several heterocycles have replaced chloride as a means of acyl activation. Notable among these are thiazolidine-2-thione $\langle 80\text{CL}159, 81\text{H}(15)1037, 89\text{TL}1369 \rangle$, piperidine *N*-oxide $\langle 71\text{TL}2697, 76\text{TL}1669 \rangle$, and 3,5-dimethylpyrazolidine $\langle 84\text{TI}927 \rangle$. Amino-ester interchange was also used successfully by Tabushi *et al.*, although the reaction times required for cyclization to occur were days to weeks $\langle 76\text{TL}4339, 77\text{TL}1049 \rangle$. An advantage of such activating groups over chloride is that HCl is not a by-product that can protonate other nitrogen atoms in the macrocycle and hamper workup.

Nitrogen can be incorporated in the macroring by inclusion of a small-ring nitrogen heterocycle such as pyridine or pyrimidine. Three approaches should be noted. If the pyridyl unit is incorporated as a 2,6-bis(methyleneoxy)pyridine derived from lutidine, the precursor will normally be a lutidine dihalide or diol. In the case of sulfur, the diol would be a dithiol. If the pyridyl unit is to be attached by 2,6-aminomethyl groups, amide formation followed by reduction is a possibility. In the event that the heterocycle will be attached directly to a macroring heteroatom, nucleophilic aromatic substitution may be useful.

Pyrido-18-crown-6 was prepared ($\sim 30\%$ yield) by reaction of 2,6-bis(hydroxymethyl)pyridine with potassium *t*-butoxide and tetraethylene glycol in (40:1) THF:H₂O $\langle 74\text{JA}6811 \rangle$. A similar strategy was used (see Section 9.31.4) to prepare a bis(pyrido)tetrathia-24-crown-8 derivative.

The ester analogue of pyrido-18-crown-6 was obtained ($\sim 80\%$ yield) by heating (45–50°C) 2,6-dichlorocarbonylpyridine and tetraethylene glycol in 1:1 benzene:THF for 2–3 days $\langle 78\text{JHC}825 \rangle$.



Scheme 5

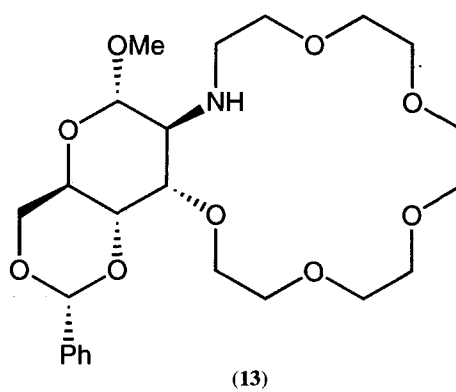
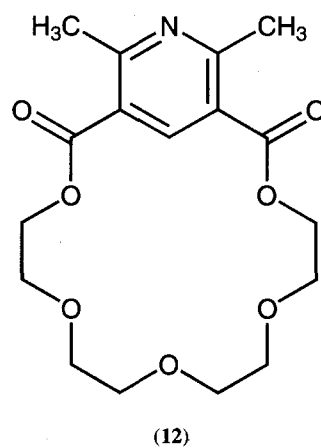
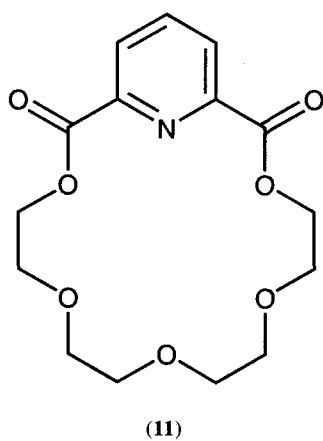
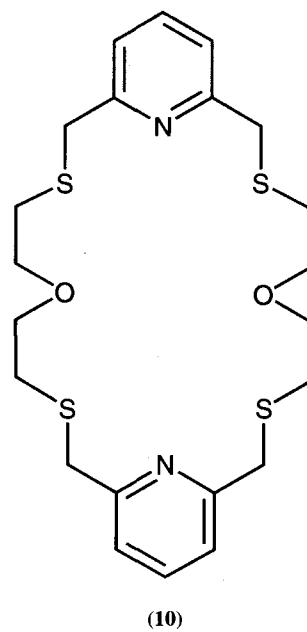
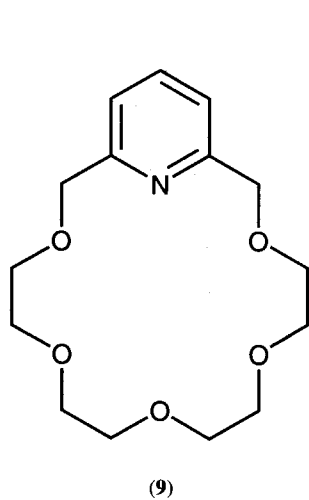
It is also interesting to note that Van Bergen and Kellogg have used the Hantzsch condensation to construct the pyridine ring *in situ* ^{<76CC964>}. Construction of the pyridine unit from the β -keto ester places the pyridine nitrogen exocyclic (**12**), unlike (**9**)–(**11**) in which the pyridine N is endocyclic.

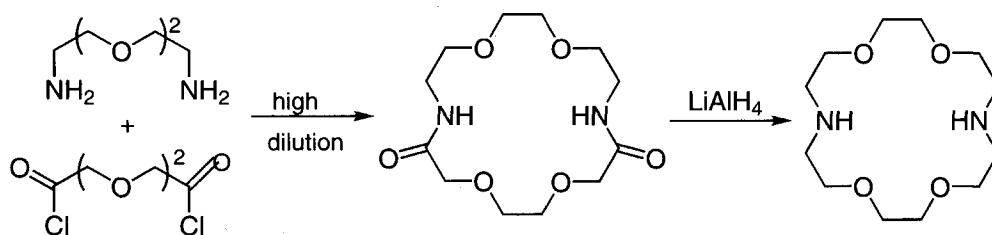
An important heterocyclic unit that has been incorporated in numerous all-oxygen crowns is the sugar. Hain *et al.* ^{<78TL625>} and Stoddart and co-workers ^{<79TL465>} included a variety of sugars as chiral appendages to macrocycles. In 1990, Bakó *et al.* have prepared examples including (**13**) in which an amino sugar is incorporated as part of the structure in such a way that the macrocyclic ring constitutes an azacrown ^{<90JCS(P1)1235>}.

9.31.3.3 Diazacrowns

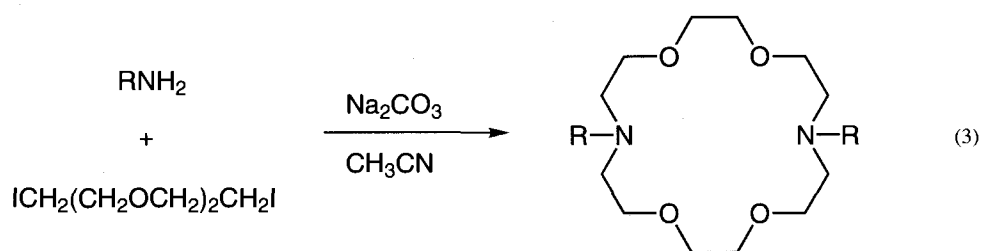
The development of the cryptands (see below) fostered an interest in the preparation of diazacrowns, as these were requisite precursors ^{<69TL2885>}. The approach used originally by Dietrich *et al.* for the preparation of cryptands was to first form 4,13-diaza-18-crown-6 and then add the third strand in a separate step. Preparation of the crown was accomplished by reaction between triglycyl chloride [$\text{ClCO}(\text{CH}_2\text{OCH}_2)_3\text{COCl}$] and triethylene glycol diamine [$\text{H}_2\text{NCH}_2(\text{CH}_2\text{OCH}_2)_3\text{CH}_2\text{NH}_2$] at high dilution. The resulting macrocyclic bis(lactam) was reduced (LiAlH_4) to give the cyclic tetraether diamine. This sequence is illustrated by Scheme 6. Formation of the cryptand is accomplished by repeating this reaction to convert the macrocycle to the macrobicyclic.

Gatto and Gokel found that the reaction of primary aliphatic amines with diethylene glycol diiodide in the presence of Na_2CO_3 directly gave diaza-18-crown-6 products (Equation (3)) ^{<84JA8240>}. If benzylamine was used as starting material, *N,N'*-dibenzyl-diaza-18-crown-6 was the product. This in turn could be cleaved by treatment with H_2 and Pd/C to give the parent diazacrown. Alkylation of the parent afforded other sidearmed derivatives. When aromatic, rather than aliphatic, amines (i.e. anilines) were used in this reaction, the only product obtained was the *N*-substituted aza-9-crown-3 product and this was isolated in low yield after a long reaction time. It is very interesting to note that Calverley and Dale had previously shown that the reaction involving triethylene glycol diiodide conducted under similar conditions gave the *N*-substituted-aza-12-crown-4 products ^{<81CC684>}. A less direct, but more versatile, synthesis of these compounds has been reported ^{<86JOC5373>}.

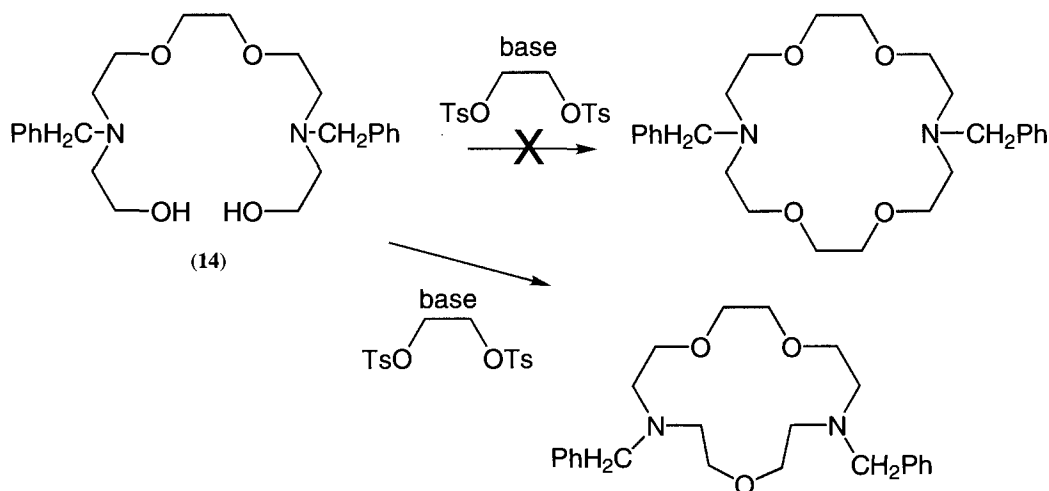




Scheme 6



Bradshaw and Krakowiak uncovered a similarly surprising capriciousness in their attempted synthesis of *N,N'*-dibenzyl-diaza-18-crown-6 (88JOC1808). The dibenzylated diol (**14**), shown in Scheme 7, was treated with 1,2-ditosyloxyethane and base in the expectation that the 18-membered ring would result from a two-bond-forming closure process. Instead, trans-tosylation apparently occurred and the isolated product was instead *N,N'*-dibenzyl-4,13-diaza-15-crown-5.



Scheme 7

Börjesson and Welch found that diazacrowns could be prepared from diols by treatment first with TsCl and then with TsNH₂. A repetition of the sequence afforded the tosyl-protected diaza-macrocycles which could then be converted into the parent structures (Scheme 8) (91ACS621).

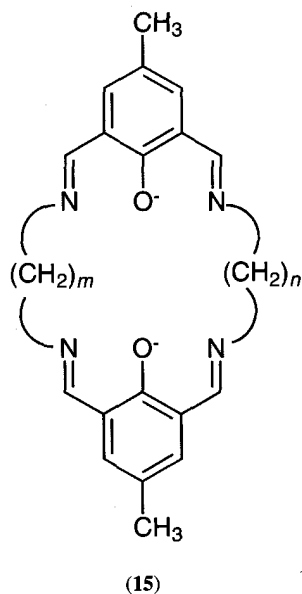
Another useful approach to azamacrocycles involves the formation of cyclic Schiff bases or imines. This approach has been widely used in the formation of all-nitrogen macrocycles, especially those of the cyclam (tetraaza-14-crown-4) family (88CSR69). An example of this approach is found in the work of Lindoy and co-workers. Diether formation by reaction of salicylaldehyde with 1,2-dibromoethane gave the diether dialdehyde. 1,4-Butanediamine was then condensed with the dialdehyde to give the bis(imine). Reduction of the imine was accomplished by using sodium borohydride in methanol to afford the diazadibenzo-16-crown-4 (Scheme 9) (75IC1322, 77AJC2095). Mixed macrocycles containing a 2,6-methyleneoxypyridine subunit and two secondary amine nitrogens have been studied by Fenton (93PAC1493).

An interesting variation of this "Schiff base" approach was reported by Okawa and co-workers

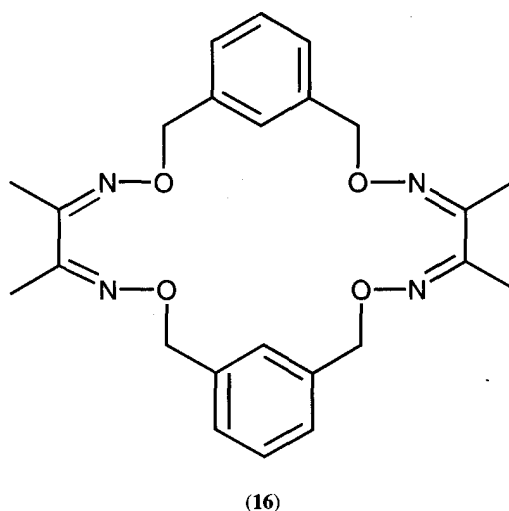


<90BCJ3337>. In this case, 2,6-diformyl-4-methylphenol is allowed to react with a diamine such as 1,3-diaminopropane. The imine formation reaction is templated by Pb(II) and formation of four bonds leading to the tetraimine occurred in 64% yield (Pb complex). In the strictest sense, this compound does not possess both O and N in the macroring, but both atoms are present in the

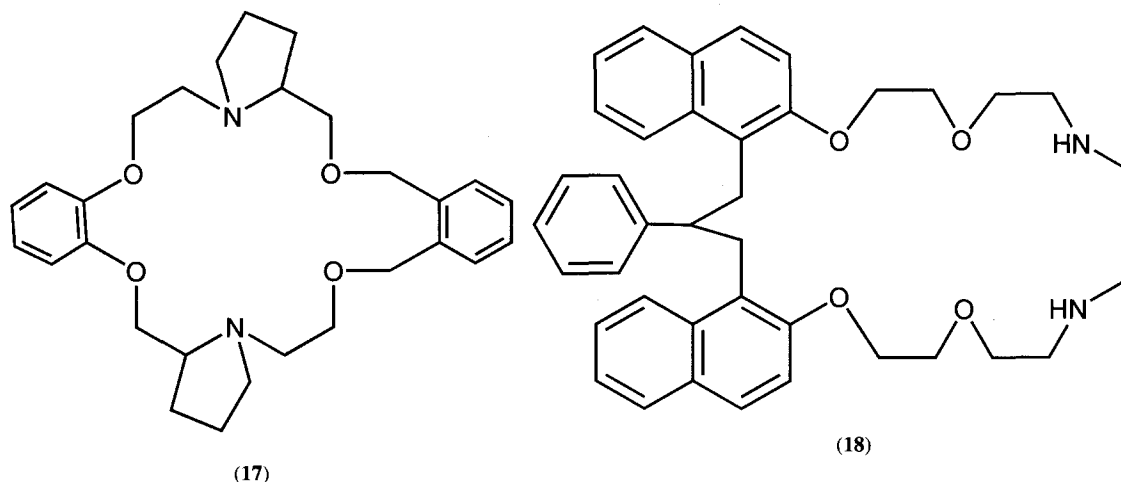
donor group array. Indeed, the compound (15) ($m = n = 3$) complexes two lead atoms. According to the solid state structure, each Pb shares both phenoxide anions and two of the four available nitrogen atoms.



An alternative method for incorporating unsaturated nitrogen is in the $C=N-O$ functional group. Two approaches were used early on to afford this substitution pattern. De Sarlo *et al.* cyclooligomerized acetonitrile to form $[C(CH_3)=N-O]_6$, an analogue of both 18-crown-6 and hexaaza-18-crown-6 which contains 12 heteroatoms (77CC549). Vögtle and co-workers used biacetyl bis(oxime) as the $C=N-OH$ precursor to compounds of type (16) (78JCR(M)1001, 78JCR(S)72). Reaction between biacetyldioxime and a pentaethylene glycol derivative gives a diaza-17-crown-7 macrocycle (structure not shown).

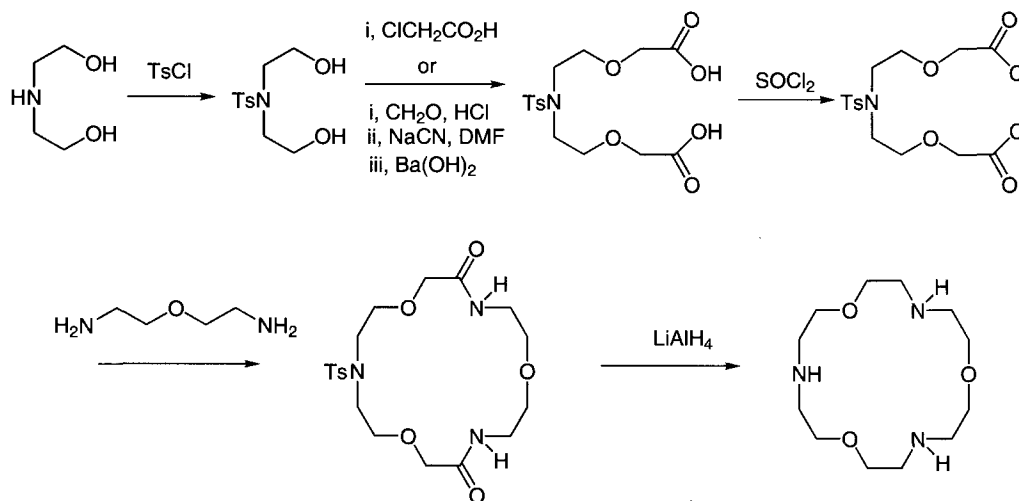


Two intriguing diazacrowns represent the interest that this class of compounds has engendered over more than two decades especially in terms of controlling macrocycle shape. Wudl and Gaeta reported the formation of a bis(amide) derived from proline (72CC107). Reduction afforded one of the earliest chiral diazacrown compounds (17). In 1993, Lockhart and co-workers prepared a diazacrown (18) which has a propeller-shaped, polyaromatic group attached (93JCS(P2)1259).



9.31.3.4 Tri- and Polyazacrowns

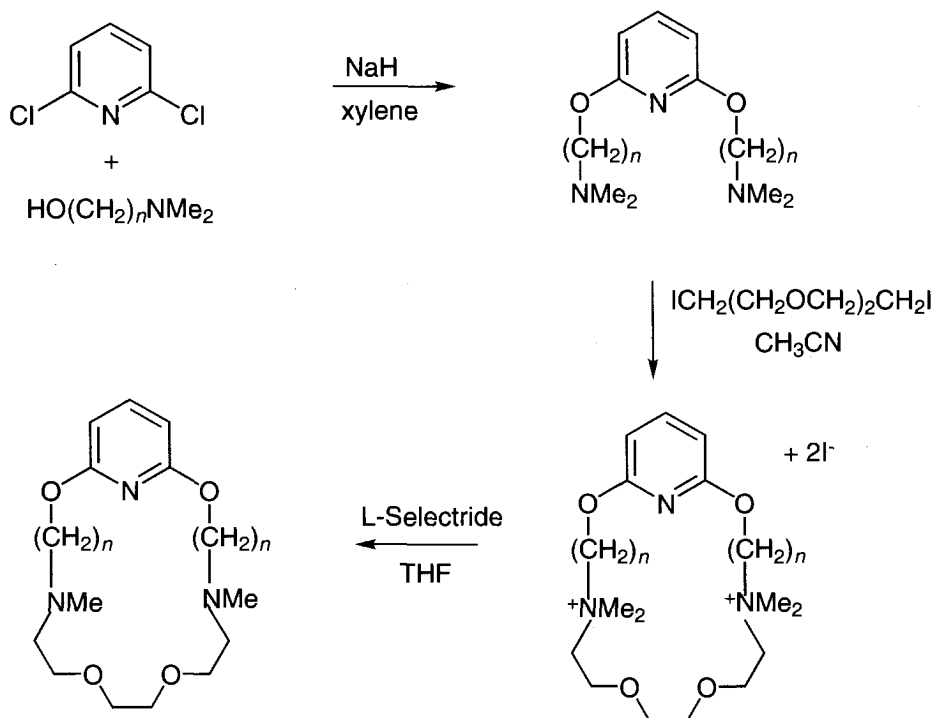
Lehn and co-workers required triaza-18-crown-6 for the preparation of the first spherand (Section 9.31.3.6). Their approach was to *N*-tosylate diethanolamine to afford $\text{TsN}(\text{CH}_2\text{CH}_2\text{OH})_2$. This was extended to $\text{TsN}(\text{CH}_2\text{CH}_2\text{OCH}_2\text{COOH})_2$ by chloromethylation, reaction with cyanide, and then hydrolysis to the acid. Further reaction with thionyl chloride afforded the diacyl chloride which was then cyclized at high dilution with 2,2'-diaminodiethyl ether. Reaction with LiAlH_4 reduced the lactams to secondary amines and detosylated nitrogen <75JA5022, 81HCA1040>. Gokel and co-workers have streamlined the synthesis by treating $\text{TsN}(\text{CH}_2\text{CH}_2\text{OH})_2$ with chloroacetic acid <89CC608>. The key was to add glass beads to the reaction mixture in this step while stirring and sonicating. Full experimental details have been reported <92MI 931-01>. Krakowiak *et al.* have reported an approach to sidearmed triazacompounds (Scheme 10) <90JOC3364>.



Scheme 10

Newkome *et al.* used nucleophilic aromatic substitution to incorporate the 2,6-pyrido unit into a triazamacrocycle which was precursor to a series of cryptands (Scheme 11) <81TL3039>. The sequence uses a tertiary aminoalcohol as the nucleophile in a sodium hydride-mediated reaction with 2,6-dichloropyridine. In the second step, the tertiary amines function as nucleophiles in a reaction of triethylene glycol diiodide. The tertiary amines are converted into quaternary ammonium salts in the process. The system must be demethylated to form the neutral crown but conditions must be such that reduction of the pyridine residue does not occur. This was accomplished by using the commercial reagents L-Selectride and Super-Hydride.

A number of multinitrogen macrocycles have been prepared over many years. Some of the earlier



Scheme 11

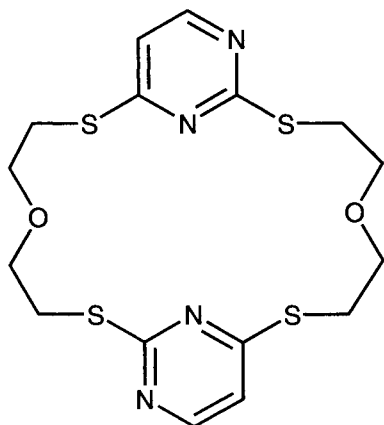
examples are noted here. A bis(pyridazine) crown (**19**) in which two of the subcyclic nitrogen atoms are turned inward and two outward was also reported by Newkome *et al.* (78JOC3362). Adam *et al.* reported a tetrabenzotetraaza-28-crown-8 (**20**) (81JCS(D)74). Buhleier *et al.* reported an 18-crown-6 derivative (**21**) in which two nitrogens were in the lactam form and two were part of a 2,2'-bipyridyl system (78CB200).

Finally, a number of interesting triaza-macrocycles have been prepared in the search for redox-switchable ligands. Ferrocene has proved to be a popular residue in this context because it may be oxidized readily and forms a cation that is stable in aqueous solution (92JA10583). Hall *et al.* have exploited this residue in a variety of macrocycles including some mixed pyridine-ferrocene cryptands (93CC1505). Beer *et al.* have attached ferrocenylmethyl as well as anthraquinylmethyl residues at each nitrogen of 4,10,16-triaza-18-crown-6 producing compound (**22**) (93JCS(D)2107). Gokel and co-workers had previously reported a number of anthraquinyl-substituted azacrown compounds (92JPO482).

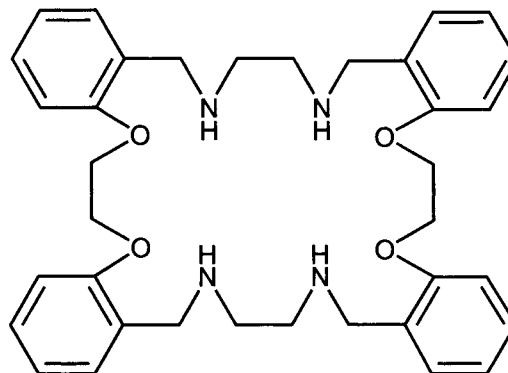
9.31.3.5 Cryptands

Heteromacrocycles represent an important point of departure from traditional heterocyclic chemistry. Heteromacrobicyclic compounds literally add another dimension to this difference. The cryptands are three-dimensional, cation-enveloping host compounds that normally contain nitrogen and oxygen donors but may contain sulfur or other heteroatoms as well. The interior or binding cavity of a cryptand is "hidden" from the external solvation shell; Lehn and co-workers thus suggested the name from the Greek *kruptos* which means "hidden" (69TL2885, 69TL2889). When the cryptand complexes sodium, the ion is called a sodium cryptate.

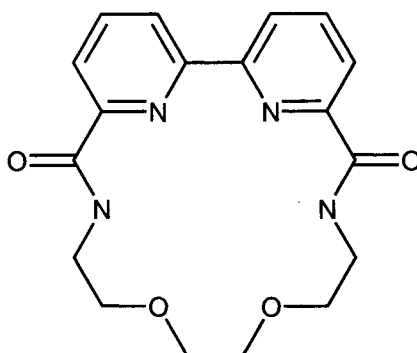
As Pedersen had done, Lehn offered a simplified nomenclature to deal with the new family of extremely complicated molecular structures. Simplified cryptand names assume that all spans contain $\text{CH}_2\text{CH}_2\text{O}$ units attached at either end by nitrogen. It is necessary only to specify how many ethyleneoxy units are present in each of the three chains. The compound $\text{N}[(\text{CH}_2\text{CH}_2\text{O})_2\text{CH}_2\text{CH}_2]_3\text{N}$ contains three molecular threads, each of which possesses two oxygen atoms. The simplified name for this compound, using a variant of the nomenclature standard for bicyclic structures, is [2.2.2]-



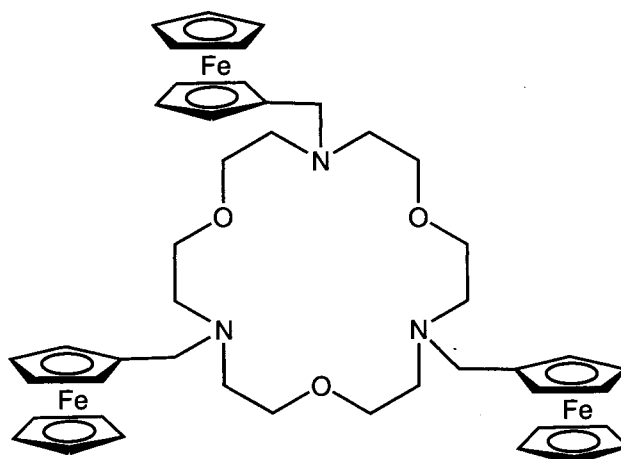
(19)



(20)



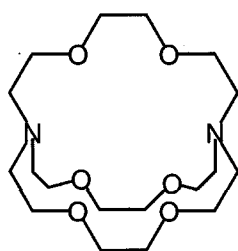
(21)



(22)

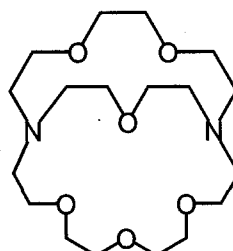
cryptand, (23). A cryptand having di-, tri-, and tetraethyleneoxy chains would be [3.2.1]-cryptand, (24).

Kulstad and Malmsten developed a remarkable, single-step synthesis for cryptands which utilized the reaction between triethylene glycol diamine and $\text{ICH}_2(\text{CH}_2\text{OCH}_2)_3\text{CH}_2\text{Cl}$ <80TL643>. They pro-



[2.2.2]

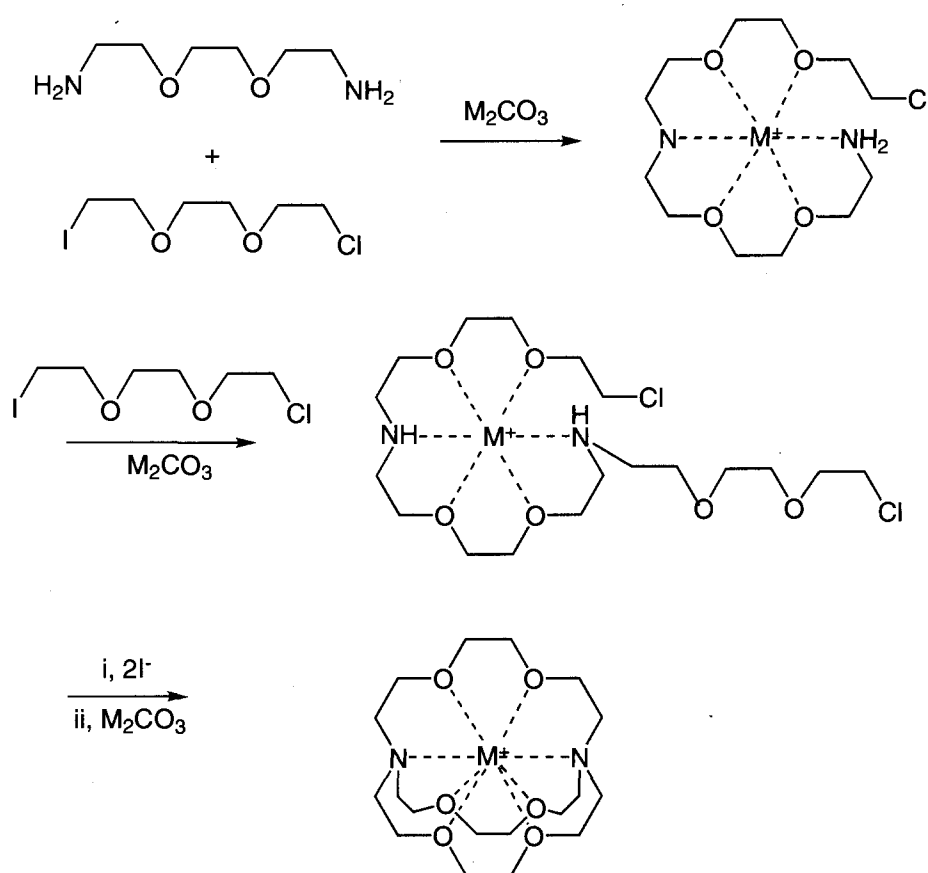
(23)



[3.2.1]

(24)

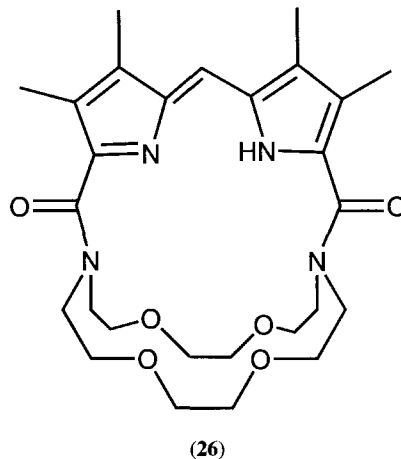
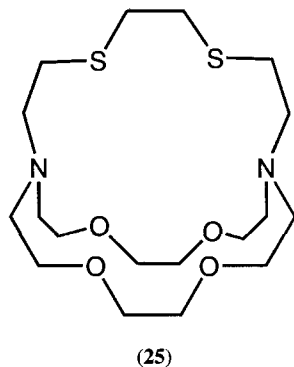
posed a mechanistic sequence for the reaction (Scheme 12) in which they presume formation of a cation-complexed, open-chained precursor which then undergoes $\text{Cl} \rightarrow \text{I}$ exchange followed by closure of both rings. This interesting approach is necessarily limited to cryptands having two identical chains. The reaction of primary amines such as $\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$ with $\text{ICH}_2(\text{CH}_2\text{OCH}_2)_3\text{CH}_2\text{I}$ gives *N,N'*-dibenzylidiaz-18-crown-6 which can be hydrogenolyzed to diaza-18-crown-6 [84JA8240].



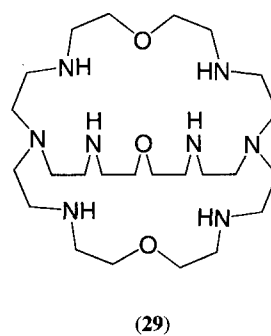
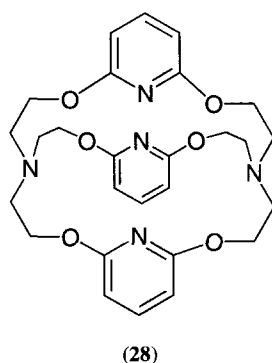
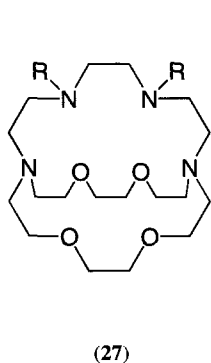
Scheme 12

A vast number of cryptands has now been prepared and it would be difficult to survey all of the examples and approaches. Only some of the variety are indicated. The dithiacryptand (**25**) was

reported in the earliest work of Lehn as a variant on the all-oxygen cryptands $\langle 69\text{TL}2889 \rangle$. Structure (26) has features of a porphyrin, a cryptand, and a macrocyclic lactam $\langle 92\text{CB}447 \rangle$.

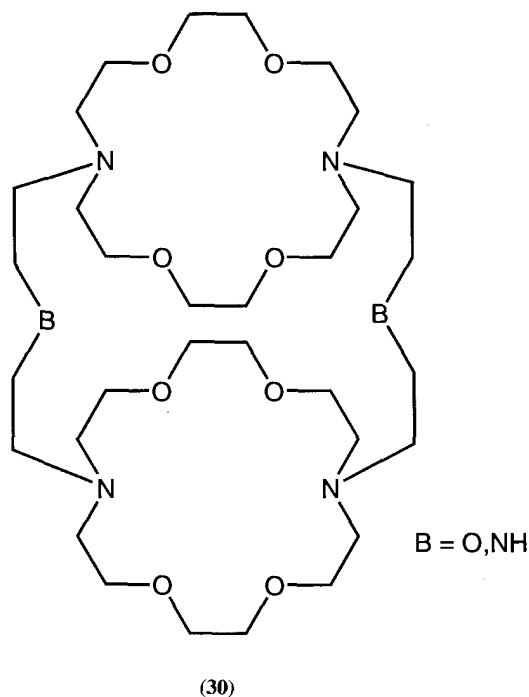


Nitrogen atoms have also been incorporated in a number of cryptands. Three examples of this are shown here. In the first case, [2.2.2]-cryptand (27) has two nitrogens in one of the chains. In the original synthesis of this compound by Lehn and Montavon, the dinitrogen chain was incorporated as $\text{ClCOCH}_2\text{NTsCH}_2\text{CH}_2\text{NTsCH}_2\text{COCl}$ by reaction with diaza-18-crown-6 $\langle 76\text{HCA}1566 \rangle$. The amide linkages were reduced using diborane and the tosylamides were cleaved using lithium in liquid ammonia. The secondary nitrogen atoms on the parent compound were then methylated using standard Eschweiler–Clark conditions. The second structure (28) represents a variation on the nucleophilic aromatic substitution approach of Newkome *et al.* described above $\langle 79\text{JA}1047 \rangle$. In this case, triethanolamine $[\text{N}(\text{CH}_2\text{CH}_2\text{OH})_3]$ was deprotonated using NaH in xylene. 2,6-Dichloropyridine served as the electrophile. The third structure (29) uses the inorganic ligand “tren” $[\text{N}(\text{CH}_2\text{CH}_2\text{NH}_2)_3]$ as the starting material. Lehn and Montavon prepared these structures (“BISTREN”) originally to be models for biological receptors $\langle 72\text{TL}4557 \rangle$. When protonated, the linear azide anion ($\text{N}=\text{N}=\text{N}^-$) can be trapped within it.



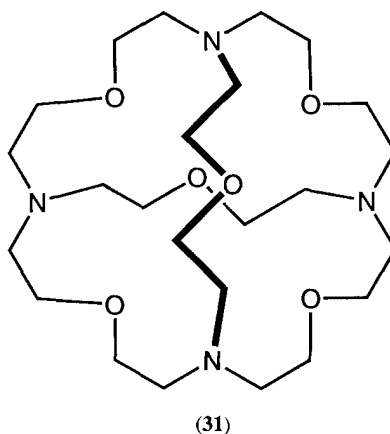
Martell and co-workers have shown that the BISTREN macrobicyclic structures can form dicobalt or dicopper complexes bound by nitrogens at opposite ends of the cryptand $\langle 82\text{IC}4253, 84\text{IC}1588, 86\text{IC}938, 88\text{IC}3630 \rangle$. Placement of the two Cu^{2+} ions within the macrocycle reduces the remaining cavity size and permits complexation of such small anions as fluoride and hydroxide.

Crowns bridged on both sides form “ditopic receptor molecules” that form “binuclear cryptate” complexes (e.g. (30)). The preparation is normally accomplished by treatment of a diazacrown with a diacid chloride. Reduction of the tetralactam affords the tetraamine $\langle 73\text{AG}(\text{E})579, 77\text{JA}8502, 79\text{CC}309 \rangle$. In particular, these structures have been probed by Sutherland and co-workers who assessed intramolecular diammonium cation binding by use of the NMR technique $\langle 79\text{CC}309 \rangle$.

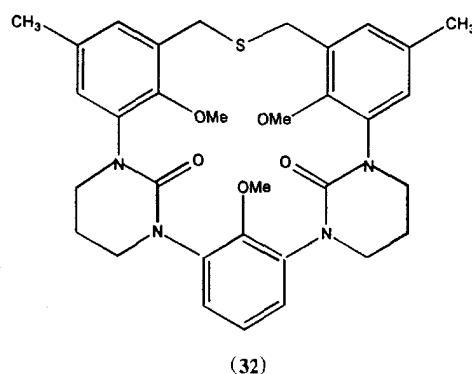
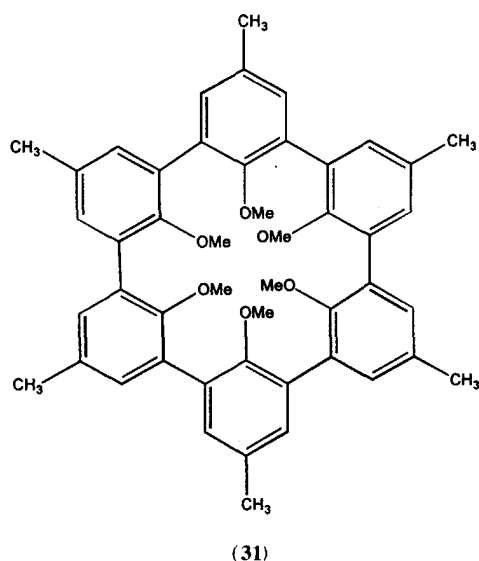


9.31.3.6 Spherands

As in the case of cryptands, the spherands (31) comprise an entire field of study and can hardly be done justice in a few paragraphs. The concept underlying this family of compounds is similar to that which led to the preparation of cryptands, namely that the ligands would be capable of enveloping a guest cation, anion, or neutral molecule. The name was coined by Graf and Lehn who described the first one (75JA5022). This compound is an architecturally interesting structure which possesses four nitrogen atoms in a tetrahedral array as well as an octahedron of oxygen atoms.



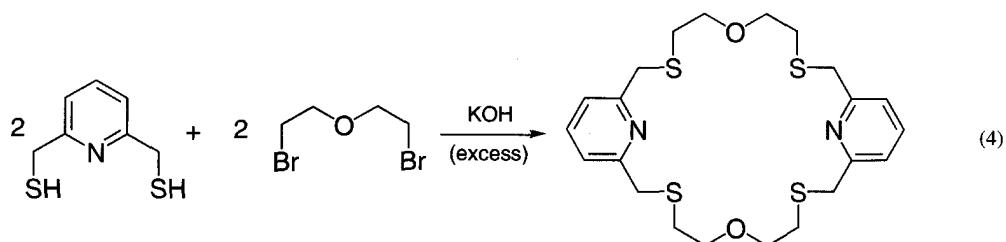
Numerous other spherands have been prepared which are beyond the scope of this chapter. In particular, the family is represented by a group of aromatic ethers of the type illustrated, prepared largely by Cram and co-workers. The first spherand of this type (32) contained six ether donor groups which were found to be in the D_{3d} conformation (85JA3645). Expansion of the family has led to many new structural types. Compound (33) contains urea donors which are more polar than aromatic ethers. Both oxygen- and sulfur-containing top bridges were used. In principle, the latter should afford a slightly larger ring size but it appears from the solid state structure of the sodium complex to turn outward, somewhat compressing the cavity (90JA5837). Despite the smaller cavity, binding of Na^+ was somewhat weaker than for the oxygen analogue.



9.31.4 AZATHIACROWNS

The incorporation of sulfur into macrocycles presents both advantages and disadvantages. From the synthetic perspective, sulfur is normally a better nucleophile in aqueous or hydroxylic media than is hydroxide or alkoxide. On the other hand, such standard crown building blocks as $\text{ClCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{Cl}$ become problematic when O is replaced by S. The high reactivity of $\text{ClCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{Cl}$ makes it difficult to handle and the exposure danger is serious. On the other hand, the corresponding thiadithiol, $\text{HSCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{SH}$, can be handled with less difficulty and deprotonation is normally facile.

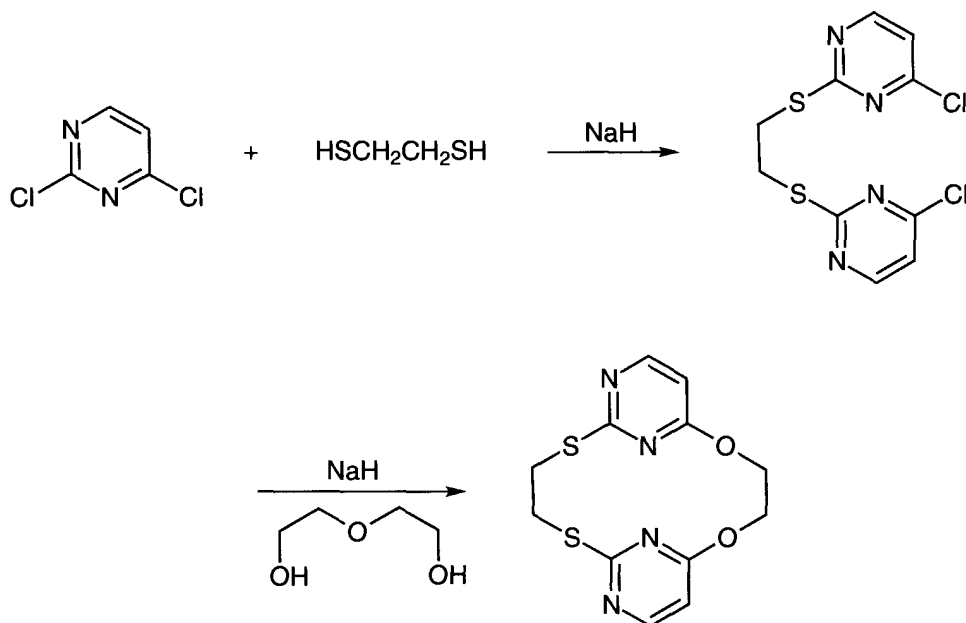
Early work in this area was undertaken by Newkome $\langle 78\text{JOC}3362 \rangle$ and by Vögtle $\langle 74\text{CZ}562 \rangle$. Weber and Vögtle showed that 2,6-bis(mercaptomethyl)pyridine could be deprotonated by KOH in a mixture of butanone and ethanol and then reacts with $\text{BrCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{Br}$ in a type of reaction we have previously characterized as a "shotgun" $\langle 76\text{CB}1803 \rangle$. The product was isolated as a crystalline solid in $\approx 10\%$ yield (Equation (4)). Mixed O, S, N heteromacrocycles incorporating the pyridine subcyclic unit were prepared by the reaction of 2,6-bis(bromomethyl)pyridine with $\text{HSCH}_2(\text{CH}_2\text{OCCH}_2)_n\text{CH}_2\text{SH}$ and KOH in degassed *t*-butanol $\langle 91\text{IC}1893 \rangle$. It is interesting to note that in the latter case, the copper complex uses pyridyl nitrogen and the two sulfur atoms as donors but not oxygen.



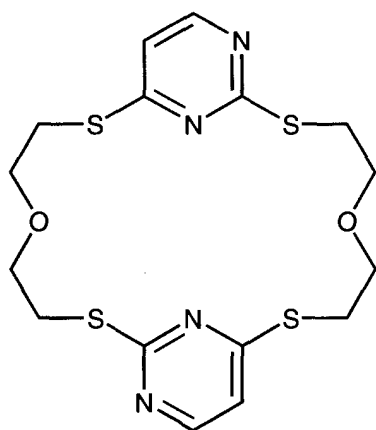
2,6-Dichloropyrimidine reacts with 1,2-dimercaptoethane in the presence of sodium hydride to give an open-chained bis(heterocycle) in which substitution has occurred at the amidine carbon (C-2) (Scheme 13) $\langle 78\text{JOC}3362 \rangle$. A second nucleophilic aromatic substitution is possible using diethylene glycol (NaH as base).

The range of structures containing oxygen, sulfur, and nitrogen is illustrated further by two macrocycles which each contain two small-ring heterocycles. The first is a symmetrical product (34) related to that described immediately above in which $\text{HSCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{SH}$ was used as the nucleophile in a direct substitution of dichloropyridazine $\langle 78\text{JOC}3362 \rangle$. The second structure (35) contains the heterocycle furan along with two sulfur atoms and two lactam nitrogens $\langle 78\text{AKZ}349 \rangle$.

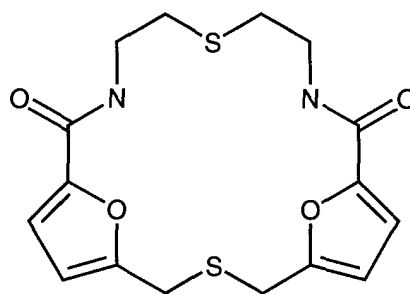
Several novel thiophene-containing macrocycles have been reported by Barker *et al.* $\langle 93\text{CC}1733 \rangle$. The preparation of these compounds was accomplished according to Scheme 14. Initial bridging of



Scheme 13



(34)

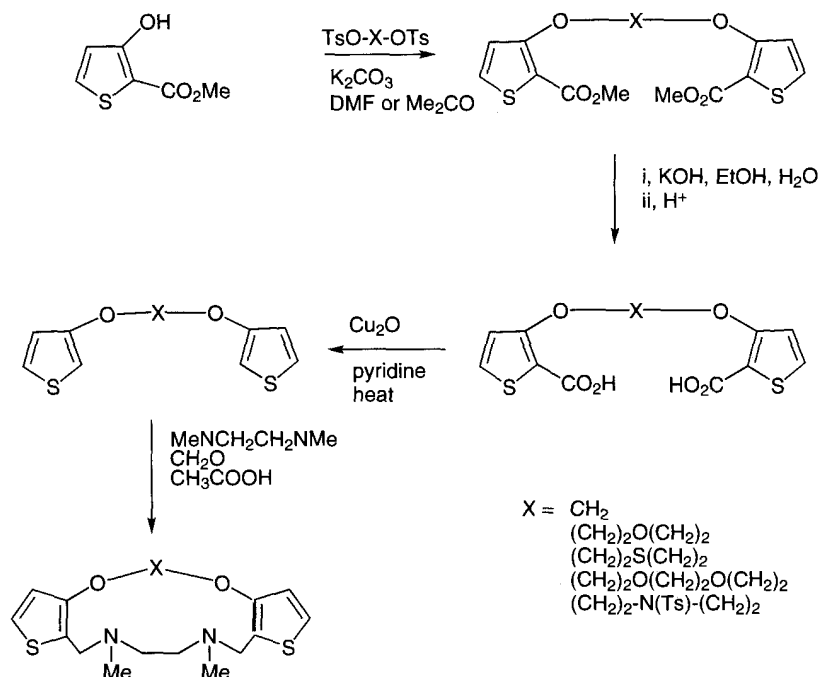


(35)

the 2-carbomethoxy-3-hydroxythiophene was accomplished by reaction with a ditosylate such as $\text{TsOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OTs}$. Once bridged, the carbomethoxy protecting group was hydrolyzed and decarboxylated by heating in pyridine in the presence of cuprous oxide catalyst. After the thiophene 2-position was revealed, Mannich reaction with $\text{CH}_3\text{NHCH}_2\text{CH}_2\text{NCH}_3$ closed the ring to afford the variety of structures shown.

9.31.5 COMPLEXATION PROPERTIES

It is always somewhat dangerous to generalize about the interests of those who prepare novel structures as so many different motivations may underlie the effort. It is reasonably safe to say, however, that a major motivation in the macrocycle area for the syntheses of so many novel structures was to develop complexing agents. All-oxygen macrocycles afforded the first general alkali metal binding structures and the aza or aza/thia macrocycles favor transition metals. A



Scheme 14

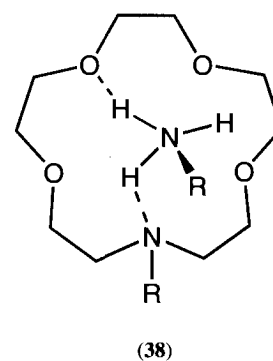
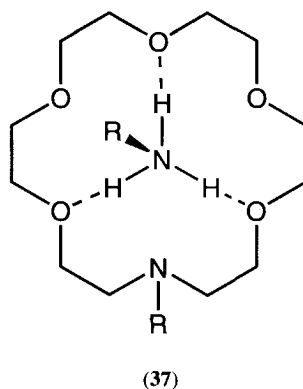
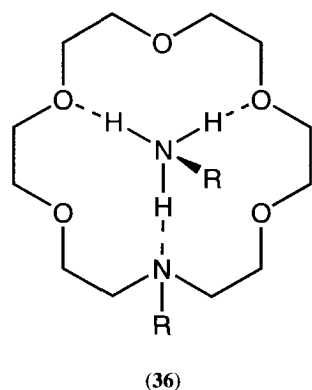
number of structures have been prepared primarily as molecular hosts. Much has been written about cation complexation by the vast family of macrocycles but the present review would be woefully lacking without some discussion of the findings.

9.31.5.1 Azacrowns

The simple, all-oxygen crown ethers bind alkali and alkaline earth metal cations as well as primary ammonium cations. In the group of cations Li^+ , Na^+ , K^+ , Ca^{2+} , potassium is usually bound most strongly in such solvents as methanol. This is due largely to the solvation enthalpy which is lowest for K^+ . In order to achieve this selectivity, small crowns such as 12-crown-4 form sandwich complexes of the type $(12\text{-crown-4})_2\text{Na}^+$ or $(\text{benzo-15-crown-5})_2\text{K}^+$. Dibenzo-30-crown-10, which seems much too large to bind potassium effectively, folds back in a "tennis-ball-seam" arrangement utilizing all of the oxygens to coordinate the cation $\langle 72\text{JCS(P2)341} \rangle$. This variability in ring size is possible since alkali metal cations bind using spherically symmetrical *s*-orbitals rather than highly directional *d*- or *f*-orbitals.

Donor group orientation is of consequence for ammonium cation binding since hydrogen bond formation has more rigid distance and orientation requirements than are apparent in alkali metal cation binding (36)–(38). The strengths of hydrogen bonds are highest when short and near linearity. A primary ammonium cation forms three identical hydrogen bonds to alternate oxygen atoms in 18-crown-6 (see Section 9.31.2.3). Replacement of an oxygen atom by nitrogen will offer the possibility of an N-H-N (e.g., (36)) rather than an N-H-O (e.g., (37)) hydrogen bond. It is unclear whether one is preferred over the other when nitrogen is secondary and aliphatic. When the pyridine subcyclic unit is present, located hydrogens show an N-H-N (e.g., (38)) bond. When the macrocyclic size is smaller than 18 atoms, the formation of three hydrogen bonds is no longer possible. Thus, binding of ammonium cation by 15-crown-5 compounds involves the formation of two hydrogen bonds rather than three.

Binding of alkali metal cations is generally weakened by an N for O replacement. On the other hand, addition of nitrogen atoms favors transition metal cation binding. Often, however, cation binding strengths must be determined in different solvents to accommodate differences in solubilities of ligands, cations, or anions. In Table 1 are recorded several cation binding constants for simple macrocycles which illustrate commonly understood binding trends. All data are for methanol solvent unless otherwise indicated.

**Table 1** Cation binding strengths for crown ethers and cryptands.

Ligand	No. of		$\log_{10} K_S$	
	O	N	Na ⁺	K ⁺
15-crown-5	5	0	1.7	1.7
18-crown-6	6	0	3.24	3.43
21-crown-7	7	0	4.35	6.08
N-benzylaza-15-crown-5	4	1	2.77	2.61
N-2-methoxyethylaza-15-crown-5	5	1	3.88	3.95
N-2-(2-methoxyethoxy)ethylaza-15-crown-5	6	1	4.54	4.68
N-benzylaza-18-crown-6	5	1	3.41	4.88
N-2-methoxyethylaza-18-crown-6	6	1	4.58	5.67
N-2-(2-methoxyethoxy)ethylaza-18-crown-6	7	1	4.33	6.07
N,N'-dibenzyl diaza-15-crown-5	3	2	3.59	3.13
N,N'-bis(2-methoxyethoxy) diaza-15-crown-5	3	2	5.09	4.86
N,N'-dibenzyl diaza-18-crown-6	4	2	2.68	3.38
N,N'-bis(2-methoxyethoxy) diaza-18-crown-6	6	2	4.75	5.46
[2.2.1]-cryptand	5	2	9.4	8.54
[2.2.2]-cryptand	6	2	8.0	10.6
[3.2.2]-cryptand	7	2	4.8	> 7

9.31.5.2 Azathiacrowns

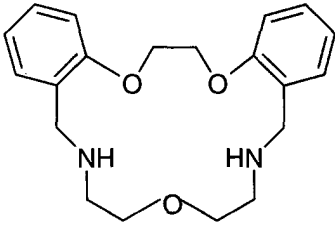
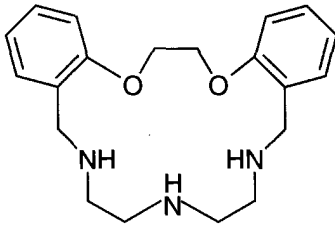
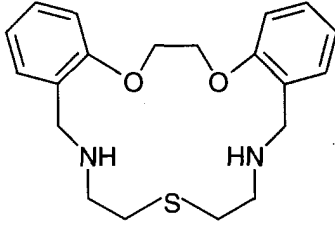
Lindoy and co-workers have prepared a large number of macrocycles having mixtures of heteroatoms, and variations in heteroatom arrangements, and length and type of spacer units (88JA8471, 92JCS(D)1869, 93JCS(D)1013, 94IC1194). They have also determined cation binding strengths for a number of transition metals with the ligands. This permits direct comparisons among cations and ligands to be made. In Table 2 are shown three dibenzocrowns that are formally 17-crown-5 derivatives. All aspects of the structure are maintained except the heteroatom at position 4 which is systematically varied from O to N to S. Cation complexation constants were determined in 95% methanol for monovalent silver and for divalent cobalt, nickel, copper, zinc, cadmium, and lead.

For all of the cations studied, altering oxygen to nitrogen increases cation binding strength. This is expected for transition metal ions and opposite to the trend observed for alkali metal cations (see above). The most dramatic increase is observed for Cu(II), the binding of which is enhanced by 10^8 by the exchange of N for O. Only a power of ten increase in binding is observed for the O → S exchange. Generally, binding strengths increase as one moves to the right along row 4 of the periodic table. Thus, binding by all three ligands generally increased from Co < Ni < Cu and then binding diminished for all ligands with Zn. Silver is a different case. It is below copper in the periodic table but is normally monovalent. It is significantly larger than Cu(II), normally fitting an 18-membered ring. Even so, changing hard oxygen to softer nitrogen or sulfur enhances cation complexation.

Obviously, much more than noted here can be gleaned from such studies. The range of cations and compounds studied means that strong and selective complexation can be achieved with a variety of synthetic heteromacrocycles.

In Table 3 are illustrated a second family of crown-5 compounds. They vary not in the identity of the heteroatoms, but in their relative placement. Ring sizes vary from 16 to 19 members and

Table 2 Stability constants for transition metal complexes of various mixed-donor macrocyclic ligands.

Structure	log K_{stab} in 95% MeOH ^a						
	Co(II)	Ni(II)	Cu(II)	Zn(II)	Cd(II)	Ag(I)	Pb(II)
	<3.5	<3.5	6.4	<3.5	5.3	7.1	5.5
	7.6	10.0	14.4	7.5	8.7	8.7	8.1
	~3.3	5.5	7.4	<3.5	4.4	8.6	4.5

^a <B-90MI 931-01>.

spacing between heteroatoms varies from one carbon to four. As above, divalent copper complexation is strongest for this family. Of course, three adjacent nitrogen atoms are available in each case. Variations in ring size are important in this series. Comparing the first and last structures in the table, it can be seen that even though the relationship of the three nitrogen atoms remains identical, the larger ring size of the latter compounds means that the donors are not optimally organized for divalent copper complexation. A similar trend can be observed for divalent cobalt.

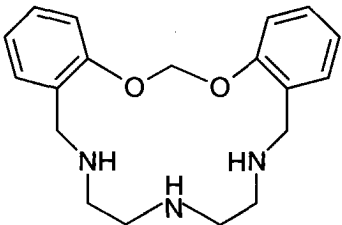
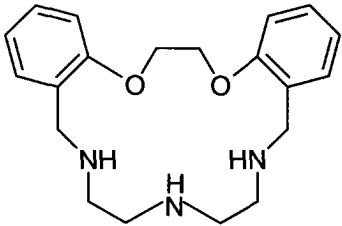
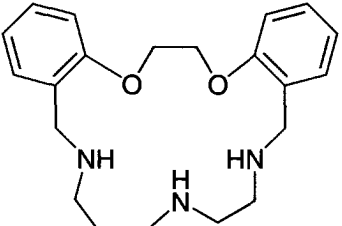
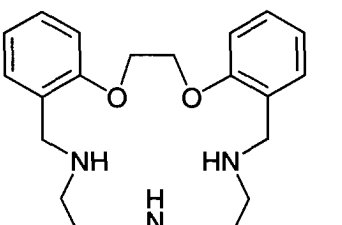
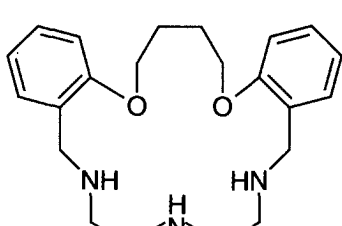
Generally, the vast families of heterocyclic structures containing O, S, and N that have been prepared are useful as cation binders. The selectivities of such molecules for alkali, alkaline earth, or transition metals depends upon ring size and the number and nature of donors. Smaller rings having more N or S atoms will favor transition metals and larger rings having all or mostly oxygen donors will favor alkali metals.

9.31.6 OTHER ASPECTS

9.31.6.1 Enterobactin Mimics

Enterobactin is a macrocyclic Fe(III) complexing agent. It is a 12-membered tris(lactone) which possesses three pendant catechol-containing sidearms. Although clearly not a ten-membered ring or higher containing N and O, a number of enterobactin analogues have been devised which coordinate cations using these elements. Work from Raymond *et al.* <84TCC49> and Shanzer and co-workers <92JA6661> has resulted in a number of novel complexands that fit the general thrust of this chapter. In particular, the complexing agent (39) known by the acronym CYCAM is a [13]ane-N₃ or triaza-13-crown-3 derivative. The catechol units readily dissociate their protons and serve as oxygen donors to the bound iron atom.

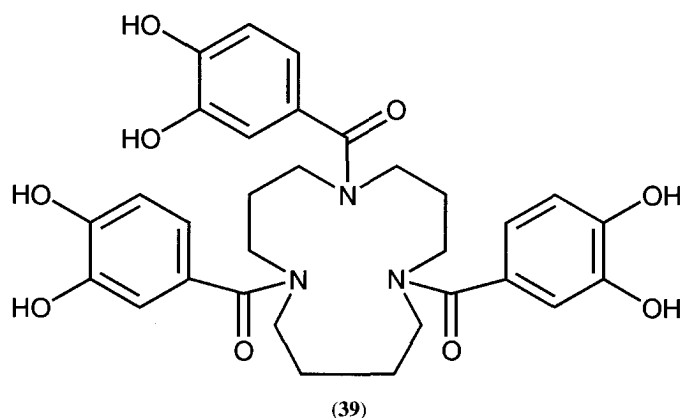
Table 3 Stability constants for transition metal complexes of N₃O₂ donor macrocycles with various ring sizes.

Structure	Ring size	Co(II)	Ni(II)	Cu(II)	Zn(II)	Cd(II)
	16	3.3 ^c	5.5 ^c	14.9 ^b	6.5 ^c	7.3 ^c
	17	5.1 ^c	~6.2 ^c	14.2 ^b	7.5 ^a	8.7 ^a
	18	7.3 ^c	9.7 ^c	14.0 ^b	7.1 ^a	7.9 ^a
	19	3.4 ^c		11.0 ^b	6.6 ^a	5.3 ^a
	19	3.5 ^c	3.5 ^c	10.5 ^b	6.0 ^a	5.0 ^a

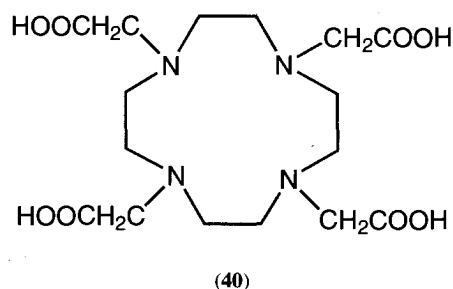
^a<88JA8471>. ^b<93JCS(D)1013>. ^c<94IC1194>.

9.31.6.2 Imaging Agents

A great economic driving force for the development of novel macrocycles is the potential for their use in complexes with gadolinium or other metals as NMR imaging agents. For the most part, these imaging agents are heterocycles that contain nitrogen only, although some compounds contain oxygen (<91T8863>). Probably the ligand best known in this context is tetra(carboxymethyl)tetraaza-



12-crown-4 (40), which is usually referred to as DOTA. Its tetraacetic acid residues make the solvation sphere of a complexed metal half oxygen and half nitrogen although only the latter is formally heterocyclic.



9.31.7 SUMMARY

It is, in a sense, impossible to summarize this section. The entire chapter is really a summary of a vast field of chemical endeavor. Compounds having a range of sizes from about nine atoms to five or six times that number have been prepared. Almost every permutation of O, S, and N has been incorporated in simple macrocycles and these heteroatoms have also been included as part(s) of small-ring heterocycles such as pyridine, thiophene, furan, etc. This chapter attempts to present a broad, if superficial, view of the possibilities and the precedents. An attempt has been made to indicate something about cation binding since this has been the driving force for much of the development in this area.

For additional reference materials the reader is referred to the following <B-82MI 931-01, B-89MI 931-01, B-90MI 931-02, B-91MI 931-01, B-93MI 931-01>.

9.32

Ten-membered Rings or Larger with One or More Oxygen and Sulfur Atoms

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and

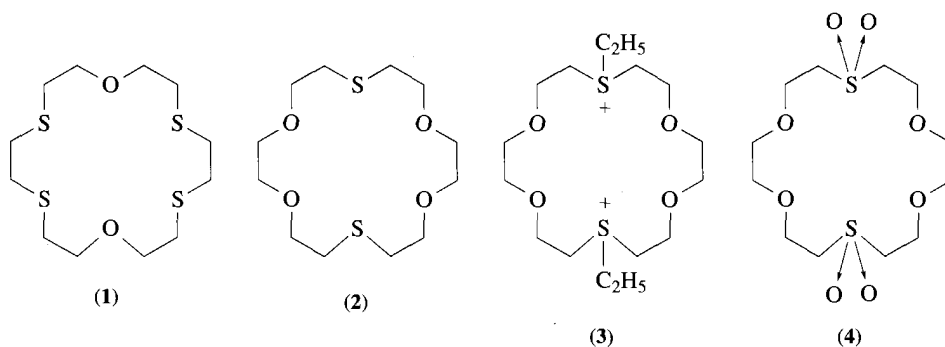
JERALD S. BRADSHAW and REED M. IZATT

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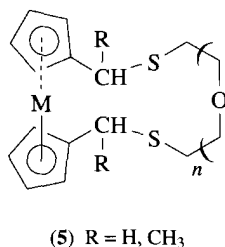
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9.32.1 INTRODUCTION

Decades before Pedersen's all oxygen-containing crown compounds were reported <67JA7071>, sulfur-containing analogues of 18-crown-6 were prepared. In 1934, Meadow and Reid prepared 7,16-dioxa-1,4,10,13,-tetrathiacyclooctadecane (**1**) <34JA2177>. In 1961, Dann *et al.* reported other sulfur analogues (**2**)–(**4**) <61JOC1991>. This early pioneering work has not received recognition because the complexation properties of those macrocycles were not known at that time. The first deliberate syntheses of crown ethers containing oxygen and sulfur atoms were conducted at the research laboratories of du Pont <68JOC2930, 70JA600, 71JOC254> and the Brigham Young University <73JHC1, 74JHC45, 74JHC649, 76JOC134>. In 1974, the group at Brigham Young published an extensive review on macrocyclic sulfide syntheses <74JHC649>. Several texts and reviews on crown ethers exist, many containing some of the molecules belonging to this chapter <74JHC649, B-79MI 932-01, B-82MI 932-01, 83TCC1>.



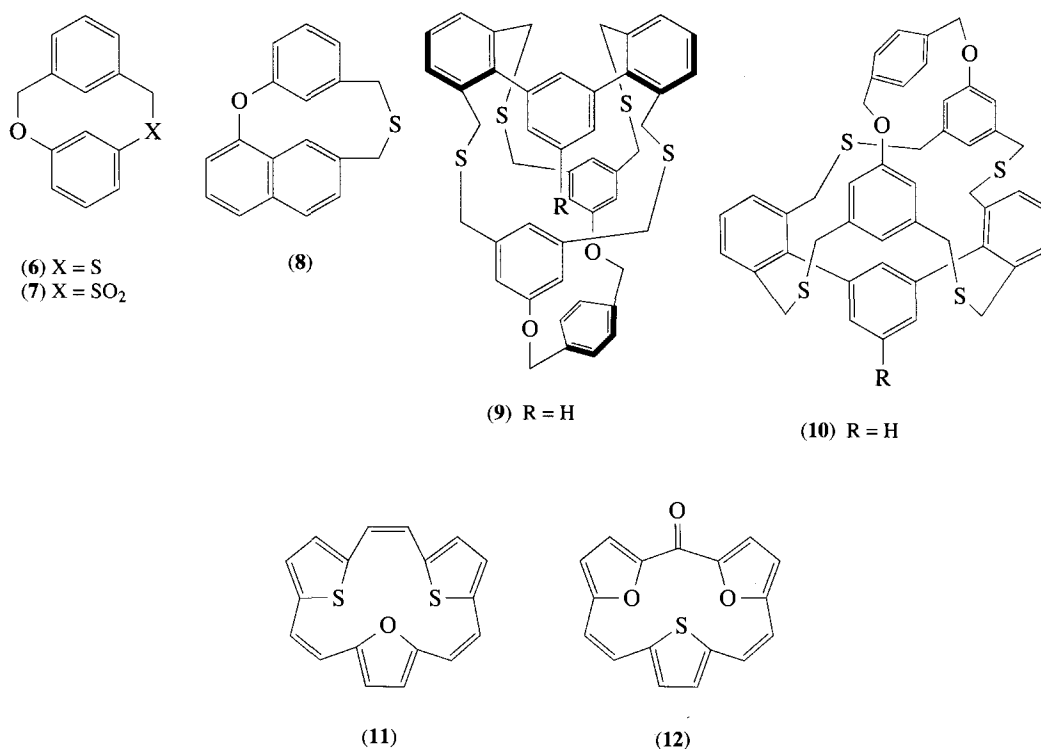
Not long after Pedersen introduced the basic crown ether structure, several research groups began making various modifications to the ring which greatly expanded the structural possibilities. A very interesting variation was the incorporation of metallocene subunits into the crown moiety as shown in structure (**5**) <79LA1094, 80PJC767>. The majority of this research was carried out by Czech *et al.* <82M965>, Sato and co-workers <82TL185, 83BCJ1459, 87CL1783>, and Izumi *et al.* <84BCJ2435>.



Vögtle and co-workers were among the first to synthesize ferrocenophanes containing both oxygen and sulfur atoms <79LA1094>. They also incorporated these two heteroatoms into [2.2]metacyclopentane structures (**6**) and (**7**) <84JOC3484> and other sulfur-containing cyclophanes such as (**8**) <85AG(E)885>. Vinod and Hart <90JA3250, 91JOC5630> have introduced oxygen and sulfur into *m*-terphenyl-based cyclophanes (**9**) and (**10**), for which they coined the term “cappedophanes”.

Annulenes such as (**11**) <65CC269, 71CC1458, 82H(19)2047> and annulenones like (**12**) <71CC1457, 73JCS(P1)2961> that contain both oxygen and sulfur heteroatoms are discussed in this chapter. Also discussed in this chapter are several small groups of substances belonging to larger classes of structures covered in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I). CHEC-I covers the following: large rings except crown ethers and heterophanes <84CHEC-I(7)709>; crown ethers and cryptands <84CHEC-I(7)731>; and heterophanes including annulenes and related species with oxygen and sulfur atoms <84CHEC-I(7)763>. This chapter concentrates on the oxygen- and sulfur-containing members of these structures covered in CHEC-I.

Several nomenclature and numbering rules have been proposed and adopted for the identification of organic compounds <B-60MI 932-01, B-60MI 932-02, B-66MI 932-01>. Conventional IUPAC rules to name macrocycles result in the assignment of unequivocal, but extremely complicated and nearly impossible names. Various researchers have avoided using cumbersome rules for naming large cyclic compounds by developing other methods <54JA5462, 59ZOB3564, 67JA7071, 80ICAL65>. The first



macrocyclic polyether synthesized by Pedersen ^{<67JA7071>} was **(13)**, which he simply called dibenzo-18-crown-6 in contrast to its more complicated IUPAC name. Alternative names for this compound are given in Table 1. Sulfur-containing analogues and derivatives of crown ethers can be named in a similar fashion to those given in Table 1. In this chapter, nomenclature is used that the relevant research groups used for their oxygen- and sulfur-containing macrocycles, as well as IUPAC names as needed. Representatives of the structures and names included in this work are shown in Figure 1.

Table 1 Examples of nomenclature methods.

Nomenclature method	(13)
Pedersen's crown ^{<67JA7071>}	dibenzo-18-crown-6
Cram's phane ^{<80ICAL65>}	1,4,7,14,17,20-hexaoxa[7.7](1,2)benzophane
Vögtle's coronand ^{<80ICAL65>}	18{O ₆ (1,2)benzeno.2 ₂ (1,2)benzeno.2 ₂ -coronand-6}
IUPAC	2,5,8,15,18,21-hexaoxatricyclo[20.4.0.0 ^{9,14}]hexacosa-1(22),9,11,13,23,25-hexaene

9.32.2 THEORETICAL METHODS

Theoretical studies of crown ethers were discussed in CHEC-I but no references to such studies for the larger rings containing both oxygen and sulfur heteroatoms were found prior to 1984. During the years 1984 to 1994, empirical force field (EFF) calculations have been used to investigate the conformations of various macrocycles ^{<B-87MI 932-01>}. These molecular mechanics (MM) cal-

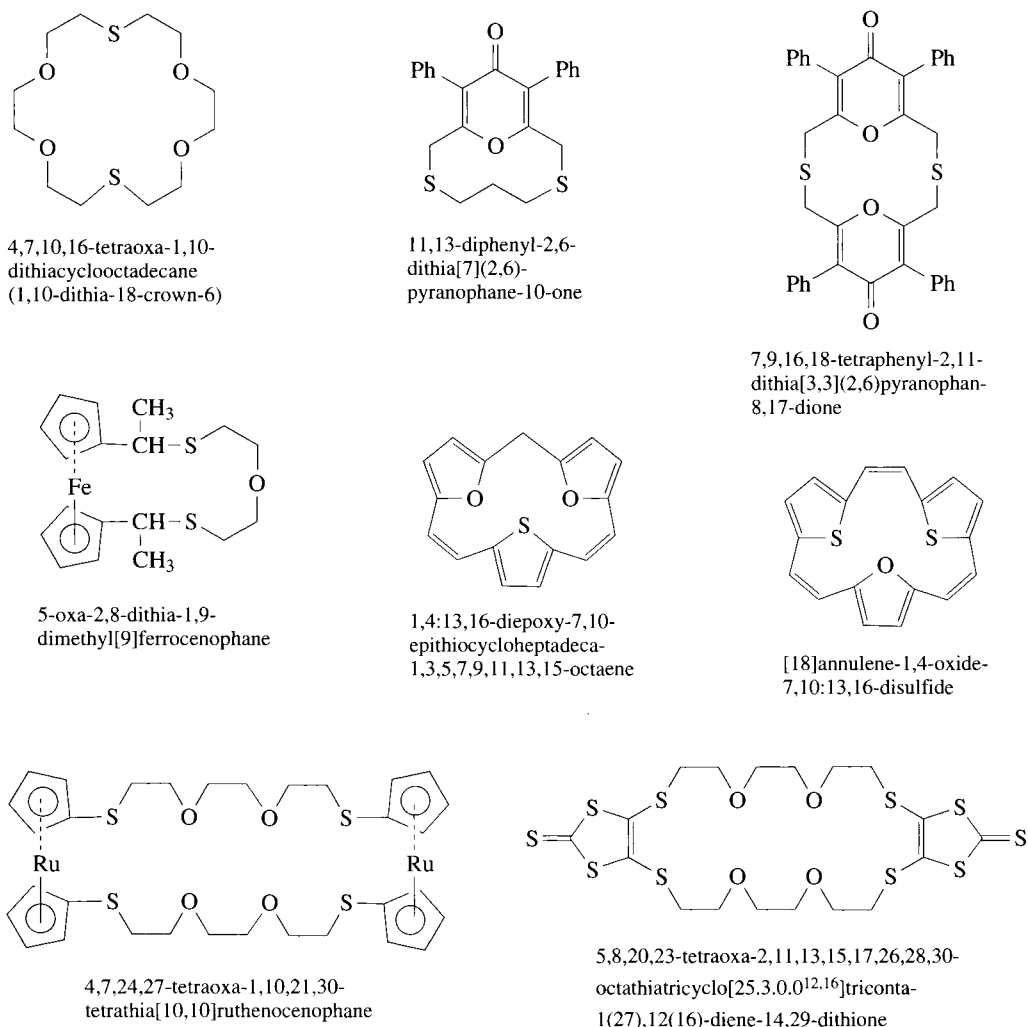
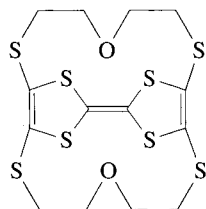
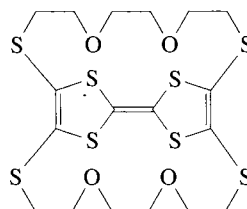


Figure 1 Examples of sulfur-containing macrocycles.

culations have also been used to aid in the design and synthesis of macrocycles <93CRV2463>. Hansen and co-workers <93JOC1359> performed molecular orbital calculations on cage compounds (14) and (15) using semiempirical methods. Using the MNDO-PM3 method introduced by Stewart <89JCC209>, they established that, in these systems, the semiempirical method was able to reproduce the experimental structures. In each case, the reported "MNDO-PM3-optimized geometries" were close to the x-ray structures with typical deviations of 0.01 Å.



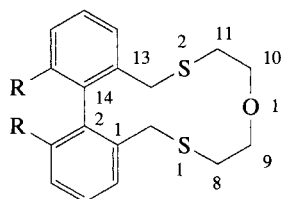
(14)



(15)

Lockhart *et al.* <94JCS(P2)1309> were able to compare molecular modeling studies (which represents the gas-phase structures) with x-ray data for compounds (16) and (17). Selected details of this comparison are given in Table 2 showing torsional angles of the thioether portions of the crowns as well as for the biphenyl rings. They were also able to study possible conformational rearrange-

ments by molecular dynamics (MD). The features studied included the populations, torsional movement, and energies of particular conformations by using simulations at various temperatures.

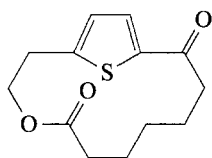


(16) R = H
(17) R = CH₃

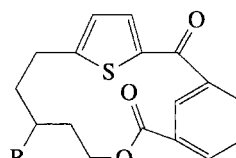
Table 2 Selected details for geometrics of (16) and (17) from crystal structure and molecular mechanics data <94JCS(P1)1309>.

		MM	X-ray
Tor 1	S(1)—C(8)—C(9)—O(1)	72.9°	70.16°
Tor 2	O(1)—C(10)—C(11)—S(2)	72.9°	66.98°
Tor 3	C(1)—C(2)—C(14)—C(13)	−94.0°	−92.75°

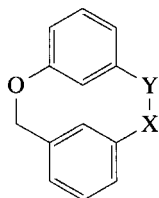
Durdyev *et al.* studied the three-dimensional structure of the two thiophene-containing macrocyclic ketolactones (18) and (19) by the method of atom–atom potential function <86IZV94>. The minimum conformational energies corresponded to the experimental structure for the crystalline compounds. Vögtle and co-workers found clear and strong differences in bond angles and lengths when they compared data collected from x-ray analysis and molecular mechanics studies <89CC65>. The results for ligands (20) and (21) are given in Table 3. Vinod and Hart have used molecular mechanics to rationalize the formation of the self-filled cappeddophane host (9). Presumably, favorable van der Waals interactions between the central *m*-terphenyl ring and the aryl rings help form the cavity <91JOC5630>.



(18)



(19) R = H, R = CH₃



(20) X = SO₂, Y = CH₂
(21) X = CH₂, Y = S

9.32.3 EXPERIMENTAL STRUCTURAL METHODS

9.32.3.1 Crystal Structures

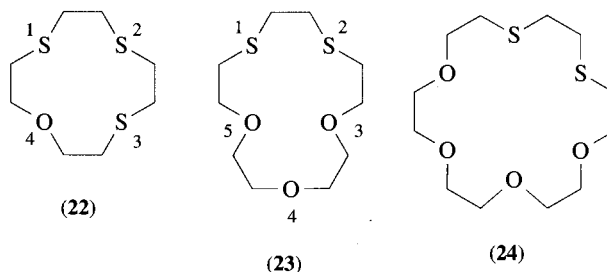
9.32.3.1.1 Crown ethers and related compounds

X-ray crystallography of macrocycles containing both oxygen and sulfur atoms has provided a window into the solid state structures of these compounds and their complexes. The crystal structures

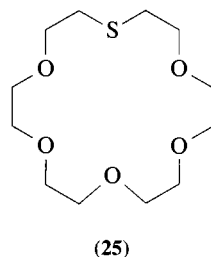
Table 3 Comparison of x-ray and MMPMI calculation results for (20) and (21).

	Distance (pm)					
	intra-annular C—C		O—C		C—S	
	MMPMI	x-ray	MMPMI	x-ray	MMPMI	x-ray
(20)	275	262	142	147	183	185
(21)	279	263	142	146	184	182

of crown ethers were discussed in CHEC-I $\langle 84\text{CHEC-I}(7)731 \rangle$. Like the cyclic ethers, the cyclic thioethers form complexes with metal ions, however, the thermodynamic stabilities of the complexes differ considerably from those of the all oxygen macrocycles. The conformational changes that occur when sulfur atoms replace oxygen atoms of the cyclic polyethers have been studied. Crystal structures for macrocycles (2) and (22)–(24) are given in Figure 2 $\langle 81\text{JHC}463 \rangle$.



In all of the above molecules, the donor heteroatoms are nearly co-planar and the sulfur atoms are directed out of the macrocyclic cavities $\langle 81\text{JHC}463 \rangle$. This causes (22) to be heart-shaped with one oxygen atom pointing into the cavity and (23), (2), and (24) to be irregularly shaped. The shortest distance across the cavity is 4.46 Å in (22) (between S(2) and O(4)), and 4.6 Å in (24). In (23), S(1), S(2), and O(3) are directed out of the cavity. The distances across the cavity range from 4.83 Å between O(3) and O(5) to 6.44 Å from S(1) to O(3) $\langle 75\text{CC}84 \rangle$. The situation is similar for (2) and (24) where all the sulfur atoms and some of the oxygen atoms point out of the cavity. Unique to (2) is the magnitude of the S—C—C—S torsion angle. This value is close to 60° while in (22) and (23), the values for chemically similar torsion angles are close to 180°. This causes the two sulfur atoms of (2) to have an S—S interatomic distance of 3.48 Å. The S—S interatomic distances for (22) and (23) are at least 4.5 Å. A result of the *gauche* conformation is the possibility of (2) functioning as a bidentate ligand, which it does when it is complexed with HgCl₂ $\langle 81\text{JHC}463 \rangle$. The bond lengths and angles of chemically similar bonds are nearly the same for (2) and (22)–(24). The average bond lengths and standard deviations calculated for those bonds are C—S, 1.806(13) Å; C—C, 1.498(15) Å; and C—O, 1.418(8) Å. The short C—O and C—C bond lengths are typical of crown ethers. The C—S bond length in (2) does, however, differ from the average value by more than two standard deviations. The C—S bond lengths in (25) (see Figure 3) (1.687(7) and 1.641(7) Å) are shorter than those in (2) and (22)–(24). The conformation of (25) is similar to that of the all oxygen 18-crown-6. The smaller C—S—C bond angles, longer C—S bond lengths, and size of the sulfur atom seem to offset each other to yield the similar conformation $\langle 81\text{AX}(\text{B})1739 \rangle$.



Compound (26) belongs to monoclinic space group C₂/C, $a = 11.578(1)$ Å, $b = 12.931(2)$ Å, $c = 16.454(1)$ Å, $B = 106.71^\circ$, $Z = 4$. The molecule has a twofold symmetry axis through the N—N

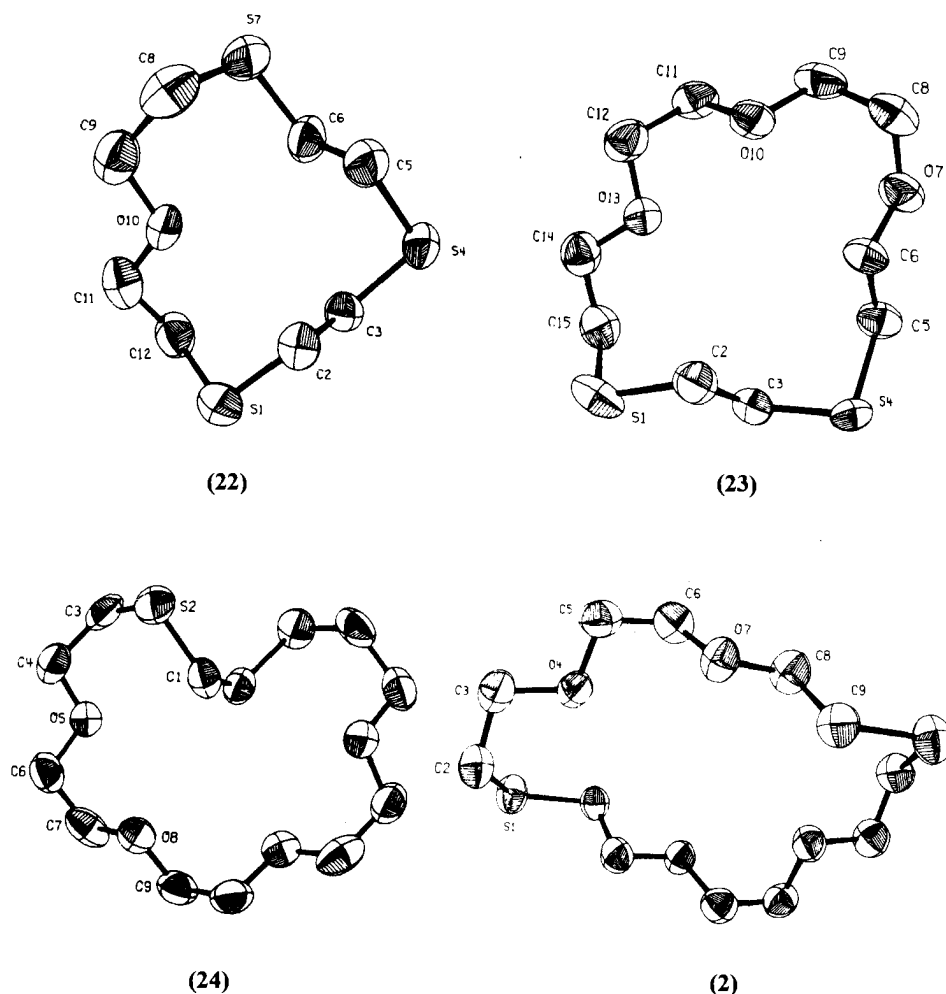
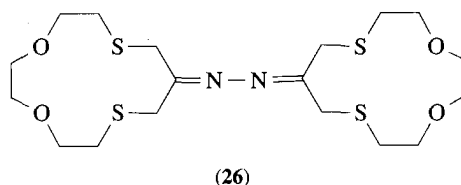


Figure 2 Solid-state structures of thiacrowns (2) and (22)–(24).

bond. The C—N—N torsional angle is 139.88° and the N—N bond distance is $1.406(3)$ Å. The macrocyclic ring adopts the usual conformations $\langle 92CC1558 \rangle$.



The replacement of sulfur for some of the oxygen donor atoms in crown ethers has been shown to change the cation selectivity pattern. This change is manifested by a decrease in the stability of complexes with group 1 and 2 metal ions and an increase in the stability of complexes with certain transition metal ions $\langle 78ICA1 \rangle$. Blake and co-workers $\langle 90JCS(D)3849 \rangle$ have studied the single-crystal x-ray structures of (23) (1,4-dithia-15-crown-5) complexed with various metal ions. It is possible that mixed sulfur and oxygen crowns will bind soft second and third row metal ions via the sulfur atoms leaving the oxygen atoms free to bind main group 1 and 2 and size-related organic cations. The crystal structure of $[Pd(23)_2]^{2+}$ shows the palladium(II) occupying a crystallographic inversion center. The palladium(II) is coordinated between the sulfur atoms of two molecules of (23) in an *exo* position with all oxygen donors directed away from the metal ion to give a relatively flattened complex. The metal–sulfur bonds are Pd—S(1), $2.3149(10)$ Å, and Pd—S(2), $2.3017(10)$ Å, with a S(1)—Pd—S(2) angle of $89.78(4)^\circ$ $\langle 90JCS(D)3849 \rangle$.

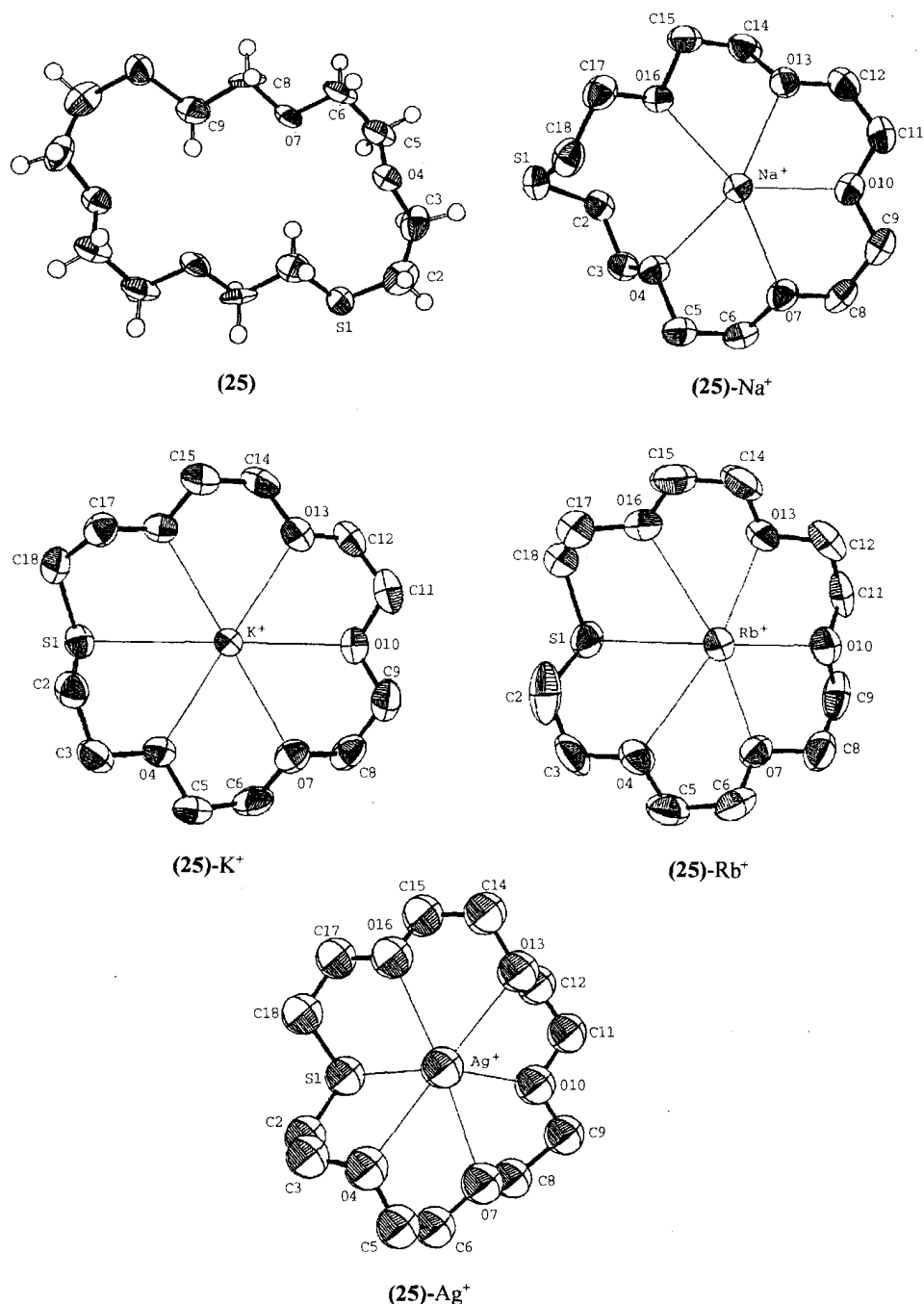


Figure 3 Solid-state structures of thiacrown (25) and the (25)-NaSCN, (25)-KSCN, (25)-RbSCN, and (25)-AgNO₃ complexes.

In the crystal structure of [RuCl(PPh₃)(23)₂]PF₆ · H₂O, the ruthenium(II) octahedrally coordinates with Cl[−] and PPh₃ ligands in the *trans* configuration. As before, ruthenium(II) is bound exocyclically to the two sulfur atoms in each macrocycle <90JCS(D)3849>.

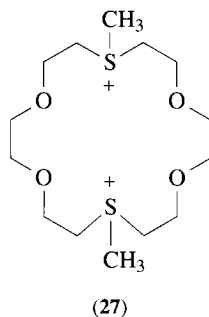
When (23) interacts with Ag⁺, two interesting complexes form <92CC1074>. The complex [Ag_n(23)_n]ⁿ⁺ is a sulfur-bridged linear polymer of [Ag(23)]⁺ units. The Ag⁺ is bound to all donor atoms in one macrocycle and a sulfur of another ring giving a formal S₂O₃S octahedral bridge coordination of Ag⁺. Each crown is coordinated to one Ag⁺ ion in an *endo* manner via two sulfur atoms and three oxygen atoms (Ag—S(2), 2.5401(15) Å; Ag—S(1), 2.7996(12) Å; Ag—O(3), 2.667(5) Å;

Ag—O(5), 2.690(4) Å; Ag—O(4), 2.492(4) Å). The bridging Ag—S(1) is 2.5951 Å. The binuclear complex of $[\text{Ag}_2(\mathbf{23})_3]^{2+}$ has distorted trigonal planar S_3 coordination at the metal ion via three sulfur-donor atoms (two from a bidentate macrocycle that is terminally bound). The Ag—S bonds are near 2.6 Å except the bridging Ag—S bonds which are near 2.45 Å <92CC1074>.

Dithia-18-crown-6 (**24**) complexes with mercury(II) and palladium(II) have been studied <81AX(B)2225>. Structure (**24**) is coordinated exocyclically to the metal ions. The bidentate thioether–mercury(II) complex has a distorted tetrahedral coordination where the two sulfur atoms occupy two positions and two chlorine atoms occupy the other two positions. The S—Hg—S angle is about 25° less than the expected tetrahedral angle with Hg—S bond lengths of 2.522(6) Å and 2.672(7) Å. The overall conformation of the complexed macrocycle is very similar to that of the uncomplexed dithiacrown ether. The mean difference between the torsion angles of complexed and uncomplexed (**24**) is about 5° . The mean bond lengths for C—S, C—C, and C—O are also very close to those of the uncomplexed macrocycle (1.8 Å, 1.49 Å, and 1.43 Å, respectively) <81AX(B)2225>. The complex of (**24**) with palladium(II) also shows the familiar exobidentate coordination where the palladium is bound to both sulfurs of two different macrocycles. All Pd—S bond lengths are 2.30 Å and all S—Pd—S bond angles are near 90° <90IC3828>.

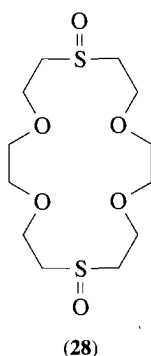
While (**24**) usually forms an exodentate complex, 1,10-dithia-18-crown-6 (**2**) usually forms an endodentate complex. The C—C, C—O, and C—S bond lengths in these complexes agree well with those of other thiacycrown ethers (1.5 Å, 1.4 Å, and 1.8 Å, respectively). The Pd—S bond lengths are similar in all complexes. These bond lengths are 2.27 Å in the $\text{Pd}(\mathbf{2})(\text{NO}_3)_2$ complex <90IC3828>, 2.30 Å in the $\text{Pd}(\mathbf{2})\text{Cl}_2$ complex <74JINC785>, and 2.39 Å in the $\text{Pd}(\mathbf{2})(\text{SCN})_2$ complex <86MI 932-01>. The $[\text{La}(\text{ClO}_4)_2(\text{H}_2\text{O})(\mathbf{2})]\text{ClO}_4$ complex has La—S average bond lengths of 3.0 Å and La—O bond lengths of 2.61 Å. The overall conformation of the macrocycle resembles that of a boat. The geometry of the whole complex is best idealized by a decatetrahedron <80JCS(D)376>. The coordination around the palladium(II) in $\text{Pd}(\mathbf{2})(\text{NO}_3)_2$ is distorted square planar <90IC3828> and in $\text{Pd}(\mathbf{2})\text{Cl}_2$ it is a *cis* square planar <74JINC785>. The complex $\text{Pd}(\mathbf{2})(\text{SCN})_2$ has a *trans* configuration <86MI 932-01>. The $\text{Cu}(\mathbf{2})\text{Cl}_2$ complex has a square planar coordination about the copper ion with Cu—S bond lengths of 2.408(2) Å <89K1577>. The Pt—S bond angles in $\text{Pt}(\mathbf{2})\text{Cl}_2$ are 2.283 and 2.285 Å. Comparison of x-ray diffraction data of $\text{Pt}(\mathbf{2})\text{Cl}_2$ and $\text{Pd}(\mathbf{2})\text{Cl}_2$ suggests that they are isostructural <89MI 932-01>.

1,10-Dimethyl-1,10-dithia-18-crown-6 (**27**) forms a complex with AuCl_4^- . This complex has a square planar geometry around the complexed AuCl_4^- <90K342>.

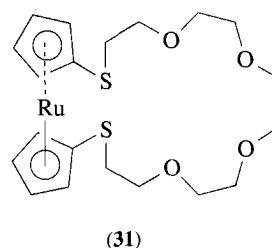
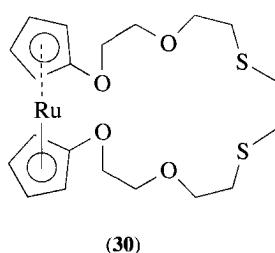
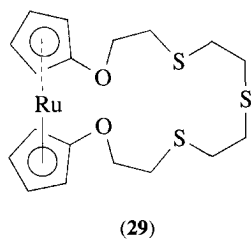


Crystal-structure analyses of (**25**) <81AX(B)1739> and its complexes with NaSCN <81AX(B)1741>, KSCN <81AX(B)1744>, RbSCN <81AX(B)1747>, and AgNO_3 <81AX(B)1750> have been carried out (Figure 3). The structure of (**25**) was discussed above with the other uncomplexed thiacycrowns. In all four complexes, the cation coordinates to the five oxygen atoms of the macrocycle. In the Na^+ complexed ligand, the sulfur atom is directed out of the cavity and does not interact with the Na^+ <81AX(B)1664>. In this case, the Na^+ ion sits in the cavity formed by the five oxygen donor atoms with the nitrogen atom of the thiocyanate ion completing the six-fold coordination of the ion <81AX(B)1741>. The sulfur–cation interaction is weak with K^+ ions even though the ion sits inside the cavity and coordinates to all six heteroatoms <81AX(B)1744>. The Rb^+ cation is located about 1.2 Å above the mean plane of the macrocycle and coordinates to all six donor atoms <81AX(B)1747>. Unlike in the K^+ and Rb^+ complexes, the S—Ag interaction in the (**25**)– AgNO_3 complex is strong and partially covalent. The Ag^+ cation sits in the cavity of the ligand and coordinates to all six heteroatoms <81AX(B)1750>. The C—C, C—S, and C—O bond lengths agree well with values obtained from related thioether complexes. All four complexes with (**25**) exhibit many of the same general features as those found in other crown ether complexes. The torsion angles about the C—C bonds are close to 60° . All bond angles are roughly tetrahedral.

X-ray analysis of 4,7,13,16-tetraoxa-1,10-dithiacyclooctadecane-1,10-dioxide (**28**) shows it to exist in two forms in its complexes with AgNO_3 and HAuCl_4 [91MI 932-01]. The β -isomer has a *cis* diequatorial structure in its complexes with the oxygen atoms of the sulfoxide groups occupying the equatorial positions. The α -form assumes a *trans* diaxial configuration in its complex with AgNO_3 and a *cis* diaxial conformation in the HAuCl_4 complex. ^1H , ^{13}C , and ^{17}O NMR spectroscopy was used to determine the solution structures of the isomers. In CDCl_3 , the α -isomer is *trans* diaxial and the β -form is *cis* diequatorial [91MI 932-01]. The structure of the 1 : 1 complex of (**28**) with HAuCl_4 has tetragonal pyramidal coordination around the gold atom and the disulfoxide is in the *cis* conformation. The compound is monoclinic space group $\text{P}2_1/b$ with $a = 8.468(2)$ Å, $b = 15.103(4)$ Å, $c = 34.609(9)$ Å, and $Z = 8$. The C—C, C—S and C—O bond lengths agree well with other thiacrown complexes. The S—O length is 1.54(3) Å. The C—S—C, O—S—C, O—C—C, and C—O—C angles are 97, 104, 109, and 110°, respectively [87K905]. The structure of the 1 : 1 complex of (**28**) with AgNO_3 has tetrahedral coordination around Ag^+ and the disulfoxide is in the *trans* diaxial conformation. The compound is monoclinic space group $\text{P}2_1/n$ with $a = 13.738(4)$ Å, $b = 9.447(4)$ Å, $c = 8.151(3)$ Å, and $Z = 2$ [87K93].



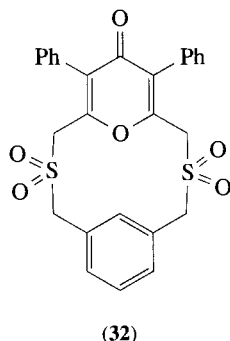
Akabori *et al.* have undertaken a study of metallocenophanes such as ruthenocenophanes (**29**)–(**31**) [85BCJ2185, 87CL1783, 89BCJ3963]. These structures can be divided into two parts: the ruthenocene moiety and the crown-like structure. In the mercury(II) complexes of (**29**) and (**30**), the mercury(II) is bound to the ruthenium atom of the ruthenocene unit opposite (and outside) of the crown ring. The Ru—Hg bond distances are near 2.70 Å with a distorted trigonal planar configuration about the mercury atom [87CL1783, 89BCJ3963]. In the mercury(II) complex of (**31**), the mercury atom is bound inside the macrocyclic ring with mercury–donor bond distances ranging between 2.8 and 3.3 Å. The distance between the ruthenium atom and the mercury atom is 4.8 Å, too long for direct metal–metal interactions [85BCJ2185]. The bond lengths of the macrocyclic ether unit agree well with reported C—C, C—S, and C—O bond lengths.



9.32.3.1.2 Miscellaneous macrocyclic compound

The crystal structure of the bis-sulfone 16,18-diphenyl-3,11-dithia[3]metacyclo[3](2,6)-pyranophan-17-one-2,2,11,11-tetraoxide (**32**) shows that the planar pyranone and benzene rings are tilted

by 60° with respect to each other. The S—O bond lengths are 1.44 Å and the S—C bond lengths are 1.8 Å (90CB1119).



X-ray crystal structure analysis of 2-oxa-10-thia[2.2]metacyclophane (**21**) shows the typical *anti* conformation of these ten-membered heterocyclic rings. The benzene rings are in a stair-stepped helical conformation. The transannular distance between hydrogen atoms inside the ring cavity is 262 pm (84JOC3484).

Vögtle *et al.* synthesized cyclophane (**20**), a close relative of (**21**). They believed that metacyclophane (**20**) would also show interesting chirotopic properties because of a helical structure caused by the C—O and C—S bonds located diagonally across the ring. The x-ray structure shows the *anti* conformation of the aromatic rings. The measured and calculated (MM) bond lengths and angles were different showing the difficulty in using theoretical methods to investigate highly strained systems. The results are listed in Table 3 (see Section 9.32.2) (89CC65).

9.32.3.2 Solution Structures

9.32.3.2.1 Nuclear magnetic resonance spectroscopy

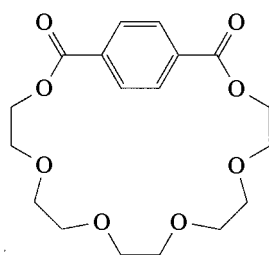
(i) Crown ethers and related compounds

Since its discovery in the 1940s, NMR spectroscopy has become the most important tool for solution structure identification and determination. Although it cannot provide the precise structural details about bond lengths and angles that x-ray or electron diffraction techniques can, an NMR spectrum rapidly provides a lot of data from which structural aspects can be deduced. One benefit of NMR spectroscopy is its speed and ease of use. 2-D, multinuclear (e.g. ^{15}N , ^{17}O , ^{23}Na , ^{195}Pt , etc.) and variable temperature NMR spectroscopy has also been used to study macrocycles and their complexes.

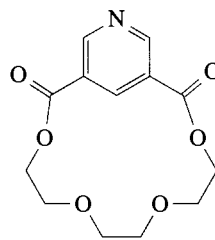
The ^1H NMR spectra for thiacrowns of the type (**2**) and (**22**)–(**25**) are very definitive. Compounds (**22**)–(**24**) have singlet peaks at $\delta = 2.7$ – 3.0 caused by the ethylene hydrogens between two sulfur atoms (73JHC1). Singlet peaks at $\delta = 3.5$ – 3.7 in (**2**) and (**23**)–(**25**) correspond to the ethylene hydrogens between two oxygen atoms. The triplet peaks at $\delta = 2.5$ – 2.8 are caused by the methylene hydrogens α to sulfur and β to oxygen while those at $\delta = 3.5$ – 3.9 by the methylene hydrogens α to oxygen and β to sulfur. These triplet NMR peaks associated with the ethylene hydrogen atoms between sulfur and oxygen heteroatoms appear to be first order for the monothia-12-crown-4 and 15-crown-5 macrocycles. Many (if not all) other sulfur-containing crown ethers appear to show complex splitting and/or broadening of the peaks associated with ethylene hydrogens between sulfur and oxygen atoms. Bradshaw *et al.* associated these observations with puckering of the rings due to the sulfur atoms being directed out of the cavity (73JHC1).

Insertion of aromatic and/or heteroaromatic subunits into crown ethers can shift the resonances of the ethylene moieties of the polyether chain upfield or downfield depending on their proximity to the ring current of the aromatic subunits. Bradshaw and Thompson observed upfield shifts of the protons on the central ethylene unit of macrocyclic cyclophane (**33**) (78JOC2456). Several other groups observed upfield shifts of the signals caused by the central hydrogen atoms of various para-cyclophanes (57JA846), hetero-*p*-carbophanes (74CL1173, 76BCJ3159) and terephthalates (78JOC2456).

Bradshaw *et al.* observed downfield shifts of the protons on the central ethylene unit of macrocycle (34), derived from pyridine and triethylene glycol <78JHC825>.



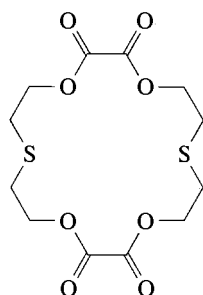
(33)



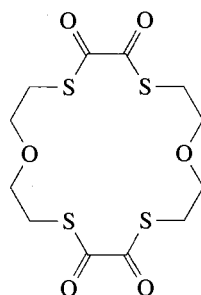
(34)

Comparison of the NMR spectra of several crown ethers or related macrocycles containing aromatic or heteroaromatic subcyclic units shows features of these compounds that are of general interest. These macrocycles have "benzylic" methylene signals that are sensitive to small steric or conformational differences because they lie in close proximity to the aromatic rings. These "benzylic" signals usually appear 0.5–1.3 ppm down field from the polyether absorptions which appear as broad multiples (or singlets) around $\delta = 3.4\text{--}3.7$ ppm.

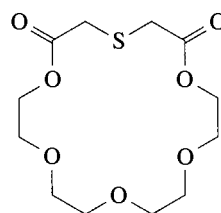
Insertion of an oxalyl moiety into the crown ethers causes some shifts in proton resonance depending on their proximity to the carbonyl group. In 1,4,10,13-tetraoxa-7,16-dithiacyclo-octadecane-2,3,11,12-tetraone (35), the protons α to the oxygen and β to the sulfur exhibit peaks at $\delta = 4.40$ in the NMR spectrum <78JHC269>. The signal for the protons α to sulfur and β to oxygen appear at $\delta = 2.90$ in (35). In (36), these proton absorptions show up at $\delta = 3.20$ and 3.70, respectively. Thus, when the sulfur atom is next to the oxalyl unit, there is a substantial downfield shift (from 2.9 to 3.7) in the signals for the proton α to the sulfur. The same downfield shift occurs for protons α to oxygen when the oxygen atom is bound to the carbonyl (from 3.2 to 4.4) <78JHC269>. In (37), the thiodiglycolate ester protons on the carbon bound to the sulfur atom (COCH_2S) gave signals at $\delta = 3.44 \pm 0.10$ <77JOC3937>.



(35)

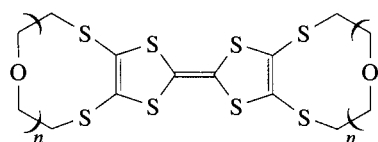
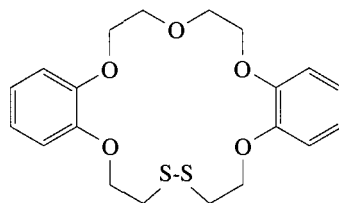


(36)

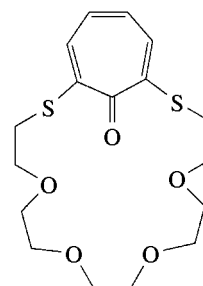


(37)

Derivatives of thiacycrown ethers, such as (38)–(40), show the expected ^1H NMR signals. In (38)–(40), the protons on carbons adjacent to the sulfur atoms exhibit the familiar triplet signals at $\delta = 3.00$ <85BCJ1343>, 3.22 <94JOC1354>, and 3.18 <92CE945>, respectively. The signals for the protons adjacent to the polyether oxygen atoms fall within the normal ranges in these compounds.

(38) $n = 3$ 

(39)



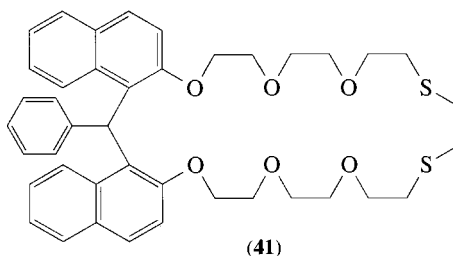
(40)

Trends in chemical shifts of ^{13}C NMR signals are somewhat parallel to those of ^1H NMR signals regarding hybridization, solvent effects, and electronegativity of substituents. ^{13}C NMR spectra for thiacrowns exhibit chemical shift ranges of $\delta = 32\text{--}35$ ppm for carbons α to the sulfur atom and β to the oxygen atom as in (2) and (23)–(25). For carbons α to the oxygen atom and β to the sulfur atom, the chemical shifts range from $\delta = 70\text{--}72$ ppm (91JA6538). Simple polyether (O—C—C—O) and thiaether (S—C—C—S) chemical shifts range from 69–73 and 31–34 ppm, respectively (84TL1991, 85BCJ3540, 91JA6538).

NMR spectral techniques are widely used to study complexation of macrocycles as well as the thermodynamic and kinetic quantities that describe host–guest interactions. Measurements of the free energy of activation for complex dissociation ($\Delta G^\ddagger$) at the ^1H NMR coalescence temperature, have been done using a variable temperature ^1H NMR procedure (B-71MI 932-01, 81JHC233). The method is advantageous for ammonium cations because the dissociation rate for most crown ether–ammonium cation complexes is within the ^1H NMR time scale and only a small amount of sample (3–5 mg) is required.

Among the various NMR spectral methods used to investigate the complexation of crown ethers with metal cations (80MI 932-01), organic cations (81TL458) and neutral molecules (82MI 932-02), ^1H NMR spectroscopy is the simplest and possibly the most accurate if it is applicable to the system under investigation and is used properly. The direct NMR method for determining $\log K$ values is advantageous in that a small amount of sample (3–5 mg) is required and useful structural information can be obtained in a short period of time (94UP 932-01).

The development of modern NMR spectroscopic techniques makes possible the study of important structural features of molecules in solution by utilizing a combination of several modern NMR experiments. For example, 1-D and 2-D NOE experiments provide information about the spatial arrangement of two atoms in a molecule if the motion of the compound is not too fast for observation in the NMR time scale (B-87MI 932-02). Complete assignment of each signal in the ^1H NMR spectrum of the propeller dithiacrown (41) was made using 2-D COSY and J-resolved spectra (90JCR(S)364). ^1H NMR spectroscopy has been used to study the complexation of thiacrowns with various metal cations such as Hg^{II} , Ag^+ , Pd^{II} (82MI 932-03, 93PAC1485) and Au^{III} (90MI 932-01).



Complexation of many ligands is usually accompanied by a significant chemical shift change in the ^1H NMR spectrum. The polyether rings usually show a smaller change in chemical shift than do any “benzylic” groups if an aromatic ring is present. Changes in chemical shifts upon complexation can depend on ring size (77T563). The effect of complexation on ^{13}C NMR spectra is small but noticeable. This, coupled with the fact that the polyether ring and “benzylic” carbons have similar chemical shifts, make ^{13}C NMR spectroscopy less suitable for studying complexation. ^{13}C NMR relaxation times and chemical shift studies have been done in order to gain information on ligand conformation, binding dynamics, and binding strengths in solution (91JA6538). This technique provides a way to identify metal binding contributions of specific binding sites in different regions of the host.

Nuclear magnetic resonances of ^7Li , ^{23}Na , ^{39}K , ^{133}Cs (85CRV271, 91CRV1721), and ^{205}Tl (85POL441) have been used to study thermodynamics of complex formation of the crown ethers. Rounaghi and Popov (81JINC911) studied the complexation of (2) and (22) with Li^+ , Na^+ , Cs^+ , Tl^+ , and Ag^+ using ^7Li , ^{23}Na , ^{133}Cs , ^{205}Tl , and ^1H NMR spectral techniques. The variation of the chemical shift with ligand/metal ion mole ratios was used to calculate the stability constants of the complexes in several nonaqueous solvents. Results of this study show no significant interaction between (22) and Li^+ as observed by ^7Li NMR spectra in six different solvents. This study also revealed a substantial decrease in complex stability of (2) with Na^+ , Cs^+ , and Tl^+ when compared to their complexes with the all oxygen analogue, 18-crown-6. This decrease was attributed to cavity size of the macrocycle (81JINC911).

Polyoxathiametallophenes are closely related to crown ethers. These thiacycrown ether-like compounds include a metallocene unit such as ferrocene or ruthenocene as a ring member in which the metal atom may play a coordination role. The ^1H NMR spectra of these compounds can be divided into two parts: the spectra of the metallocene unit and the spectra of the thiacycrown ether-like moiety. Sulfur-containing ferrocenophanes and ruthenocenophanes show many of the same spectral features as their crown ether counterparts. The ^1H NMR spectra of ferrocenophanes (42)–(74) show the familiar ^1H NMR signals of $\delta = 2.5\text{--}3.2$ and $\delta = 3.4\text{--}4.1$ for protons of the type $\text{S}-\text{CH}_2\text{CH}_2-\text{O}$, and $\text{S}-\text{CH}_2-\text{CH}_2-\text{O}$, respectively. Ferrocenophanes (47), (57)–(59), (64), (65) and (71) have signals at $\delta = 2.7\text{--}3.0$ for the ethylene protons between two sulfur atoms; whereas (43)–(45), (49), (50), (53)–(55), (61)–(63), (67)–(69) and (72)–(74) exhibit at $\delta = 3.4\text{--}4.0$ for protons on ethylenes between two oxygen atoms (80PJC767, 82M965, 82TL185, 83BCJ1459, 84TL1991, 91TL3775). Ruthenocenophanes (75)–(82) also show proton resonances like the ferrocenophanes listed above (84TL1991, 85BCJ3540, 89BCJ3963).

Proton resonances for the cyclopentadienyl (Cp) rings of the metallocenophanes show some differences in chemical shifts between the two rings. The signals for the α and β protons of the Cp rings in ferrocenophanes (42)–(55) and (60)–(63) were observed as narrow multiplets or as singlets at $\delta = 3.90\text{--}4.35$ (80PJC767, 82TL185). In ferrocenophanes (56)–(59), (64)–(69) and (70)–(74), the α and β protons of the Cp rings appear to be triplets with chemical shifts of $\delta = 3.8$ to 4.25 (83BCJ1459). These proton signals were observed between $\delta = 4.6\text{--}4.8$ in ruthenocenophanes (75)–(77) (84TL1991) and between $\delta = 4.27\text{--}4.9$ in (79)–(82) (85BCJ3540, 89BCJ3963).

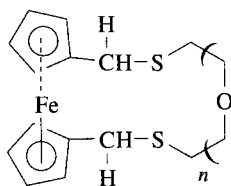
^{13}C NMR spectroscopy of the ruthenocenophanes and ferrocenophanes show the following ranges for the carbon resonances: $\text{C}-\text{O}$, $\delta = 70\text{--}72.4$ and $\text{C}-\text{S}$, $\delta = 30\text{--}34$ (84TL1991, 85BCJ3540). The chemical shifts for the Cp carbon atoms seem to depend upon the metal atom (iron or ruthenium) and which heteroatom is bound to the Cp ring. The bridgehead carbon (C_b) exhibits carbon resonances at $\delta = 88\text{--}90.5$ when bound to a sulfur atom in ruthenocenophane. This same carbon (C_b) of the ruthenocenophane unit when bound to an oxygen exhibits a signal at $\delta = 126.8\text{--}128.5$. The bridgehead carbons of a ferrocene unit exhibit signal absorbances at $\delta = 83.0\text{--}91.0$ when bound to a sulfur (80PJC767) and $\delta = 85.0\text{--}86.0$ when bound to a methylene carbon (91TL3775). The α carbons (C_a) of the Cp rings of the ruthenocene moiety exhibit signals at $\delta = 77$ and 60 when C_b is bound to a sulfur atom or an oxygen atom, respectively (84TL1991, 85BCJ3540). The α carbons of the ferrocene units exhibit signals at $\delta = 66\text{--}73$ and the β carbons exhibit resonances between $\delta = 68\text{--}74$ (80PJC767, 91TL3775). The β carbons of the ruthenocenophanes have signals at $\delta = 72\text{--}73$ and $64\text{--}66$ when the bridgehead carbon is bound to a sulfur or an oxygen atom, respectively (84BCJ421, 85BCJ3540, 80PJC767, 82M965).

Complexation properties of metallocenophanes have been investigated by NMR spectroscopy. The addition of silver nitrate to (52)–(55) in acetonitrile- d_3 causes a deshielding shift in the ferrocene Cp ring protons as well as the methylene protons next to the sulfur atom. This deshielding effect increases almost linearly in response to an increase of silver nitrate concentration until molar equivalence is achieved. Little change in chemical shift occurs after a 1 : 1 molar ratio suggesting that a 1 : 1 complex formed. The Cp ring protons of (54) and (55) appeared as singlets in both the complex and uncomplexed forms, while the ferrocene ring protons in the silver complex of (53) appeared as a separated triplet pair suggesting a tilt deformation of the Cp rings in order to accommodate the ion. The large deshielding of the cyclopentadienyl protons has been associated with electron transfer from the iron atom of the ferrocene to the silver ion. Similar downfield shifts of Cp ring carbons were observed by ^{13}C NMR spectroscopy supporting the idea that there is electron transfer from the iron and sulfur atoms to the silver cation (84BCJ421).

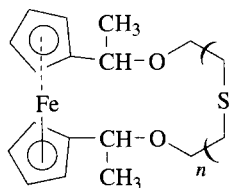
^1H NMR spectra (DMSO- d_6) of the Ag^+ complexes of ruthenocenophanes (81) and (82) suggest no interaction between the ruthenium and the complexed silver ion. In this case, the methylene protons attached to sulfur atoms were shifted more than the protons of the ruthenocene nucleus. ^1H NMR spectra of the mercury(II) complexes of (80)–(82) suggest that there is significant interaction between ruthenium and the mercury(II). The β protons of the Cp rings were shifted further downfield than the α protons, and the ethylene protons exhibited very little downfield shift (85BCJ3540).

Variable temperature ^1H NMR spectroscopy has been used to study the conformational mobility of (19). When $\text{R} = \text{CH}_3$ in (19), the molecule is conformationally rigid in solution as shown by an unaltered ^1H NMR spectrum when increasing the temperature to 413 K (88MI 932-01). The five carbons in the chain of diphenylpyranophane (83) are less conformationally mobile at 213 K than at room temperature. According to the NMR spectrum at 213 K , rotation about the $\text{C}_2\text{--C}_3$ axis is no longer possible (90CB1587). Ring inversion barriers for the helical pyridinophanes (84), (86), and (87) all lie at 88 kJ mol^{-1} , while that of (85) is 95 kJ mol^{-1} (88AG(E)976).

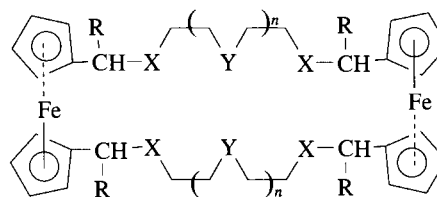
Coalescence temperatures, free energies of activation, coupling constants, and chemical shifts



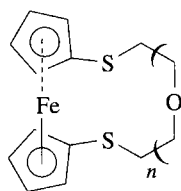
- (42) $n = 1$
 (43) $n = 2$
 (44) $n = 3$
 (45) $n = 4$



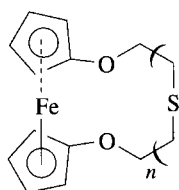
- (46) $n = 1$
 (47) $n = 2$



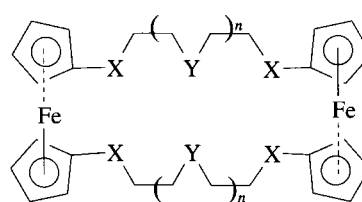
- (48) $R = H, X = S, Y = O, n = 1$
 (49) $R = H, X = S, Y = O, n = 2$
 (50) $R = H, X = S, Y = O, n = 3$
 (51) $R = CH_3, X = S, Y = O, n = 1$



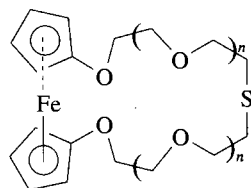
- (52) $n = 1$
 (53) $n = 2$
 (54) $n = 3$
 (55) $n = 4$



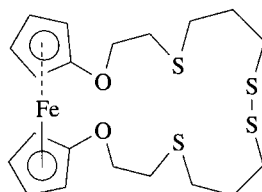
- (56) $n = 1$
 (57) $n = 2$
 (58) $n = 3$
 (59) $n = 4$



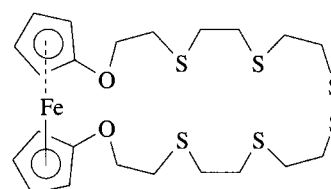
- (60) $X = S, Y = O, n = 1$
 (61) $X = S, Y = O, n = 2$
 (62) $X = S, Y = O, n = 3$
 (63) $X = S, Y = O, n = 4$
 (64) $X = O, Y = S, n = 2$
 (65) $X = O, Y = S, n = 3$



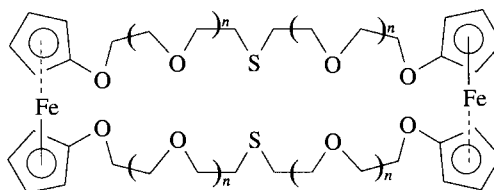
- (66) $n = 0$
 (67) $n = 1$
 (68) $n = 2$
 (69) $n = 3$



(70)



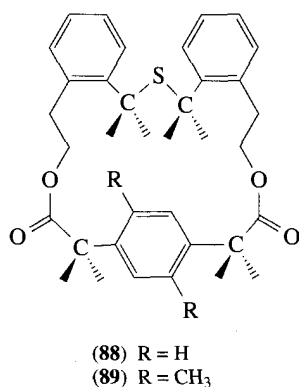
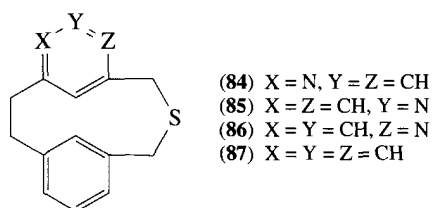
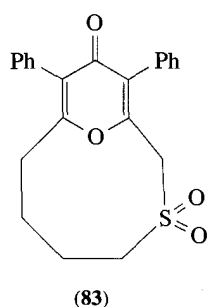
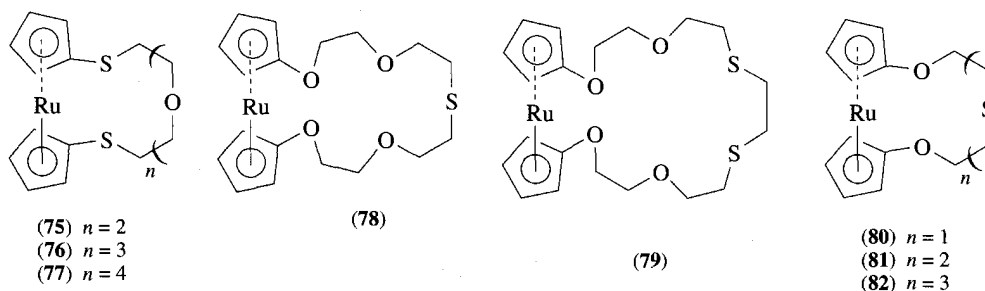
(71)



- (72) $n = 1$
 (73) $n = 2$
 (74) $n = 3$

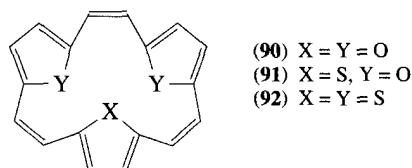
were obtained on 19,22-dimethyl-3,15-dioxa-9-thia-2,16-dioxo-6,7,11,12-dibenzo[17]paracyclophan-6,11-diene (**89**) and its unsubstituted homologue (**88**) in order to study long range asymmetry effects. The results show the non-equivalence of methylene protons that are separated by eight bonds from an aromatic center of asymmetry <75CL615>.

Structure identification and characterization still constitute the main use of ^1H NMR spectroscopy as shown by the difference between the spectra of the two cappedophane conformers (**9**) and (**10**). The ^1H NMR resonances of the three vicinal aromatic protons on the central ring of the *m*-terphenyl unit of cappedophane (**9**) are deshielded because they lie within a cavity of aromatic rings. The distinction between (**9**) and (**10**) is apparent from their ^1H NMR spectra <91JOC5630>.



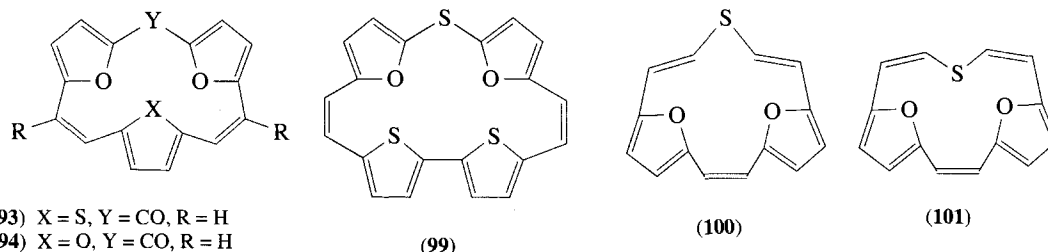
(ii) Miscellaneous macrocyclic compounds

The aromatic nature of various [18]annulenes containing oxygen and sulfur as heteroatoms has been investigated by ^1H NMR spectroscopy. Catalin models of macrocycles (11) and (90)–(92) suggest that [18]annulene trisulfide (92) and [18]annulene oxide disulfide (11) are not planar, [18]annulene dioxide sulfide (91) may be nearly planar, and [18]annulene trioxide (90) is planar. The ^1H NMR and ultraviolet–visible (UV–VIS) spectra of these compounds confirmed the aromaticity of [18]annulenes (90) and (91) and the nonaromatic nature of (11) and (92). The UV–VIS spectrum of (11) indicates that it is more planar and conjugated than (92) <65CC269, 65CC492, 66AJC257, 66AJC1461>.



Extensive ^1H NMR spectral analyses of annulenes (91) and (93)–(101) have shown annulenes (95)–(99) and (101) to be atropic <82H(19)2047> and (91) to be diatropic <73JCS(P1)1786>. Annulenone (94) <73JCS(P1)2961> and thia[15]annulene (100) <82H(19)2047> were found to be paratropic and planar,

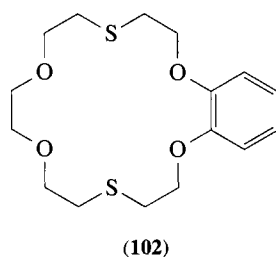
while annulenone (**93**) fails to support any paramagnetic ring current. Development of ring current was reported to be a function of the ability of these compounds to adopt a flat or nearly planar geometry <73JCS(P1)2961>.



- (93) X = S, Y = CO, R = H
 (94) X = O, Y = CO, R = H
 (95) X = Y = S, R = H
 (96) X = O, Y = S, R = 4H
 (97) X = Y = S, R = CO₂CH₃
 (98) X = O, Y = S, R = CO₂CH₃

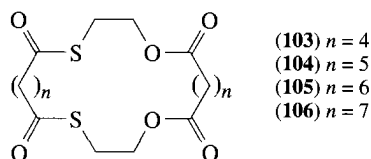
9.32.3.2.2 Vibrational spectroscopy

Infrared (IR) spectroscopy has been applied to crown ethers to better understand conformation and structure aspects of the complexed and uncomplexed ligands. Early investigations of crown ethers by IR were carried out by Pedersen and some examples are given in CHEC-I <84CHEC-I(7)731>. Comparison of IR spectra of free and complexed dithia-18-crown-6 (**2**) has been recorded in order to determine the mode of its coordination to various metals. The bands of stretching vibrations of the C—S, C—O—C, C—C—O moieties in Yb²⁺, Sm²⁺, Tm²⁺, and U³⁺ complexes with (**2**) are displaced relative to the band for the free host <90MI 932-01, 91MI 932-02>. In a study using the divalent lanthanide complexes, stronger displacement in the IR spectra for the all oxygen 18-crown-6 over its thiacrown analogues was observed indicating a greater binding strength for 18-crown-6 <90MI 932-01>. In complexes with Ag⁺ and palladium(II) ions, the C—O stretching wavenumber is nearly the same as that of free (**2**). Bands in the range where metal–oxygen vibrations usually appear (450–600 cm⁻¹) were absent and bands in the range of 200–400 cm⁻¹ (metal–sulfur vibrations) appear indicating that the sulfur atoms of the host are coordinated to the metal ion <82MI 932-03>. This same result was found in a copper complex of (**102**). The x-ray structure of this complex shows the copper bound to the sulfur atoms forming an exodentate complex <89MI 932-02>.



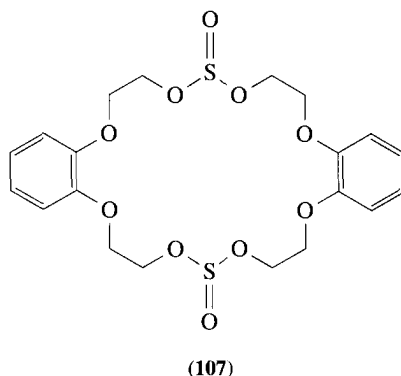
IR spectral data of the mercury(II) and silver(I) complexes of ruthenocenophanes (**80**)–(**82**) have been used to help determine the extent of interaction between the ruthenium atom of the ruthenocene unit and the encapsulated metal ion. The Cp—Ru—Cp ring tilting band around 430 cm⁻¹ is very instructive in these studies <85BCJ3540>.

The binding properties of sulfur- and oxygen-containing lactones (**103**)–(**106**) have been investigated by IR spectroscopy. The IR spectrum of the mixtures of each of the dithiolactones and metal salts of mercury(II), silver(I), and lead(II) indicated no binding of mercury(II) or lead(II), but (**103**) and (**105**) bound AgNO₃ as shown by displacement of the thiolactone absorption band <85JOC5476>. Raman spectroscopy has found limited use in the study of oxygen- and sulfur-containing macrocycles. The Raman spectrum at 100 K shows one peak at 164 cm⁻¹ associated with the symmetric stretching mode of I₂ in the iodine complex of 1,10-dithia-18-crown-6 (**2**) <92ICA23>.



9.32.3.2.3 Electronic spectroscopy

The majority of UV spectroscopic studies on macrocyclic rings containing oxygen and sulfur atoms has been done on annulenes and annulenones. The main thrust of this type of research has been to determine the planarity and hence the aromatic properties of these compounds. UV spectral studies done on annulenes (91) and (95)–(101) and annulenones (93) and (94) support the ^1H NMR results discussed earlier <73JCS(P1)1786, 73JCS(P1)2961, 82H(19)2047>. UV–VIS spectroscopy has been used, although not widely, to study the complexation of sulfur-containing crown ethers and ruthenocenophanes. According to Serguchev *et al.* <88MI 932-02>, the introduction of sulfide groups in macrocyclic polyethers substantially increases the stability of their complexes with iodine. Measurements carried out on UV–VIS spectrophotometers show stability constants of about 10^2 with enthalpies of formation up to 30 kJ. Absorption spectra of the 22-membered sulfonyl dibenzo crown (107) suggest that the metal cations coordinate to the oxygen of the $\text{S}=\text{O}$ groups outside the macrocyclic cavity <91ZOB2042>.



Electronic spectral data have been obtained on sulfur-containing ruthenocenophanes to determine the interaction between metal cations and the ruthenium atom of the ruthenocene moiety. In the mercury(II) complexes of (80)–(82), the wavelengths of maximum absorption exhibit a blue shift of about 8–34 nm along with an increase in their molecular coefficients when compared to the free ligands. This, coupled with the fact that others have observed an intense band at 200 nm in the ruthenocene– HgCl_2 complex, which is not found in the UV spectrum of free ruthenocene, suggests interaction of the ruthenium atom with HgCl_2 . Comparisons made between the all oxygen analogues of (80)–(82) indicate that the stronger $\text{S}—\text{Hg}$ interaction weakens the $\text{Ru}—\text{Hg}$ interaction <85BCJ3540>. This result is expressed by a maximum absorption for complexes of (80)–(82) in a longer wavelength range than those of the all-oxygen analogues.

9.32.3.2.4 Other experimental structural methods

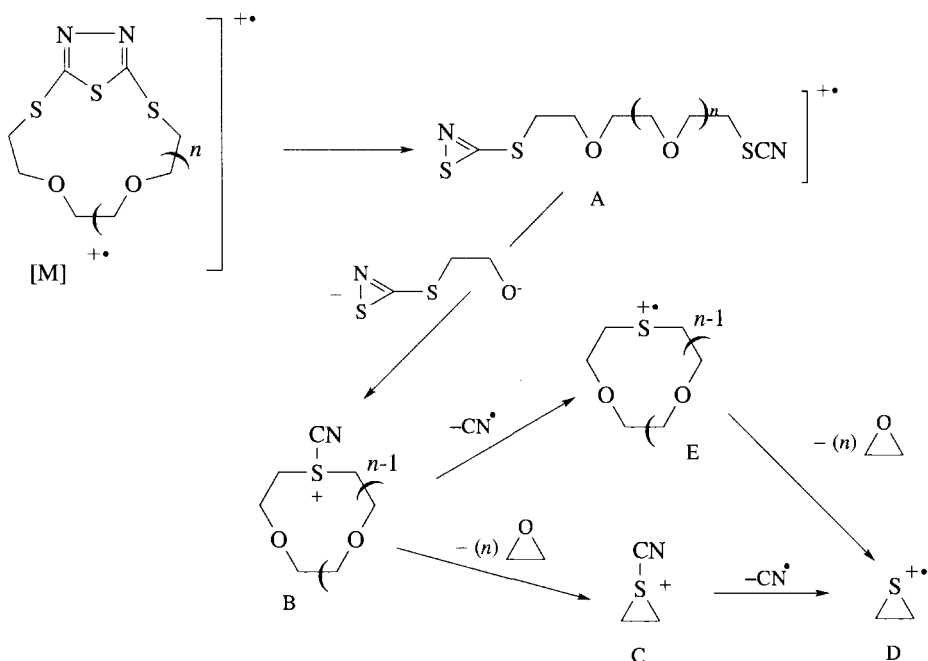
Mass spectrometry has been widely used for the elucidation of the structures of macrocycles with both oxygen and sulfur as heteroatoms. However, in most cases only molecular compositions are reported and detailed fragmentation patterns are scarce. The mass spectra of macrocyclic polyethers have been evaluated and fragmentation patterns compared <76JCS(P2)206>. Within the series of compounds studied, molecular ion peaks were always observed. Only small differences in the mass spectra of compounds with different aromatic ring substitutions were observed. A protonated

Scheme 1

(108) $n = 1$
 (109) $n = 2$

(110)

(111) $n = 1$
 (112) $n = 2$
 (113) $n = 3$



Scheme 2

Fragmentation pathways for ferrocenophanes (**43**) and (**44**) have been proposed ^{<82M965>} and are given in Scheme 3. As seen in Scheme 3, both compounds exhibit peaks at $m/z=134$ and

Table 4 Selected ions in the mass spectra (18 eV) of (108)–(110) (see Scheme 2) <87OMS(22)269>^a.

<i>Ion assignment</i>	(108)	(109)	(110)
[M] ⁺	264 (28)	308 (18)	308 (100)
[M-SH] ⁺	231 (55)	275 (36)	275 (32)
B	130 (40)	174 (33)	174 (7)
[B-C ₂ H ₄ O] ⁺	86 (50)	130 (39)	130 (11)
[B-2C ₂ H ₄ O] ⁺		86 (53)	86 (23)
E	104 (20)	148 (10)	148 (3)
[E-C ₂ H ₄ O] ⁺	60 (65)	104 (28)	104 (4)
[E-2C ₂ H ₄ O] ⁺		60 (28)	60 (12)

^aData are listed as *m/z* (relative intensity, %).**Table 5** Selected ions in the mass spectra (18 eV) of (111)–(113) <87OMS(22)269>^a.

<i>Ion assignment</i>	(111)	(112)	(113)
[M] ⁺	440 (30)	528 (32)	616 (11)
[M-H ₂ O] ⁺	442 (7)	510 (<1)	598 (2.1)
[M-CH ₃ O] ⁺	410 (10)	498 (4)	586 (1.3)
[M-SH] ⁺	407 (6)	495 (11)	583 (7)
[M-C ₂ H ₃ O] ⁺	397 (47)	485 (35)	573 (27)
[M-C ₂ H ₅ OS] ⁺	363 (40)	451 (2.2)	539 (2.4)

^aData are listed as *m/z* (relative intensity, %).

78. The mass spectra of [18]annulene derivatives (11) and (90)–(92) were reported in 1967 and fragmentation patterns were discussed <67AJC2669>.

Plasma desorption mass spectrometry (PDMS) has been used for the characterization of macrocycles and their complexes. PDMS seems to be able to produce molecular ions reliably giving a semiquantitative picture of the compounds with very minimal fragmentation. PDMS has been used to compare the binding of various metal ions to individual hosts <92JOC6403, 92TL3035>.

9.32.4 THERMODYNAMICS ASPECTS

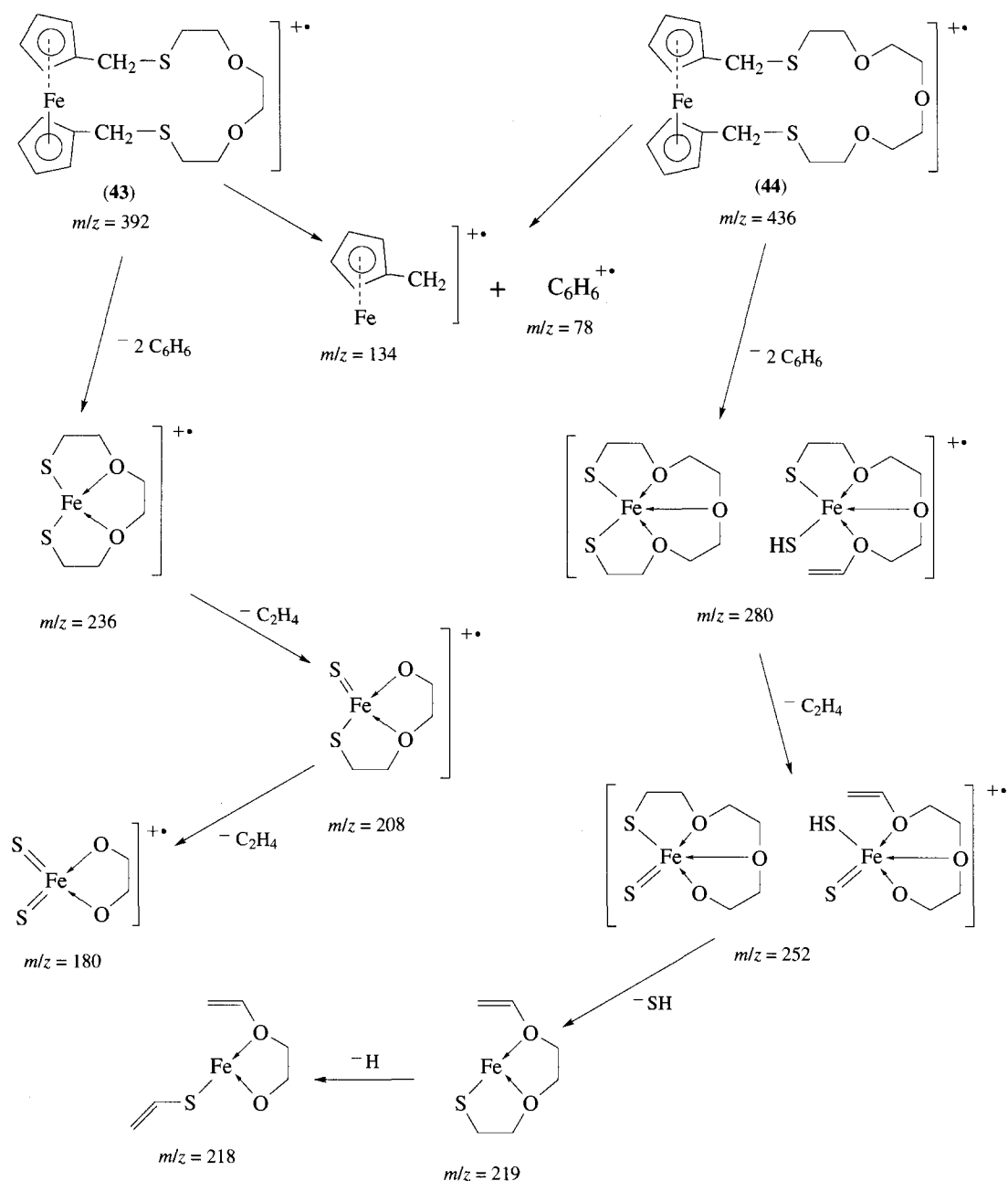
9.32.4.1 Intermolecular Forces

9.32.4.1.1 Melting and boiling points

The boiling and melting points of heterocyclic rings containing ten or more members, with both oxygen and sulfur as heteroatoms, have been reported, but only from the standpoint of compound characterization. To date, the boiling and melting points of these compounds have not been investigated from an "intermolecular forces" point of view. The main thrust of research dealing with these macrocycles concerns their synthesis as well as their complexation properties. Large compilations of melting and boiling points are available in reviews on these molecules <B-82MI 932-01, 74JHC649> and the references cited therein. For comparison, a few select structural types along with their respective melting points are listed in Figure 4.

In 1963, Dale reported that the melting points of macrocycles are related to their conformations and that the melting point can be expressed as $T_m = \Delta H_m / \Delta S_m$ <63JCS93>. Dale points out that a large ΔS of fusion will equate to a low melting point or a small ΔS of fusion will mean a high melting point because the heat of fusion will likely remain nearly constant for all compounds of a certain series. In the liquid state, the larger more labile macrocycles will have several equivalent conformations and thus a higher entropy of fusion corresponding to a lower melting point.

Generally, as the ring size increases within a series of compounds, the melting point decreases. This can be seen by comparing the melting points of crowns (114), (119), and (126), of thiodiglycolate



Scheme 3

macrocycles (131)–(134), and the metallocenophane series (57)–(59) (see Figure 4). This phenomenon is probably due to more flexibility in the large rings.

Melting points seem to increase as the number of sulfur atoms increases within a series of the same ring size. This is shown by comparing the sets of compounds (114), (22), (115), and (117); (119), (120), (122), and (124); (126), (24), and (25); (133) and (135); (136) and (80); and (137) and (81). Bradshaw and Hui point out that the larger sulfur atoms may cause these rings to become less flexible thereby reducing the number of possible conformations in the liquid state. They also observed in their 1974 review, that the more symmetrical macrocycles had the higher melting points <74JHC649>.

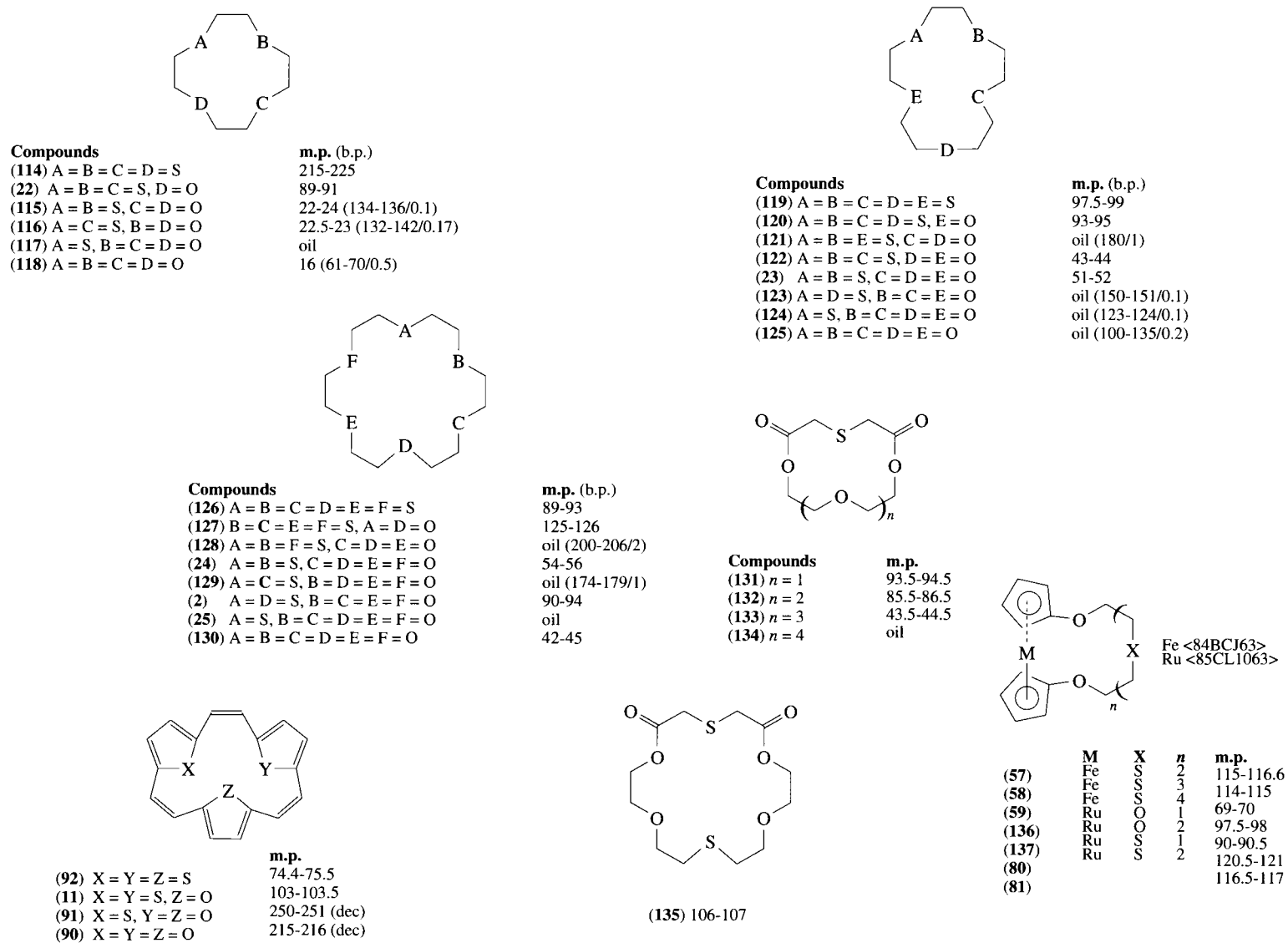


Figure 4 Melting points (boiling points/mm Hg) (°C) for selected macroheterocycles <74JHC649, B-82MI 932-01, 84BCJ63, 85CL1063>.

9.32.4.1.2 Solubility

While the solubilities of oxygen- and sulfur-containing macrocycles may have been investigated, their behavior in various solvents is usually associated with purification, separation, or complexation. Solvents that have been utilized in recrystallization of thiacyclic ethers include: hexane, heptane, and benzene. For the crown ether derivatives of the tetrathiafulvalenes, solvents include: H_2O , CH_3OH , $\text{C}_2\text{H}_5\text{OH}$, CH_2Cl_2 , and CH_3CN , for the metallocenophane crown ethers: hexane and $\text{C}_2\text{H}_5\text{OH}$, and for the annulenes: hexane, $\text{C}_2\text{H}_5\text{OH}$, cyclohexane, dioxane, and CH_3OH . These solvent lists are not intended to be extensive.

9.32.4.1.3 Chromatographic behavior

Chromatography in its various forms has been widely used for the separation and purification of macrocycles. Some typical conditions include various mixtures of the following solvents on silica gel or alumina (basic or neutral): thiacyclic ethers: benzene, CHCl_3 , hexane, ethyl acetate, and CH_2Cl_2 ; thiacyclic diesters: hexane, CHCl_3 , and ether; metallocenophanes: benzene, ether, CHCl_3 , hexane, acetone, toluene, and ethyl acetate. The aforementioned conditions are not an extensive review of the literature.

9.32.4.2 Complexation Thermodynamics

Most of the research on oxygen- and sulfur-containing macrocycles has been the investigation of their complexation properties. The majority of thermodynamic investigations concern $\log K$, ΔH and ΔS values for the interactions of macrocyclic hosts with various guests. The insertion of sulfur atoms in the crown ethers produces dramatic effects on K values for metal ion–ligand interaction $\langle 78\text{ICA1} \rangle$. Little or no interaction is found between alkali or alkaline earth ions and sulfur-containing macrocycles in aqueous solution. Stabilities of Ag^+ and mercury(II) complexes are increased while those of Tl^+ and lead(II) are reduced when compared to the all oxygen analogues. As previously mentioned, x-ray analysis indicates that, in many instances, the sulfur atoms are directed out of the macrocycle cavity prohibiting inclusion type binding. If the sulfur atoms were directed into the ring, a greatly decreased cavity size would result. The stoichiometry of complex formation can give information on the type of binding that is occurring.

Understanding the interactions between ions and macrocyclic ligands requires a study of various parameters governing the reactions. Several reviews containing compilations of thermodynamic and/or kinetic data for macrocycle–ion interaction have been published $\langle 74\text{CRV}351, 85\text{CRV}271, 91\text{CRV}1721, \text{B-79MI } 932\text{-01}, 95\text{CRV}2529 \rangle$. The exhaustive reviews published by Izatt and co-workers tabulate $\log K$, ΔH , and ΔS values measured by various techniques up to the year 1994.

Izatt and co-workers investigated the macrocyclic effect as defined by Cabbiness and Margerum $\langle 69\text{JA}6540 \rangle$ by comparing the stabilities of a number of oxygen- and sulfur-containing macrocycles to their open-chain analogues $\langle \text{B-79MI } 932\text{-01} \rangle$. They note that, if the sulfur atoms are directed out of the macrocyclic cavity, no macrocyclic effect is expected $\langle 78\text{ICA1} \rangle$.

Ferrocenophanes and ruthenocenophanes containing oxygen and sulfur donor atoms exhibit many of the same complexing characteristics as do the related crown ethers. X-ray, ^1H NMR, electronic, and IR spectral and metal picrate extraction studies show enhanced binding affinities for various transition metals (Ag^+ , Hg^{II} , Cu^{II} , etc.) and very little interaction with alkali and alkaline earth metal ions $\langle 84\text{BCJ}63, 84\text{BCJ}421, 85\text{BCJ}2185, 89\text{BCJ}3963 \rangle$.

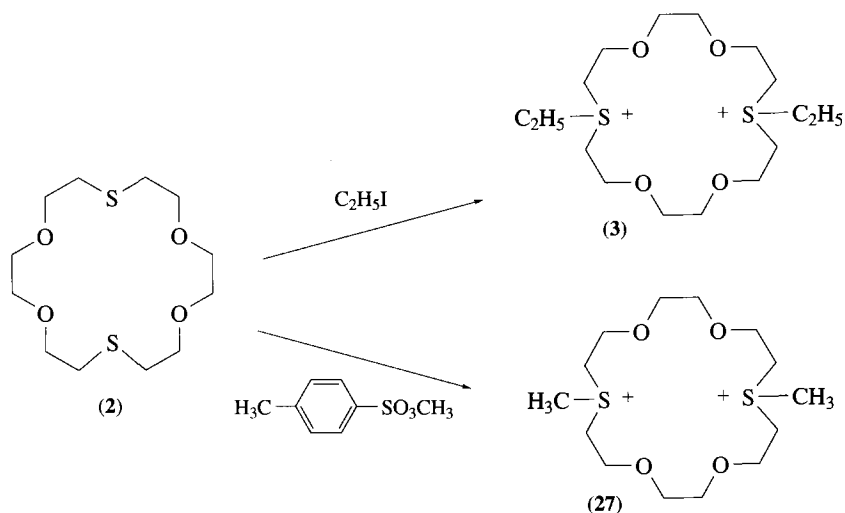
The complexing abilities of thiacyclic ethers and related macrocycles depend on several factors that have not been fully investigated. These factors include ligand cavity size, spatial distribution of binding sites within the ring, types of donor atoms, “hard and soft acid–base rule”, cation diameter, solvent, macrocycle conformation, and other factors $\langle \text{B-77MI } 932\text{-01}, \text{B-81MI } 932\text{-01} \rangle$.

9.32.5 REACTIVITY

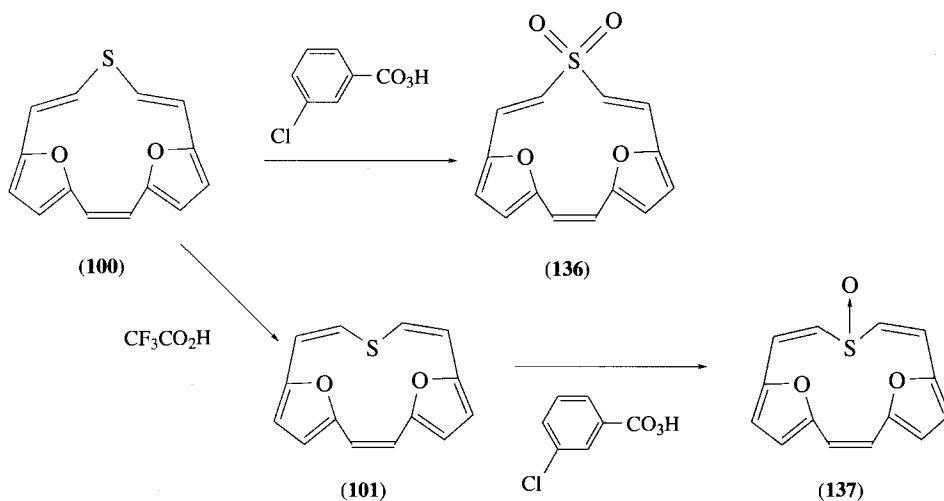
9.32.5.1 Functional Group Reactivity

Oxygen- and sulfur-containing macrocyclic compounds show much of the same functional group chemistry expressed in the simple acyclic systems. For example, as shown in Scheme 4, the macroring

sulfur atoms are typical nucleophiles and interact with alkyl halides or tosylates to give the sulfonium ions $\langle 61JOC1991 \rangle$. Oxidation of sulfur-containing macrocycles can occur at the sulfur atom as in the conversion of (2) to (4) $\langle 34JA2177 \rangle$. Oxidation of sulfur-containing annulenes (100) and (101) to give sulfone (136) and sulfoxide (137), respectively, are shown in Scheme 5. No thermal isomerization occurred in (100) or (101) up to 150°C as shown by variable temperature NMR spectroscopy. In the presence of trifluoroacetic acid, isomerization of (100) to (101) occurred at room temperature $\langle 82H(19)2047 \rangle$. In a similar oxidation, Massa *et al.* generated disulfone (139) from cyclic disulfide (138). Pyrolysis of disulfone (139) gave monosulfone (83) and desulfurized macrocycle (140) as outlined in Scheme 6 $\langle 90CB1587 \rangle$.



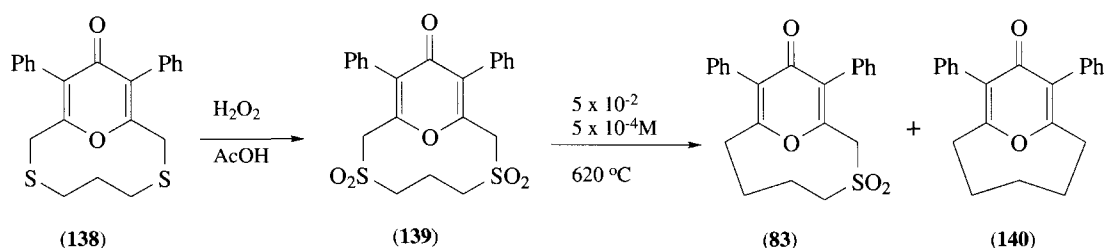
Scheme 4



Scheme 5

9.32.5.2 Complexation

Without question, the most remarkable reactions of the oxygen- and sulfur-containing crown ethers and related compounds are with metal cations. Their complexation ability is, in part, derived from the three-dimensional topology of the macrocyclic cavity as defined by the oxygen and sulfur atoms. As mentioned previously, the oxygen- and sulfur-containing crown ethers and metallo-

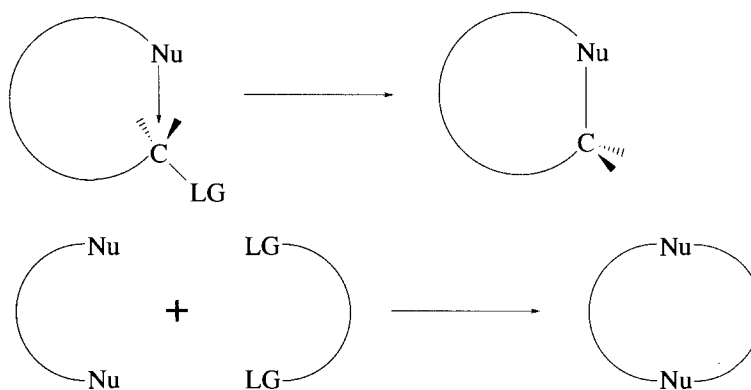


Scheme 6

cenophanes interact preferentially with transition metals while the all-oxygen analogues have affinities for alkali and alkaline earth metal ions. X-ray crystal data (Section 9.32.3.1) suggest that the 1,4-dithiacrowns like (**24**) usually form exodentate complexes between the metal ion and the adjacent sulfur atoms. Endodentate complexes are usually formed when the sulfur atoms are on opposite sides of the macrocyclic cavity as in 1,10-dithia-18-crown-6 (**2**). With alkali and alkaline earth metal ions, the interaction appears to be between the metal cation and the oxygen atoms. Extensive reviews of thermodynamic and kinetic data for the complexation of all types of macrocyclic ligands with metal cations are given in three reviews $\langle 85\text{CRV}271, 91\text{CRV}1721 \rangle$. Complexation of certain metallocenophanes and metal ions takes place between the guest metal ions and the oxygen and sulfur donor atoms and/or the iron or ruthenium of the metallocene unit of the host $\langle 84\text{BCJ}421, 85\text{BJC}3540, 87\text{CL}1783, 89\text{BCJ}3963 \rangle$. The metal ion complexing abilities of the metallocenophanes provide the possibility for interaction between two metal centers yielding redox active host molecules capable of selective cation recognition $\langle 94\text{CRV}279 \rangle$.

9.32.6 SYNTHESIS OF COMPOUNDS AND COMPARISON OF ROUTES AVAILABLE

CHEC-I gives possible synthetic avenues to the monocyclic crown ethers and heterophanes $\langle 84\text{CHEC-I}(7)763 \rangle$. In general, the various synthetic schemes are those typical of large ring formation and are accompanied by polymerization and low yields. These schemes usually involve some type of modified $\text{S}_\text{N}2$ route (Williamson thioether synthesis $\langle 74\text{JHC}45 \rangle$) as shown in Scheme 7 where Nu is an electron-donating group, such as oxygen or sulfur, and LG is a leaving group, such as a halide or tosylate.



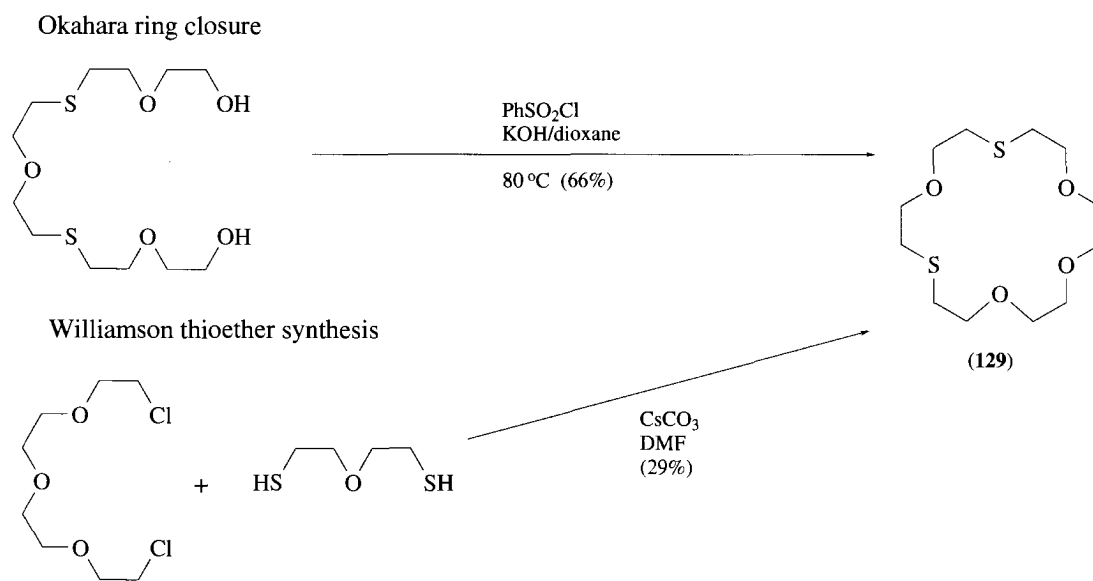
Scheme 7

Synthetic concepts and pathways have been developed to help elucidate and control the difficulties that arise when creating macrocyclic rings. Among them, the “template effect” $\langle 72\text{TL}1793, 80\text{CC}176, 80\text{CC}259 \rangle$, the “caesium effect” $\langle 80\text{CC}466, 81\text{JOC}4481 \rangle$, the “rigid group principle” $\langle 51\text{JCS}200, 74\text{JCS(P}1)2578 \rangle$, the “high dilution effect” $\langle 83\text{TCC}1 \rangle$ and other effects $\langle 81\text{TL}3035 \rangle$ have proven to be valuable. Some synthetic strategies for the construction of oxygen- and sulfur-containing mac-

rocycles have been reviewed (74JHC649, 77CRV513, 79CRV37, B-82MI 932-01, 83TCC1, B-92MI 932-01). Examples given in this review are representative and in many cases can be modified and extended to other compounds.

9.32.6.1 Synthetic Techniques for Macrocyclic Synthesis

Approaches to the polyether sulfides via templated strategies have enjoyed limited success. Metal template synthesis has been defined as reactions which depend on, or can be, significantly enhanced by a particular geometrical orientation imposed by metal coordination. If such coordination shifts the position of equilibrium then it has been called a thermodynamic template effect. If the metal ion directs the steric course of cyclization then it is a kinetic template effect (64JA3651). For the all-oxygen analogues, the ideal template ion is the one that best fits into and interacts with the cavity of the macrocyclic product. These are the alkali metal ions. Sulfur-containing macrocycles often do not have well-defined cavities and they do not complex with the hard metal cations. For these reasons, the template procedure has shown little success in the synthesis of these macrocycles. Many macrocycles are formed by multistep procedures, and hence a composite of many synthetic strategies may be involved including templated reactions. In such cases, the role of the metal ion may be difficult to define. Nakatsuji *et al.* observed a temperature dependence during the synthesis of monothia-15-crown-5 and 18-crown-6 macrocycles by the reaction of a thiaoligoethylene glycol and benzenesulfonyl chloride in base (the Okahara ring closure method) (Scheme 8). The optimum temperature range was found to be 80–100 °C (82BCJ627). 1,7-Dithia-18-crown-6 (**129**) was obtained in a 66% yield by this method (82BCJ627) as compared to a 29% yield by the traditional Williamson thioether synthesis (74JHC45) (Scheme 8).



Scheme 8

A similar yield (65%) for (**129**) was realized using caesium to promote ring closure (81JOC4481). Kellogg and co-workers observed dramatic increases in the yields of several sulfur-containing macrocycles using the “caesium effect.” Both aryl and alkyl thiols are deprotonated by Cs₂CO₃ and CsHCO₃ in DMF to form caesium thiolates. A typical reaction involves the simultaneous addition of the dithiol and dibromide to a 10% excess of Cs₂CO₃ suspended in DMF. The success of the caesium ion approach is shown by the fact that the synthesis of a variety of sulfur-containing macrocycles was significantly improved using this technique (B-92MI 932-01). It was suggested that the caesium thiolates are most likely present in DMF as solvent-separated, highly reactive ion pairs and that this was probably not a templated cyclization reaction (87JOC4230, 88ACR141). Kellogg emphasized that reactants containing the S—CH₂CH₂—X moiety, where X is a leaving group, are dangerous vesicants and must be handled with extreme care.

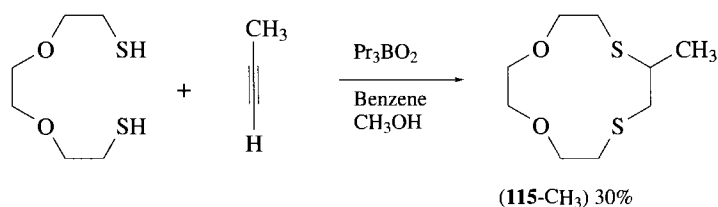
Another method employed to increase yields of macrocyclizations is the “high dilution” technique. This procedure employs a fast reaction between equimolar concentrations of very reactive reagents

in a large enough excess of solvent to provide a low stationary state concentration. Simultaneous addition of reactants can be achieved by motorized burettes to deliver metered quantities at a slow rate <81JCR(S)314>. Vögtle and co-workers have published a review of the high dilution technique <83TCC1>. The high dilution procedure is frequently used in concert with the template or caesium method. Introduction of rigid groups, such as aromatic or heteroaromatic rings, into any of the reactants restricts their conformational degrees of freedom and further increases the yields of the high dilution reactions <51JCS200, 74JCS(P1)2578>.

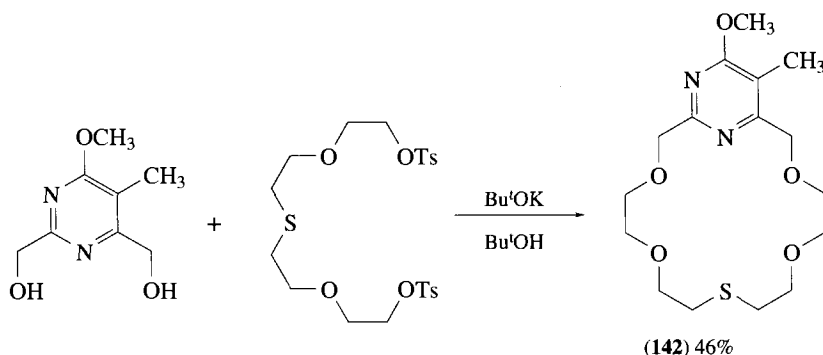
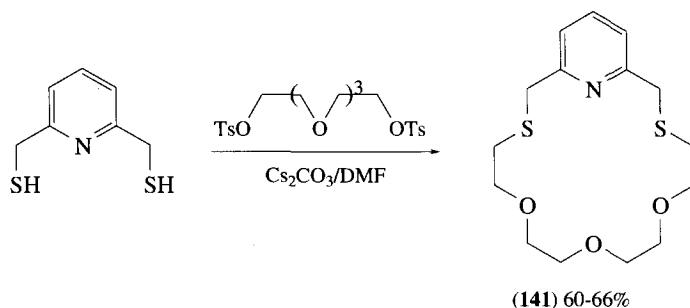
9.32.6.2 General Synthetic Schemes

In addition to Scheme 8, Schemes 9–16 contain general methods for the preparation of the various classes of oxygen- and sulfur-containing macrocycles mentioned in this chapter as follows:

- (i) Cyclization by reacting a dimercaptan and an alkylacetylene (Scheme 9) <92SL233>.
- (ii) Preparation of thiacycrown ethers with pyridine and pyrimidine units (Scheme 10) <94IC4351, 94JHC1047>.



Scheme 9



Scheme 10

- (iii) Cyclization by reacting a diacid dichloride and a sulfur-containing diol to give a dithiacrown diester (Scheme 11) <76JCS(P1)2505>.

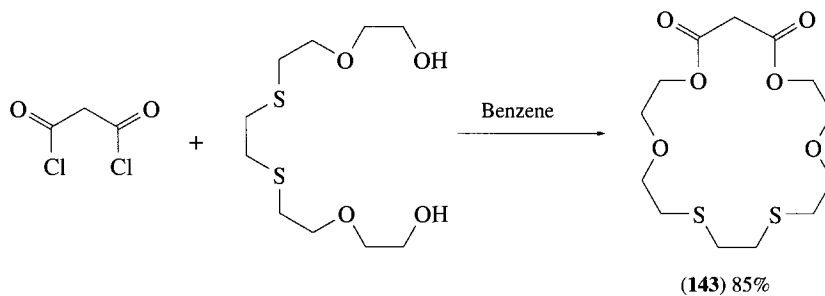
- (iv) Cyclization by treating 2,6-pyridinedicarbonyl dichloride with a sulfur-containing diol to give a thiapyridino-18-crown-6 diester (Scheme 12) <78JHC825>.

(v) Preparation of thiacycrown ethers containing a tetrathiafulvalene unit (Scheme 13) <85BCJ1343, 92JOC6403>.

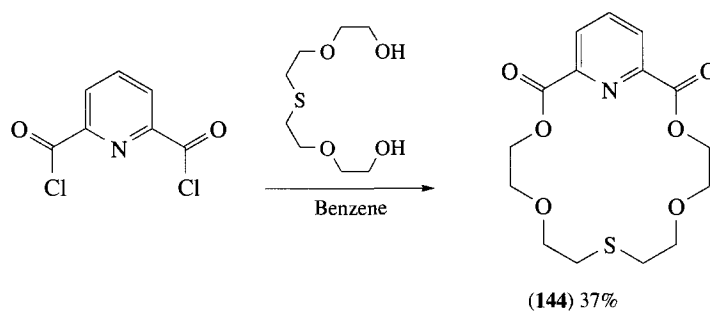
(vi) Preparation of a thiacycrown ether complex with molybdenum (Scheme 14) <90JCS(D)3789>.

(vii) Preparation of thiacycrown ethers containing a metallocene as part of the macrocoring (Scheme 15) <84BCJ421, 84TL1991>.

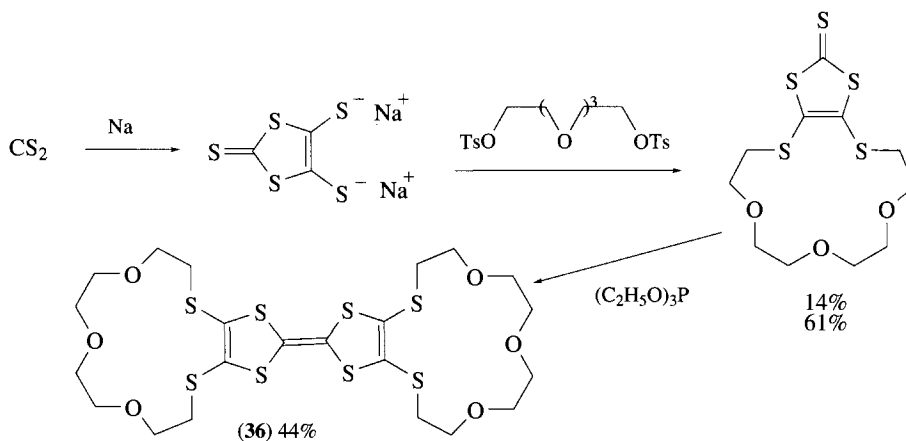
(viii) Preparation of sulfur-containing anulenes (Scheme 16) <71CC1457>.



Scheme 11



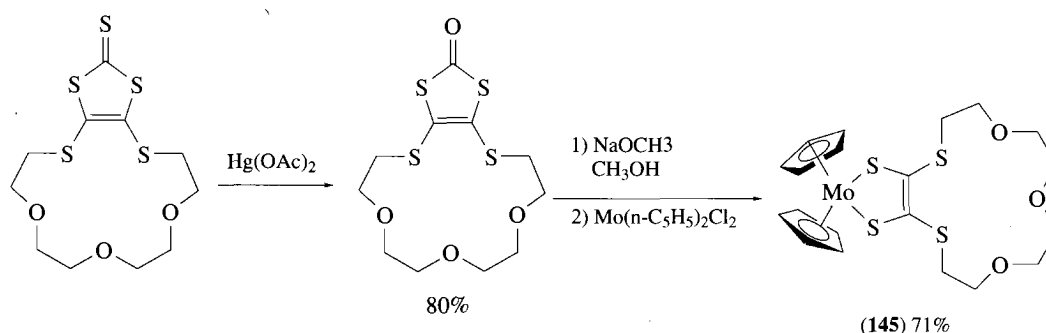
Scheme 12



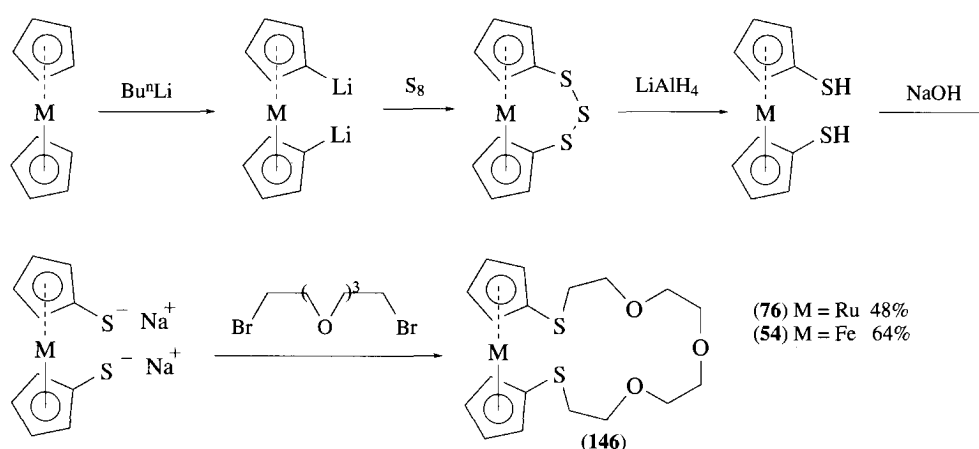
Scheme 13

9.32.7 APPLICATIONS

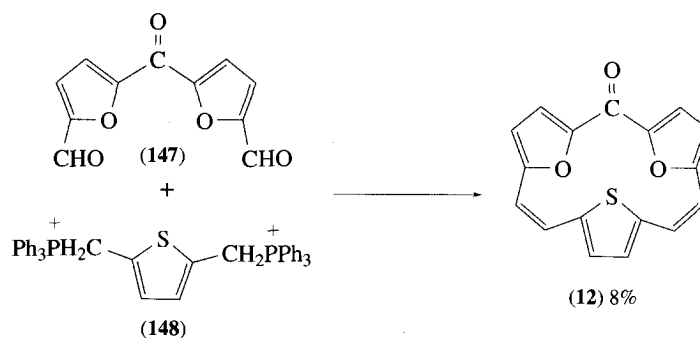
Most of the applications of the oxygen- and sulfur-containing macrocycles center on the interactions of those compounds with various cations. Since ring size, substituents, number and type of



Scheme 14



Scheme 15



Scheme 16

donor atoms can be altered to provide host compounds with a wide variety of properties, these ligands are ideally suited for applications involving various types of complexation interactions.

Environmental and biological concerns caused by various metal ions have provoked a great deal of effort in the development of ion selective electrodes. These electrodes, using neutral macrocyclic carrier molecules, have found important clinical and environmental applications [79JEC91, 82JEC99, 84JA6978]. The ability to chemically modify macrocyclic ligands offers the possibility to design and synthesize new carrier molecules with the necessary selectivities for ions not presently accessible to measurement. Introduction of sulfur into the crown ether moiety has made possible ion selective electrodes for rare earth and heavy metal ions [86MI 932-02, 87MI 932-03, 88CL409, 88MI 932-03, 88MI 932-04, 89JCS(P1)1675]. Oue and co-workers [89JCS(P1)1675] have synthesized a number of lipophilic thiacycrown ether derivatives for use as neutral carriers by use of the caesium method described by Butler and Kellogg [81JOC4481]. The selectivities of these Ag^+ electrodes were shown to be similar despite differences in the structures of the 15-, 16-, and 18-membered mono- or dithiacrowns used

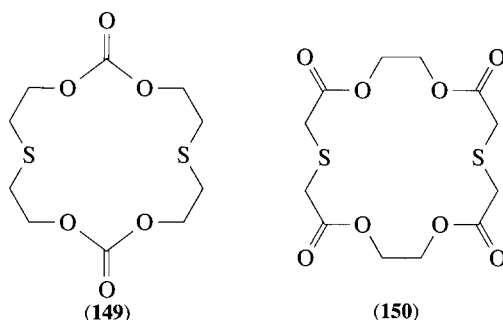
as carriers. These thiacrown-based Ag^+ selective electrodes appear to have superior selectivity to that of the Ag_2S -based Ag^+ electrodes <89JCS(P1)1675>. 1,7-Dithia-12-crown-4 (**116**) (see Figure 4) has shown good selectivity for iron(III) when compared to various alkali and alkaline earth cations <88MI 932-03>.

Liquid-liquid extraction techniques are used in some cases for the industrial separation, concentration and recovery of metals. Introduction of sulfur into the polyether macrocycles has increased the selectivity of those compounds toward the thiophilic metal ions such as Ag^+ , Hg^{II} , Au^{III} and Pd^{II} <B-79MI 932-01, 87MI 932-04, 88MI 932-05>.

A large-scale use of crown ethers for industrial applications is limited by the expense of these compounds. The cost can be greatly reduced by attaching the ligand to a solid support. In this case, the crown ether can be used and renewed for further use without a significant decrease in overall binding ability. Several macrocyclic polyethers attached to polymer supports have been prepared and used successfully as catalysts, exchangers and absorbents <83MI 932-01, 92MI 932-02, 92MI 932-03, 93MI 932-01>. As expected, the poly (thiacrown ether)s exhibited excellent complexation properties for metal ions like Pd^{II} , Ag^+ , and Au^{III} <92MI 932-02>. The group at Wuhan University in China has investigated platinum complexes of polysiloxane-supported thiacrowns and their catalytic behavior in hydrosilylation reactions of the alkenes <92MI 932-03, 93MI 932-01>.

Sulfur-containing macrocycles bound to silica gel are highly selective concentration and purification ligands for Pd^{II} , Hg^{II} and Ag^+ . These immobilized macrocycles efficiently removed Au^{III} and Pd^{II} from solutions of HCl and FeCl_3 . Similarly, Ag^+ , Au^{III} and Pd^{II} were separated by these columns and selectively eluted from the columns with purities of 99.9%. It was also shown that Pd^{II} can be removed from industrial silver electrolyte solutions with 99.9% purity in one pass through these columns <91ANC1014>.

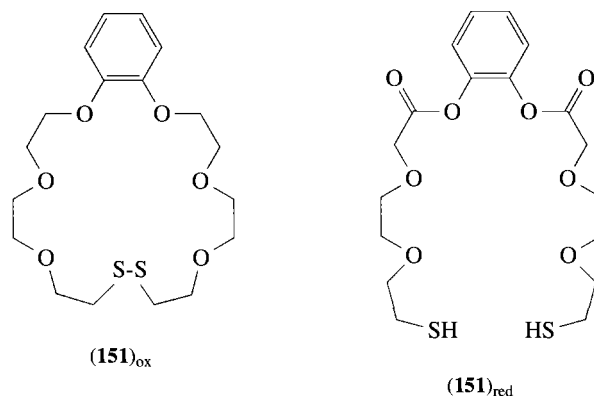
In 1961, Eastman Kodak found that diesters and tetraesters, such as (**149**) and (**150**), increased the sensitivity of silver halide emulsions already sensitized with gold compounds <61BP588242>. Hengel investigated the correlation between complex formation in aqueous solutions and photographic activity <83MI 932-02>.



Liquid membranes which provide highly selective separations have been reported <82MI 932-04, 82MI 932-05, 86MI 932-03, 88ANC1694>. The following parameters which affect ion transport have been investigated and reviewed: host-guest complex stability, host-guest concentration, anion type, membrane configuration, proton ionization of acidic hosts, membrane solvent type and receiving phase composition <86MI 932-03>. Transport selectivities have been observed by crown ethers with cavities no larger than that of 21-crown-7 for cations which best fit the ligand cavity provided the host-guest stability constant is not too large. Addition of large lipophilic groups serves to minimize loss of macrocycle carrier to the water phases and does not significantly alter transport fluxes or selectivities. As expected, selective transport of the softer cations Ag^+ , Pb^{II} , etc. over alkali and alkaline earth cations is achieved by the oxygen- and sulfur-containing crowns <81MI 932-02>. Complexation stability and selectivity are functions of solvent type, donor atom type and ratio of cavity to cation radii <86MI 932-03>. Sulfur-containing macrocycles have been found that selectively transport lead(II) over alkali and alkaline earth cations in a bulk liquid membrane system. Recovery of palladium is important because of its applications in catalytic converters, its resistance to corrosion, and its use as a catalyst <87MI 932-05>.

The use of a disulfide in a macrocycle such as in (**151**) provides the possibility of reductive ring opening which can be important in cation transport. Shinkai *et al.* <85JA3950> investigated redox mechanisms and their application to membrane transport. They demonstrated that the rate of Cs^+ transport was regulated by the interconversion of (**151**)_{ox} to (**151**)_{red} in the membrane phrase. Thus, electrochemically controlled processes may switch ion transport on or off. Ion transport may also

be switched on or off by photochemical induced conformational changes <86MI 932-03>. Moreover, liquid membranes containing proton-ionizable carrier molecules provide a means of transporting ions against their concentration gradients and transport can be switched on or off by the pH of the media <86MI 932-03>. Much of membrane transport research using macrocyclic carriers is concerned with modeling the transportation of ions of biological interest <81MI 932-02>. Nature employs both cyclic and noncyclic molecules that bind selectively to various metal cations to perform various biochemical functions including transport of ions across membranes.



Macrocycles should be able to selectively remove metal ions when present in biological systems at toxic levels. It should be possible to remove Hg^{II} or Pb^{II} from an environment containing biologically important cations such as Na^+ , K^+ , Ca^{II} , Fe^{II} , Fe^{III} , Cu^{II} , Zn^{II} , and Mg^{II} . The use of synthetic macrocycles to introduce metals into the body also deserves some consideration. However, toxicity studies of such carriers would be required.

Macrocycles containing oxygen and sulfur atoms have unique complexation properties between the all oxygen crown ethers which complex the hard cations and their all sulfur analogues which complex certain radioactive cations. The complexation of ^{99}Tc by the all sulfur crown ligands has provided a means to deliver the radioisotope in order to improve Tc-based diagnostic imaging agents for the heart, liver, kidney, and brain. The all sulfur-containing ligands do not react with the biologically important metal ions <B-92MI 932-04>.

The ability of crown ethers to convert hydrophilic metal ions into large hydrophobic cationic species soluble in organic solvents of low polarity has been widely exploited in organic synthesis. Problems of cosolubility between reactant and reagent can be overcome allowing the reaction to be carried out under mild conditions. Reagent solubilization, phase transfer catalysis, anion activation, cation inhibition, along with several of the applications previously discussed are covered in CHEC-I <84CHEC-I(7)763>.

ACKNOWLEDGMENTS

The authors are indebted to the Office of Naval Research and Department of Energy for supporting their research programs. They also thank Krystyna Pawlak for her help in the literature search for this review.

9.33

Rings containing Selenium or Tellurium

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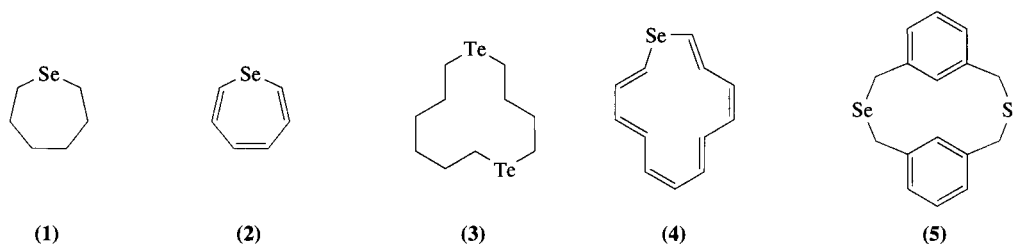
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9.33.1 INTRODUCTION

Since almost no large or medium-sized rings containing selenium or tellurium were covered in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I), this chapter reviews those

compounds in *Chemical Abstracts* containing selenium or tellurium in a seven or larger membered ring for the period 1967 to July 1994.

Nomenclature in such compounds follows two main pathways: for seven-membered rings, the saturated compound (1) is called selenepane (tellurepane), while the fully unsaturated compound (2) is selenepin (tellurepin); analogously, the eight-membered rings are selenocanes and selenocins; the nine-membered rings would be the selenonanes and selenonins. For larger rings, heteracycloalkane or heteraannulene are used, for example (3) would be called 1,6-ditelluracyclododecane, while (4) is selenal[13]annulene. Similar naming is used for cyclophanes, thus (5) is 2,11-diselena[3.3]metacyclopentane.



Most of the work on such compounds has been directed towards their synthesis, with some emphasis on their conformations and reactions. Unlike the smaller rings, aromatic examples are absent.

9.33.2 THEORETICAL METHODS

Whilst molecular mechanics methods are popular, little has been done on selenium and tellurium containing ring compounds, because the additional parameters required over sulfur compounds are not well documented. HYPERCHEM, for example, changes the covalent radii on going from $S = 0.99 \text{ \AA}$ to $Se = 1.14 \text{ \AA}$ to $Te = 1.33 \text{ \AA}$, the van der Waals radii from $S = 1.97 \text{ \AA}$ to $Se = 1.97 \text{ \AA}$ to $Te = 2.07 \text{ \AA}$, and the dissociation energies of nonbonded interactions of two identical atoms; most other parameters are not changed. The results obtained therefore must be viewed with some caution $\langle 88TL5587, 89TL1551 \rangle$. An *ab initio* MO calculation using the STO-3G basis set has been carried out for the fully unsaturated eight and nine rings of 1,2-diselenocin and 1,2,3-triselenonin, respectively $\langle 90JOC263 \rangle$.

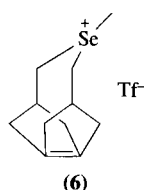
9.33.3 EXPERIMENTAL STRUCTURAL METHODS

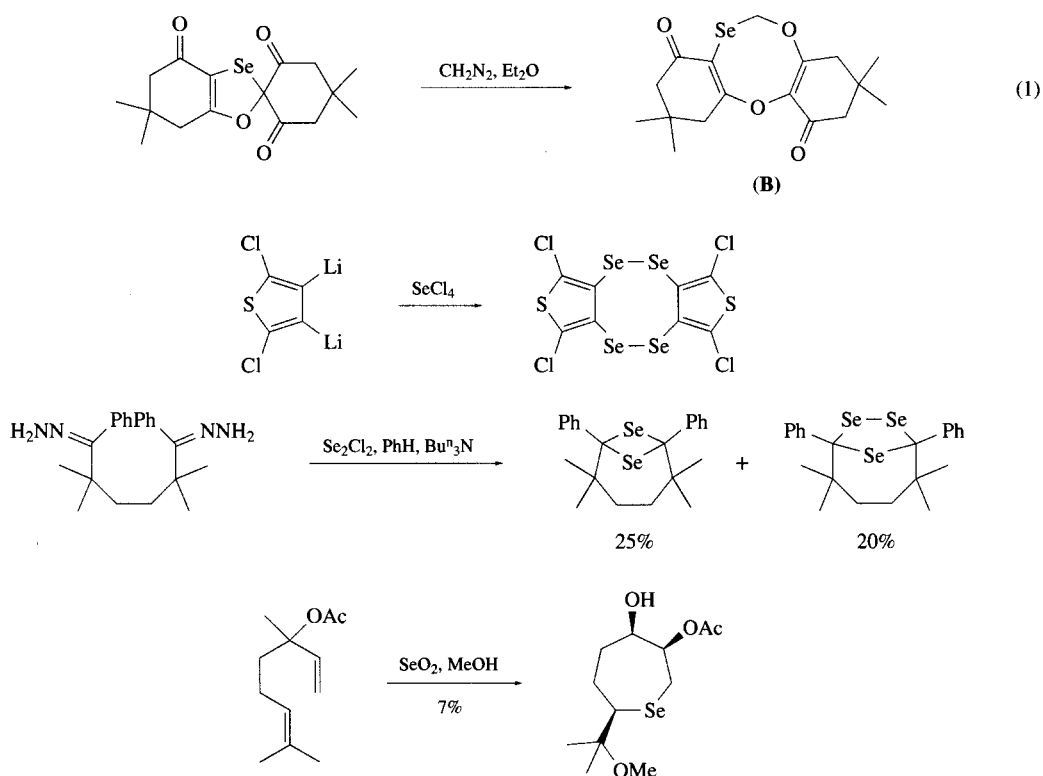
9.33.3.1 X-ray Structure Determinations

These are discussed in order of ring size:

(i) Seven-membered rings: the trisubstituted selenepane, at the end of Scheme 1, adopts a twist-chair with a C—Se distance of $1.98 \text{ \AA}$ and a C—Se—C angle of $100\text{--}103^\circ$ $\langle 89T5073 \rangle$.

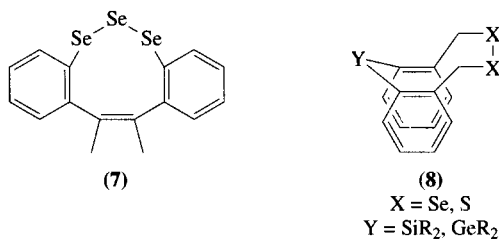
(ii) Eight-membered rings: 1,3,5,7-tetraselenocane also assumes a twist-chair with a mean C—Se distance of $1.94 \text{ \AA}$ ($1.91\text{--}1.98$), and a mean C—Se—C angle of 99.8° ($98.0\text{--}101.5$) $\langle 78AX(B)2634 \rangle$. In compound (6), which has a pyramidized double bond, the C—Se—C angle is 111.4° , about 12° larger than normal. The five-membered rings pucker strongly, and the C—C—Se angles also open 6° to about 115° . The C—Se bonds are also about $0.05 \text{ \AA}$ longer than normal $\langle 87JA5524 \rangle$. The structure of the dioxaselenocin of Equation (1) is also known $\langle 87CPB4967 \rangle$.





Scheme 1

(iii) Nine-membered rings: compound (7) is a *syn*-[3.2]orthocyclophane in the solid state, in which the nine-membered ring adopts a tub-like shape. The C—Se and Se—Se bond lengths are 1.924 Å and 2.326 Å, respectively, and the Se—Se—C and Se—Se—Se angles are 101.5° and 106° respectively [90JOC263]. Structures for five compounds of type (8) are known [85JOM(290)25, 86JOM(301)273, 88JOM(347)33], and have the same approximate twist boat–boat conformation. Three of the five appear to have a donor–acceptor (X→Y) interaction, and shorter intermolecular X–Y distance.

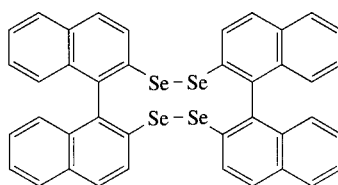


(iv) 10-Membered rings: the diselena (and dithia) orthocyclophane (9) has an *anti* conformation in which the 10-membered ring adopts a chair–chair conformation [89TL1551]. The analogous compound (10), which lacks the constraining benzene rings, adopts a twist–twist boat conformation, where the oximes are *trans* [94AX(C)304].



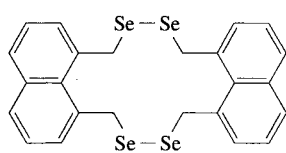
(v) 12-Membered rings: much of the work on the larger rings centers along the conformation of the ring. 1,3,7,9-Tetraselena-cyclododecane, [12Se₄], exists in two distinct crystal conformers, [3333] and [66] in Dale's notation [80IJ3], in which there are two close Se···Se distances of 3.69 Å

<88CJC2956, 89JA6582>. The diselena[3.3]metacyclophane (**5**) has been compared with the dithia-analogue <82CJC362>. They both adopt *syn* conformations, and the diselena compound has a slightly larger $X\cdots X$ distance of 7.22 Å vs. 6.97 Å, internal hydrogen distance of 2.84 Å vs. 2.71 Å, and internal carbon distance of 3.15 Å vs. 3.05 Å compared with the dithia compound, though its benzene rings are inclined at a slightly smaller angle of 19.1° vs. 20.6°. The 0.153 Å longer C—Se bond results in a C—Se—C bond angle 3.0° smaller than the dithia compound. The crystal structures of both the 8,17-dimethoxy derivative <91CB2583> and a nickel complex <89JOC393> of 2,11-diselena [3.3](2,6)pyridinophane also indicate that they exist in the *syn* conformation. The ring in the tetraselenide (**11**) appears to be somewhat strained relative to diphenyldiselenide, since it has a smaller C—Se—Se—C dihedral angle, 74.5° vs. 97° <91JHC433>, though other distances and angles appear to be normal.

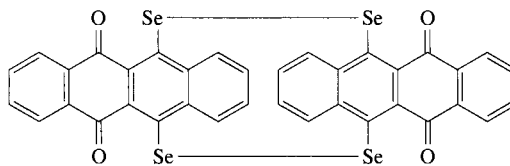


(11)

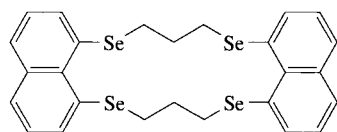
(vi) 14-Membered rings: 1,4,8,11-tetraselenacyclotetradecane, [14Se₄], exists as a single conformer, a [3434] quadrangle with the four corners occupied by selenium, giving significant $Se\cdots Se$ contact, 3.411 Å <89JA6582>. In the tetraselena 14-ring compound (**12**), the Se—Se distance is 2.315 Å, and the dihedral angle at Se—Se is 88.1°. The hydrogens of the 1,8-naphthalene methylene groups are in close contact, 1.96 Å <72AX(B)1509>. The bistriselenide (**13**) is a paracyclophane and thus has bent aromatic rings, with Se—Se—Se angle of 105.1° <84JOM(260)293>.



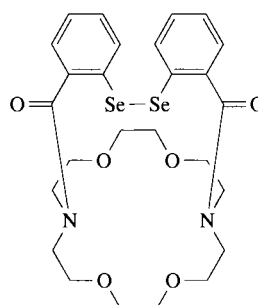
(12)



(13)



(14)



(15)

(vii) 16-Membered rings: 1,5,9,13-tetraselenacyclohexadecane, [16Se₄], is partially disordered but with one conformational type with [3535] quadrangles. The shortest $Se\cdots Se$ is 3.45 Å <89JA6582>. Its copper(II) trifluoromethanesulfonate complex displays square planar coordination of copper by the four selenium atoms, and has a [4444] conformation with Cu—Se distances of 2.46 Å, and Se—Cu—Se angle of 88.4°. Prolonged standing of [16Se₄] with Cu(CF₃SO₃)₂ gave [16Se₄]²⁺ [(SO₃CF₃)[−]]₂, which has three almost linear selenium atoms, permitting greater charge delocalization, indicated by the short $Se\cdots Se\cdots Se$ distances of 2.669 Å and 2.592 Å <90JA3706, 91JOM(411)147>. The dinaphtho annelated derivative of [16Se₄], (**14**), adopts a *syn* conformation <93JCS(P1)2145>.

(viii) 18-Membered rings: 1,3,7,9,13,15-hexaselenacyclooctadecane, [18Se₆], has very unusual irregular geometry, in contrast to the symmetrical quadrangular shapes above. The two sides of the ring display different characters <88JA2990, 89JA6582>. The cryptand (**15**) has the two selenium atoms

in an 18-ring in which the dihedral angle about the Se—Se bond is 99.7° . Tomoda and Iwaoka suggest that the hypervalent property of the selenium atom greatly affects the shape of the host cavity in the solid state $\langle 90CC231 \rangle$.

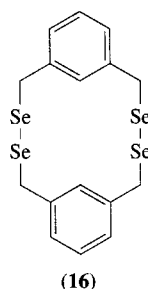
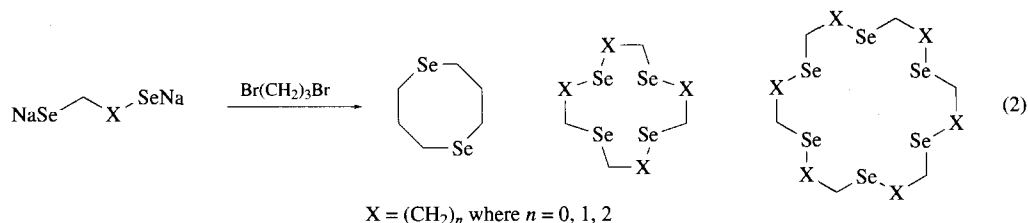
(ix) Larger membered rings: 1,5,9,13,17,21-[24Se6] has [4848] geometry and is a single conformer $\langle 89JA6582 \rangle$.

9.33.3.2 NMR Spectra

Variable temperature NMR studies have been extensively used to examine conformational changes to the rings, and are discussed in Section 9.33.4. Since nearly all papers use proton and carbon spectra to characterize the compounds discussed above, relatively little data will be given here, only that which is influenced by the chalcogen or is unusual.

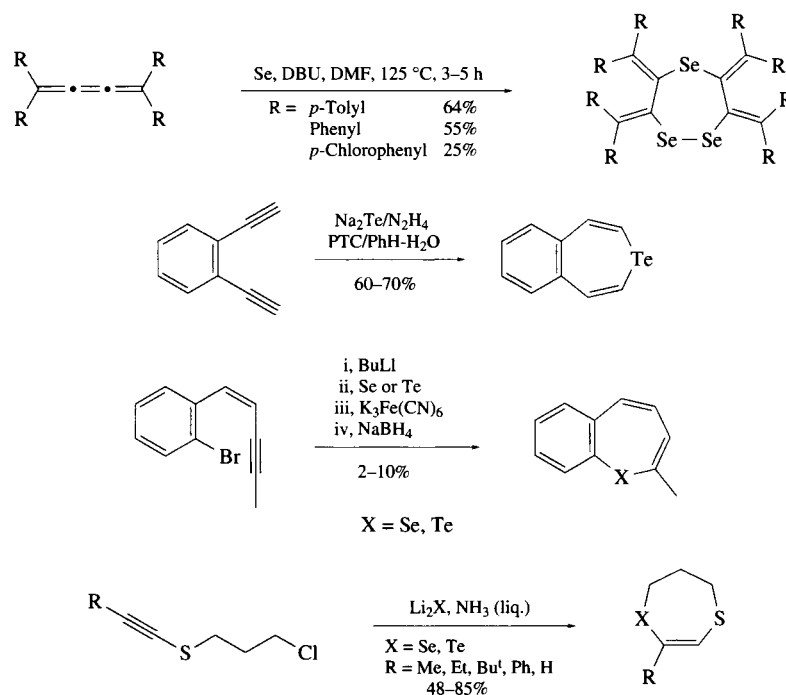
9.33.3.2.1 Proton spectra

For the saturated compounds shown in Equation (2), typically $-\text{CH}_2-\text{CH}_2-\text{Se}$ appears at δ 2.9–2.6, $-\text{CH}_2-\text{CH}_2-\text{Se}$ at δ 2.2–2.0, and $-\text{Se}-\text{CH}_2-\text{Se}$ at δ 3.7 $\langle 89JA6582 \rangle$. In the smaller rings, 1,5-[8Se2] and 1,6-[10Se2], the corresponding protons are deshielded slightly δ 3.0–2.7, δ 2.4–2.0 and 3.3–2.9, δ 2.3–1.9, respectively $\langle 93T1605 \rangle$. For 1,5-[8Te2], the shifts are δ 2.8–2.7 and δ 2.2–2.1 $\langle 91TL4537 \rangle$. There are many examples of $\text{Ar}-\text{CH}_2-\text{Se}$ shifts in cyclophanes, and typically the benzylic protons appear at δ 4.0–3.5 for Ar = benzene or pyridine, δ 4.8–4.0 for naphthalene and δ 3.8–3.6 for furan $\langle 87BCJ4027, 89T1611 \rangle$. These are not much different from the thia compounds. An additional selenium, i.e. $\text{Ar}-\text{CH}_2-\text{Se}-\text{Se}-$ deshields slightly, δ 4.00 vs. δ 3.78 for (16) vs. (5) $\langle 76CJC238, 80CJC1398 \rangle$. Very few examples containing $-\text{C}=\text{CH}-\text{Se}-$ or $-\text{C}=\text{CH}-\text{Te}$ appear to exist, Scheme 2 has two examples, where δ is 6.25 and 6.75, respectively $\langle 81RTC368, 88TL1935, 91CC802, 93CC1493 \rangle$. In 3-benzotellurepine, the $-\text{CH}=\text{CH}-\text{Te}$ protons appear at δ 7.6 and δ 6.75, respectively $\langle 91CC802 \rangle$. Unsubstituted benzo-selenepines are not yet known $\langle 93CC1493 \rangle$.



9.33.3.2.2 Carbon spectra

In the saturated compounds shown in Equation (2), typically $-\text{CH}_2-\text{CH}_2-\text{Se}$ appears at δ 23–26, $-\text{CH}_2-\text{CH}_2-\text{Se}$ at δ 29–32, and $-\text{Se}-\text{CH}_2-\text{Se}$ at δ 13–14 $\langle 89JA6582 \rangle$. In the smaller rings, 1,5-[8Se2] and 1,6-[10Se2], the corresponding carbons are at δ 23.4, δ 30.9, and δ 28.1, δ 30.2, respectively $\langle 93T1605 \rangle$. For 1,5-[8Te2], the shifts are δ 4.9 and δ 34.1 $\langle 91TL4537 \rangle$. Selenium and tellurium shield the attached

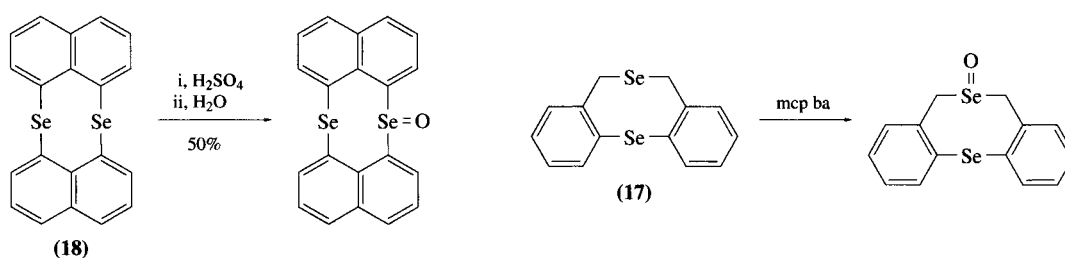


Scheme 2

carbon. In cyclophanes, the benzylic carbons, $\text{Ar-CH}_2\text{-Se}$ typically appear at δ 30–22 $\langle 80\text{CJC1398, 89TL1611} \rangle$ and $\text{Ar-CH}_2\text{-Te}$ appears at δ 14–12 $\langle 93\text{CL263} \rangle$. sp^2 -Carbons attached to selenium appear at δ 140–138 and to tellurium at δ 153–145 $\langle 89\text{T1611, 93CL263} \rangle$.

9.33.3.2.3 ^{77}Se and ^{125}Te spectra

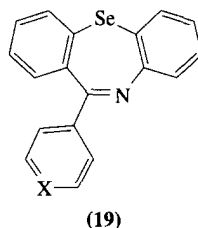
Most often, these spectra are reported relative to Me_2Se and Me_2Te , respectively. Chemical shift ranges are large, and whilst useful as reference data, are somewhat difficult to classify. Selenium chemical shifts are reported for the saturated selenium coronands in Equation (2), δ 215–137 in solution, δ 327–115 in the solid state $\langle 89\text{JA6582} \rangle$, for the smaller rings, 1,5-[8Se2] and 1,6-[10Se2], δ 141 and 166 $\langle 93\text{T1605} \rangle$, respectively, and for tellurium in 1,5-[8Te2] δ 164 $\langle 91\text{TL4537} \rangle$. As might be expected, the selenium and tellurium shifts in these latter small ring dications appear dramatically downfield to δ 806, δ 1202 and δ 1304, respectively. In the cyclophanes, $\text{ArCH}_2\text{SeCH}_2\text{Ar}$ appears at δ 450–260 $\langle 88\text{TL5587, 89T1611} \rangle$. For the dibenzo-8-ring- X_2 -compounds of type (17), when $\text{X} = \text{Se}$ the ArSe appear at δ 352–382 and the $-\text{CH}_2\text{Se}-$ at δ 380–400 $\langle 91\text{CL1649} \rangle$, whereas when $\text{X} = \text{Te}$, they appear at δ 565–553 and 703–677, respectively $\langle 93\text{CL263} \rangle$ (Scheme 3).



Scheme 3

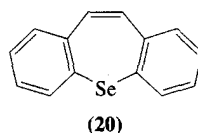
9.33.3.3 Mass Spectra

Most papers reporting mass spectral data indicate that the compounds give molecular ions (see e.g. <80CJC1398, 87BCJ4027, 89JA6582>). Few papers bother to report fragment peaks; however, they are reported for a series of selenacyclophanes, which eject selenium atoms <89T1611>, and for compound (19), which also first loses selenium <76TL3141>.



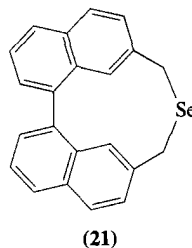
9.33.3.4 Ultraviolet Spectra

Dibenzo[*b,f*]selenepine (20) has been studied in detail, and a comparison has been made between the calculated and observed transitions for the planar and boat conformers; the latter fits better <74ZN(A)1371>.



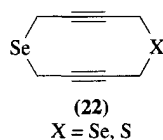
9.33.3.5 Circular Dichroism Spectra

The circular dichroism (CD) spectra of the selenium-9-ring-binaphthyl (21) has been compared with the thia and oxa analogues <78JCS(P2)304, 78TL3161, 81JCS(P2)1621>, and has principal bands at 232(+717) nm ($10^{-3}\theta$), 255(−279) nm ($10^{-3}\theta$), 277(−56) nm ($10^{-3}\theta$), and 297(−97) nm ($10^{-3}\theta$).



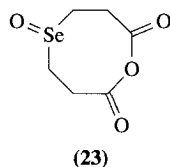
9.33.3.6 Photoelectron Spectra

The photoelectron (PE) spectra of the diselena and selenathia compounds (22) have been compared with their thia and oxa analogues. The lowest energy bands correspond to the two lone pair ionizations at about 8.4 eV, followed by four π ionizations between 8.9 eV and 10.1 eV, which have been assigned <91CB365>.



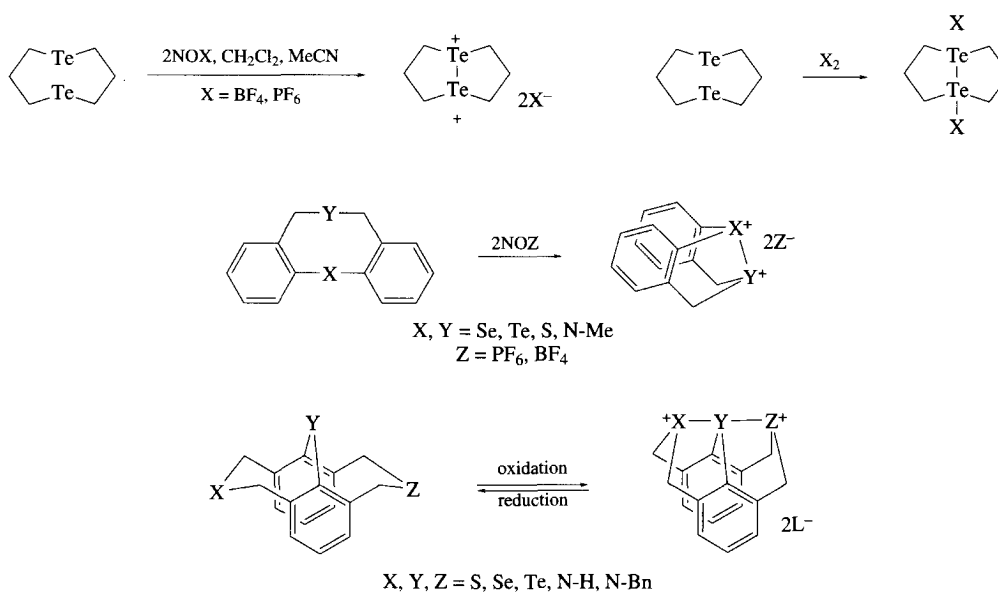
9.33.3.7 Electron Spectroscopy for Chemical Analysis (ESCA)

The eight-ring compound (**23**) has been studied by ESCA which has selenium $3d$ and $3p_{3/2}$ binding energies of 58.6 eV and 164.2 eV, respectively, very similar to those obtained for many other selenium containing compounds <71MI 933-01>.

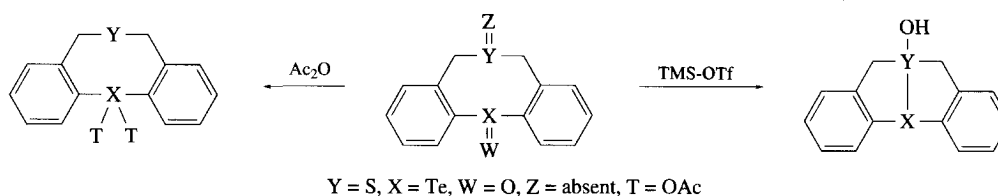


9.33.3.8 Oxidation Potentials and Cyclic Voltammetry (CV)

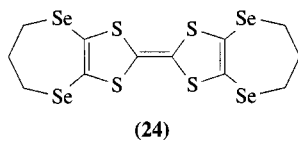
Some systems in which the heteroatoms are suitably close for transannular oxidation, for example some of those in Schemes 3–5, have been studied by CV. 1,5-[8Se2] shows only one reversible oxidation peak at the remarkably low potential of +0.25 V, unlike 1,4-[6Se2] which has an irreversible wave at +0.86 V similar to many other selenium containing compounds. This is ascribed to a transannular Se—Se bond formation (cf. Scheme 4) <90CL549>. The dibenzo compounds shown in Scheme 4 also undergo remarkably easy reversible oxidation and reduction <90TL2307, 91CL1649, 92JA3117>. The CV for the interesting TTF derivative (**24**) has been published <88JOC201> and showed one reversible wave with peak potentials of +0.18 V and +0.11 V, at slightly less potential than the sulfur analogues.



Scheme 4

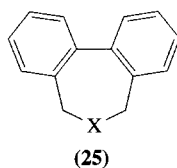


Scheme 5



9.33.3.9 ESR Spectra

The solid state ESR spectrum of the TCNQ complex of (25; X = Te) shows a strong sharp signal with $g = 2.0025(\pm 3)$ <92T3155>. The cation radical of (18) generated in H_2SO_4 gave $g = 2.0248$ <91TL4345>.

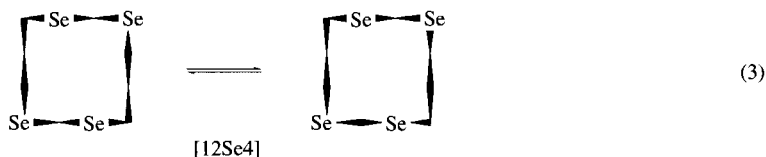


9.33.4 THERMODYNAMIC ASPECTS

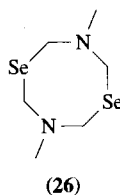
There is a fairly large volume of material on conformations and some on chromatography.

9.33.4.1 Conformational Aspects

Several solid-state conformations were discussed in Section, 9.33.3.1. Variable temperature (VT) NMR spectra have been used extensively to determine conformational changes and their energetics, where the process occurs on the NMR timescale. However in the more flexible larger rings, this is frequently not the case. Thus, whilst ring inversion barriers for the PdCl_2 complex of selenane (six-ring) could be obtained from VT NMR studies, those for selenepane (seven-ring) could not <86JCS(D)205>. Similarly, of the coronands shown in Equation (2), only 1,3,7,9-[12Se4] showed suitable NMR behavior. The 5,5,11,11-tetramethyl derivative on cooling below 165 K split the $\text{Se-CH}_2\text{-CH}_2\text{-}$ protons into two signals at δ 2.72 and δ 3.10, which with $T_c = 167$ K gives $\Delta G_c^\ddagger = 7.6$ kcal mol $^{-1}$, very similar to the barrier in cyclododecane (7.3 kcal mol $^{-1}$) itself. Neither ^{13}C nor ^{77}Se spectra proved useful here. The exchange process is believed to be a rotation of two sides (Equation (3)) <88CC1087, 89JA6582>.

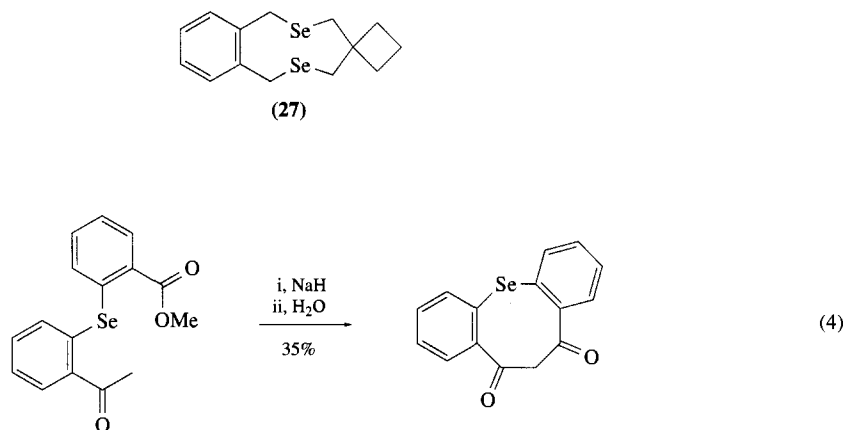


The diazadiselenacyclooctane (26) shows an AB quartet at 240 K, where $J = 12.4$ Hz and $\Delta\nu = 14.5$ Hz, and with $T_c = 258$ K gives $\Delta G_c^\ddagger = 14.4$ kcal mol $^{-1}$ for the interconversion of the crown and chair-boat forms, almost identical values to the thia analogues <66CC803>.



The spiro compound (27) has been studied by VT ^{13}C and ^{77}Se NMR. The latter yields two signals at 218 K at δ 253 and δ 236 which coalesce at 278 K, giving $\Delta G_c^\ddagger = 11.7$ kcal mol $^{-1}$ for the inversion

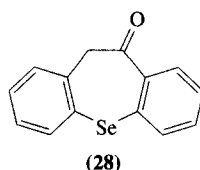
of the nine-ring $\langle 92\text{JHC}967 \rangle$. In the eight-membered ring diketone in Equation (4), the boat inverts with $\Delta G_c^\ddagger = 10.1 \text{ kcal mol}^{-1}$, based on the AB for the protons, $\Delta\nu = 717 \text{ Hz}$, $T_c = 234 \text{ K}$ $\langle 85\text{ZN}(\text{B})858 \rangle$. The eight-membered ring of (17) and its mono- and ditellura analogues, exist in boat and chair conformers in about equal amounts, which are easily seen in their ^1H , ^{13}C , ^{77}Se , and ^{125}Te spectra $\langle 91\text{CL}1649, 92\text{CL}151, 93\text{CL}263 \rangle$.



The cyclophanes have been more extensively studied and reviewed $\langle 83\text{MI} 933-01 \rangle$. The metacyclopentane (5) was originally studied in 1975 at 90 MHz and at -110°C $\langle 75\text{TL}1363 \rangle$. Its restudy at 250 MHz raised T_c from -96°C to -86°C , but more importantly enabled the internal aromatic proton for both the *syn* and the *anti* isomers to be seen, giving, for the *syn* to *anti* conversion, $\Delta G_{187}^\ddagger = 8.3 \text{ kcal mol}^{-1}$. This was in excellent agreement with the value found, $8.2 \text{ kcal mol}^{-1}$, from the VT ^{77}Se spectra, in which $\Delta\nu = 2736 \text{ Hz}$, and $T_c = -70^\circ\text{C}$ $\langle 88\text{TL}5587 \rangle$. Even the ^{77}Se spectra were unfortunately not able to freeze out the bridge wobble. T_c for this process has been estimated at -120°C to -125°C , based on studies on the analogous cyclophanes in which one and then both benzenes are replaced by 2,6-pyridines $\langle 89\text{JOC}393 \rangle$ for which the barrier for the *syn* to *anti* pyridine flip is too small to measure, but solubility of the pyridinophanes is sufficient to measure the bridge wobble. From the observed AB for the methylene protons, the bridge wobble is estimated to have a barrier of about $8.9 \text{ kcal mol}^{-1}$ for the dipyridinophane, $8.1 \text{ kcal mol}^{-1}$ for the monopyridinophane, and hence suggests a value of about $7.3 \text{ kcal mol}^{-1}$ for (5). Several other cyclophanes were studied by VT ^{13}C and ^{77}Se NMR, but did not yield conclusive results $\langle 89\text{T}1611 \rangle$. The tetraselenide (16) has also been studied by VT ^1H NMR $\langle 76\text{CJC}238, 83\text{CJC}1598 \rangle$, and predominantly is *syn* in solution and the solid state. The barrier for the bridge rotation is 10 kcal mol^{-1} , somewhat higher than for (5), but about $2.3 \text{ kcal mol}^{-1}$ lower than for the analogous tetrasulfide. Probably there is a significant lone pair–lone pair interaction which gives the higher barrier in the dichalcogenide bridges.

9.33.4.2 Chromatography

Separation of numerous cyclic methylene sulfides and selenides, including 1,3,5,7-[8Se4] and 1,3,5,7,9-[10Se5], by reversed phase HPLC is reported. The retention times and capacity factors depend on the ring size, and the number and type of heteroatoms, generally rising with ring size going from sulfur to selenium $\langle 83\text{ZN}(\text{B})719 \rangle$. Similar studies have been made for a series of compounds derived from (28), dibenzoselenenepins, in relation to oxa and thia analogues $\langle 84\text{JC}309, 85\text{JC}113 \rangle$.

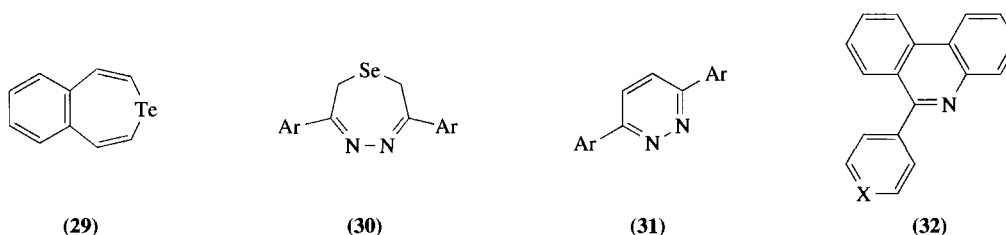


9.33.5 REACTIONS

Not surprisingly, these reactions are mostly derived from the moderately weak C—Se or weak Se—Se bonds, and thus mostly involve the heteroatom.

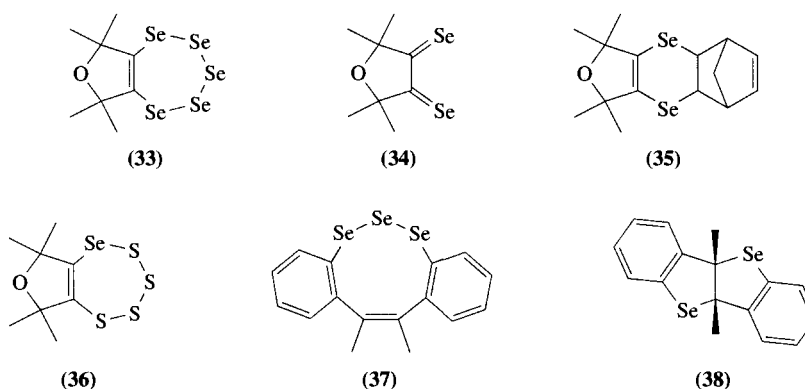
9.33.5.1 Elimination of the Heteroatom to form an Aromatic Species

The tellurepin (**29**) spontaneously eliminates tellurium over 2–3 days in solution at room temperature to give naphthalene in a manner similar to borepins and benzophosphepines <91CC802>. Higher temperatures (about 200°C) are required to eliminate selenium from (**30**) <72JHC1427> and from (**19**) <84JHC1321> to give the aromatic products (**31**) and (**32**), respectively.



9.33.5.2 Elimination of the Heteroatom to form a Nonaromatic Species

Most of these examples are either photolyses or thermolyses of polychalcogenides. Thus irradiation of the pentaselenepin (**33**) gives the diselenone (**34**), which can be trapped by norbornadiene in 60% yield to give (**35**) <87TL5699>. When the related mixed seleno-thia compound (**36**) is used, deselenization is observed in a greater amount than desulfurization and gives a mixture of dihydro-1,4-dithiins and dihydro-1,4-thiaselenins <87TL4833>. Photolysis or thermolysis of (**37**) gives the *cis*-pentalene derivative (**38**) by extrusion of one selenium atom and intramolecular addition of the remaining selenium (radicals) across the double bond <90JOC263>.

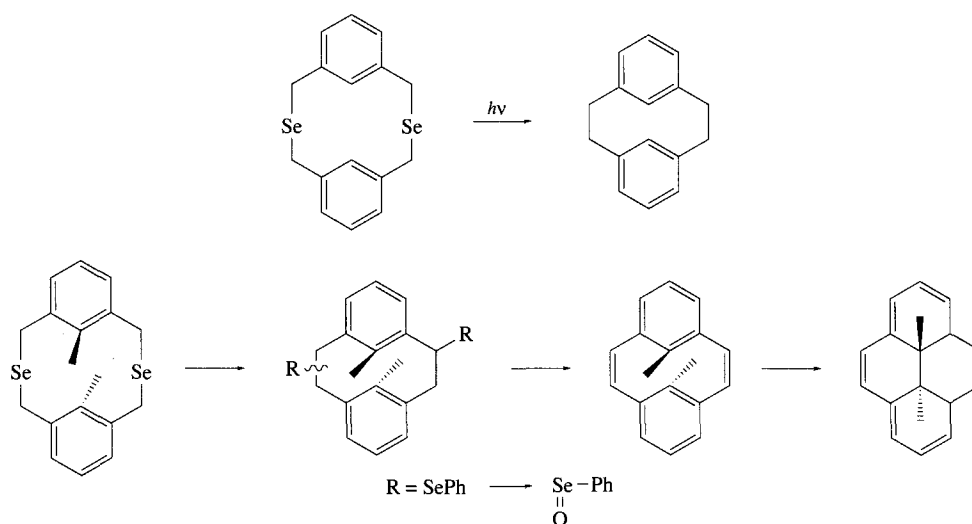


9.33.5.3 Elimination of the Heteroatom in Heterocyclophanes

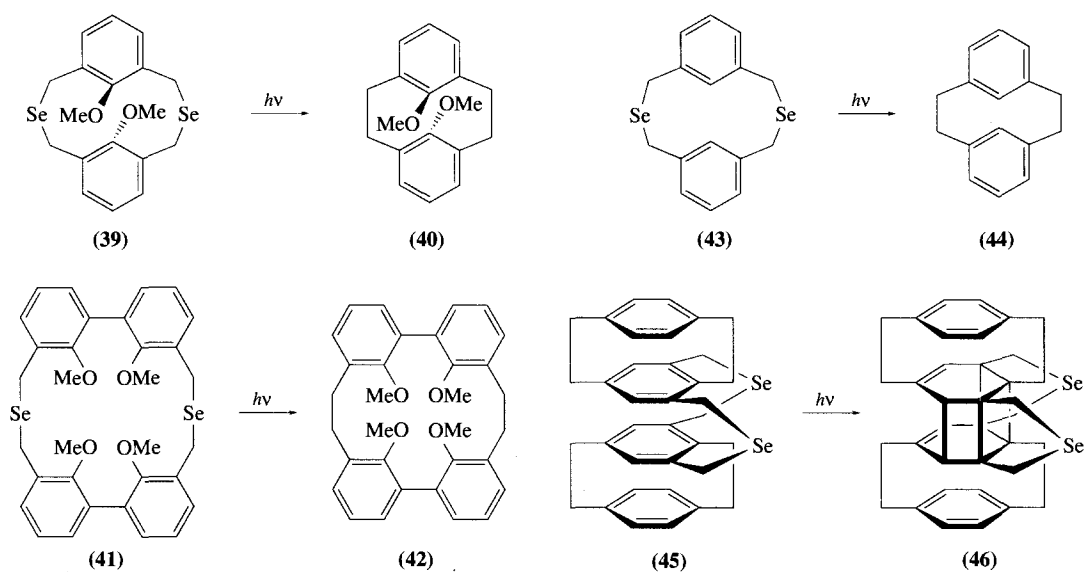
Cyclophanes have been given their own section because of the interest in these compounds, and the fact that so many cyclophanes have been prepared by elimination of the heteroatoms from the thiacyclophanes. With the improved yields of selenacyclophanes, obtained via the selenocyanate discussed in Section 9.33.6.1, selenacyclophanes should play a more important role in the synthesis of cyclophanes in the future.

It should be noted that heterocyclophanes are attractive intermediates because it is often more difficult to form the C—C bond in the cyclophanes directly, than to go via the nucleophilically accessible C—Het—C bond. Moreover, the ring size of the heterocyclophane is larger and hence

the latter is usually less strained than the corresponding cyclophane, and better yields are normally obtained. There are three methods to extrude selenium from the selenacyclophanes: (i) Photodeselenation using tris(dimethylamino)phosphine or trialkylphosphites. This is usually carried out in THF at room temperature with a high pressure Hanovia-type mercury lamp. On the mmol scale, this method usually gives good yields (50–100%), but like all photolyses can give problems on a large scale. (ii) Flash pyrolysis at 650 °C under reduced pressure; yields are generally low (10–20%). (iii) A benzyne-induced Stevens rearrangement, in which benzyne is generated from anthranilic acid with isopentyl nitrite in refluxing 1,2-dichloroethane. These three methods are compared <83TL2593, 87BCJ4027>; however, method (iii) for the metacyclophanes has an advantage in that it is easily scaled up and the resulting product can either be hydrogenolyzed to the saturated cyclophane with Raney nickel <87BCJ4027>, or can be oxidized to the selenoxide with MCPBA, and then eliminated in refluxing toluene to give the alkene <87TL5119>. Using the latter procedure gives alternate access to the bridged annulene shown in Scheme 6. Sometimes the photodeselenation works extremely well, e.g. for the rather rigid examples (39) to (40) and for (41) to (42) the yields are quantitative; whereas for the more flexible (43) to (44), the yield is only 16% <87BCJ4027>. In the case of the triple-layered cyclophane (45), irradiation did not give deselenation but rather photodimerization to give 47% of (46) <86T1731> (Scheme 7).

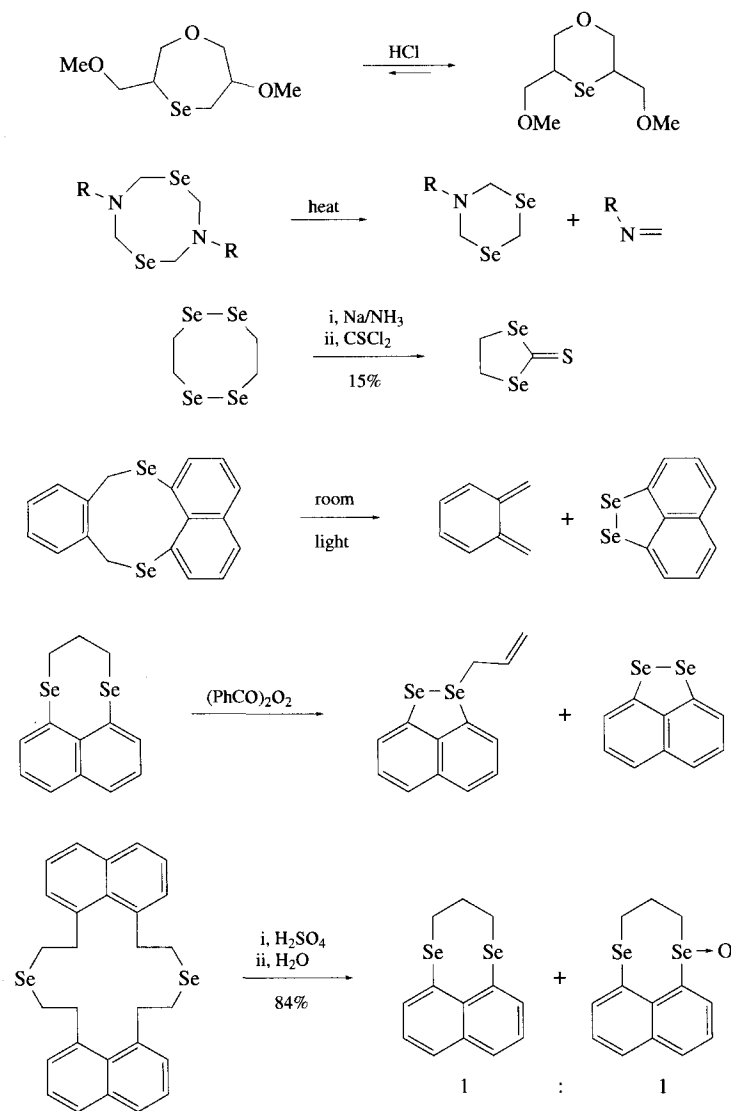


Scheme 6



Scheme 7

Some of these reactions seem somewhat unpredictable and unrelated, but presumably are driven by the lower energy of the smaller rings. They are collected in Scheme 8 $\langle 72\text{CR}(\text{C})1700, 79\text{JCS}(\text{P}1)1206, 80\text{JOC}2632, 92\text{CL}1437, 93\text{JCS}(\text{P}1)2145, 93\text{JOC}5291 \rangle$.



Scheme 8

Oxidation of the diselenide (**18**), shown in Scheme 3, does not cleave the ring, unlike the last example of Scheme 8, but gives 50% of the selenoxide along with 50% return of starting material $\langle 91\text{TL}4345 \rangle$. Similarly, (**17**) gives the selenoxide with MCPBA $\langle 91\text{CC}1052 \rangle$. If the heteroatoms are sufficiently close, then NOBF_4 or NOPF_6 can oxidize them to give a dication with a transannular $\text{M}-\text{M}$ bond (Scheme 4) $\langle 89\text{CC}1789, 90\text{CL}393, 91\text{TL}4537, 92\text{CL}151, 92\text{JA}3117, 93\text{TI}605 \rangle$. These cations act as oxidants from which the diselenide or telluride can be recovered. When I_2 or Cl_2 is used as the oxidant (Scheme 4), the product is the dihalogeno ditelluride (**6**). The dications may be hydrolyzed to the oxide by water, and the oxide converted to the cations by concentrated H_2SO_4 $\langle 90\text{TL}2307$,

91CL1649). The oxides also react with TMS-OTf <92JCS(P1)2247> and similar species <91CC98, 91JA6337, 93JA9826> or with Ac₂O <92CL501>, as shown in Scheme 5.

9.33.5.6 Complexation with Heavy Metals

Very few complexes involving large-ring heterocycles with metals are reported. 2,11-Diselena[3.3](2,6)pyridinophane has been complexed with nickel and copper forming a complex where the metal is surrounded octahedrally by two pyridine nitrogens, two seleniums, and two oxygens from water <89JOC393>. 2,11-Diselena[3.3]orthocyclophane forms a complex where (η^6 -benzene) ruthenium is attached to the two selenium atoms <93IC3648>. The complexing ability of various selenacrown ethers towards cobalt, copper, nickel, palladium, silver, and mercury ions was examined <89CL1667>. Selenacrowns exhibit greater selectivity for methylmercury(II) cations than the corresponding thiacycrown ethers. The PdX₂ complexes of selenepane (1) have been prepared; VT NMR studies indicate probable fast selenium inversion <86JCS(D)205>.

9.33.5.7 Other Reactions

There are many papers which contain large-ring selenium compounds that involve functional group transformations which do not involve the selenium atom. One example being the many reactions of (28), for example reduction to the alcohol, elimination to the alkene, Grignard reactions, etc., which produce derivatives which have been used in neurotropic and psychotropic studies <69CCC3801>.

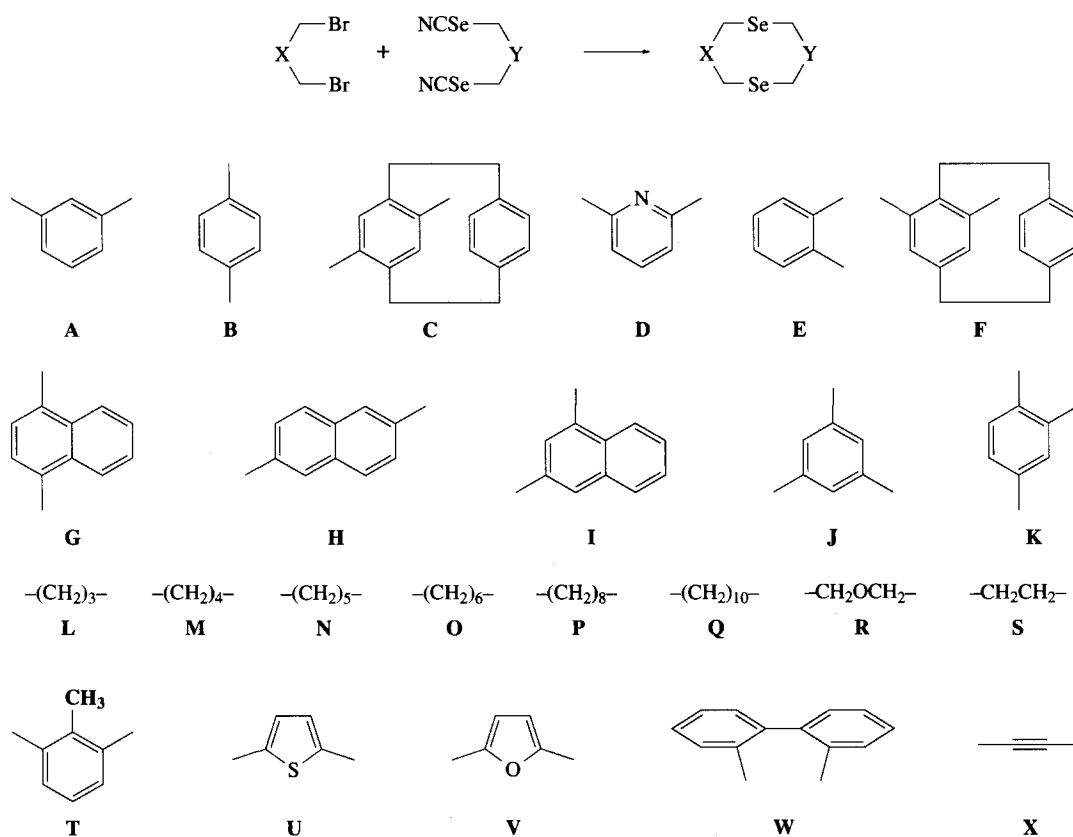
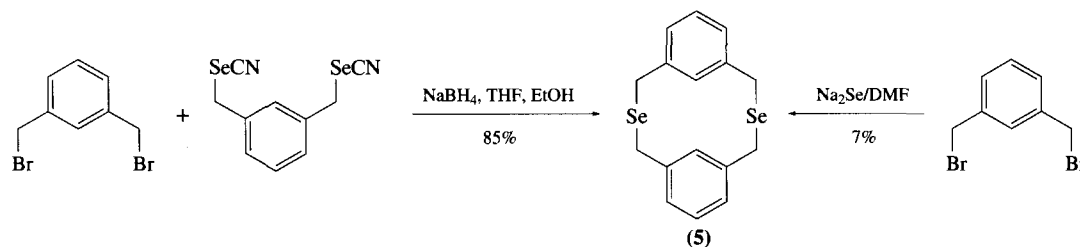
9.33.6 SYNTHESIS

Selenium and tellurium can be introduced into organic compounds as the element, as a reduced (—Se^-) species, or as an oxidized (SeO_2) species. Use of the reduced form is by far the most common and will be discussed first. In forming the ring, the C—Se—C bond can be premade and thus not be involved in the ring-closure step. More commonly, the C—Se—C bond is formed during the ring-closure step. The latter is discussed first.

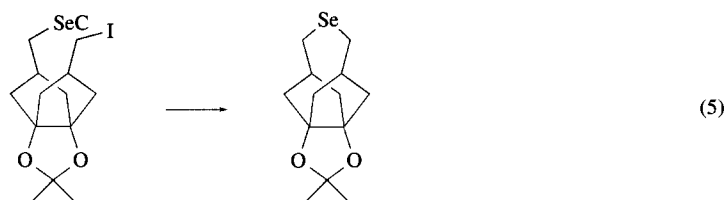
9.33.6.1 Synthesis of Rings in which Formation of a C—Se Bond is the Ring-closure Step

Sodium selenide (Na_2Se) or telluride themselves are difficult to use because they react fairly quickly with air and moisture, and although they can be reacted with halides, it is not the best route. Selenocyanates can be reduced *in situ* by NaBH_4 to form selenolate, which like thiolate is an excellent nucleophile, and thus the same solution can displace a halide. Whereas the reaction <75TL1363, 80CJC1398> of *m*-xylylene bromide with sodium selenide only gave 7% of (5), conversion of half of the bromide to the bis-selenocyanate first, and then coupling as shown in Scheme 9, gave 85% yield of (5) <82TL5571>. This method, developed by Misumi and co-workers <87BCJ4027>, can also be used for nonsymmetrical examples and for purely aliphatic cases. Without doubt, it is the best method, usually giving yields of cyclic product of 80–100%. Some examples of couplings are (see Scheme 9 for X and Y): where XY or YX = AA(85%), AB(81%), BB(73%), AC(68%), BC(74%), AD(93%) <82TL5571>; EE(83%), AE(78%), AF(78%), CC(64%), CF(63%), GG(80%), HH(41%), BG(77%), AG(98%), BI(79%), AI(81%), JJ(67%), JK(55%), AL(48%), AM(100%), AN(100%), AO(87%), AP(53%), BQ(79%), DP(78%), SO(70%), RR(60%) <87BCJ4027>; TT(55%) <87TL5119>; UU(100%), VV(100%), DD(96%), WW(95%), DU(100%), EU(100%), AU(100%), BU(100%),

DW(100%), UW(97%), EW(95%), AW(98%), BW(95%) <89T1611>; ER₂(10%) <89CL1667>; XX(46%) <91CB357>. For other examples see <85JA4802, 86T1731, 91CB2583, 91CC860, 91CL1461, 92JHC967, 93JCS(P1)2145>. An example of an intramolecular coupling to give an eight-membered ring in 70% yield is shown in Equation (5) <87JA5524>.



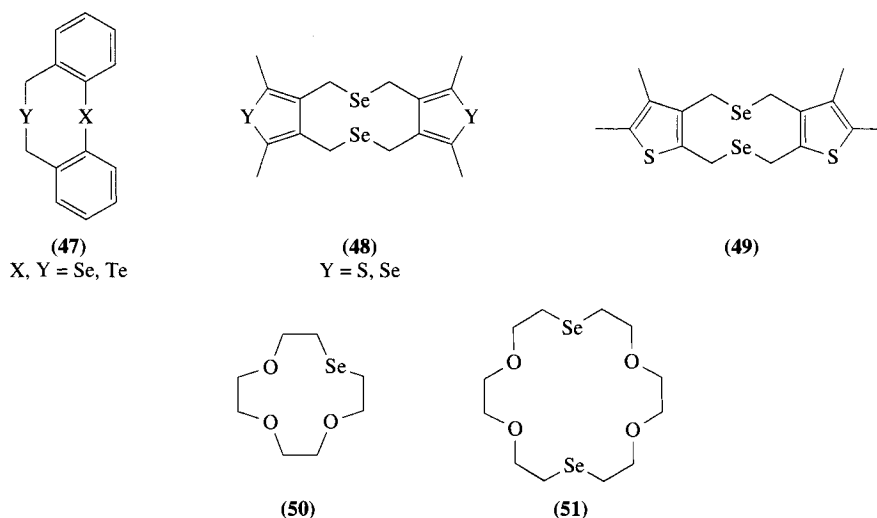
Scheme 9



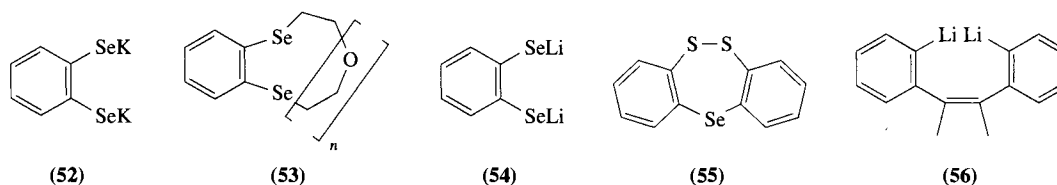
Pinto and co-workers <89JA6582> prepared a novel series of selenium coranands by generating the bis-selenolate by reduction of the selenocyanate in liquid ammonia using sodium (Equation (2)).

Although the selenocyanate method is now preferable, examples of use of sodium selenide or telluride in ethanol are prevalent, especially if higher oligomers are required, for example CH_2Cl_2 yields $(\text{CH}_2\text{Se})_n$, where $n = 3, 4, 5, \dots$ <82ZAAC(488)60>. Often diselenides or ditellurides are formed by air oxidation of the intermediate selenols. This can sometimes be avoided by introduction of

NaBH_4 partway through the reaction, to reduce back to selenolate <91TL4537>. At least one example of a good yield using Na_2Se in ethanol has been reported, to give 71% of (47; $\text{X} = \text{Y} = \text{Se}$) from the corresponding bis(bromomethyl)diphenylselenide <91CC1052>. Sodium telluride has been similarly used for (47; $\text{X} = \text{Se}, \text{Te}$; $\text{Y} = \text{Te}$) <93CL263>. Sometimes elemental selenium is reduced *in situ*, for example, selenepane (1) was obtained in 5% yield from 1,6-dibromohexane and the product of selenium, NaOH and $\text{NaSO}_2\text{CH}_2\text{OH}$ (Rongalite) <86JCS(D)205>. The dibenzo derivatives (25; $\text{X} = \text{Se}$) <85OPP270> and (25; $\text{X} = \text{Te}$) <92T3155> were prepared similarly. Aqueous sodium hydrogen selenide in dioxane on a bis(bromomethyl)thiophene gave some of the 10-membered ring compound (48; $\text{Y} = \text{S}$) <77H(6)1349>; whereas, selenium and NaBH_4 in ethanol were used to obtain 16% of (48; $\text{Y} = \text{Se}$) <84CS53>, and 40% of (49) <82CS176>. Gaseous H_2Se bubbled into a solution of sodium ethoxide gave the seleno-crowns (50) and (51) in 16% and 28% yields, respectively <89MI 933-01>.

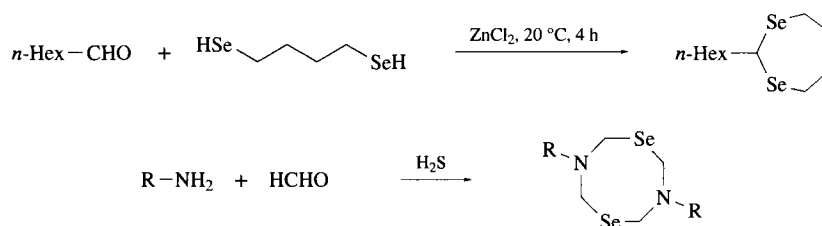


When selenium is next to an aryl ring, it can be introduced by way of an organometallic intermediate. Thus reaction of a zirconocene, R_2ZrPh_2 , with selenium powder and then Bu^tOK gave the bis-selenolate (52), which with various bromoethylethers gave a series of benzo crown selenoethers (53) where $n = 1-3$ in 20–46% yields <91PS247>. Sometimes, however, the products are not always obvious; the dilithio derivative (54) with $\text{Pd}(\text{Ph}_3\text{P})_2\text{Cl}_2$ yielded 53% of (55) <90JCR(S)332>, while (56) with selenium gave the nine-membered ring, triselenide (7), in up to 68% yield depending upon how much selenium was used <90JOC263>.



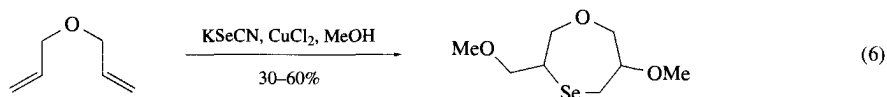
A number of rings have been made where selenium itself or a selenol intermediate adds across a multiple bond (Scheme 2) <81RTC368, 88TL1935, 91CC802, 93CC1493>.

Selenols will also add across carbonyl bonds (Scheme 10) <72CR(C)1700, 85T4793>.

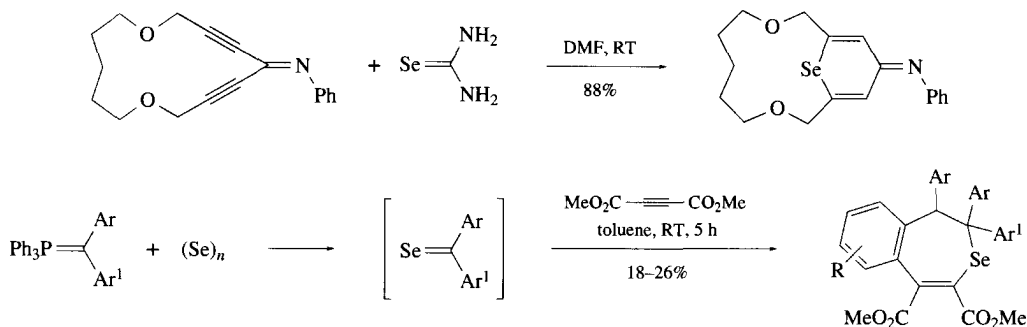


Scheme 10

Potassium selenocyanate acts as a source of a selenium atom in an interesting addition across alkenes (Equation (6)) <79JCS(P1)1206>.



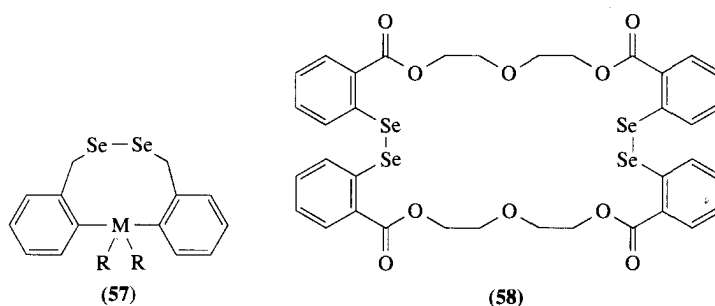
Selenoureas <90JOC2567> and selenones (derived from a phosphorus ylide and selenium) <92TL1333> can also act as selenium sources for addition across triple bonds (Scheme 11).



Scheme 11

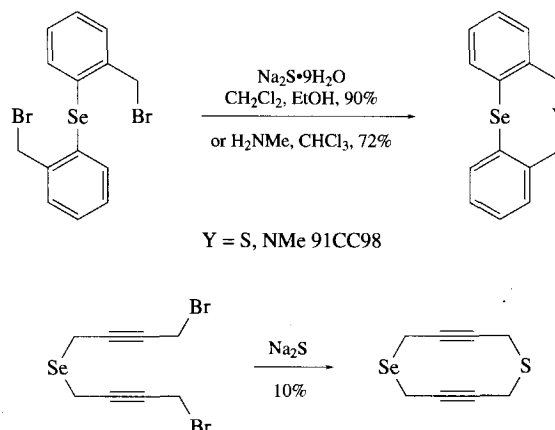
Use of oxidized species of selenium in the synthesis of selenium containing macrocycles is less common, but SeCl_4 <89POL2817>, Se_2Cl_2 <92CL2289>, and SeO_2 <89T5073> have all been used (Scheme 1).

If a cyclic 1,2-diselenide is required, this can easily be obtained by oxidation of a bis-selenol or bis-selenolate. If the latter are benzylic, then displacement of halide is best. Selenium itself with $\text{NaBH}_4/\text{EtOH}$ was used to give (**57**; $\text{M} = \text{Si}$) <86JOM(301)273>, while reduction of the selenocyanate (which is probably the easiest route) with $\text{NaBH}_4/\text{EtOH}$ and then oxidation of selenolate with O_2 gave (**16**) <76CJC238>. In the cases of (**58**) and (**10**), in which the selenium atoms are joined directly to aryl rings, for (**59**) the selenocyanate was reduced with NaBH_4/HCl and then O_2 was used <90CC231>, while for (**10**) the dilithio-aromatic was treated with selenium and then with O_2 <91JHC433>. The yields in these four cases were, however, not great (<20%).



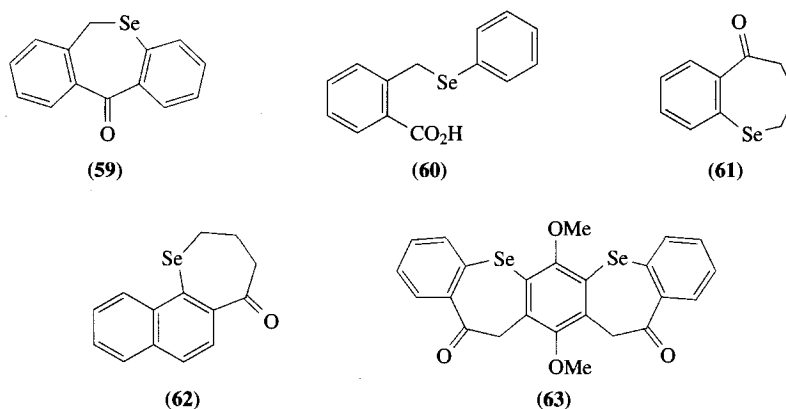
9.33.6.2 Synthesis of Rings in which Formation of a C—Se Bond is not the Ring-closure Step

Many types of reactions can close rings, those discussed below have a preformed C—Se—C bond in one of the fragments, and this is not involved in the ring-closure step. The simplest conceptually involve nucleophilic displacement on halides, for example with Na_2S or MeNH_2 (Scheme 12) <90TL2307, 91CB357, 91CC98>. Similar reactions have been carried out on tellurium containing fragments <92CL151>.



Scheme 12

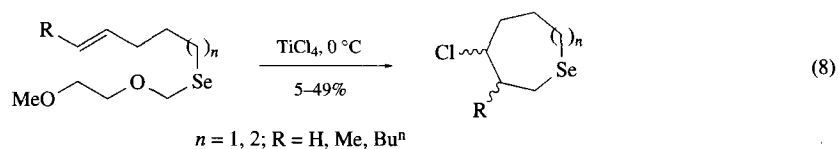
Friedel–Crafts cyclization of seleno-substituted aryl derivatives of acetic acids has produced a wide variety of benzannelated selenacycloalkanones, for example (59) was obtained in 49% yield from (60) <69CCC2122> with phosphoric acid; (28) <69CCC3801> was similarly obtained in 47% yield. Examples of monobenzannelated and naphthannelated types, for example (61) and (62), are also documented <69CR(C)532, 71BSF2689, 71BSF2699>, as well as polycyclic examples, for example (63) <92BCJ1794>.

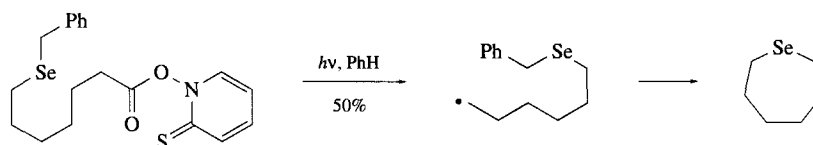


Dicarbonyl compounds have been used as ring-closure intermediates, for example in the β -diketone synthesis in Equation (4) <87CB1151> and formation of the selenadiazepine from the bis-acetophenone shown in Equation (7) <72JHC1427>.



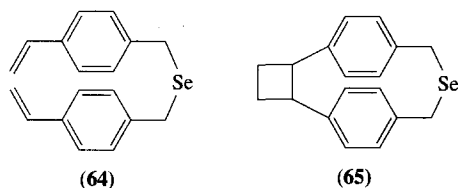
Reactive intermediates have also been used: Lewis acid acts on (2-methoxyethoxy)methylselenides to generate an intermediate α -selenocarbenium ion, which cyclizes intramolecularly onto alkenes or alkynes (Equation (8)) <94JOC1011>. Intramolecular homolytic substitution at selenium of the radical, derived from a thiohydroxamic ester, was used to prepare selenopane (Scheme 13) <92CC57>.





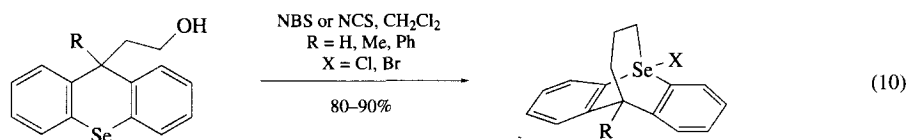
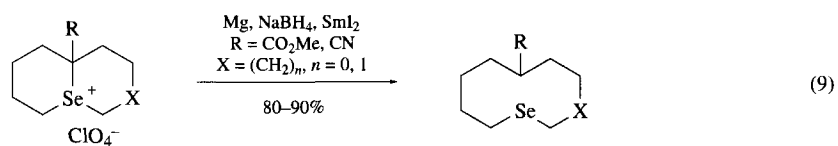
Scheme 13

Photolysis of the styrene derivative (**64**) in benzene in the presence of benzophenone gave about 50% of the interesting cyclophane (**65**) $\langle 92\text{PS}(67)257 \rangle$.

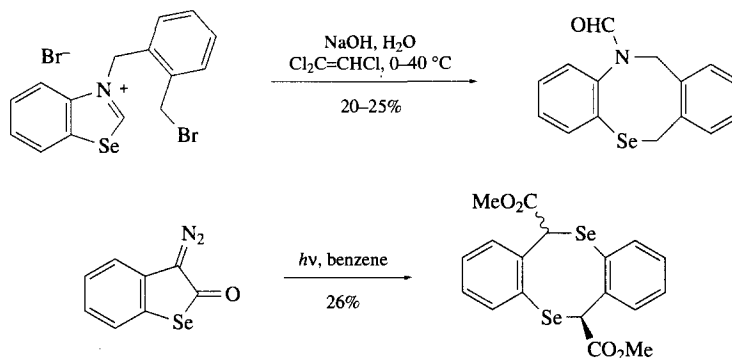


9.33.6.3 Syntheses Involving Transformation of a Selenium-containing Ring

Conceptually, one of the simplest methods to generate a large ring is cleavage of the common bond of two fused rings; indeed cleavage of a selenonium salt, where the selenium is at the bridgehead has been used to make nine- and ten-membered rings (Equation (9)) $\langle 90\text{TL}3027, 92\text{JCR}(\text{S})393, 92\text{PS}(67)169 \rangle$. Likewise, a new ring can also be formed by cyclization onto the selenium atom as shown in Equation (10) $\langle 84\text{H}(22)1473 \rangle$.

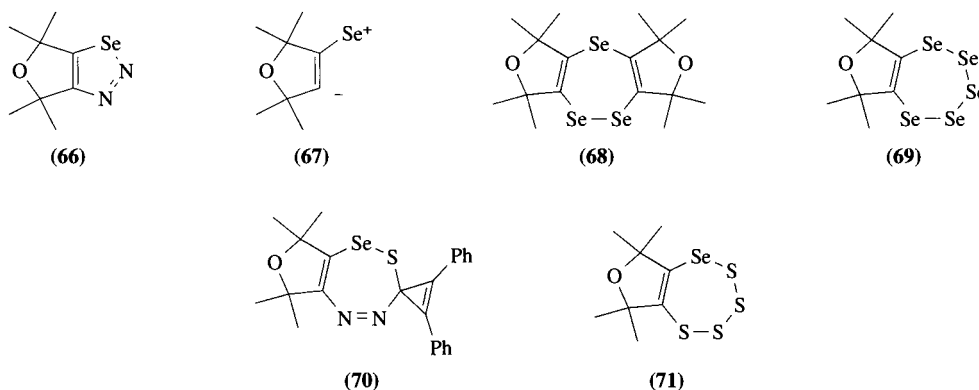


There are several examples where one ring is opened and then recyclized to give a new larger ring; base-induced ring expansion of quaternized benzoselenazoles gives the benzoselenazocine shown in Scheme 14 [⟨80TL2429⟩](#), while photolysis of the diazoselena ketone, also shown in Scheme 14, gives a route to selenocins [⟨89JOC240⟩](#).

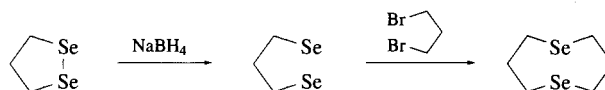


Scheme 14

Thermolysis of the selenadiazole (**66**) proceeds by way of the 1,3-dipolar intermediate (**67**), which can be trapped with a variety of species to yield heterocycles with many heteroatoms such as 58% of (**68**) or 8% of the pentaselenapin (**69**) <87TL5699>. Reaction of the intermediate with molten sulfur gave 39% of the mixed heterocycle (**70**) <87TL4833>, while with diphenylcyclopropenethione 90% of (**71**) was obtained <87TL4707>.



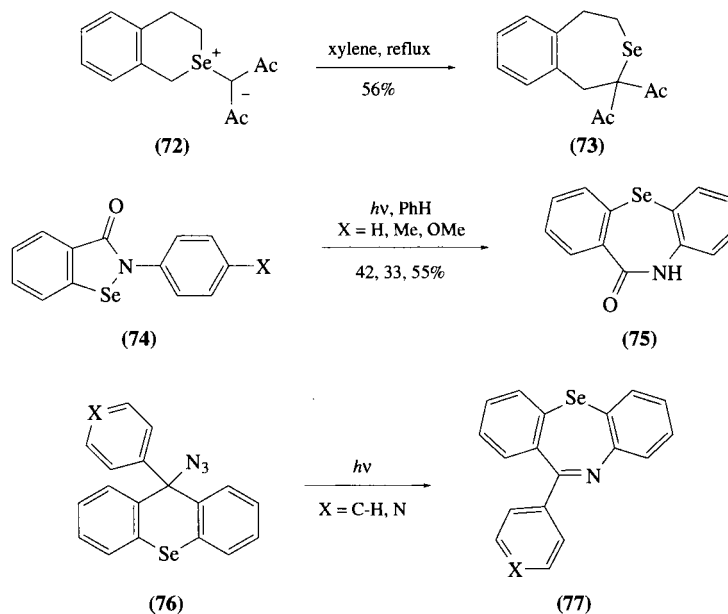
Since 1,2-diselenides on reduction with NaBH_4 give diselenolates, 1,3-diselenolane acts as a small ring suitable for conversion to a larger one as shown in Scheme 15 <89CC1789>.



Scheme 15

Diazomethane can break open 1,3-oxaselenoles and form in quantitative yield the eight-membered dioxaselenocine shown in Equation (1) <83H(20)1959, 87CPB4967>.

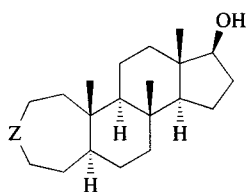
It is also possible to expand five- or six-membered rings with fragments already attached to the molecule; for example, heating the diacetylmethanide (**72**) (which is a cyclic *exo*-selenium ylide) gives the benzoselenepine (**73**) <90JCS(P1)39>, while irradiation of the selenazolone (**74**) in benzene gives the amide (**75**) <86BCJ2179>, and heating the selenoxanthene (**76**) gives the dibenzoselenoazepine (**77**) (Scheme 16) <76TL3141, 84JHC1321>.



Scheme 16

9.33.7 UNUSUAL AND INTERESTING COMPOUNDS

Many compounds derived from the dibenzoselenenpins (**59**) and (**28**) have been prepared because of their potential neurotropic and psychotropic activity (see <70CCC3721> and 44 preceding papers). Compound (**63**) is a potential precursor for infrared dyes for semiconductor lasers used in optical recording media <92BCJ1794>. The seleno and telluro A-homosteroids (**78**) have been synthesized and tested for androgenic activity. The seleno compound is active whereas the telluro derivative is not. Steric rather than electronic factors seem to dominate <72JMC368>.



(**78**)
Z = Se, Te

9.34

Rings containing Phosphorus

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9.34.1 INTRODUCTION

The eclectic nature of molecules containing phosphorus in seven- and larger-membered rings has necessitated the use of broad subject headings for this chapter. The inclusion of numerous structural diagrams in the text, however, will assist the reader in locating material of interest. A comprehensive review by Caminade and Majoral of phosphorus-containing macrocycles and cryptands has been published <94CRV1183> and there are two important earlier reviews by Gallagher <87MI 934-01> and Quin <B-88MI 934-01> concerning the stereochemical aspects of heterocyclic phosphorus compounds.

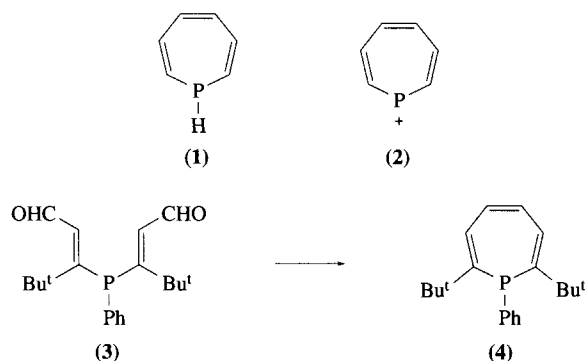
9.34.2 PARENT RINGS WITH ONE PHOSPHORUS ATOM

9.34.2.1 Seven-membered Rings

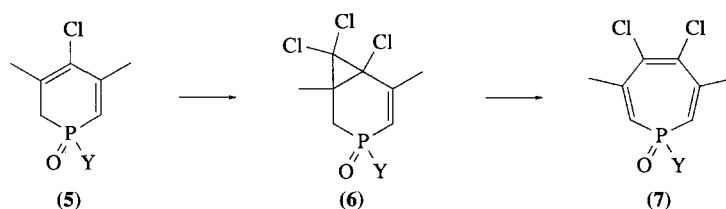
9.34.2.1.1 Monocyclic derivatives

The parent 1*H*-phosphhepin (**1**) is not known, although there is evidence for the phosphatropylium ion (**2**) from collision activation experiments between phosphorus and benzene in the gas phase

<92JA7582>. The reductive coupling of (3) by the McMurray reaction gave the substituted phosphepin (4) as a distillable oil that crystallized in 8–10% yield after purification by HPLC <84AG(E)894>.

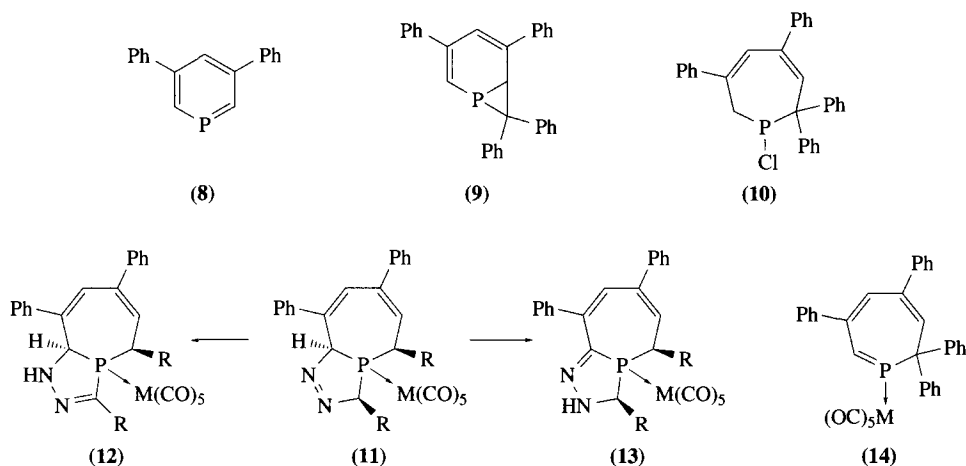


The addition of dichlorocarbene to the 1,2-dihydrophosphinine-1-oxides (5; Y = MeO, Ph) under phase transfer conditions, followed by alkaline dehydrochlorination of the intermediate (6; Y = MeO, Ph), afforded the phosphepin-1-oxides (7; Y = MeO, Ph) in 3–5% yields <87JOC3983>. A number of related compounds have been prepared similarly <93S931>.

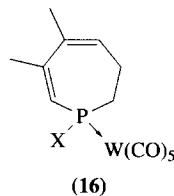
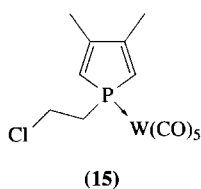


3,5-Diphenyl- λ^3 -phosphinine (8) reacts with diphenyldiazomethane to give the 1-phosphanorcaradiene derivative (9); the latter, when treated with hydrogen chloride, affords (10). When co-ordinated to zerovalent metals in the complexes $[M(CO)_5(8)]$ (M = Cr, Mo, W) diazomethane and monosubstituted diazomethanes react to give (11; M = Cr, Mo, W); the latter, depending upon R and the solvent from which they are recrystallized, undergo 1,3-H shifts producing the isomeric hydrazones (12; M = W) and (13; M = Cr, Mo, W). The reaction of $[M(CO)_5(8)]$ (M = Cr, Mo) with diphenyldiazomethane produces $[M(CO)_5(9)]$ (M = Cr, Mo), which are in equilibrium with the complexes (14; M = Cr, Mo); (14; M = Cr, Mo) react reversibly with hydrogen chloride to give $[M(CO)_5(10)]$ (M = Cr, Mo) <87AG(E)1134>. The crystal structure of (11; M = W, R = H) has been determined.

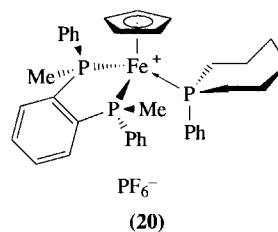
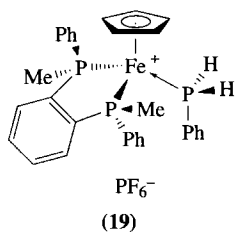
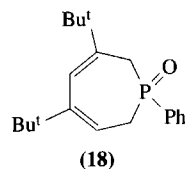
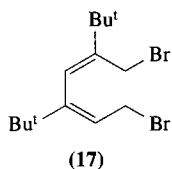
In the presence of aluminum trichloride, the 1- β -chloroethylphosphole complex (15) rearranges



into the 6,7-dihydrophosphepin derivative (**16**; X = Cl), which, upon methanolysis, yields the phosphinite complex (**16**; X = OMe) <85TL3461, 92SL363>.

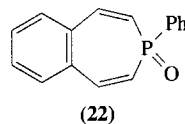
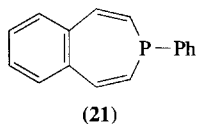


Substitution of the bromine atoms in (**17**) by disodium phenylphosphide, followed by oxidation of the intermediate phosphine with hydrogen peroxide, gave (**18**) in 10% yield, along with two other unidentified products <94CC67>. Phenylphosphine, in the complex (**19**), reacts with 1,6-dibromohexane in the presence of KOBu^t to give the 1-phenylphosphepane complex (**20**) in 63% yield <95OM1434>.



9.34.2.1.2 Fused benzo and dibenzo derivatives

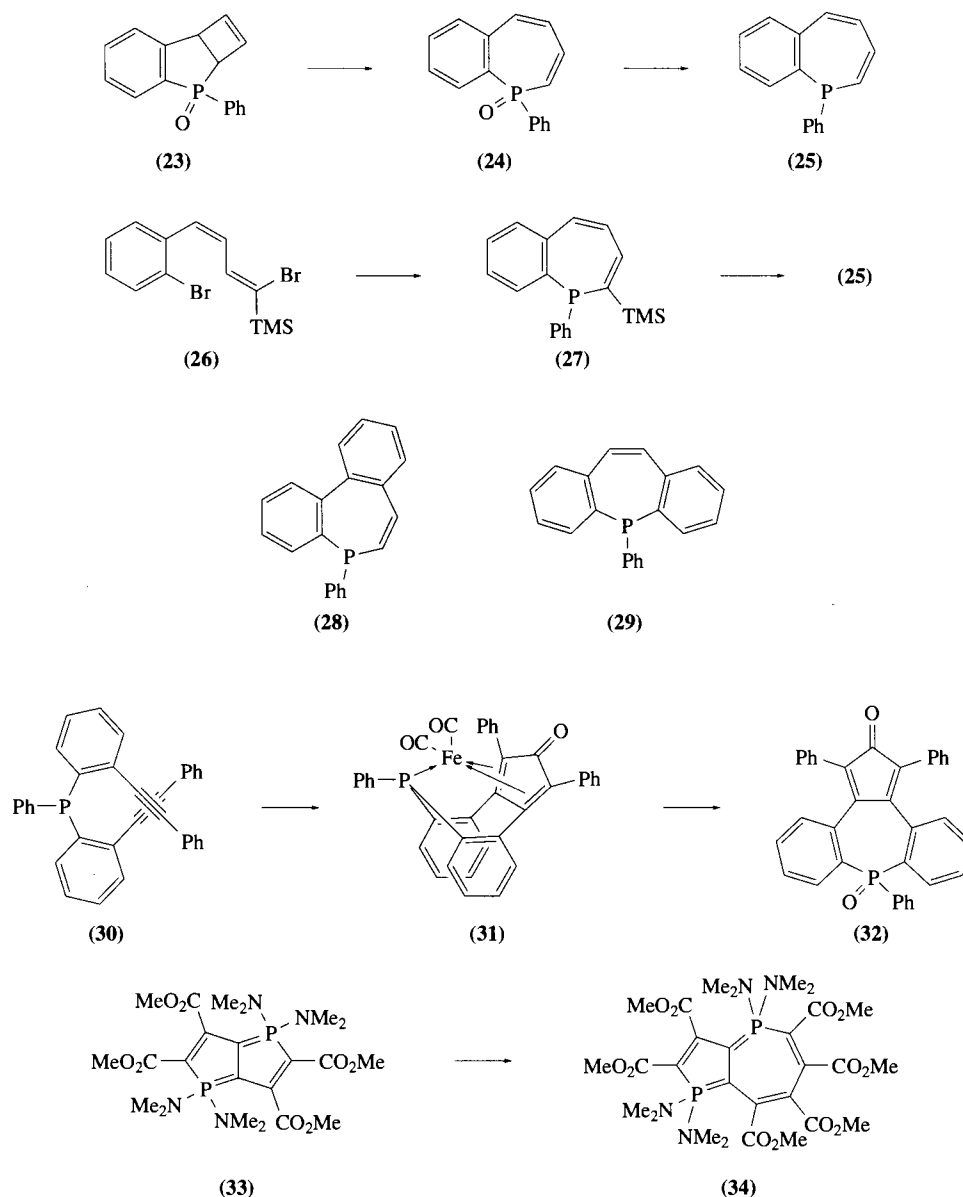
The 3-benzophosphepin (**21**) was the first phosphepin derivative to be isolated. Thermally labile (**21**) ($t_{1/2}$ ca. 120 min in decalin at 80°C) was synthesized by the base-catalyzed addition of phenylphosphine to 1,2-diethynylbenzene. The stable oxide (**22**) was also prepared <83TL2545>.



Flash vacuum pyrolysis of (**23**) results in valence isomerization and ring-opening to give the 1-benzophosphepin oxide (**24**) in 85% yield; (**24**) was reduced with trichlorosilane to 1-phenyl-1-benzophosphepin (**25**) in 80% yield <91CC1227>. The phosphepin (**25**) (but not the phosphepin oxide (**24**)) is thermally labile in solution, decomposing into naphthalene and, presumably, cyclopoly(phenylphosphine) ($t_{1/2}$ ca. 90 min in toluene at 80°C). Compound (**25**) has also been prepared from (**26**) by lithiation, treatment with dichlorophenylphosphine to give (**27**), and desilylation of (**27**) with tetra-*n*-butylammonium fluoride. The dibenzophosphepins (**28**) and (**29**) were prepared similarly and were found to be stable for 20 h in toluene at 60°C <93CC1817>.

Photolysis of the phosphine (**30**) with iron pentacarbonyl in THF afforded (**31**) in 40% yield <83CB1923>. The structure of (**31**) was determined by x-ray crystallography. Oxidative decomposition of (**31**) with cerium(IV) or oxygen gave the free phosphepin oxide (**32**).

Dimethylacetylene dicarboxylate inserts into a P—C bond of the diphosphapentalene (**33**) to give the diphosphaazulene (**34**), which was characterized by x-ray crystallography <91ZN(B)197>.

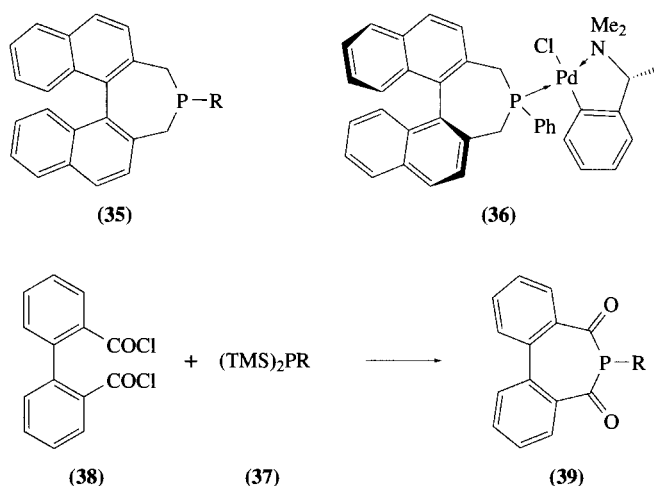


The atropisomeric dinaphthophosphepins ($\pm$)-(35) ($R = \text{Me}, \text{Ph}$) can be prepared from 2,2'-dimethyl-1,1'-dinaphthyl by lithiation and addition of the respective dichlorophosphine $\langle 94\text{TA}511, 94\text{JOC}6363 \rangle$. The resolutions of ($\pm$)-(35) ($R = \text{Me}, \text{Ph}$) were accomplished by the method of metal complexation with use of an optically active ortho-metallated palladium(II)-amine complex. The absolute configuration of (*S*)-(-)-(35) ($R = \text{Ph}$) was determined from the x-ray crystal structure of (36). The optically active phosphepin in conjunction with rhodium(I) is an effective auxiliary for the asymmetric hydroformylation of styrene.

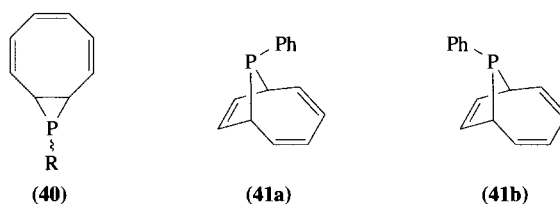
The bis(trimethylsilyl)phosphines (37; $R = \text{Ph}, \text{Bu}^t$) react with the diacyl dichloride (38) to give the dibenzophosphepin derivatives (39) $\langle 87\text{CC}1753 \rangle$.

9.34.2.1.3 Bicyclic systems

Dipotassium cyclooctatetraenide in THF reacts with dichlorophenylphosphine to give (40; $R = \text{Ph}$), which upon warming stereoselectively isomerizes into (41a) $\langle 66\text{JA}3832, 73\text{JA}4292 \rangle$. Rapid gas phase pyrolysis of (41a) at 480°C , or heating at 100°C overnight in chloroform containing hydrogen chloride, causes inversion at phosphorus and formation of (41b). Pure (41b) was obtained via

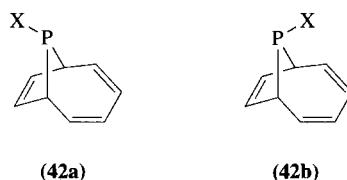


its palladium(II) chloride derivative. Diastereomers **(41a)** and **(41b)** react with retention of the configuration at phosphorus with methyl iodide and hydrogen peroxide to give the characteristic methiodides and oxides, respectively, but **(41a)** and **(41b)** give the same oxide with air, i.e. the oxide of **(41b)**.



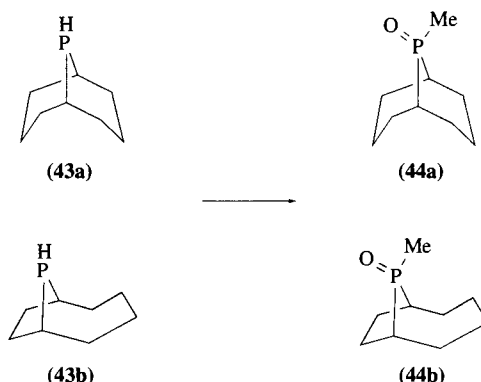
Conformational barriers in cations of the type $[\text{Rh}(\text{COD})\text{L}_2]^+$ containing **(41a)** or **(41b)** have been investigated by ^1H , ^{13}C , and ^{31}P NMR spectroscopy $\langle 90\text{JOM}(385)131 \rangle$. A correlation exists between the diastereomer of the complex and the $\text{Rh}-\text{P}$ rotational barrier and the catalytic activity and selectivity of isomerization and hydrogenation of 1-hexene. In subsequent work, the unusual ^{31}P NMR chemical shifts of 7-phosphanorbornene compounds have been rationalized by *ab initio* chemical shielding calculations $\langle 93\text{JA}11984 \rangle$.

Diethylaminodichlorophosphine reacts with cyclooctatetraenyldilithium to give the diastereomers **(42a; X = NEt₂)** and **(42b; X = NEt₂)** $\langle 84\text{JOM}(273)1 \rangle$. The *syn* diastereomer **(42a)** is halogenated by phosphorus(III)-bromide or -chloride or $\text{KF}/[18]\text{-crown-6}$ to give the corresponding halophosphines as unequal mixtures of diastereomers. The stereochemistry of the substitution of the chloro compound with lithium alkyls, phenolates, thiophenolates, and alcoholates was investigated. The compound **(42b; X = Bu^t)** substitutes carbon monoxide in $\text{Fe}_2(\text{CO})_9$ with retention of configuration at phosphorus; whereas **(42a; X = Bu^t)** co-ordinates with inversion $\langle 85\text{TL}1039 \rangle$.

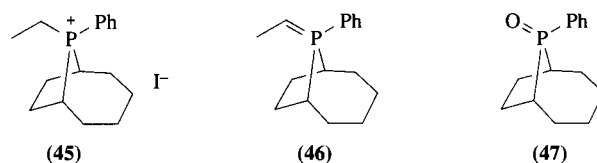


The mixed isomers **(43a)** **(43b)** react with aqueous formaldehyde and sulfuric acid to give the corresponding bis(hydroxymethyl)phosphonium salts that were individually converted into the corresponding methylphosphine oxides **(44a)** and **(44b)** by heating at 150°C for 13 h in 36% sulfuric acid $\langle 93\text{JCS}(D)2563 \rangle$. Although 90% of **(43b)** was converted into **(44b)** under these conditions, only 10% of **(43a)** was converted into **(44a)**.

The crystallographically characterized salt **(45)**, after hydrogenation over 10% Pd/C, was converted into the ylide **(46)** by deprotonation; the ylide reacted with straight-chain or α -mono-

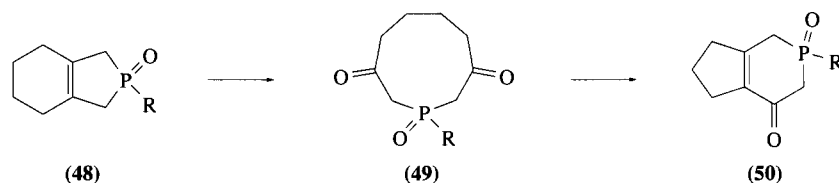


substituted aliphatic aldehydes with formation of *E*-alkenes with 94–96% selectivity giving (47) as by-product (93JOC1985). More general applications of this synthesis will require an inexpensive source of the 9-phosphabicyclo[4.2.1]nonane skeleton (82TL4915, 85CB97).



9.34.2.2 Nine-membered Rings

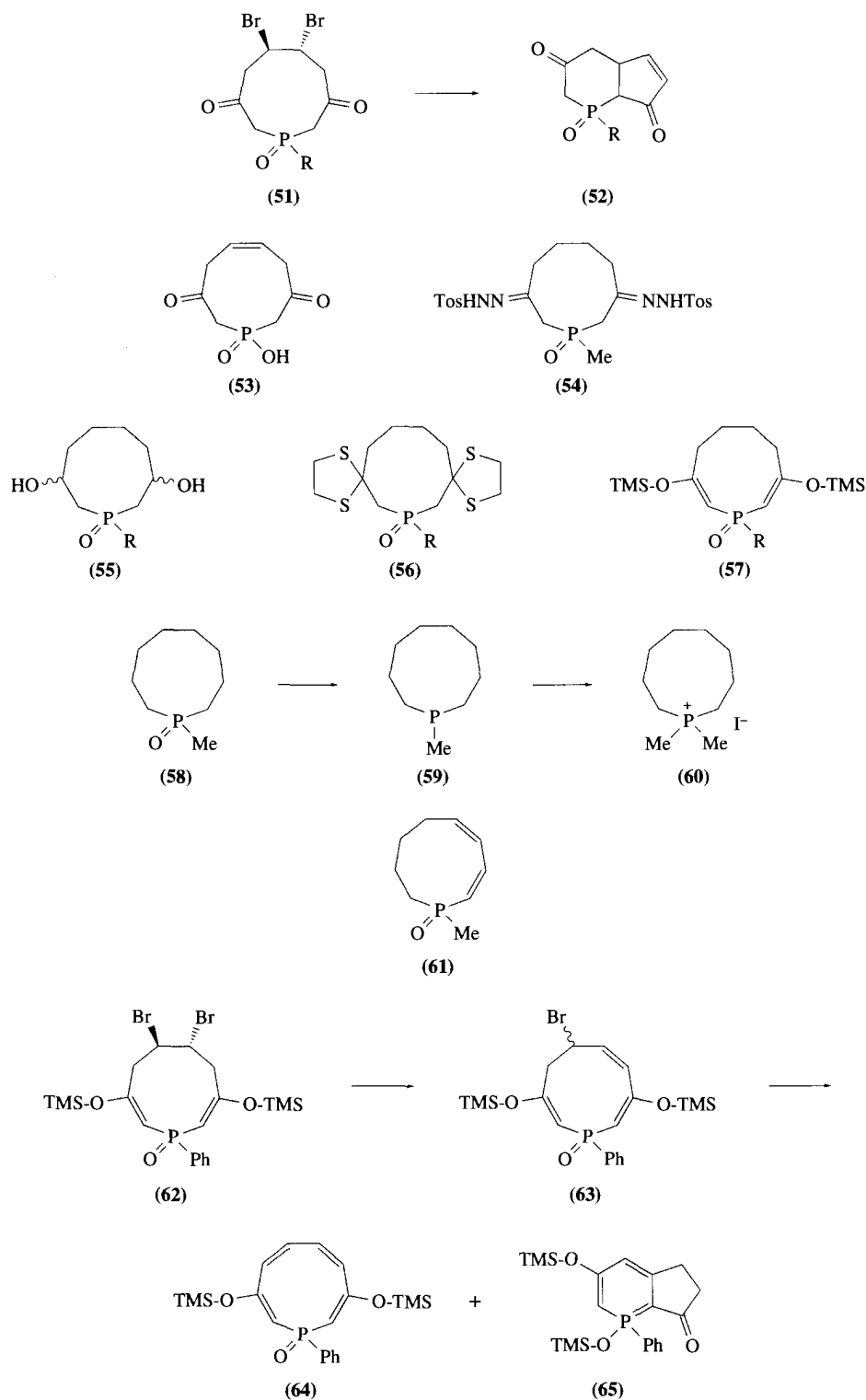
Oxidative ring-opening of the bicyclic phospholenes (48; R = OH, Me, Ph) by ozonolysis affords the phosphonane diones (49; R = OH, Me, Ph), which were found to be valuable intermediates for the synthesis of other nine-membered rings (82JOC905, 82JA1893).



Under acidic or basic conditions, (49; R = Me, OH) undergo intramolecular aldol condensations to give (50; R = Me, OH). Similarly, (51; R = Me, Ph) reacts with triethylamine to give (52; R = Me, Ph) rather than the desired phosphonane diones. Debromination of (51; R = OH) with zinc in acetic acid gave crystalline (53) in 89% yield. The crystal structure of (49; R = Me) revealed a twist-chair conformation of the nine-membered ring in the solid state, but rapid conformational interconversion was observed in solution for this and other phosphonanes (82JA1893). The bis(tosylhydrazone) (54), upon borohydride reduction, regenerated (48; R = Me), but the reduction of (49; R = Me, Ph) with H₂/Raney nickel gave the phosphonane diols (55; R = Me, Ph) as diastereomeric mixtures. The diones (49; R = Me, Ph) reacted with 1,2-ethylenedithiol in the presence of BF₃·OEt₂ as catalyst to give the bis(dithioketals) (56; R = Me, Ph) and with bis(trimethylsilyl)acetamide under neutral conditions at room temperature to give the enol silyl ethers (57; R = Me, Ph). Raney nickel in boiling ethanol desulfurizes (56; R = Me) to give the phosphonane oxide (58), which can be reduced to the free phosphonane (59) with diphenylsilane; quaternization of (59) with methyl iodide gives the phosphonium iodide (60). Spectroscopic evidence for the single product of dehydration of the diol (55) with POCl₃—pyridine supports the formulation of the diene (61).

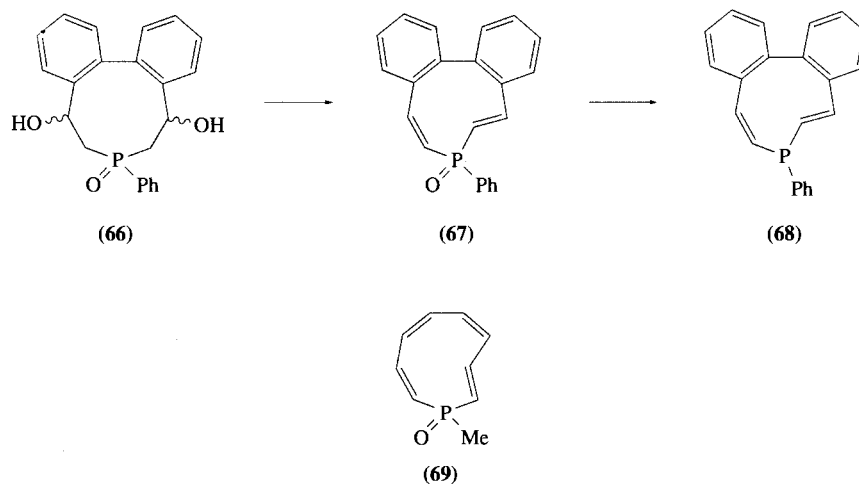
Silylation of (51; R = Ph) led quantitatively to (62), which, when reacted with triethylamine (1 equiv.) gave (63) as a diastereomeric mixture (84JOC3157). Full debromination of (62) was achieved by lengthy exposure to triethylamine, which resulted in the formation of the unstable all-*cis* phosphonin oxide (64) and bicyclic (65) in almost equal amounts.

The dibenzophosphonane oxide (66) smoothly dehydrates to the crystalline oxide (67) (23% yield); the latter can be reduced to the free dibenzophosphonin (68) with HSiCl₃—pyridine. Both (67)



and (68) display the *cis-trans* configuration and severe twisting from planarity prevents attainment of electronic delocalization [82JOC905].

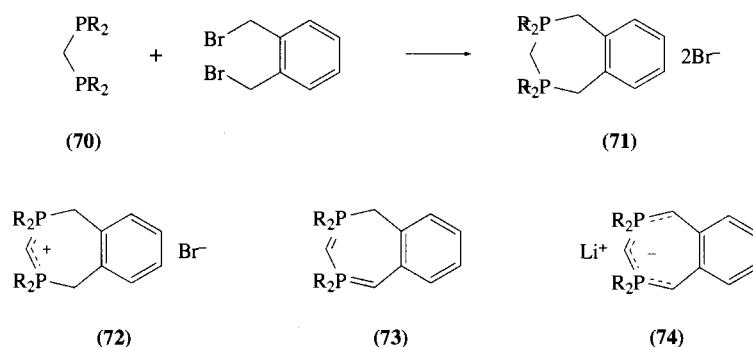
The phosphonin oxides (69; R = Bu^t, Ph) are the first recognizable products of the reaction of (40; R = Bu^t, Ph) with peroxides [83JA5960, 86PS(27)109]. The oxides are stable below -15°C , but undergo intramolecular cycloaddition to give *trans*-3*a*,7*a*-dihydrophosphindoles on warming to room temperature. A similar rearrangement occurs for (40; R = *c*-C₆H₁₁, Me) [85CB97].



9.34.3 RINGS WITH TWO OR MORE HETEROATOMS

9.34.3.1 Cyclic Quaternizations and other Condensations

The diphosphenomethanes (**70**; R = Me, Ph) react with 1,2-xylylene dibromide to give the bis(phosphonium) salts (**71**; R = Me, Ph) <82OM1266>. By stepwise deprotonation of the salts, the mono-, bis- <81CB1428>, and tris-ylides <82OM1266> (**72**)–(**74**) have been prepared; (**74**) has been used as a ligand for transition metal ions <82OM1266, 83AG(E)907>.



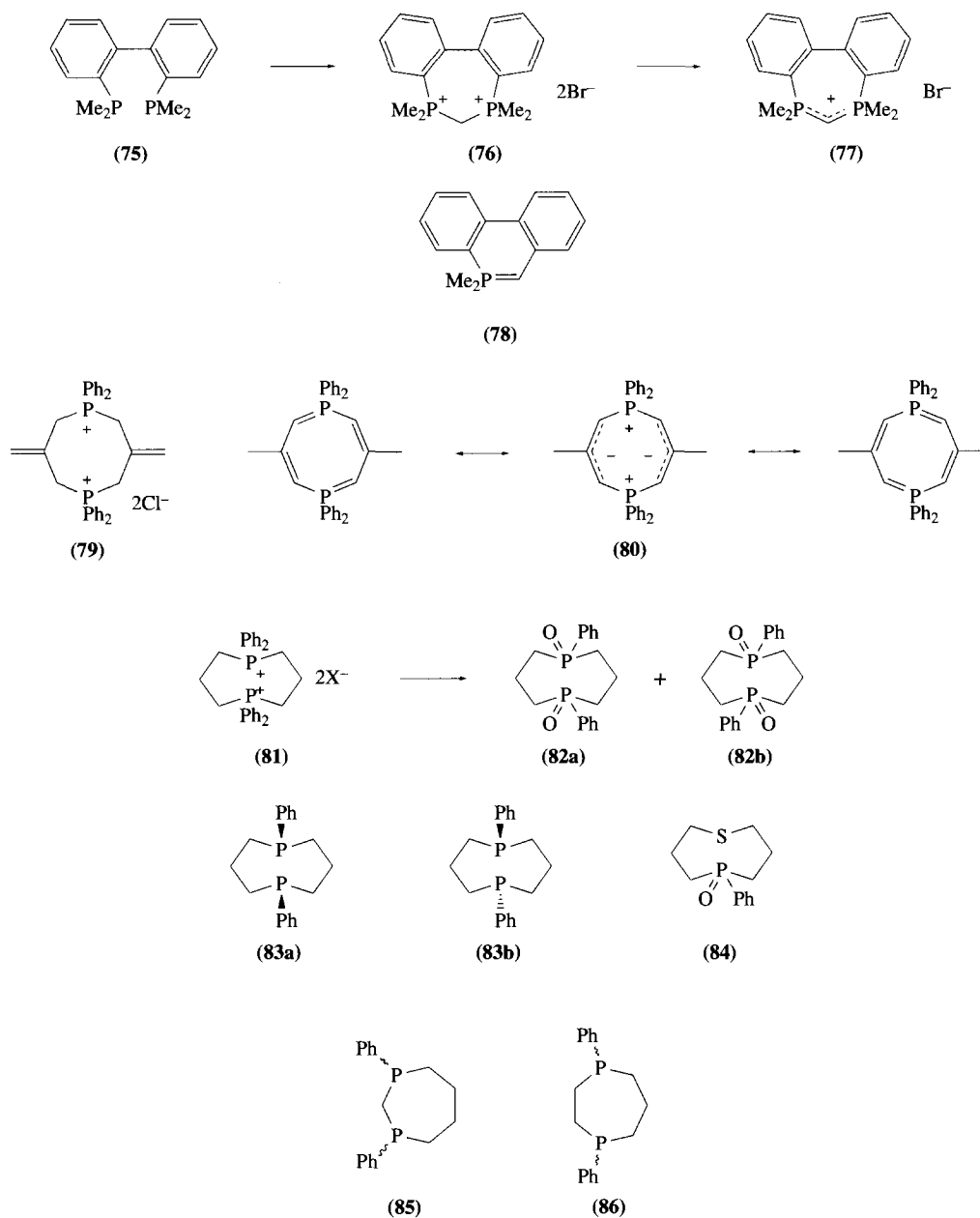
The biphenylphosphine (**75**) undergoes similar cyclic quaternization with methylene dibromide to give the dissymmetric salt (**76**), which can be monodeprotonated to give dissymmetric (**77**); further deprotonation of (**77**) gave 9,9-dimethyl-9 λ^5 -phosphaphenanthrene (**78**) <82CB1367>.

1,5-Bis(λ^5 -phospha)cyclooctatetraene (**80**) was prepared by double deprotonation of (**79**) with strong base <92OM986>. The crystal structure of (**80**) $\cdot$ 0.5Et₂O revealed a puckered tub-like conformation of the eight-membered ring with two conjugatively isolated methallylic fragments.

The bis(phosphonium) salts (**81**; X = Br, I) <89PS(44)235, 91PS(56)27> were prepared from 1,3-bis(diphenylphosphino)propane and the appropriate 1,3-dihalopropane in boiling DMF. Alkaline hydrolysis of (**81**) afforded the *cis* and *trans* bis(phosphine oxides) (**82a**) (**82b**), which were separated by chromatography and individually reduced to the corresponding bis(tertiary phosphines) (**83a**) (**83b**) with HSiCl₃ <89PS(44)235> or LAH <91PS(56)27>. The crystal structures of (**82a**) and (**83b**), and the thia compound (**84**), revealed boat–chair conformations for the three compounds in the solid state.

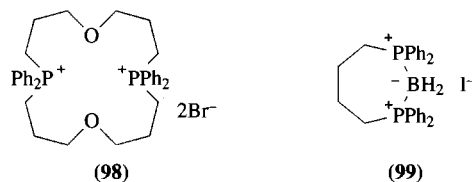
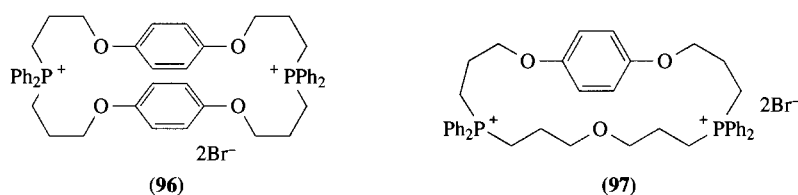
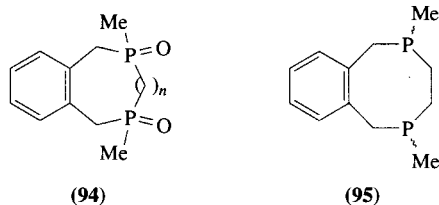
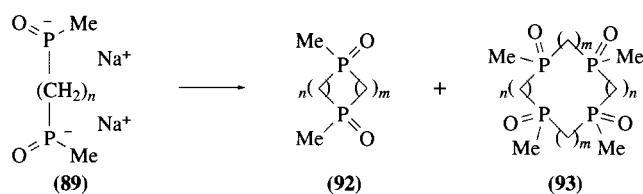
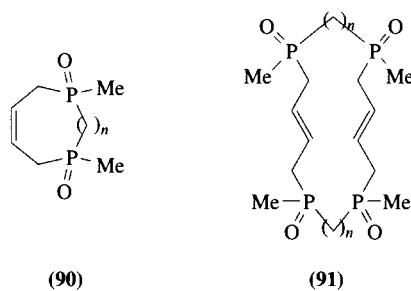
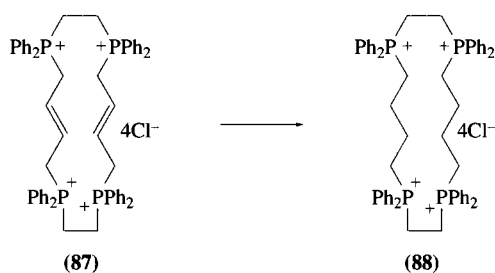
The bis(tertiary phosphine) (**85**) has been synthesized in 35% yield by treatment of dilithium methylenebis(phenylphosphide) with 1,4-dichlorobutane: a single diastereomer was observed in the ³¹P NMR spectrum of (**85**) <86CB2832>. Similar reactions between dilithium 1,2-ethylene- and 1,3-propylene-bis(phenylphosphide) and the appropriate α,ω -dihaloalkane yielded (**86**) as a mixture of two diastereomers <87PS(30)389>.

An 80% yield of (**87**) was obtained by the condensation of 1,2-ethylenebis(diphenylphosphine) with *cis*- or *trans*-1,4-dichlorobut-2-ene <87TL1259>. Catalytic hydrogenation of (**87**) over Raney



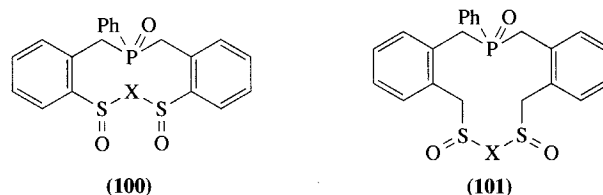
nickel afforded the saturated macrocycle (88). Treatment of the salts (89; $n = 2, 3$) with the same alkylating agent under high-dilution conditions gave a mixture of (90; $n = 2, 3$) and (91; $n = 2, 3$), which were reduced to the corresponding saturated 1,4-butylene compounds $\langle 88\text{TL6247, 93BSF647} \rangle$. The salts (89; $n = 2, 3$) react with the appropriate α, ω -dibromoalkanes to give the saturated rings (92; $n, m = 2, 3$) and (93; $n, m = 2, 3$). Following similar strategies, 1,2-bis(bromomethyl)benzene gave with (89; $n = 2, 3$) the 1,2-xylidyl compounds (94; $n = 2, 3$) $\langle 93\text{PS}(78)\text{I19} \rangle$. The diastereomers of (94; $n = 2, 3$) were separated by chromatography; (94; $n = 2$) was reduced with LAH/CeCl₃ to the bis(tertiary phosphine) (95).

In related work, the macrocyclic bis(phosphonium) salts (96)–(98) were prepared in 16–40% yield $\langle 84\text{NJC191} \rangle$. Numerous macrocyclic poly(phosphonium) salts have been synthesized in remarkably high yields in similar condensations $\langle 75\text{MI 934-01} \rangle$. Alkaline hydrolysis of (96) afforded the *cis* and *trans* diastereomers of the corresponding bis(phosphine oxide), which were separated by chromatography, individually reduced with hexachlorodisilane to the corresponding bis(tertiary phosphines), and reoxidized with methyl iodide. The reaction of 1,4-bis(diphenylphosphino)butane with Me₂S · BH₃/I₂ in benzene affords the boronium iodide (99) in 74% yield $\langle 85\text{ICA293} \rangle$.

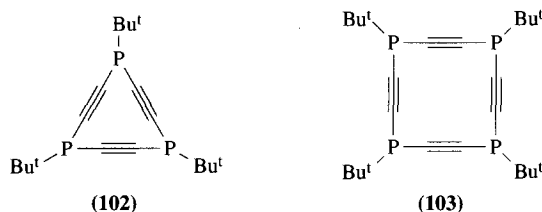


The two families of macrocyclic phosphine oxide disulfoxides (**100**; $X = (CH_2)_{2-4}$, 1,2-xylyl, 1,3-xylyl) and (**101**; $X = (CH_2)_{3-5}$, 1,2-xylyl, 1,3-xylyl) have been prepared stereoselectively for comparisons of three-point binding abilities with monoalkylammonium ions [92TL2107, 93PAC461, 93JA7900]. Compound (**101**; $X = 1,2\text{-xylyl}$) also binds halide ions [94JA4069].

The nine- and 12-membered tri- and tetraphosphapericyclines (**102**) and (**103**) were obtained in low yields in three steps from *t*-butylmagnesium chloride and trichlorophosphine [90JA7823]. Only

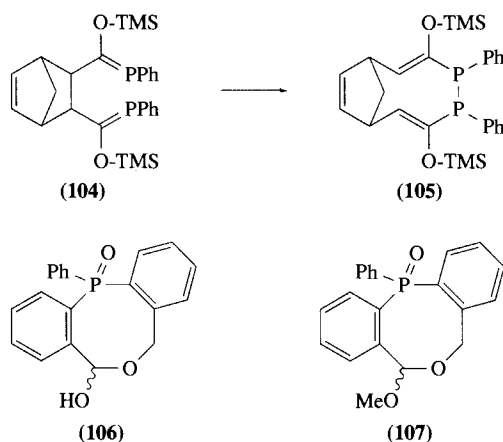


the *cis,trans* diastereomer of **(102)** was isolated. No evidence of equilibration of the two possible diastereomers of **(102)** was observed on the ^{31}P NMR time scale up to 50°C . For **(103)**, although the four possible stereoisomers were present in the crude reaction mixture, the all-*trans* isomer was isolated by fractional crystallization. The molecular structures of *cis,trans*-**(102)** and all-*trans*-**(103)** were determined by x-ray crystallography.



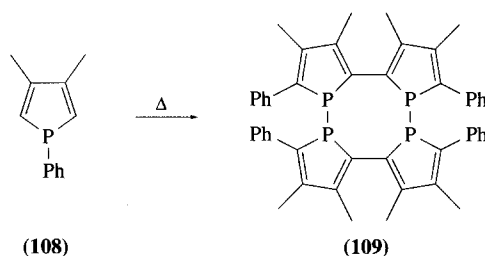
Ring enlargement by the hetero-Cope-rearrangement of **(104)** afforded **(105)** in 82% yield <84ZAAC(510)123>. The compound **(104)** was prepared in two steps from norbornene dicarboxylic dichloride and phenylbis(trimethylsilyl)phosphine.

Bis(2-formylphenyl)phenylphosphine undergoes acid-catalyzed hydration into **(106)**, which is converted into **(107)** under similar conditions in methanol <82CC1170>.

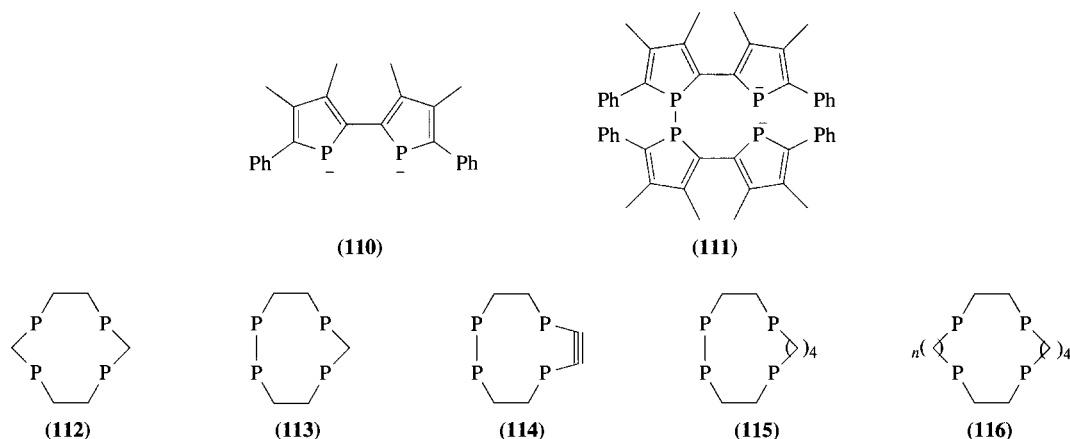


3,4-Dimethyl-1-phenylphosphole **(108)**, when heated at 160°C for 170 h, produces red crystals of **(109)** in ca. 20% yield <82JA2077>. The crystal structures of **(109)** <83JCS(D)841> and the penta-carbonylmolybdenum(0) derivative have been determined. Six-unit mixed chains containing four thiophene and two phospholyl rings have also been prepared <90AG(E)655>.

One or both of the P—P bonds in **(109)** can be cleaved by sodium naphthalenide in THF to yield

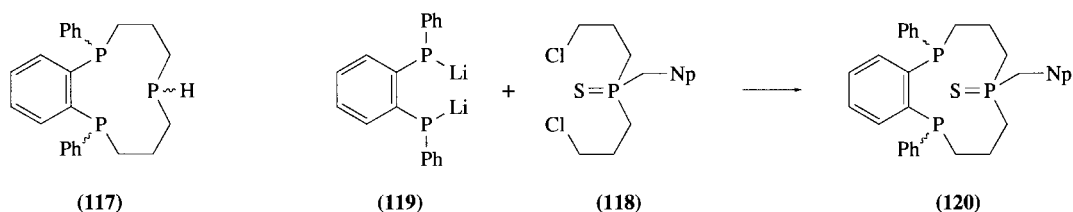


the dianions (**110**) and (**111**) that react with dibromomethane to give (**112**) or (**113**) in 45 and 80% yield, respectively (abbreviated structures are given henceforth) <94JA3306>. The reaction of (**110**) with tetrachloroethylene unexpectedly gave (**114**) in 25% yield, which was structurally characterized. The dianion (**111**) can also be converted by treatment with 1,4-dibromobutane into the 12-membered compound (**115**); the latter in turn can be used to prepare larger macrocycles, i.e. (**116**; $n = 1-4$). Since the phosphorus atoms in these macrocycles are included in phosphole rings, they invert close to room temperature, which means that the macrocycles can adapt their configurations to the stereochemical requirements of metals.



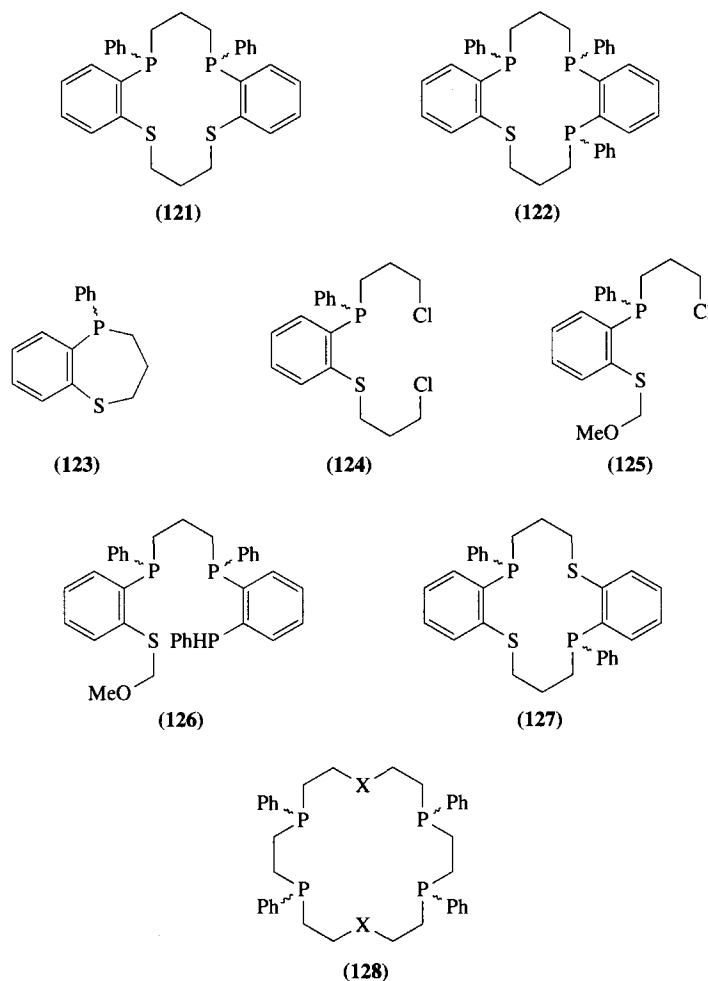
9.34.3.2 High-dilution Condensations of Organophosphides

An interesting and effective strategy was used to prepare the heterocycle (**117**) <85IC1613>. Treatment of α -naphthylmethylphosphine with two equivalents of 1-bromo-3-chloropropane afforded after sulfurization (**118**), which condensed under high-dilution conditions with the bisphosphide (**119**) to give (**120**); removal of the α -naphthylmethyl group from (**120**) with potassium naphthalenide, followed by the sulfur with LAH/TMS-Cl, afforded (**117**) as a mixture of two diastereomers. A number of transition metal complexes of (**117**) were isolated. A similar P_2N macrocycle has been reacted with $CpFe(CO)_2I$ and $Cp^*Fe(CO)_2I$ under photochemical conditions <94JOM(468)199>.



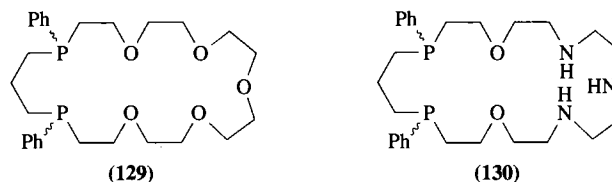
The *cis*- P_2S_2 macrocycle (**121**) was synthesized as a mixture of R^*,R^* and R^*,S^* diastereomers from 1-mercapto-2-(phenylphosphino)benzene by deprotonation and treatment with 1,3-dihalo-propanes: depending upon the base and halo-alkane employed, strapping at phosphorus or sulfur could be achieved in the first step <85JA2141>. The P_3S macrocycle (**122**), together with a trace of (**123**), was prepared by the high-dilution condensation of (**124**) with dilithium 1,2-phenylenebis(phenylphosphide). On the other hand, the conversion of (**125**) into (**126**), followed by deprotection at sulfur and ring closure with 1,3-dichloropropane, afforded the *trans*- P_2S_2 macrocycle (**127**). The structures of (R^*,S^*)-(**121**) and $[Pt\{(R^*,S^*)-(\mathbf{127})\}](PF_6)_2 \cdot C_6H_6$ were determined by x-ray crystallography. Because of the highly stereoselective formation of R^*,S^* (meso) diastereomers of products of dilithium 1,2-phenylenebis(phenylphosphide) with electrophiles, (**122**) was also considered to be predominantly of the R^*,S^* stereochemistry. In later work, the synthesis and coordination chemistry of other 14-membered P_2S_2 -macrocycles was reported <94JCS(D)3031>.

The reaction of dipotassium 1,2-ethylenebis(phenylphosphide) with bis(2-chloroethyl)amine in THF at room temperature led to the 18-membered P_4N_2 macrocycle (**128**; $X = NH$), for which four of the five possible diastereomers were isolated <83ICAL17>. The crystal structure of one of the



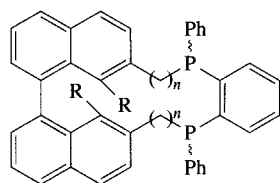
diastereomers in the complex $[\text{Ni}(\mathbf{128})](\text{BPh}_4)_2 \cdot 2\text{MeCO}$ was determined: the two nitrogen atoms of the macrocycle were not coordinated to the nickel.

The synthesis and characterization of the diastereomers (**128**; $\text{X} = \text{S}$) and several cobalt(II) and nickel(II) complexes have been described $\langle 84\text{JCS}(\text{D})575, 84\text{JCS}(\text{D})995, 85\text{JCS}(\text{D})1425 \rangle$. This work has been reviewed $\langle \text{B-90MI 934-01}, 94\text{CRV}1183, 86\text{PAC}1429 \rangle$. The high-dilution syntheses of (**129**) and (**130**) were achieved from dilithium 1,3-propylenebis(phenylphosphide) and the appropriate terminal dichloro-heterosubstituted-alkanes $\langle 86\text{JA}8302 \rangle$. The crystal structures of $(\pm)\text{-}[\text{PtCl}_2\{(\text{R}^*, \text{R}^*)\text{-}(\mathbf{129})\}]$ and one enantiomer of $(\pm)\text{-}[\text{Ni}(\text{NCS})_2\{(\text{R}^*, \text{R}^*)\text{-}(\mathbf{130})\}](\text{NCS})_2$ were determined.

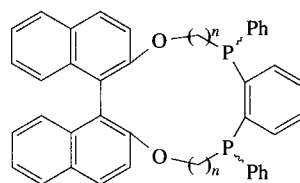


The 16- and 18-membered P_2 macrocycles (**131**; $n = 2$ and $\text{R} = \text{Me}$ or OMe ; $n = 3$, $\text{R} = \text{OMe}$) have been synthesized from the corresponding terminal *p*-toluenesulfonate esters and dilithium 1,2-phenylenebis(methylphosphide) under high-dilution conditions $\langle 92\text{CB}679 \rangle$. The compounds (**131**; $n = 3$, $\text{R} = \text{OMe}$) were obtained in 87% yield. X-ray crystal structure analyses of the C_1 and C_2 diastereomers of (**131**; $n = 2$, $\text{R} = \text{Me}$) and the C_1 diastereomer of (**131**; $n = 2$, $\text{R} = \text{OMe}$) and its nickel(II) chloride adduct were performed. In later work, the compounds (**132**; $n = 2\text{--}6$) were prepared in optically active form from (*S*)-1,1'-binaphthyl-2,2'-diol and square-planar complexes

of the type $[MCl_2(132; n = 2-5)]$ were isolated and characterized by NMR, CD, and selected x-ray crystal structure determinations (94HCA409, 94CB1411, 94TA189).

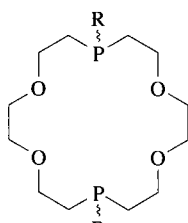


(131)

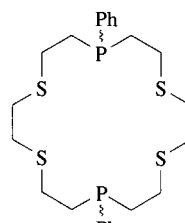


(132)

The phosphino-crown ethers and thioethers (133; R = Bn, *c*-C₆H₁₁, Ph) and (134) were prepared in one step from the appropriate dilithium organophosphides and 1,2-bis(2-chloroethoxy)ethane or 1,2-bis(2-chloroethylthio)ethane, respectively (92TL3621).



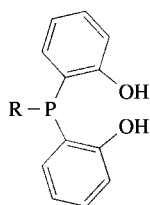
(133)



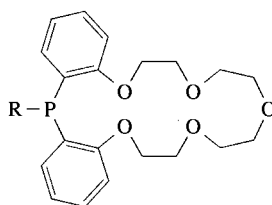
(134)

Treatment of (135; R = Bu^t, Ph) with sodium hydride followed by the appropriate ditosylate afforded the dibenzophospha-crown ethers (136; R = Bu^t, Ph) and (137; R = Ph) (83RTC326). These compounds are capable of solubilizing lithium ions in chloroform.

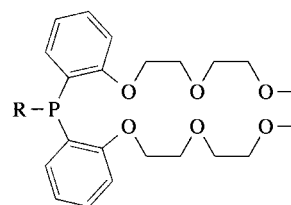
The macrocycle (139; X = P(O)OMe) was prepared in 34% yield from (138) and 1,4-dibromobutane (93JA6995). Treatment of (139; X = P(O)OMe) with TMS-I and sodium hydroxide gave (139; X = P(O)ONa) and reduction of (139; X = P(O)OMe) with LAH followed by quaternization with methyl iodide afforded the bis(dimethylphosphonium) salt (139; X = PMe₂⁺I⁻). The binding abilities of (139; X = P(O)ONa and PMe₂⁺I⁻) towards substituted naphthalenes were investigated.



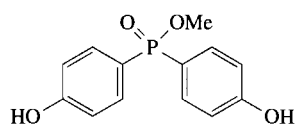
(135)



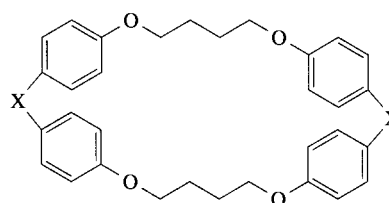
(136)



(137)



(138)

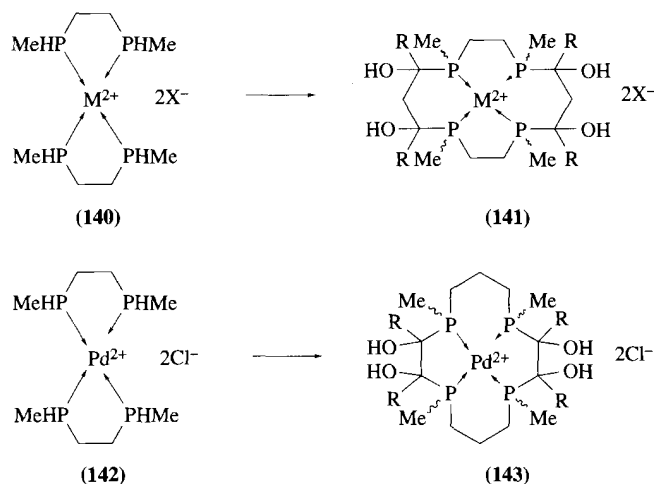


(139)

9.34.3.3 Metal Template Syntheses

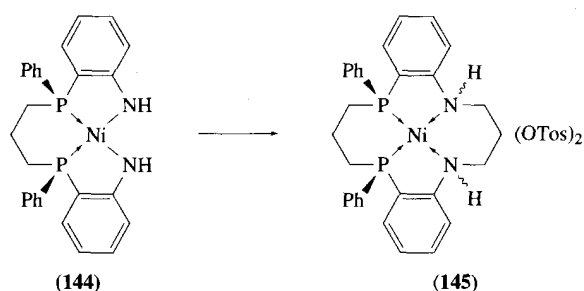
The stable complexes (140; M = Ni, X = Br and M = Pd, X = Cl) react with malondialdehyde tetramethyl acetal in the presence of acid or acetylacetone with formation of the complexes (141; M = Ni, X = Br and M = Pd, X = Cl and R = H, Me), which contain up to eight chiral centres

<83IC3624>. The reactions with malondialdehyde did indeed result in complex mixtures of diastereomers, but with acetylacetone only two diastereomers were obtained for both metal salts: the structure of the palladium compound was determined by x-ray crystallography. Interestingly, the reaction of $[\text{Pd}(\text{acac})_2]$ with 1,2-ethylenebis(methylphosphine) in the presence of hydrochloric acid gave a single diastereomer of the macrocyclic complex. The use of biacetyl in the condensation of the bis(secondary phosphine) complex was unsuccessful. On the other hand, the complex (142) reacts with biacetyl or bibenzoyl to give (143; $\text{R} = \text{Me}, \text{Ph}$), but not with acetylacetone to give the expected 16-membered macrocyclic complex. The macrocycles could not be displaced from the palladium complexes of types (141) or (143); treatment of (141) with cyanide regenerated the bis(secondary phosphine) and (143) did not react under the conditions tried.



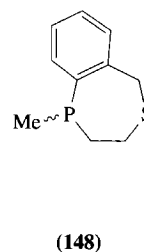
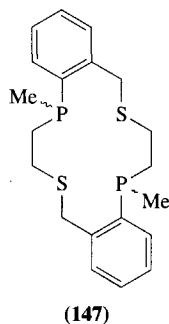
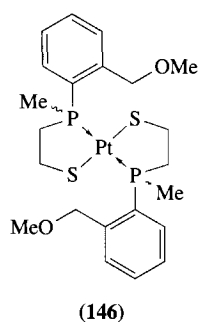
In subsequent work, in order to reduce the number of product diastereomers from eight to six, a strategy was adopted in which appropriate tertiary phosphine complexes of nickel-, palladium-, and platinum-containing terminal carbonyl groups (protected as their ketals) were reacted with chelating bis(secondary phosphines): the addition of acid-generated carbonyl groups that underwent cyclizations in the usual way to give macrocyclic tetra(tertiary phosphine) complexes. As before, however, the macrocycles could not be liberated from the metals <84IC3304>.

The cyclic alkylation of the amido complex (144) of R^*,S^* stereochemistry with the 1,3-propylenebis(*p*-toluenesulphonate) gave the corresponding R^*,S^* diastereomer of the complex (145), from which the macrocycle was liberated with aqueous cyanide <85CC439>. The structure of (144) and the free macrocycle were determined. Interestingly, the R^*,R^* form of (144) could not be prepared.

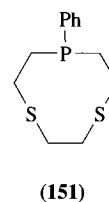
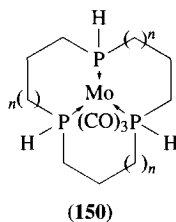
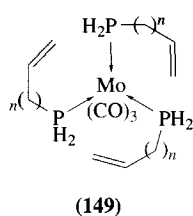


Treatment of the complex (146), which was isolated as a mixture of diastereomers with (R^*,R^*) -*cis*: (R^*,S^*) -*cis*: (R^*,R^*) -*trans*: (R^*,S^*) -*trans* = 1:1:3:4, with boron tribromide resulted in 83.5% cyclization at sulfur <92IC1411>. The intermediate complexes, after treatment with cyanide, yielded (R^*,R^*) - and (R^*,S^*) -(147) (1.5% yield), $(\pm)$ -(148) (6% yield), and $(\pm)$ -(148) $\cdot \text{BBr}_3$ (76% yield). The structures of the latter and the complex $[\text{Ni}\{(R^*,R^*)\text{-(147)}\}](\text{ClO}_4)_2 \cdot \text{Me}_2\text{CO}$ were determined by x-ray crystallography.

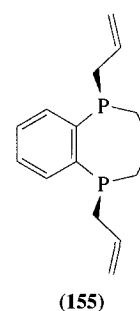
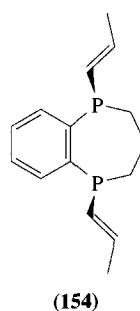
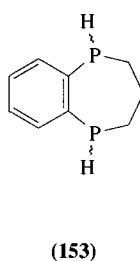
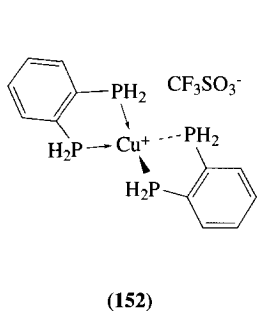
Free radical initiated cyclotrimerization of allyl- and but-2-enyl-phosphine in the complexes (149; $n = 1, 2$) yielded the macrocyclic P_3 complexes (150; $n = 1, 2$), respectively <89IC2811>. Complex (149,



$n = 1$) was characterized by x-ray crystallography. It was not possible to displace the free ligands from the metal complexes. The PS_2 macrocycle (151) was synthesized by reacting tetramethylammonium bis(2-thiolatoethyl)phenylphosphine with molybdenum hexacarbonyl and treating the resulting complex with 1,2-dichloroethane, but the ligand could not be liberated from the metal <93CC54>. Accordingly, the nine-membered ring was prepared directly in 44% yield from the phosphinothiol and 1,2-dichloroethane in the presence of caesium carbonate.



The cyclic alkylation of 1,2-phenylenebis(phosphine) in the complex (152) with 1,3-dibromopropane under basic conditions gives a variety of phosphines after the displacement from the metal, including the bis(secondary phosphine) (153) and the R^*, S^* diastereomers of the bis(tertiary phosphines) (154) and (155); the crystal structure was determined of the square-planar complex *anti*- $[\text{Ni}\{(R^*, S^*)\text{-(154)}\}_2](\text{ClO}_4)_2 \cdot \text{CH}_2\text{Cl}_2$ <95MI 934-01>.

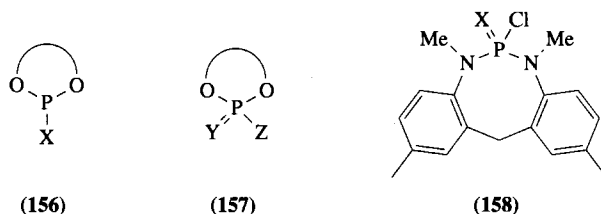


9.34.3.4 Cyclic Phosphonites and Related Compounds

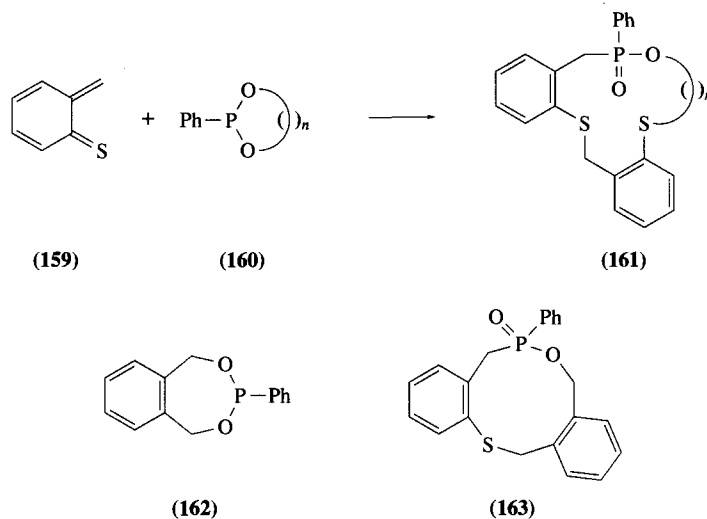
A great variety of seven- and larger-membered rings containing the phosphonyl, phosphoryl, thiophosphoryl, or iminophosphoryl groups have been prepared from the appropriate halophosphorus compounds and deprotonated diols <94CRV1183>. The types of compounds within the category can be represented by the diagrams (156) and (157).

N,N-Dimethyl-*p*-toluidine reacts with phosphoryl chlorides at 130°C to give (158; X = O, S) in

ca. 68% yields <86PS(26)185, 87JCS(P1)1547>. The crystal structures of the two compounds have been determined.



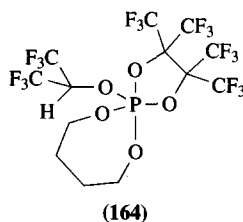
Addition of two equivalents of the valence isomer of benzothiete, (159), to the cyclic phosphonites (160; $n = 2-5$) affords the macrocycles (161; $n = 2-5$) <89TL155, 91CB377>. In the case of the 1,3,2-dioxaphosphepin (162), 10-membered (163) is formed by an intramolecular rearrangement.



Reviews are available of conformational investigations and the stereochemistry of heterocyclic phosphorus compounds <87MI 934-01> and compounds containing seven and larger rings, including cyclic phosphonites and related compounds <B-88MI 934-01>; eight-membered rings have been treated separately <92PS(68)155>.

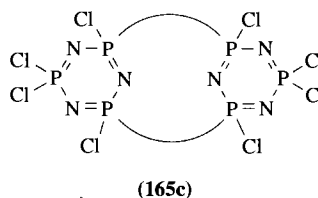
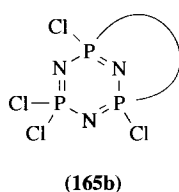
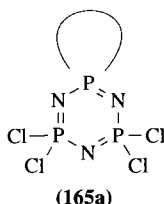
9.34.3.5 Cyclic Oxyphosphoranes

Two reviews are available of pertinent information on cyclic oxyphosphoranes containing five- to eight-membered rings, including oxygen, sulfur, and nitrogen as heteroatoms <90PS(53)437, 92MI 934-01>. The pentaoxyphosphoranes, for example (164), are useful models for intermediates in phosphate ester hydrolyses.

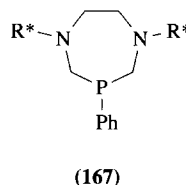
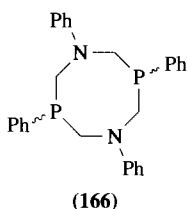


9.34.3.6 Cyclic Phosphazene Derivatives

Cyclic triphosphazatrienes condense with difunctional reagents such as linear diamines, diols, and aminoalcohols to give spirocompounds (**165a**), ansa compounds (**165b**), and macrocyclic compounds (**165c**) <90PS(47)119, 90PS(53)333, 90JMS245, 90JMS253>.

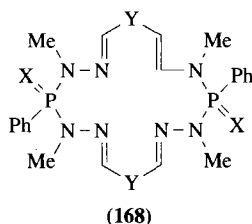


The Mannich reaction for the aminomethylation of CH-acidic compounds has provided numerous tertiary phosphine-containing macrocycles <84ZC365>. For example, the reaction of bis(hydroxymethyl)phenylphosphine with aniline or (*R*)-(+)- or (*S*)-(–)-*N,N'*-bis(1-phenyl-1-ethyl)-ethylenediamine in boiling acetonitrile or ethanol gives the 1,5-diaza-3,7-diphosphacyclooctane (**166**) (77% yield) <80TL1409> or the optically active 1,5-diaza-3-phosphacycloheptanes (**167**; *R** = (*R*)- or (*S*)-PhCHMe) (92% yield) <80TL3467>, respectively. Nickel carbonyl and molybdenum carbonyl complexes of (**166**) were reported.



9.34.3.7 Polyazaphosphorus Macrocycles

A general synthesis has been described of symmetrically and unsymmetrically functionalized 18-, 20-, 22-, and 30-membered rings containing P—N—N linkages and involving either [1 + 1], [2 + 2], or [3 + 3] condensations between phosphadihydrazides and 1,2-, 1,3-, 1,4-, or 1,11-dialdehydes <90JA5618>. The variety of rings isolated are of the type (**168**; Y = O, S) where the nature of Y determines the size of the macrocyclic rings. The reader is referred to two detailed reviews on this substantial topic <92MI 934-01, 94CRV1183>.

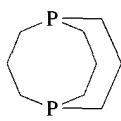


9.34.4 BICYCLIC SYSTEMS WITH BRIDGEHEAD PHOSPHORUS

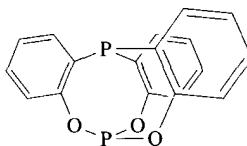
9.34.4.1 Bridgehead Tertiary Phosphines

Treatment of allylphosphine in benzene with a radical initiator, such as AIBN, gives mainly PH₃, but also (**169**) <82PS(12)227>. The bicyclic bis(tertiary phosphine) was characterized by ³¹P, ¹³C, ¹H NMR and mass spectral data.

The C₃ tertiary phosphine (**170**) was obtained in moderate yield following a one-pot procedure involving successive quenching of lithium 2-bromophenolate with phosphorus trichloride and phos-



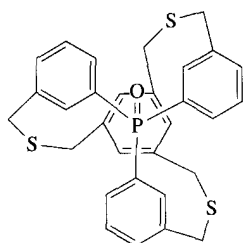
(169)



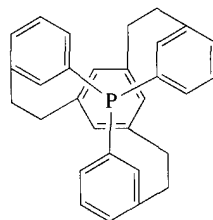
(170)

phoryl chloride under high-dilution conditions $\langle 88\text{AG(E)835} \rangle$. The barrier to racemization of the C_3 phosphine was estimated as $11.8 \text{ kcal Mol}^{-1}$ (49.4 kJ mol^{-1}) at 0°C , but diastereomers were not observed when the phosphines were reacted with a homochiral palladium(II) complex.

High-dilution coupling of 1,3,5-tris(mercaptomethyl)benzene with tris[(3-bromomethyl)phenyl]phosphine oxide afforded the thiacyclopentane (171) in 17% yield $\langle 88\text{TL5101} \rangle$. Compound (171) was converted into the C_3 phosphapha[2.2.2]cyclophane (172) in three steps, but, again, diastereomeric complexes were not observed when the latter was reacted with a homochiral palladium(II) complex.

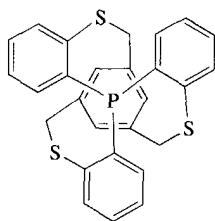


(171)

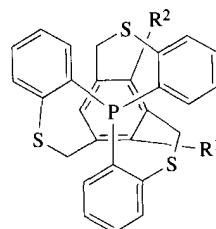


(172)

The base-promoted high-dilution condensation of tris(2-mercaptophenyl)phosphine with 1,3,5-tris(bromomethyl)benzene yielded the phosphaphane (173) in up to 15% yield $\langle 90\text{JA6406, 91JA2672} \rangle$. In the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of (173), a through-space coupling between the carbons of the basal aromatic ring and the phosphorus was observed. The crystal structure of (173) indicated that the phosphorus was pyramidalized in the direction of the basal aromatic ring, which accounted for the surprisingly large down-field shift of the phosphorus in the ^{31}P NMR spectrum. The inward direction of the lone pair in (173) contrasts with the outward direction of the lone pair in (172). Accordingly, attempted oxidation at phosphorus in (173) failed, the trisulfone being formed instead. A variable temperature NMR investigation of (173) in DMSO-d_6 indicated a lower limit to racemization of $21.98 \text{ kcal mol}^{-1}$ (92 kJ mol^{-1}). The phosphaphanes (174; $\text{R}^1 = \text{NO}_2$, $\text{R}^2 = \text{H, Br, NO}_2$) were prepared similarly $\langle 93\text{JOC3502} \rangle$; the nitro compound was reduced with titanium(III) chloride to the amine. The crystal structures of (174; $\text{R}^1 = \text{NO}_2$, NH_2 , $\text{R}^2 = \text{H}$) were determined. The enantiomers of (174; $\text{R}^1 = \text{NO}_2$, $\text{R}^2 = \text{H}$) were separated by chiral HPLC and were found to have considerable stability, i.e. $E_{\text{inv}} > 25.99 \text{ kcal mol}^{-1}$ ($108.8 \text{ kJ mol}^{-1}$).



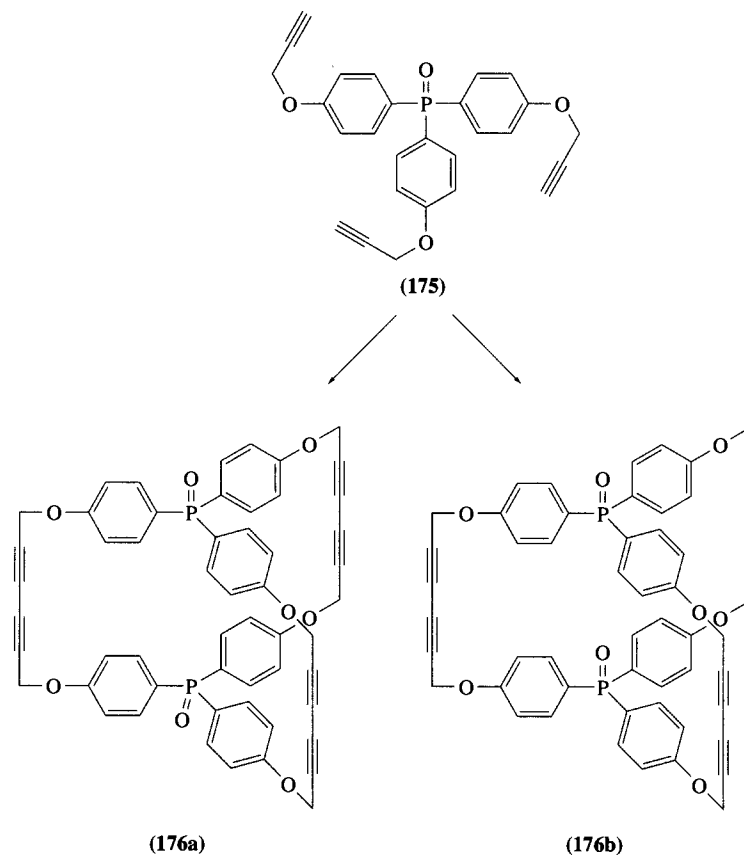
(173)



(174)

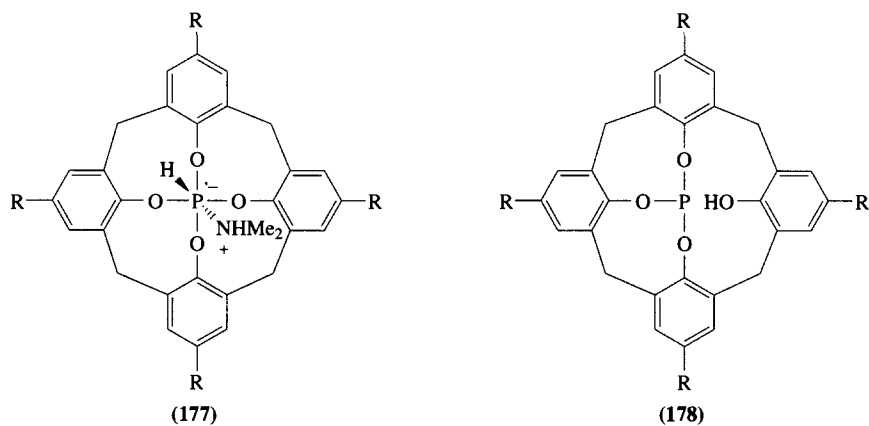
The phosphine oxide (175) reacts with copper(II) acetate in pyridine at 60°C (2 h) under high-dilution conditions to give the macrobicyclic bis(phosphine oxides) (176a) and (176b) in 14% yield and 7% yields, respectively $\langle 89\text{JA9132, 90JA8931} \rangle$. Catalytic hydrogenation of (176a) and (176b) over 5% Pd/CaCO_3 afforded the corresponding compounds with saturated bridges. X-ray crystal structure determinations on (176a), (176b), and the *endo-exo* diastereomer of the saturated compound, confirmed the dispositions of the $\text{P}=\text{O}$ groups. Whereas (176a) and (176b) displayed pronounced helicity, the saturated form was distorted only slightly from C_{3v} symmetry. The host-

guest behavior of the diastereomers of the four macrobicycles with substituted phenols and dichlorodiphenyltin was investigated by ^1H and ^{31}P NMR spectroscopy and association constants were determined.



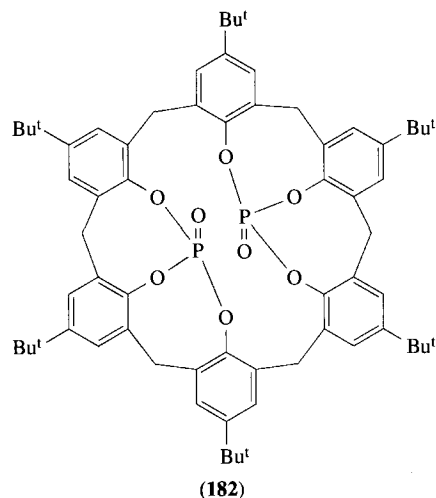
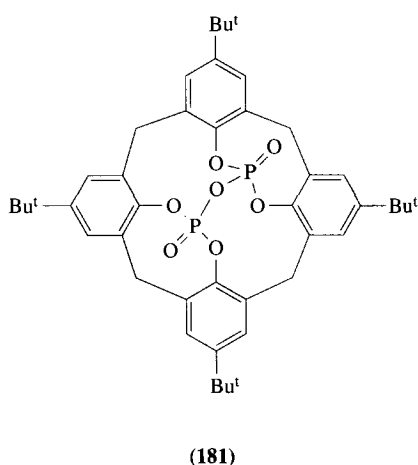
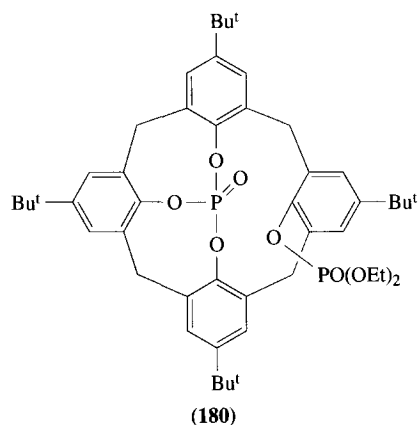
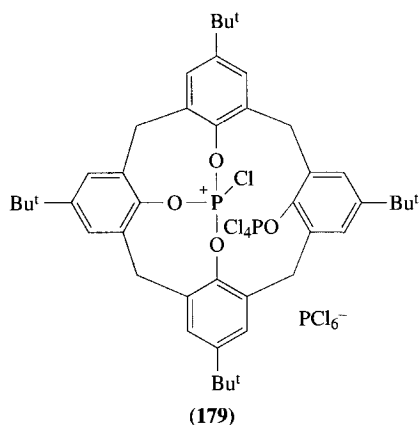
9.34.4.2 Calixarene Phosphites and Related Compounds

The reaction of calix[4]arene or its *p-t*-butyl derivative with tris(dimethylamino)phosphine gives the basket zwitterionic six-coordinate phosphorus derivatives (**177**; $\text{R} = \text{H}$, Bu^t) <90JA9422, 91CC562, 93PS(75)253, 94IC2657>. The attempted deprotonation at phosphorus with *n*-butyllithium to give the basket aminophosphorane with four basal P—O bonds was unsuccessful (the NH proton was removed), but trifluoroacetic acid or heat yielded the bicyclic phosphite (**178**; $\text{R} = \text{H}$, Bu^t). The crystal structures of (**177**; $\text{R} = \text{H}$) and the oxidized form of (**178**; $\text{R} = \text{H}$) were determined. The P—H atom in (**177**; $\text{R} = \text{Bu}^t$) is inside the basket.



Treatment of *p-t*-butylcalix[4]arene with phosphorus pentachloride afforded (179), which underwent ethanolysis to give (180); the crystal structure of (180) was determined (93PS(84)217).

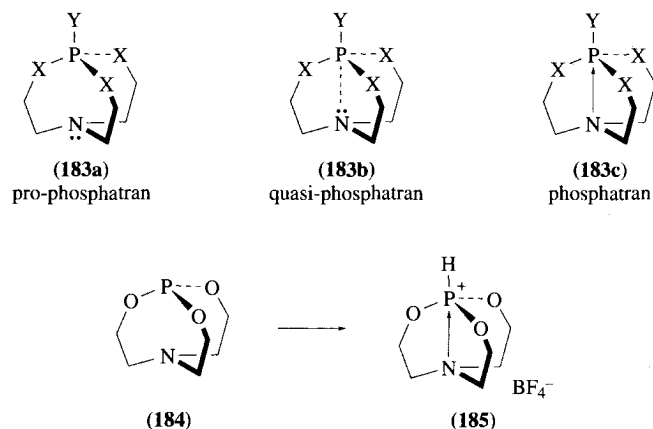
Vacuum pyrolysis of the dialkylphosphate esters of *p-t*-butylcalix[4]arene and *p-t*-butylcalix[6]arene resulted in the phosphorus polybridged compounds (181) and (182), which displayed dynamic processes (93CC13). The structure of (182) was determined by x-ray crystallography. Related compounds having a phosphorus atom in the bridgehead position have also been prepared (92PS(71)7).



9.34.4.3 Phosphatranes and Related Compounds

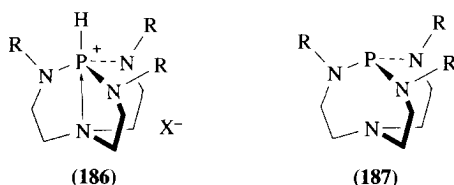
These compounds, which are conveniently known by their trivial names as indicated for the structures (183a)–(183c), have unusual basicities and reactivities because of the various degrees of delocalization of the bridgehead nitrogen lone pair into the three-centre, four-electron bond systems along the molecular axes in each case (93ACR483). The unusual basicity of the phosphorus in a phosphatrane was indicated by the attempted alkylation of the unstable phosphite (184) with trimethyl- or triethyloxonium tetrafluoroborate, which gave (185); the proton originated from the reaction of the oxonium salt with unreacted triethanolamine in the reaction mixture (77JA6607, 86JOC4287). It was not found possible to deprotonate (185) with sodium methoxide or 1,8-bis(dimethylamino)naphthalene.

Boron trifluoride, Et_3Si^+ , or a proton binds with the phosphate analogue of (184) to form the trigonal bipyramidal transannulated phosphatrane having a P—O—B , P—O—Si , or P—O—H

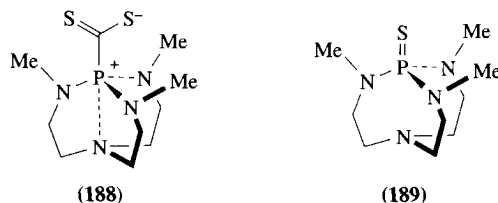


bond, respectively <85JA7084, 90PS(49/50)163, 86JA4918>. The phosphorus sulfide of (184) behaves similarly towards these reagents.

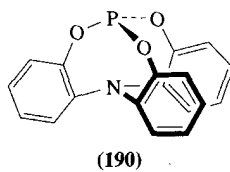
The compounds (186; R = H, Me, Bn and X = Cl) were prepared in almost quantitative yields when chlorobis(dimethylamino)phosphine was reacted with the appropriate tris(2-aminoethyl)amine in the presence of triethylamine for 1 h at room temperature <89JA3478, 91ZAAC(605)163>. The compound (186; R = H, X = OTf) was prepared in 99% yield by reacting *tris*(dimethylamino)phosphine, tris(2-aminoethyl)amine, and triflic acid in dichloromethane for 15 min at room temperature. The salts (186; R = H, Me, Bn and X = Cl) can be deprotonated with potassium *t*-butoxide to the neutral proazaphosphatranes (187; R = H, Me, Bn), which are ca. 10^7 times more basic than any other known phosphine derivative due to the stability of the transannulated salts (186; R = H, Me, Bn) <90JA9421>. The compound (187; R = H) polymerizes on attempted isolation, but (187; R = Me, Bn) are stable sublimable solids. The syntheses and crystal structure determinations of a variety of *P*-oxidized prophosphatranes and quasiphosphatranes have been performed <89PS(41)21, 89ZAAC(578)75, 90IC2214, 92JA3129>.



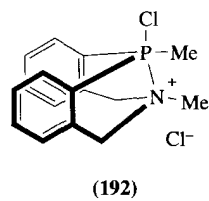
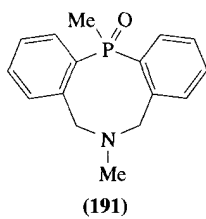
The variable basicity of (187; R = Me) due to the flexible transannular bond is believed to play an important role in the superior catalytic activity of this compound for the cyclotrimerization of phenylisocyanate <93AG(E)896>. The relative stability of (188) has been attributed to its partially annulated structure (P—N 3.250 Å) <92JA3129>. The reaction of the proazaphosphatran (189) with methyl iodide gave both the annulated $\text{P}^+ \text{—S—Me}$ and open $\text{N}^+ \text{—Me}$ regioisomers <93JA1660>.



The prophosphatran (190) has been prepared by the reaction of *tris*(2-hydroxyphenyl)amine with tris(dimethylamino)phosphine <87HCA1063> or phosphorus trichloride <88POL679>. High-dilution conditions were not required for the synthesis of this air-sensitive compound by either route. The corresponding phosphate was prepared similarly from phosphorus oxychloride <87HCA1063, 88POL679>.



The dibenz[*cf*][1,5]azaphosphocine (**191**) reacts with thionyl chloride to give a solution of (**192**); the ^{31}P and ^1H NMR data for (**192**) are consistent with the transannular N—P bond <86TL5221>.



9.35

Rings containing Arsenic, Antimony, or Bismuth

MICHAEL PABEL and S. BRUCE WILD

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9.35.1 INTRODUCTION

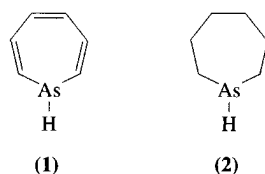
Seven-membered and larger rings containing arsenic, antimony, and bismuth range from organo-metallic rings to inorganic rings with organic substituents. Moreover, because of the breadth and rather specialized nature of the subject, little systematic chemistry has been undertaken. This review

emphasizes synthetic aspects of work on organometallic compounds of these elements in order to give an overview of the variety of interesting molecules involved. For more detailed accounts of the earlier work, however, the reader should consult Mann's *The Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony, and Bismuth* (B-70MI 935-01) and Volume 13/8 of *Methoden der Organischen Chemie (Houben-Weyl)*, which is entitled "Metallorganische Verbindungen As, Sb, Bi" (78HOU(13/8)). A review of cyclic arsenic-containing ligands has also been published (89MI 935-01). The chemistry of organic arsenic, antimony, and bismuth compounds has also been discussed in detail (B-94MI 935-01).

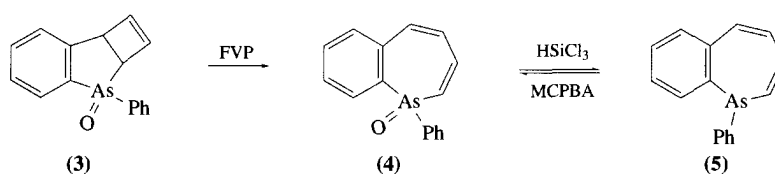
9.35.2 RINGS WITH ONE ARSENIC ATOM

9.35.2.1 Seven-membered Rings

The parent compounds 1*H*-arsepin (1) and arsepane (2) are known only as their fused benzo derivatives.

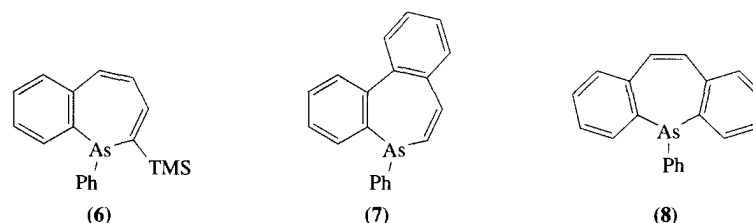


Flash vacuum pyrolysis (FVP) of dihydrocyclobut[*b*]arsindole (3), which was prepared from 1-phenylarsindole by irradiation with methyl acrylate followed by hydrolysis and oxidative decarboxylation of the adduct, affords 1-phenylbenzo[*b*]arsepin-1-oxide (4) and naphthalene in 27–40% yield depending on conditions (Scheme 1) (93H(36)2677). Reduction of the arsepin oxide with trichlorosilane gives 1-phenylbenzo[*b*]arsepin (5) in 75% yield; *m*-chloroperbenzoic acid (MCPBA) reconverts the tertiary arsine into the oxide in 80% yield. The arsine oxide (4) is stable, even when heated to 200°C for 24 h, but the arsine (5) decomposes in toluene at 80°C with $t_{1/2} \sim 10$ min according to ^1H NMR spectroscopic analysis. Compound (5) was also prepared by desilylation of (6) with tetra-*n*-butylammonium fluoride in aqueous THF; (6) was prepared from a 1,6-dibromohexatriene precursor by lithiation and addition of dichlorophenylarsine (93CC1817). The dibenzo[*b,d*]arsepin (7) was similarly prepared; the dibenzo[*b,f*]arsepin (8) was obtained from *cis*-*o,o*-dibromostilbene by lithiation and addition of dichlorophenylarsine. The dibenzoarsepins (7) and (8) are far more stable than (5) and remained unchanged when heated at 60°C for 20 h in toluene.



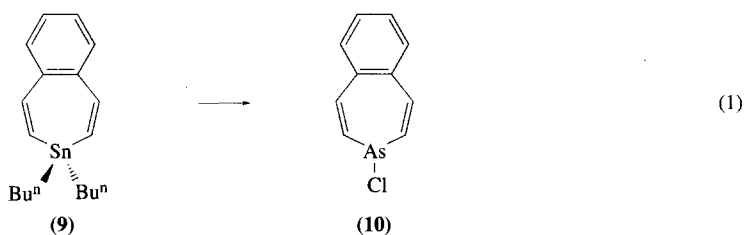
FVP = flash vacuum pyrolysis
MCPBA = *m*-chloroperbenzoic acid

Scheme 1

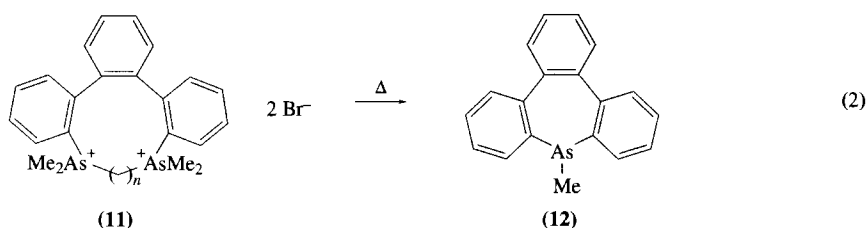


The reaction of di-*n*-butylbenzo[*d*]stannepin (9) with 1 equiv. of AsCl_3 in chloroform at 0°C affords 1-chlorobenzo[*d*]arsepin (10) and di-*n*-butyltin dichloride (Equation (1)) (92AG(E)1642). The

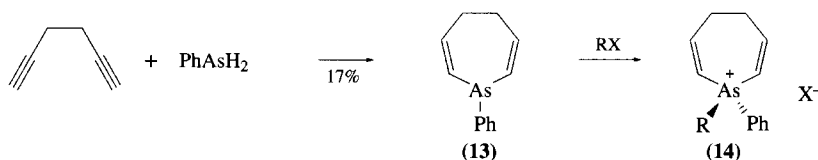
arsepine, which decomposes with $t_{1/2} = 50$ min at 25°C , was identified by the similarity of its ^1H NMR spectrum with that of the more stable stibepin (see Section 9.35.4.1).



The cyclic diarsonium dibromides (**11**; $n = 1$ or 2) undergo ring contraction when heated with formation of 9-methyltribenzo[*b,d,f*]arsepin (**12**), m.p. $159\text{--}160^{\circ}\text{C}$ (Equation (2)) <65JCS6342>. The arsepin forms an unstable monohydrated methiodide and a stable yellow methiopicate.



The AIBN-initiated cycloaddition of hexa-1,5-diyne with phenylarsine in boiling benzene for 7 h affords 1-phenyl-4,5-dihydroarsepin (**13**) (b.p. $68\text{--}70^{\circ}\text{C}/0.01$ mm Hg) (Scheme 2). The compound was characterized by IR, MS, and ^1H NMR spectroscopy, and by quaternization with methyl iodide and benzyl bromide, which gave the respective arsonium salts (**14**; $\text{R} = \text{Me}$ or Bn ; $\text{X} = \text{I}$ or Br) <73TL1455>.



Scheme 2

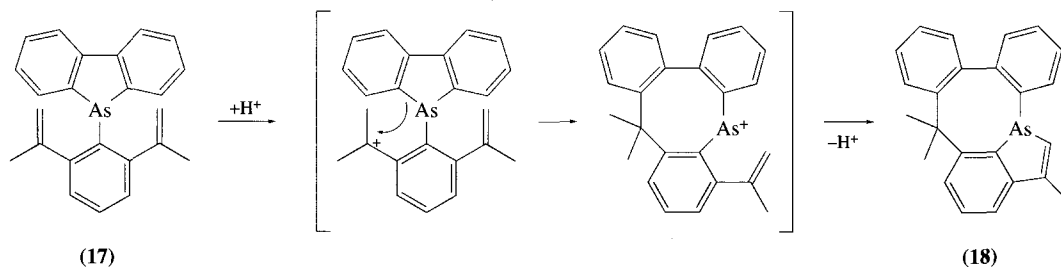
2,2'-Dilithiobibenzyl condenses with dichlorophenylarsine to give 10,11-dihydro-5-phenyl-dibenzo[*b,f*]arsepin (**15**) <53JCS1130>. There are two forms of the arsine, m.p. $59\text{--}59.5^{\circ}\text{C}$ and $78.5\text{--}79^{\circ}\text{C}$. Isomeric 5,7-dihydro-6-phenyldibenz[*c,e*]-arsepin (**16**; $\text{X} = \text{Ph}$) was prepared from 2,2'-bis(bromomethyl)biphenyl and phenylarsinebis(magnesium bromide) <50JCS1923>. The heterocyclic ring in (**16**; $\text{X} = \text{Ph}$) is much more stable than that in (**10**). The former, when boiled in hydroiodic acid for 2 h, gave the 6-iodo derivative (**16**; $\text{X} = \text{I}$); under similar conditions (**15**) rapidly breaks down with formation of bibenzyl and arsenic triiodide.



9.35.2.2 Eight-membered Rings

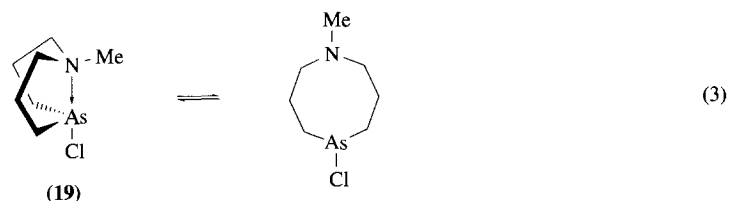
In a novel reaction, the tertiary arsine (**17**), which was prepared from 9-chloroarsafluorene and 2,6-bis(isopropenyl)phenyllithium, reacts with methanesulfonic acid in glacial acetic acid to give

(18) (Scheme 3) <90AG(E)689>. In this reaction, the initial attack of the protonated isopropenyl group takes place at the *ipso*-position of the arsafluorene unit resulting in an eight-membered ring containing an arsenium ion that then attacks the terminal carbon atom of the second isopropenyl group. A crystal structure determination on (18) revealed an almost planar arsinole unit attached to a central eight-membered ring system with a highly distorted boat conformation.



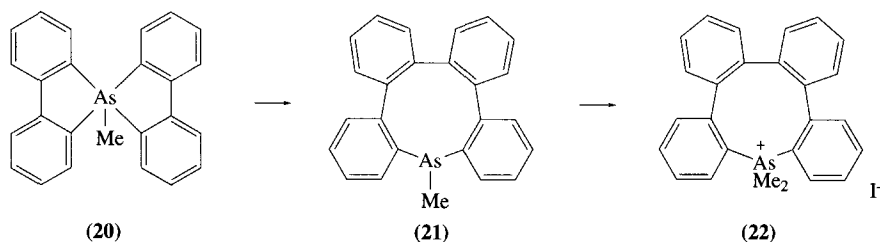
Scheme 3

The metallocane (19) (Equation (3)) has been prepared from $MeN(CH_2CH_2MgCl)_2$ and arsenic trichloride in low yield (<1%) by simultaneous addition of the two reagents to a large volume of toluene with vigorous stirring <94POL365>.



9.35.2.3 Nine-membered Rings

The thermal decomposition of methylbis(2,2'-biphenylene)arsenic(V) (20) at $250^\circ C$ produces a colorless sublimate of methyl(2,2''-o-quaterphenylene)arsine (21) in 94% yield; with methyl iodide after 2 h in the refrigerator, (21) gave the arsonium iodide (22) in 86% yield (Scheme 4) <68CB121>.

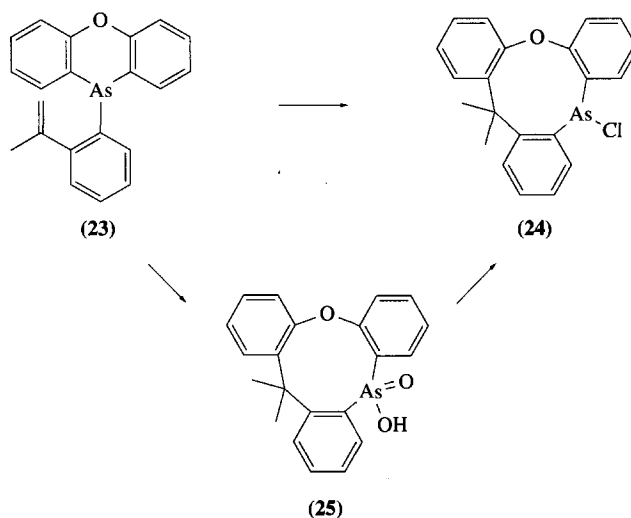


Scheme 4

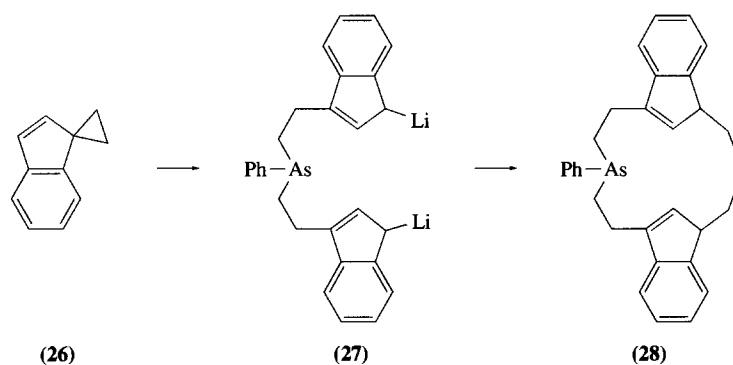
The *ipso*-attack on the activated isopropenyl group of the phenoxarsine (23) with $TiCl_4$ in cyclohexane led to (24). The same compound was obtained when the arsinic acid (25), which was generated by formic acid-catalyzed ring expansion of (23) followed by oxidative workup, was reduced with PCl_3 (Scheme 5) <90AG(E)689>.

9.35.2.4 14-membered Rings

In work directed towards the synthesis of chelating bis(indenyl) ligands containing additional tertiary arsine donors, "indenylcyclopropane" (26) was converted into the arsine (27); treatment of (27) with 1,3-dibromopropane under high-dilution conditions gave the 14-membered heterocycle (28) in 17% yield after column chromatography on silica (Scheme 6) <85CB4507>.



Scheme 5



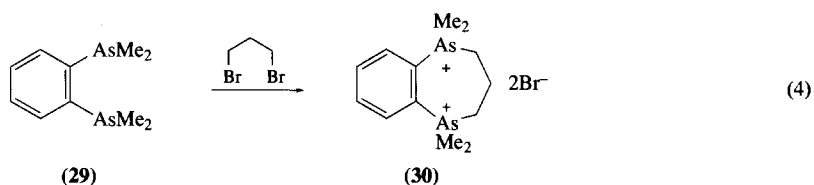
Scheme 6

9.35.3 RINGS WITH TWO OR MORE HETEROATOMS

9.35.3.1 Cyclic Quaternization of Bis(tertiary arsines)

9.35.3.1.1 Derivatives of 1,2-phenylenebis(dimethylarsine)

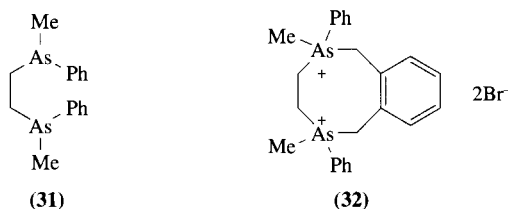
1,2-Phenylenebis(dimethylarsine) (**29**) and 1,3-dibromopropane (1 equiv.), when heated together at elevated temperatures, react with cyclic quaternization and formation of 2,3,4,5-tetrahydro-1,1,5,5-tetramethyl-5*H*-1,5-benzodiarsepinium dibromide (**30**) (Equation (4)) <50JCS682>. The thermal decomposition of the salt was not investigated.



9.35.3.1.2 Derivatives of 1,2-ethylenebis(methylphenylarsine)

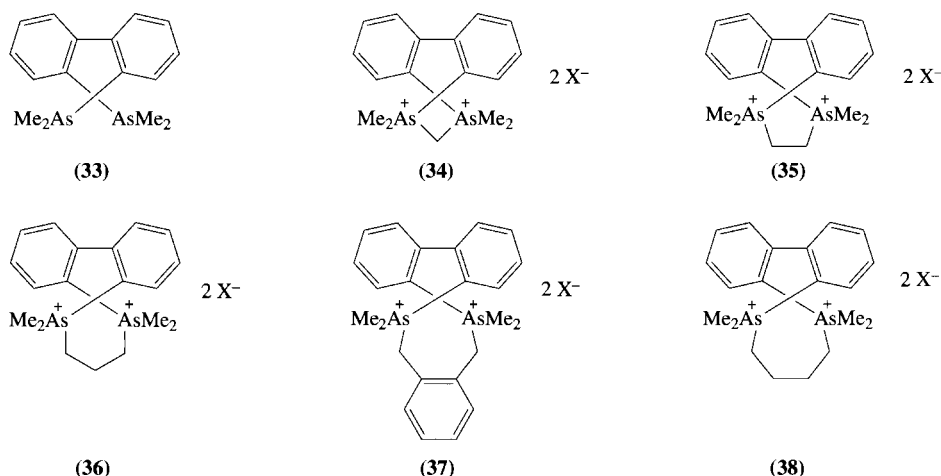
1,2-Bis(methylphenylarsino)ethane (**31**) undergoes rapid cyclic quaternization with 1,2-xylylene dibromide at 100°C to give 1,2,3,4,5,6-hexahydro-2,5-dimethyl-2,5-diphenyl-2,5-benzodiarsepinium

dibromide (**32**), as well as a yellow resinous material <55JCS401>. The products of the thermal decomposition of (**32**) under reduced pressure were not identified. Isomerism in (**31**) and (**32**) was not discussed.



9.35.3.1.3 Derivatives of 2,2'-biphenylenebis(dimethylarsine)

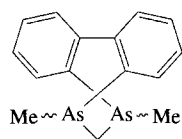
The ready quaternization of 2,2'-biphenylenebis(dimethylarsine) (**33**) with alkylene dibromides to give cyclic diarsonium bromides can be attributed to the favorable disposition of the dimethylarsino groups attached to the nonplanar biphenyl rings. Thus, when heated with methylene, ethylene, propylene, or 1,2-xylylene dibromide at 100°C for some hours, the corresponding cyclic diarsonium dibromides (**34**–**38**; X = Br) were formed from (**33**) in high yields <58JCS3838; 61JCS2762>.



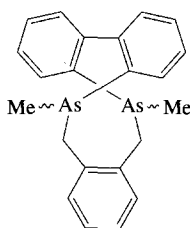
The lack of coplanarity of the biphenyl rings causes the salts to possess molecular dissymmetry. The salts were resolved with appropriate optically active acidates and subsequently reconverted into the optically active dibromides by ion exchange chromatography <63JCS2833>. The three salts (**34**)–(**36**) show an increase in optical stability as the length of the bridge increases. Thus, at 70°C the activity of an aqueous solution of (**34**) fell from $[\alpha]_D + 29$ to $+3.07$ in 2 h, whereas that of (**35**) at 100°C fell from $[\alpha]_D + 50.8$ to $+5$ in 60 h and a solution of (**36**) could be kept in a sealed tube at 150°C without perceptible change in activity. In view of these results, it is significant that only (**34**) showed an apparent biphenyl band in the UV absorption spectrum.

With aqueous silver oxide, the dibromides (**34**–**36**; X = Br) afford the hydroxides (**34**–**36**; X = OH) <61JCS2762>. The thermal decomposition of the salts proceeded in a manner markedly dependent on the length of the bridge. Thus, (**34**; X = Br) decomposes above its melting point at reduced pressure with loss of methyl bromide to give the seven-membered bis(tertiary arsine) (**39**) <58JCS3838>, which can exist as (*R*^{*}, *R*^{*}) and (*R*^{*}, *S*^{*}) diastereomers. The product gave a chelated covalent dibromopalladium(II) complex, however, which implies stereoselective formation of (*R*^{*}, *S*^{*})-(**39**) unless the (*R*^{*}, *R*^{*}) complex was inadvertently lost during workup. The salt (**34**; X = OH) decomposes similarly when heated above its melting point. Thermal decomposition of (**37**; X = Br) also yields the expected product: ten-membered (**40**). When the eight-, nine-, and ten-membered cyclic diarsonium bromides (**35**; X = Br), (**36**; X = Br), and (**37**; X = Br) were heated above their melting points, however, ring contraction occurred giving 9-methyl-9-arsafluorene (**41**) (and traces of the corresponding 9-bromo compound) and trimethylarsine and dimethylvinyl arsine, respectively. The

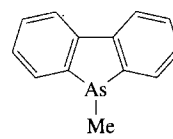
salt (38; X = Br) also underwent ring contraction to (41). The dihydroxides (35; X = OH) and (36; X = OH) behaved irregularly when heated above their melting points; (35; X = OH) decomposed smoothly into (33) and (36; X = OH) gave biphenyl as the only identifiable product.



(39)



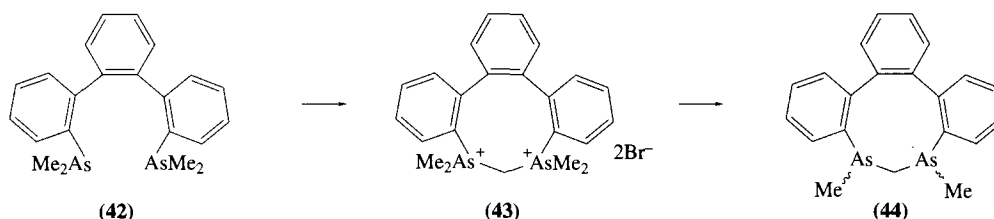
(40)



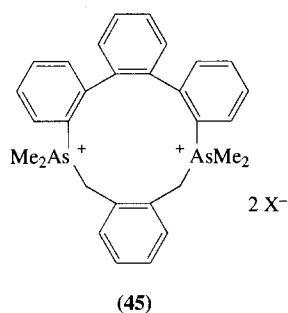
(41)

9.35.3.1.4 Derivatives of 1,2-terphenyl-2,2'-ylenebis(dimethylarsine)

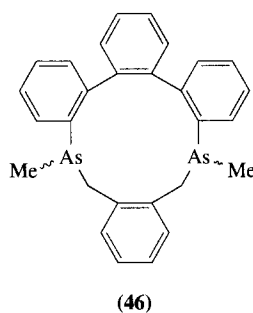
Cyclic diquaternization of 1,2-terphenyl-2,2'-ylenebis(dimethylarsine) (42) with 1 equiv. of dibromomethane (at 100°C for 8 h) gave nine-membered 10,11-dihydro-9,9,11,11-tetramethyl-9*H*-tribenzo[*d,f,h*][1,3]diarsoninium dibromide (43) (Scheme 7) <65JCS6342>, which on decomposition at 245°C (0.1 mm Hg) lost methyl bromide giving 10,11-dihydro-9,11-dimethyl-9*H*-tribenzo[*d,f,h*][1,3]diarsonin (44). Similar cyclic diquaternization of (42) with *o*-xylylene dibromide gave 12-membered (45), which thermally decomposed into (46) <65JCS6342>.



Scheme 7



(45)

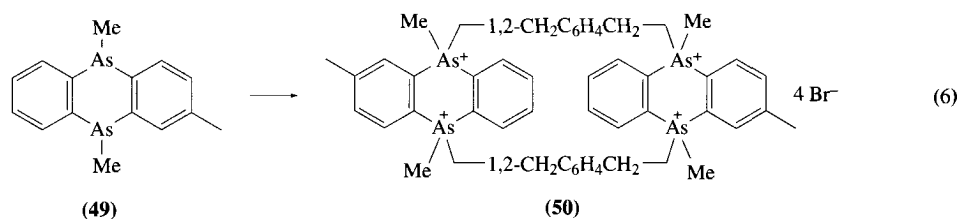
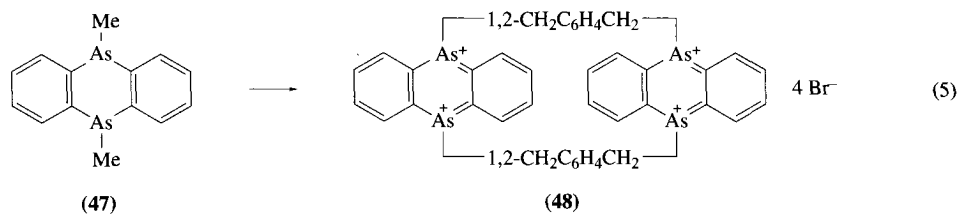


(46)

9.35.3.1.5 Derivatives of 5,10-dihydro-5,10-dimethylarsanthrene

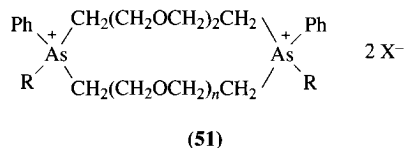
5,10-Dihydro-5,10-dimethylarsanthrene (47; X = Br) reacted with 2 equiv. of 1,2-xylylene dibromide (2 h at 160°C) with loss of methyl bromide to give the arsanthrenium tetrabromide (48) in 64% yield (Equation (5)) <55JCS411>. The corresponding tetraiodide and tetrapicrate decahydrate salts were also isolated. Calculations showed that the two parallel arsanthrene units in (48) should be ~290 pm apart and the suggestion was made that the shape and size of the cation may be associated with the stability of the colorless tetrapicrate decahydrate, which became orange upon attempted dehydration. It would be of great interest to determine the crystal and molecular structures of these unusual compounds. 5,10-Dihydro-2,5,10-trimethylarsanthrene (49) reacted with 1 equiv.

of 1,2-xylylene dibromide under milder conditions (1.5 h at 100°C) to give the regular tetraarsonium tetrabromide (**50**) (Equation (6)), which gave a cream-colored tetraiodide and a solvent-free tetrapicrate.



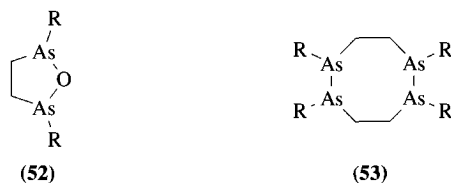
9.35.3.1.6 Derivatives of other bis(tertiary arsines)

Cyclic diquaternization of a glycol ether-based bis(tertiary arsine) with the appropriate organic dibromides produced the crown-like bis(arsonium) salts (**51**; R = Me or Et). Proton NMR data are reported for the bromide and tetraphenylborate salts <91JGU1032>.



9.35.3.2 Reductive Cyclization of 1,2-Ethylenebis(arsinic acids)

The reduction of the arsinous acid anhydride (**52**; R = Me or Ph) or the corresponding arsinic acids with 50% hypophosphorous acid (H₃PO₂) in ethanol affords the tetraarsacyclooctanes (**53**; R = Me or Ph), respectively <70ZAAC(377)278>. The molecular weights of the two colorless solids were determined in benzene with good agreement between observed and calculated values.

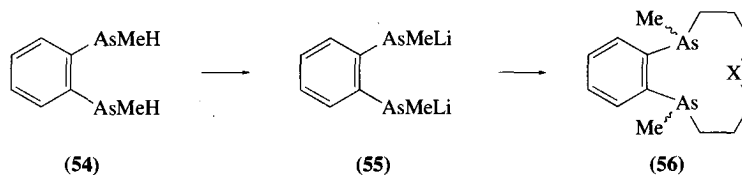


9.35.3.3 High-dilution Condensations of Arsenides

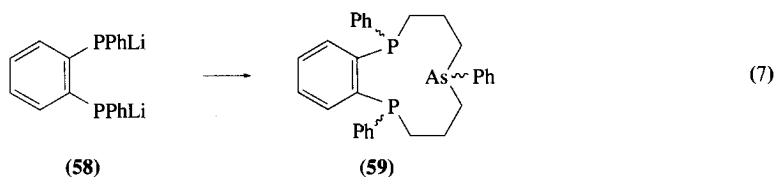
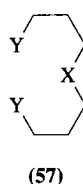
9.35.3.3.1 Derivatives of 1,2-phenylenebis(methylarsine)

Treatment of 1,2-phenylenebis(methylarsine) (**54**) with 2 equiv. of *n*-butyllithium in THF generates the bis(arsenide) (**55**) (Scheme 8), which under high-dilution conditions can be used to

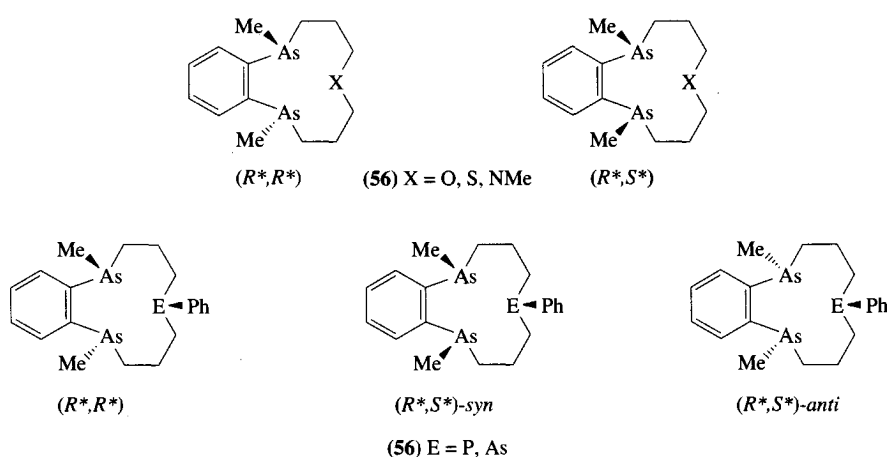
prepare the 11-membered heterocycles (**56**; X = AsPh, PPh, S, O, or NMe) by treatment with the bis(electrophiles) (**57**; X = AsPh and Y = Br, PPh and Cl, S and OMs, O and OMs, or NMe and Cl), respectively. A similar reaction between the bis(phosphide) (**58**) and the electrophile (**57**; X = AsPh, Y = Br) afforded (**59**) (Equation (7)) <80CC449, 80JA7012>.



Scheme 8



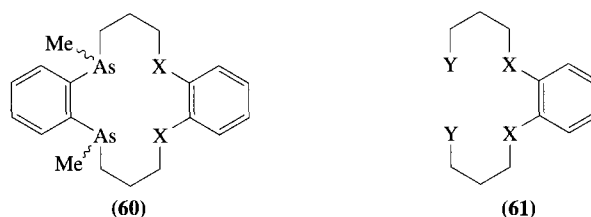
Due to the relatively high barriers to inversion of tertiary phosphines and arsines <72JA291>, compounds (**56**) and (**59**) can exist as stable diastereomers, (R^*,R^*) and (R^*,S^*) for the bis(tertiary arsines) (**56**; X = S, O, or NMe) and (R^*,R^*), (R^*,S^*)-*syn*, and (R^*,S^*)-*anti* for the heterocycles containing three chiral stereocenters (**56**; X = AsPh or PPh) and (**59**) (Figure 1).

Figure 1 Diastereomers of (**56**).

An interesting feature of the reactions of the bis(arsenide) (**55**) and the bis(phosphide) (**58**) is the stereoselective nature of many of their reactions with bis(electrophiles). Thus, except for (**56**; X = S), where a trace of the (R^*,R^*) diastereomer was evident, the reactions in each case afforded the

(R^*,S^*) diastereomers with complete selectivity. Moreover, for the compounds containing three chiral stereocenters there was considerable stereoselectivity in favor of the (R^*,S^*)-*anti* diastereomer. For (**56**; X = AsPh), (R^*,S^*)-*syn*:(R^*,S^*)-*anti* = 5:4; for (**56**; X = PPh) and for (**59**), the corresponding ratios were 5:1 and 100:1 (no detection of minor diastereomer by NMR spectroscopy), respectively. The chelating (R^*,S^*) diastereomers in each case were identified by preparing molybdenum(0) carbonyl derivatives. The (R^*,S^*)-*syn* diastereomers of the ligands gave fully coordinated *fac*-tricarbonylmolybdenum complexes and the (R^*,S^*)-*anti* forms the As_2 - or P_2 -chelated *cis*-tetracarbonylmolybdenum complexes.

Along similar lines, several 14-membered *cis*- As_2X_2 macrocycles (**60**; X = O, S, or AsMe) were prepared by reacting the bis(arsenide) (**55**) or the bis(phosphide) (**58**) with the bis(electrophiles) (**61**; X = O and Y = OMs, S and OMs, or AsMe and Cl) <81JOC860>. The yields of the heterocycles were consistently lower for the derivatives of (**55**) (20–40%) than for those of (**58**) (30–60%).

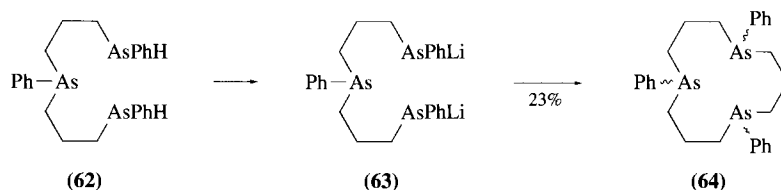


Once again, the syntheses of (**60**; X = O or S) proceeded with complete (R^*,S^*) diastereoselection at arsenic. The tetra(tertiary arsine) (**60**; X = AsMe) was isolated as a mixture of three diastereomers in which it was assumed, on the basis of the previous examples, that the incoming arsenido–arsenic stereocenters adopted the (R^*,S^*) relative configuration and the electrophile–arsenic stereocenters arbitrary configurations.

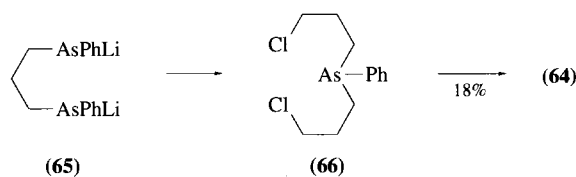
When the bis(phosphide) (**58**) was reacted with the arsenic substrate (**61**; X = AsMe and Y = Cl), the compound (**60**; X = PPh) was isolated as a mixture of diastereomers each of which had the (R^*,S^*) relative configuration at phosphorus. Chromatographic separation of the mixture followed by fractional crystallization of the material in the major fraction gave a small quantity of a single diastereomer, m.p. 138.5–139.5°C, in which the arsenic–methyl groups were believed to be *trans* to one another.

9.35.3.3.2 Derivatives of bis(3-phenylarsinopropyl)phenylarsine

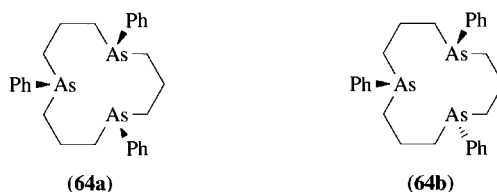
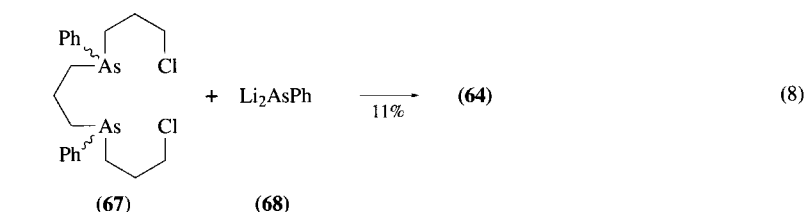
By application of the dilution principle, a series of potentially chelating heterocyclic tertiary arsines containing three, four, and six arsenic donors has been synthesized from bis(3-phenylarsinopropyl)phenylarsine (**62**) and related compounds <81AG(E)118, 85CB2692>. Thus, treatment of (**62**) with 2 equiv. of *n*-butyllithium gave (**63**), which with 1,3-dichloropropane gave the tri(tertiary arsine) (**64**) (Scheme 9). Compound (**64**) was also obtained in lower but significant yields from lithium 1,3-propylenebis(phenylarsenide) (**65**) and bis(3-chloropropyl)phenylarsine (**66**) (Scheme 10) and from the bis(3-chloropropyl)bis(tertiary arsine) (**67**) with dilithium phenylarsenide (**68**) (Equation (8)). The ^{13}C NMR spectrum of crude (**64**) indicated the presence of the two possible diastereomers (**64a**) and (**64b**), which, however, defied separation by column chromatography.



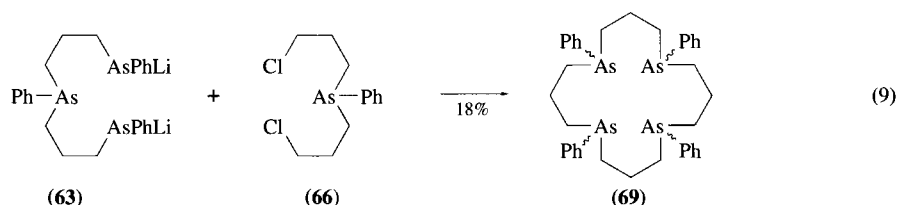
Scheme 9



Scheme 10



Condensation of (63) with (66) afforded the 16-membered tetra(tertiary arsine) (69) (Equation (9)). From the crude product, a crystalline fraction having m.p. 106.5°C was isolated. A detailed NMR investigation of this fraction, however, indicated that it consisted of a mixture of two of the four possible diastereomers of (69).

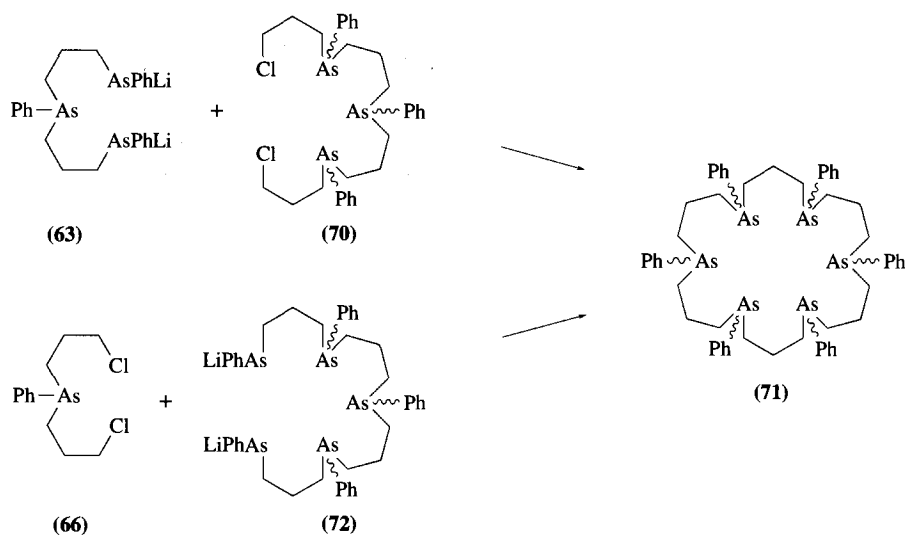


As a final accomplishment, the reaction between (63) and the bis(electrophile) (70) afforded the 24-membered hexa(tertiary arsine) (71) in 15% yield. A 6% yield of (71) resulted from the reverse condensation, that is, the reaction of (66) with the bis(arsenide) (72) (Scheme 11). The product was isolated by column chromatography and characterized by elemental analysis and MS. The ease with which the heterocycles (64) and (69) and (71) can be purified by column chromatography is an important physical property that distinguishes them from similar tertiary phosphines and opens up the possibility for the complete separation of diastereomers.

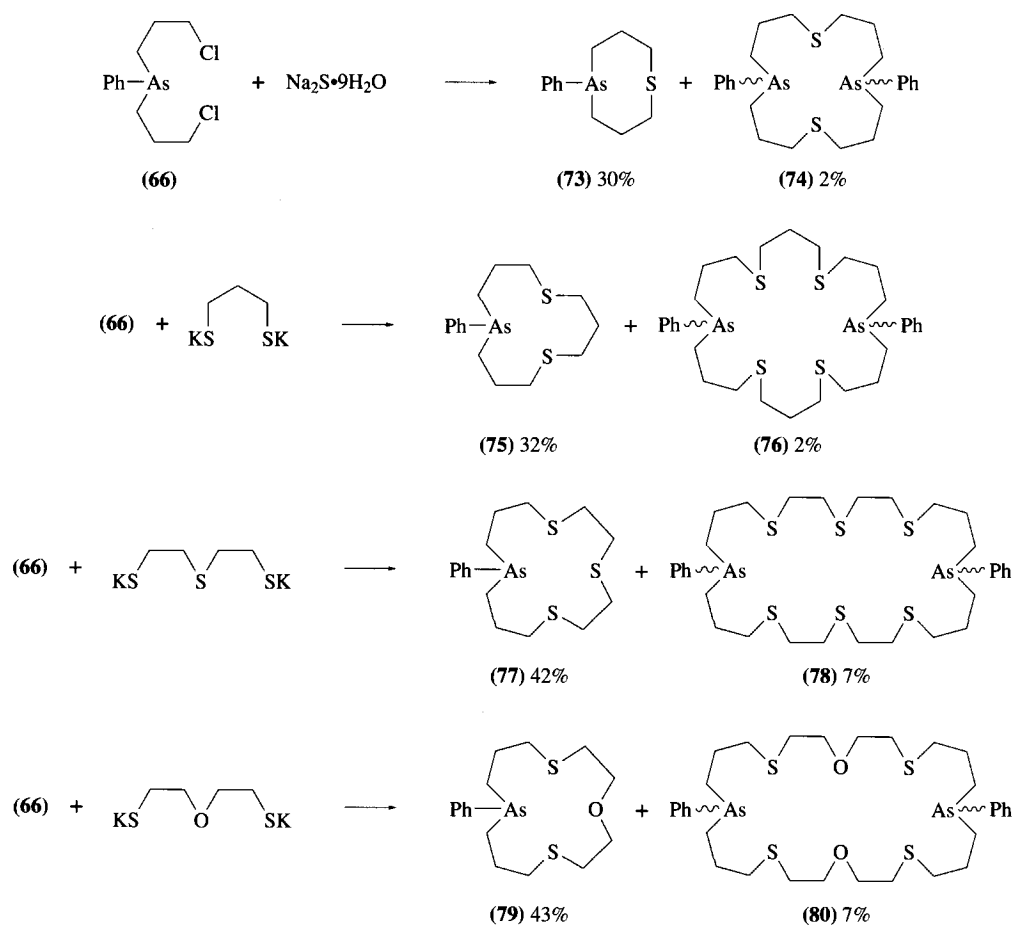
9.35.3.4 High-dilution Condensations of Sulfides

In seeking to produce stable iron(0) complexes for the activation of arenes, a variety of interesting arsenic-sulfur heterocycles has been synthesized. Thus, with use of bis(3-chloropropyl)phenylarsine (66) as the electrophile, the potentially chelating macrocycles (73)–(80) were prepared under high-dilution conditions in ethanol at 70°C from sulfide or various thiolates (Scheme 12) <81TL5035, 85CB2703>. The products were purified on alumina columns with use of benzene-diethyl ether as eluant. Except for crystalline (75), (77), and (78), the products were oils.

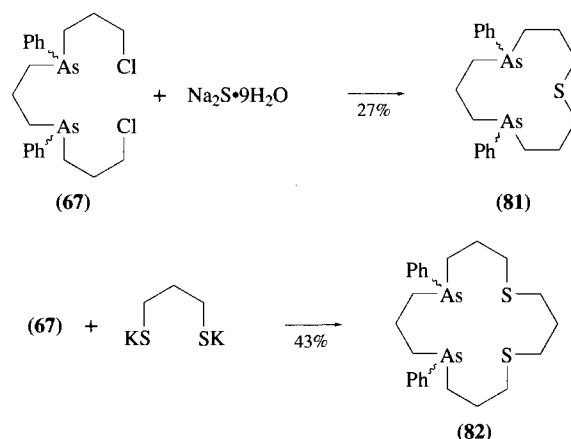
Under similar conditions, (67) afforded (81) and (82) with the appropriate substrates (Scheme 13) and (70) gave (83) with sodium sulfide (Equation (10)). Detailed analysis of the ¹³C NMR spectrum of (82) indicated an equimolar mixture of (*R**,*R**) and (*R**,*S**) diastereomers.



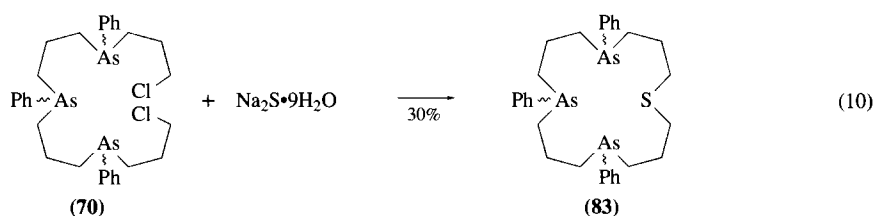
Scheme 11



Scheme 12

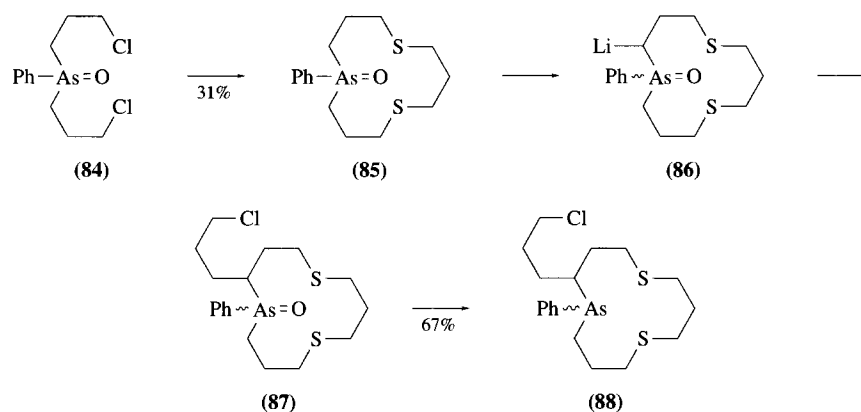


Scheme 13



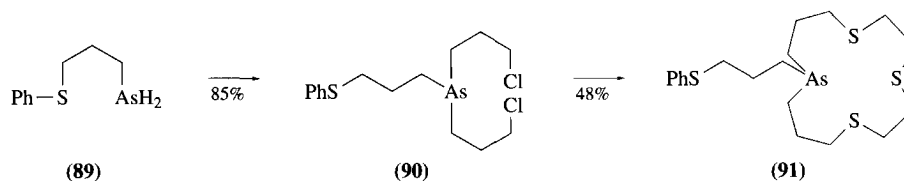
The titanium(IV) chloride adducts of (75) and (79), after reduction with diethylaluminum chloride, catalyzed the dimerization of isoprene and the trimerization of butadiene as effectively as other η^5 -cyclopentadienyl-based tertiary arsine ligands [84TL1971].

Interesting chemistry has been observed in the process of attaching pendant donors and propylene chloride substituents to arsenic-sulfur heterocycles [85CB2714]. The arsine oxide (84) was converted into the heterocycle (85) by reaction with 1,3-propane dithiol in the presence of potassium hydroxide. Deprotonation of this compound with LDA at -50°C to -35°C afforded the 2-lithio intermediate (86), which with 1 equiv. of 1-chloro-3-iodopropane over 12 h at -25°C , gave (87). Reduction of (87) in chloroform with sulfur dioxide gave (88) as a colorless oil (Scheme 14).



Scheme 14

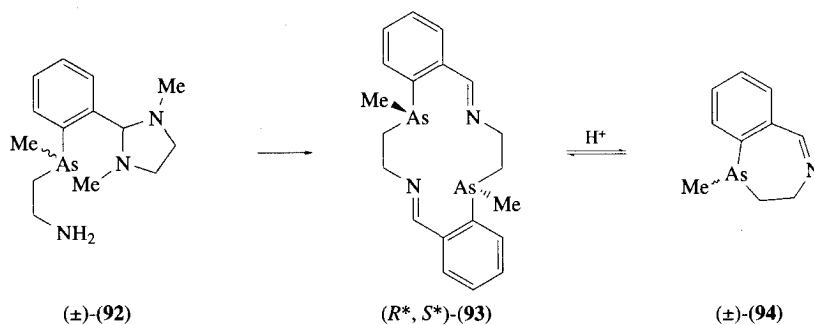
The primary arsine (89) was synthesized from sodium arsenide (NaAsH_2) and (3-chloropropyl)phenyl sulfide in liquid ammonia. Without isolation, (89) was converted into the bis(3-chloropropyl)arsine (90) and subsequently into the 14-membered crystalline heterocycle (91) under the usual conditions with bis(2-thioethyl) sulfide (Scheme 15).



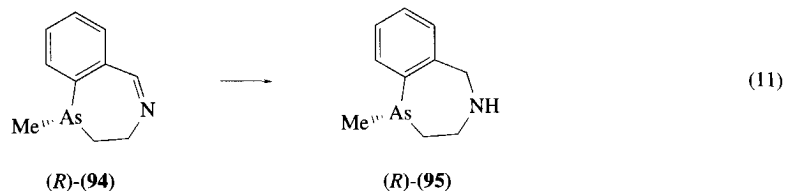
Scheme 15

9.35.3.5 Schiff-base Condensations

When the imidazolidine ($\pm$)-(92) is heated in vacuo at 80°C, it is transformed quantitatively into the achiral 14-membered *trans*-As₂N₂ macrocycle (*R*^{*},*S*^{*})-(93) (Scheme 16); the macrocycle, in chloroform in the presence of a trace of acid, rearranges quantitatively into ($\pm$)-2,3-dihydro-1-methyl-4,1-benzarsazepine (94), which cannot be isolated because of quantitative reformation of (*R*^{*},*S*^{*})-(93) upon removal of solvent [88JA4346]. Nevertheless, treatment of a solution of (94) in diethyl ether with LAH afforded the corresponding tetrahydroarsazepine (95), which was isolated as a colorless oil having b.p. 115°C (0.04 mm Hg). The acid-catalyzed monomer-dimer rearrangement is believed to proceed by a stepwise mechanism involving a 1,3-diazetidene intermediate, as has been proposed for the dimerization of 3,4-dihydro-5*H*-2-benzazepine [69JA4941]. Analogous 14-membered macrocycles containing oxygen [70ICA226] and sulfur [85ICAL5, 87IC2963] in place of the AsMe group in (94) behave similarly with respect to the monomer-dimer rearrangement; only 3,4-dihydro-5*H*-2-benzazepine and 3,4-dihydro-1,4-benzoxazepine are stable enough to be isolated. The optically pure enantiomers of (93), (94), and (95) were also isolated. Unlike (*R*^{*},*R*^{*})-(93), which spontaneously transforms into less-soluble (*R*^{*},*S*^{*})-(93), (+)- and (−)-(93) are individually stable and rearrange into the optically pure enantiomers of (94) in the presence of acid. The enantiomers of (93) were also prepared with complete stereoselectivity in an asymmetric synthesis involving (*R*^{*},*S*^{*})-(93) and an optically active palladium(II) complex containing *ortho*-metallated (*R*)-[1-(dimethylamino)ethyl]naphthalene in the presence of acid.



Scheme 16



9.35.3.6 Metal-template Dimerizations

The palladium(II) template dimerization of the thiolato ligands in (96) with boron tribromide, which proceeds via internal nucleophilic displacements of bromide from an intermediate bis(benzyl bromide) complex, affords the 14-membered *trans*-As₂S₂ macrocycle (*R*^{*},*R*^{*})-(97) (Figure 2) as air-

stable crystals after displacement from the metal (50% yield), along with seven-membered ($\pm$)-(98) in 38% yield (87JA4321). No trace of (R^*,S^*)-(97) was detected in the product, although when a solution of (R^*,R^*)-(97) was exposed to aqueous hydrochloric acid, less-soluble (R^*,S^*)-(97) crystallized in quantitative yield in a typical second-order asymmetric transformation owing to epimerization at arsenic under the haloacid conditions. Similar cyclizations of the optically pure forms of (96) afforded the optically pure enantiomers of (97) in 66% yield, $[\alpha]_D \pm 180$ (CH_2Cl_2), together with a 13% yield of the corresponding enantiomers of ($\pm$)-(98), $[\alpha]_D \pm 32.5$ (CH_2Cl_2). The stereoselectivities and yields of the various forms of the 7- and 14-membered rings were rationalized in terms of the relative stabilities of intermediate and product complexes.

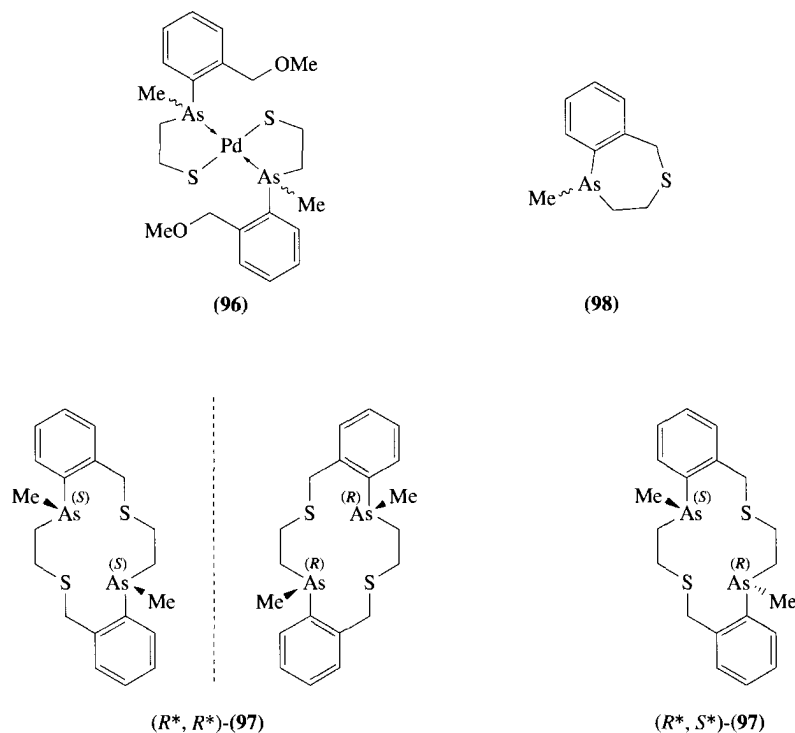
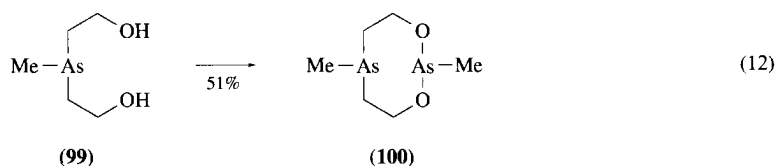
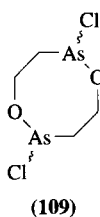
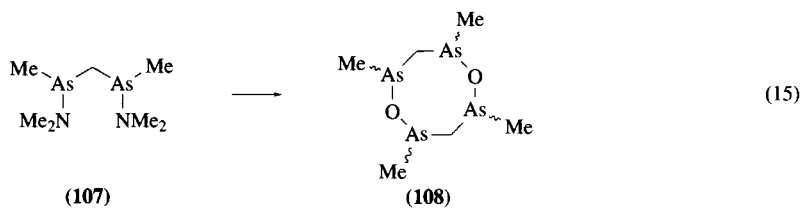
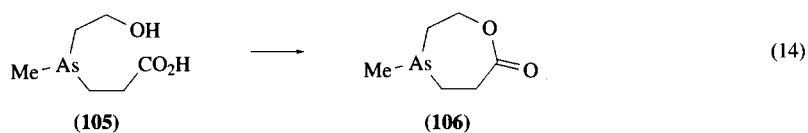
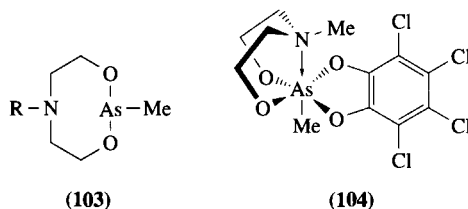
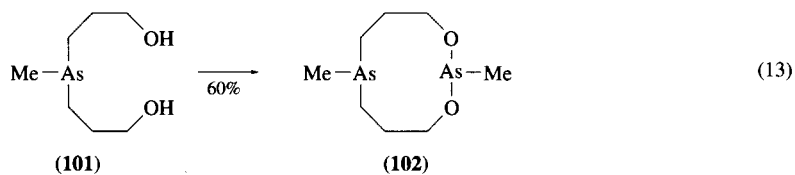


Figure 2 Stereoisomers of (97).

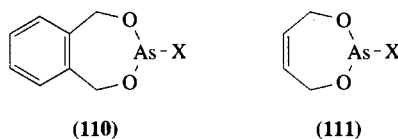
9.35.3.7 Cyclic Esters of Arsenic(III) and Arsenic(V) Acids and Thioacids

Aminoarsines of the type $\text{RAs}(\text{NR}_2)_2$ are versatile reagents for the preparation of cyclic organo-arsenic compounds when reacted with appropriate hydroxo compounds (82S173). For example, the diol (99) reacts with $\text{MeAs}(\text{NMe}_2)_2$ to give the cyclic eight-membered arsonous acid ester (100) (Equation (12)) and similarly the diol (101) gives ten-membered (102) (Equation (13)) (83ZAAC(501)89). The related arsenic(III) compound (103) (84ZAAC(513)35) and the arsenic(V) compound (104) are also known (85CJC636). Dehydration of the arsine (105) affords the seven-membered lactone (106) (Equation (14)) (83ZAAC(501)89). Another interesting reaction is the hydrolysis of the bis(aminoarsine) (107) into the eight-membered cyclic arsonous acid anhydride (108) (b.p. 110–112°C, 0.2 mm Hg) (Equation (15)) (70ZAAC(377)120, 75ZAAC(412)202). The related compound (109) was formed in 23% yield when dichloro(2-hydroxyethyl)arsine was treated with triethylamine (70ZAAC(377)273).

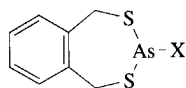




A variety of substituted dioxarsepins of types (110) and (111) have been synthesized $\langle 84\text{IZV}1779, 79\text{ZAAC}(458)29 \rangle$. Detailed analyses of conformational equilibria have been undertaken for many of the compounds $\langle 83\text{IZV}2507 \rangle$. According to variable-temperature IR, Raman $\langle 83\text{JGU}1835 \rangle$, dipole moment, and ^{13}C NMR measurements $\langle 84\text{IZV}1779 \rangle$, 2-chloro- and 2-bromo-substituted compounds of this type adopt chair conformations with axial arrangements of the exocyclic bond at arsenic. Aryl-substituted compounds exist as almost equimolar mixtures of chair and twist conformers. The chair conformation of (110; X = Ph) in the solid state has been established by x-ray crystallography $\langle 87\text{MI} 935-01 \rangle$.

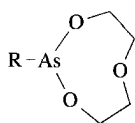


The reaction of 1,2-xylylenedithiol with arsenic(III) halides and various dialkyl esters of arylarsonic acids under anhydrous conditions gives the corresponding halo- or aryl-substituted dithiarsepins (112), respectively $\langle 88\text{IZV}182 \rangle$. As found for the analogous dioxarsepins, halo substituents reduce conformational lability.

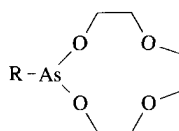


(112)

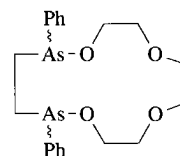
The condensation of dichlorophenylarsine <83JGU2520> or bis(dimethylamino)methylarsine <82S173> with the glycol ethers $\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_n\text{CH}_2\text{OH}$ ($n = 1$ or 2) in benzene in the presence of triethylamine gives the 8- and 11-membered heterocycles (113) and (114) as distillable oils in 53% and 36% yields, respectively. 1,2-Bis(chlorophenylarsino)ethane and $\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_2\text{CH}_2\text{OH}$ react under similar conditions to give 14-membered (115).



(113)

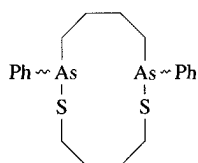


(114)

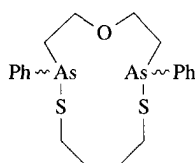


(115)

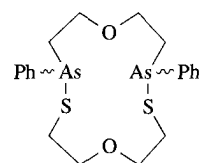
The reaction of terminal alkylene bis(chlorophenylarsines) with various terminal alkylene and alkylene ether dithiols in the presence of pyridine affords remarkably good yields of the heterocycles (116)–(122) with normal reactant concentrations <86JGU91>. The 12-membered heterocycle (116) was obtained as a crystalline solid, m.p. $106\text{--}108^\circ\text{C}$. The mass spectra of the macrocycles show intense peaks corresponding to the molecular ions and vibrational spectroscopy confirmed the presence of the As—S bond in each case.



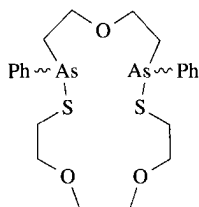
(116) 57%



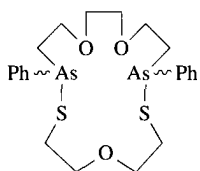
(117) 33%



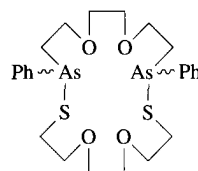
(118) 62%



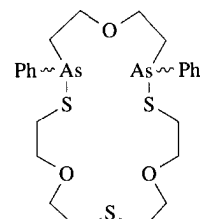
(119) 76%



(120) 68%

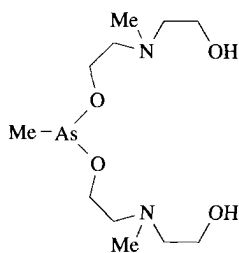


(121) 75%

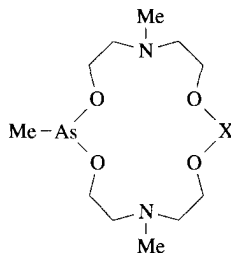


(122) 75%

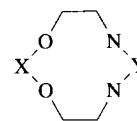
With use of the dilution principle, the diol (123) was converted by reaction with $\text{MeAs}(\text{NMe}_2)_2$ or $\text{Me}_2\text{Si}(\text{NMe}_2)_2$ into the respective 16-membered rings (124; $\text{X} = \text{AsMe}$ or SiMe_2) <84CZ13>. The two reagents were added simultaneously in tetrahydrofuran over 72 h, giving the macrocycles in 32% ($\text{X} = \text{AsMe}$) and 40% ($\text{X} = \text{SiMe}_2$) yields. The related 10-membered rings (125; X or $\text{Y} = \text{AsMe}$ or SiMe_2) were prepared similarly.



(123)



(124)



(125)

Condensation of the bis(2-aminoethyl)arsonous acid ester (**126**) with acetylacetone in the presence of a trace of formic acid gave (**127**) in 58% yield <87CZ273>.



9.35.3.8 Macrocyclic Arsa-aza-oxa Cryptands

The reaction of $N(\text{CH}_2\text{CH}_2\text{AsPh}_2)_3$ (**128**) with gaseous HI produces $[\text{HN}(\text{CH}_2\text{CH}_2\text{AsI}_2)_3]\text{I}$ (**129**), which upon hydrolysis with aqueous ammonia in tetrahydrofuran, gives $[\text{N}(\text{CH}_2\text{CH}_2)_3]_8(\text{As}_4\text{X}_4)_6$ (**130**; $\text{X} = \text{O}$) (Figure 3) <82CC382>; with $\text{H}_2\text{S}/\text{NEt}_3$, the cryptand (**130**; $\text{X} = \text{S}$) is obtained <83JOM(252)153>. The compounds were characterized by IR, FIR, Raman, ^1H NMR, and mass spectroscopy. In addition, the crystal and molecular structure of (**130**; $\text{X} = \text{O}$) was determined. In the solid state, each molecule of (**130**; $\text{X} = \text{O}$) consists of six eight-membered As_4O_4 rings that are connected together by the triethylamine groups linked to arsenic, giving another six 16-membered ring (Figure 3). The reaction of (**130**; $\text{X} = \text{O}$) with $[\text{Cr}(\text{CO})_5\text{THF}]$ gives the adduct $[\text{Cr}(\text{CO})_5(\text{130}; \text{X} = \text{O})]$ in which the chromium group is attached to one of the arsenic atoms and appears to be situated *endo* to the cryptand <86CB766>. With use of appropriate starting materials, similar methyl-substituted cryptands were prepared <86JOM(299)51>.

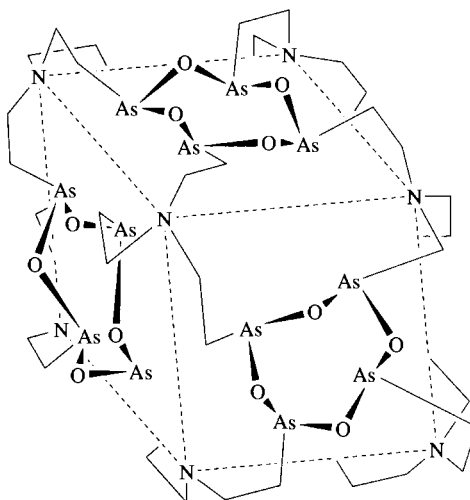


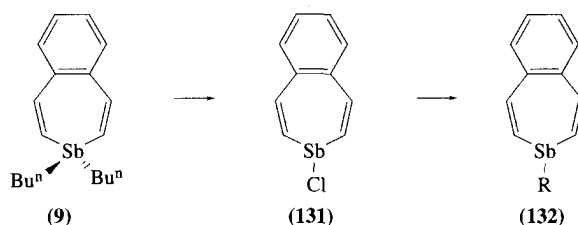
Figure 3 Molecular structure of (**130**; $\text{X} = \text{O}$). (Reproduced by permission from *J. Organomet. Chem.*, 1986, **299**, 51.)

9.35.4 RINGS CONTAINING ANTIMONY

9.35.4.1 Benzo[*d*]- and Dibenzo[*b,d*]-stibepins

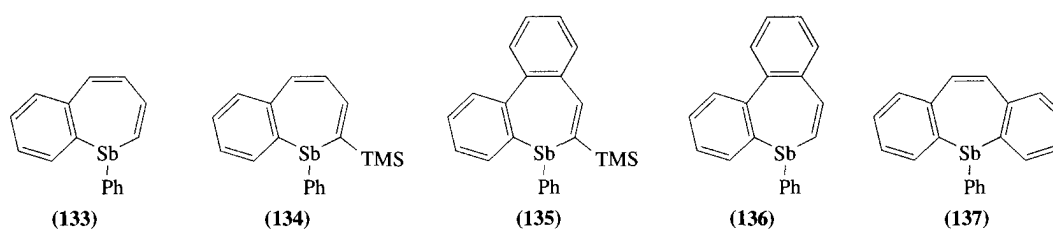
The reaction of di-*n*-butylbenzo[*d*]stannepin (**9**) with 1 equiv. of SbCl_3 in chloroform at 0°C affords 1-chlorobenzo[*d*]stibepin (**131**) and dibutyltin dichloride (Scheme 17) <92AG(E)1642>. An x-ray crystal structure determination on (**131**) revealed a boat-like conformation of the stibepin ring. The marked alternation between the single and double bond lengths in the structure of (**131**) is

consistent with a low degree of conjugation in the ring. Compound (**131**) was converted by treatment with methyl or *n*-butyllithium into the derivatives (**132**; R = Me or Buⁿ), respectively. The alkyl derivatives (**132**) decompose in CDCl₃ at 25°C into naphthalene and unidentified antimony-containing products by a first-order process with $t_{1/2}$ = 370 min (R = Me) and 660 min (R = Buⁿ), respectively.



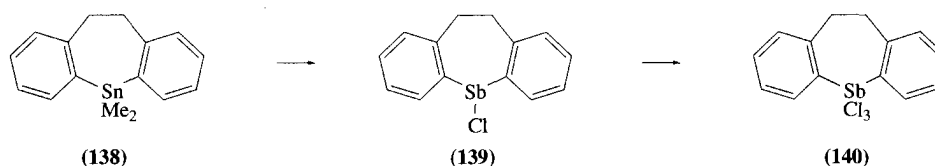
Scheme 17

1-Phenylbenzo[*b*]stibepin (**133**) has been prepared by desilylation of (**134**), which was prepared from a 1,6-dibromohexatriene precursor <93CC1817>. Similar desilylation of the dibenzo compound (**135**) with fluoride afforded (**136**). Isomer (**137**) was obtained from *cis*-*o,o'*-dibromostilbene by lithiation and addition of dichlorophenylstibine. Whereas (**133**) decomposes into naphthalene during isolation by column chromatography, the dibenzo compounds (**136**) and (**137**) withstand heating in toluene at 60°C for 20 h.



9.35.4.2 Dihydro-5*H*-dibenzo[*b,f*]stibepins

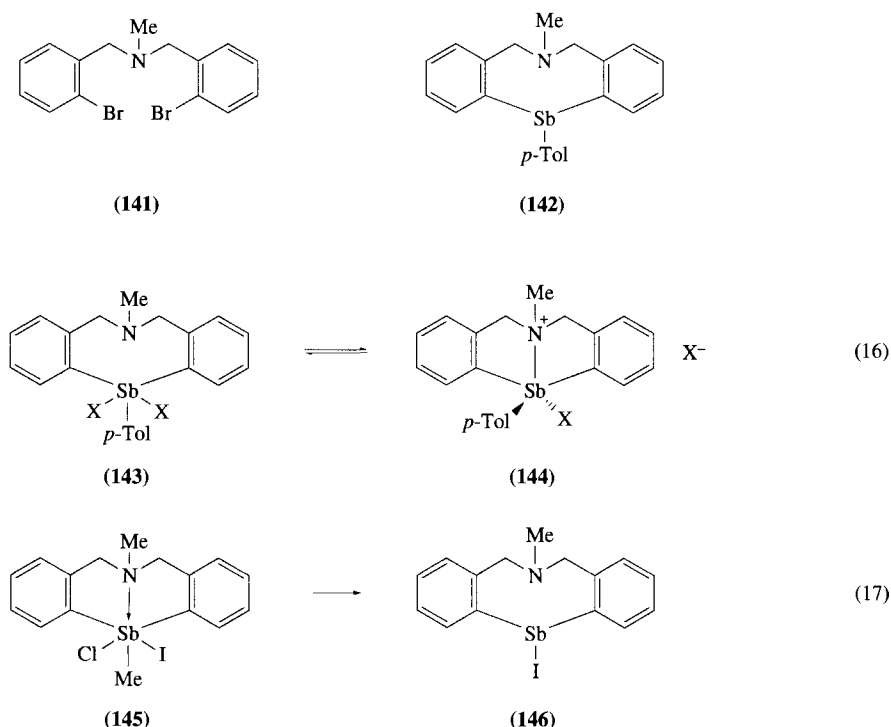
A mixture of 5,5-dimethyl-10,11-dihydro-5*H*-dibenzo[*b,f*]stannepin (**138**) and antimony trichloride, when heated to 150°C at 15 mm Hg, affords, with elimination of dichlorodimethyltin (which sublimes from the reaction vessel), 5-chloro-10,11-dihydro-5*H*-dibenzo[*b,f*]stibepin (**139**), as colorless needles having m.p. 138°C (Scheme 18) <73JOM(55)139>. The stibepin (**139**) in chloroform, when heated with an equimolar amount of suluryl chloride, gave the 5,5,5-trichloro compound (**140**) which was isolated as a colorless crystalline solid <77JOM(136)173>. Unlike other cyclic compounds of the type R₂SbCl₃, the stibepin (**140**) does not react with tetramethylammonium chloride to form the corresponding tetrachloroantimonate salt. Steric hindrance around the antimony atom in the trichlorostibepin was given as the reason for the failure of the addition reaction. The ¹²¹Sb Mössbauer spectrum of (**140**) and related compounds of the general formulas [Me₄N][SbR₂Cl₄] and SbR₂Cl₄ has been reported <79JCS(D)1925>.



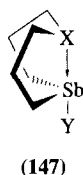
Scheme 18

9.35.4.3 Stibocanes

The one-pot reaction between di(2-bromobenzyl)methylamine (**141**), *n*-butyllithium, and antimony trichloride, followed by *p*-tolyllithium, afforded (**142**) in 23% yield <88TL5401>. Halogenation of (**142**) yielded the corresponding dihalides (**143**; X = Cl, Br or I) and the reaction of (**143**; X = Cl or Br) with SbCl₅ or AgBF₄ resulted in the formation of compounds with Sb—N bonds (**144**; X = Cl or Br) (Equation (16)). Treatment of (**143**; X = Cl) with KF in DMF gave the difluoro compound (**143**; X = F). The structure was assigned to the compounds (**143**) on the basis of ¹H NMR spectroscopy. The most reasonable structure for (**143**; X = I) was determined to be the ionic formulation (**144**; X = I). The addition of benzyltrimethylammonium chloride to (**144**; X = Cl) converted it back into the neutral compound (**143**; X = Cl). Methyl iodide oxidatively adds to (**142**); subsequent reductive elimination of methyl chloride from the intermediate (**145**) yields the iodostibine (**146**) in quantitative yield (Equation (17)) <89TL4841>.



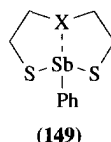
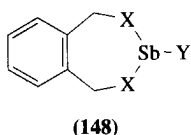
A series of eight-membered stibocanes (**147**; X = NMe and Y = Cl or Br, NBn and Cl, NBUⁱ and Cl, S and Cl) has been prepared from reactions between appropriate di-Grignard reagents and antimony(III) halides <94POL365>. The yields ranged from 3% to 16%. The crystal structure of the compound (**147**; X = NMe and Y = Cl) indicated a structure based on the trigonal bipyramid with the Sb—N distance 238.5(2) pm.



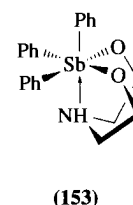
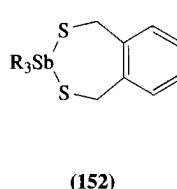
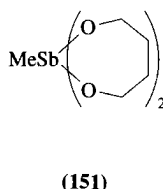
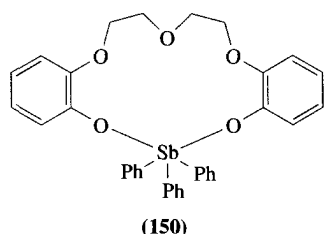
9.35.4.4 Cyclic Esters of Antimony(III) and Antimony(V) Acids and Thioacids

Various benzodioxo- and benzodithiastibepins (**148**; X = O or S, Y = alkyl or halide) have been isolated from reactions of the *o*-xylylene diols and dithiols with antimony(III) halides <87IZV423, 87IZV2342>. Similar reactions with maleic or phthalic acid give cyclic diesters <84ZN(B)600, 84ZN(B)754>. Detailed IR and Raman spectroscopic investigations have been performed on the cyclic dithiolates

(149; X = O or S) <85JOM(295)33, 86SA(A)1255, 87JOM(320)273>. The spectra for the ether and thioether compounds were very similar, although it was not possible to conclude whether the heteroatom in each case was coordinated to the antimony.



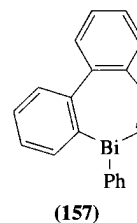
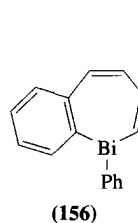
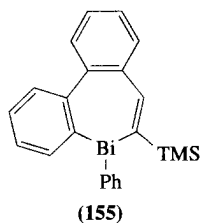
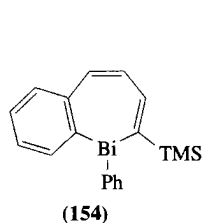
The 14-membered cyclic antimony(V) ester (**150**) was obtained in 75% yield from the reaction between the disodium salt of (*o*-HOC₆H₄OCH₂CH₂)₂O and Ph₃SbCl₂ <80IZV1446>. The crystal and molecular structures of the compound have been determined. The antimony(V) esters (**151**) <90ZAAC(585)65> and (**152**) <87IZV1380> have also been isolated. The reaction of Ph₃Sb with diethanolamine in the ratio 1 : 2 in boiling benzene gives (**153**), which was characterized by x-ray crystallography <91ZAAC(605)137>. A similar compound has been prepared by reaction of (*p*-Tol)₃SbCl₂ with a bis(2-hydroxyphenyl)amine <90CL1721>.



9.35.5 RINGS CONTAINING BISMUTH

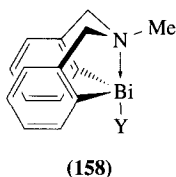
9.35.5.1 Benzo[*d*]- and Dibenzo[*b,d*]-bismepins

Desilylation of the compounds (**154**) and (**155**) with tetra-*n*-butylammonium fluoride in THF affords moderate yields of the 1-phenylbenzo[*d*]- and dibenzo[*b,d*]bismepins (**156**) and (**157**), respectively; (**154**) and (**155**) were prepared from 1,6-dibromohexatriene precursors <93CC1817>. As for the analogous arsenic and antimony compounds, the α -silyl-substituted compounds are more stable than the desilylated compounds and the dibenzo compound is much more stable than the benzo compound.



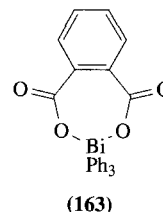
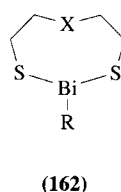
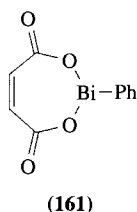
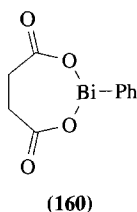
9.35.5.2 Bismocanes

The azabismocanes (**158**; Y = F, Cl, I, Me, or Ph) were prepared from bis(2-bromobenzyl) methylamine in two steps involving treatment with *n*-butyllithium and the addition of bismuth(III) chloride <89TL4841>. The compounds (**159**; R = Me, Bn, Prⁱ or Buⁱ, Y = Br or I) were prepared from the appropriate Grignard reagent and bismuth(III) halide <94POL365>.



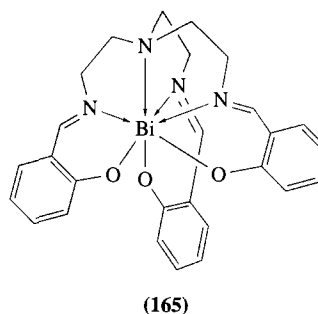
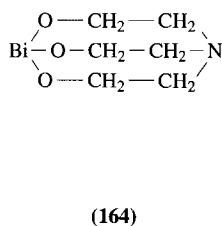
9.35.5.3 Cyclic Esters of Bismuth(III) and Bismuth(V) Acids and Thioacids

In the reaction of triphenylbismuth with succinic or maleic acid, two phenyl groups are cleaved and the cyclic esters **(160)** and **(161)** are produced in 15% and 99% yields, respectively <80ZN(B)1000>. Reactions between bis(2-thioethyl)ether or sulfide with $\text{PhBi}(\text{OEt})_2$ (at -30°C) or $\text{MeBi}(\text{OEt})_2$ (at RT) afford the cyclic dithiolates **(162)**; $\text{R} = \text{Ph}$ or Me , $\text{X} = \text{O}$ or S <85JOM(290)133, 86SA(A)1255>. The light-sensitive compounds have been investigated by mass spectrometry and by vibrational and ^{13}C NMR spectroscopy. The crystal structure of **(162)**; $\text{R} = \text{Ph}$ and $\text{X} = \text{O}$ reveals an eight-membered ring in the chair-chair conformation with the $\text{Bi}-\text{O}$ distance 297(1) pm.



Triphenylbismuth carbonate reacts with phthalic acid in boiling acetone to give the cyclic ester **(163)** in 58% yield after recrystallization from aqueous alcohol <51JA4470>.

The bicyclic pro-atrane-like bismuth(III) compound **(164)** was prepared from bismuth hydroxide and triethanolamine <40JA2707>. In **(165)**, which was characterized by x-ray crystal structure analysis, bismuth(III) has the coordination number 7 <94AJC1799>.



9.36

Rings containing Silicon to Lead

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Australian National University, Canberra, ACT, Australia

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9.36.1 INTRODUCTION

A great variety of seven-membered and larger heterocyclic rings containing silicon, germanium, or tin have been synthesized. A search of *Chemical Abstracts*, volumes 97–120 (1982–1994), produced 801 references on the subject—256, including some pertinent earlier works and later articles not yet abstracted, were selected for this overview. Few references to lead compounds were found. For a comprehensive account of the organometallic chemistry of silicon, the reader should consult parts 1 and 2 of *The Chemistry of Organic Silicon Compounds* (edited by S. Patai and Z. Rappoport) (B-89MI 936-01). The following list of review articles are also helpful to workers in the field—the titles (authors) and references to the articles follow: “Recent results in the heterocyclic chemistry of germanium” (J. Satgé) (82BSB1019); “Structural chemistry of organosilicon heterocyclic compounds” (O. A. D’yachenko and L. O. Atovmyan) (83MI 936-01); “Organo-1,3,2-dioxasilane heterocycles” (R. H. Cragg and R. D. Lane) (84JOM(267)1); “Recent developments in the structural chemistry of Si compounds” (V. E. Shklover and Y. T. Struchkov) (87JOM(322)269); “Structure and reaction controlled by strong sigma/pi interactions” (H. Sakurai) (87PAC1637); “C-Heterocyclic tin compounds: a review” (V. G. K. Das, L. K. Mun and N. S. Weng) (88MI 936-01); “Organotin heterocycles” (K. C. Molloy) (91AOC(33)171); and, “Reactivity of penta- and hexa-coordinated silicon compounds and their role as reaction intermediates” (C. Chuit, R. J. P. Corriu, C. Reye and J. C. Young) (93CRV1371).

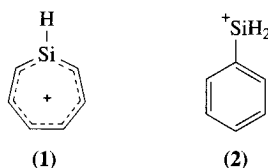
Because of the interrelationship of much of the material presented here, subheadings have been kept to a minimum—the reader is requested to use the structural diagrams as a guide to the content.

9.36.2 PARENT RINGS WITH ONE GROUP 14 HETEROATOM

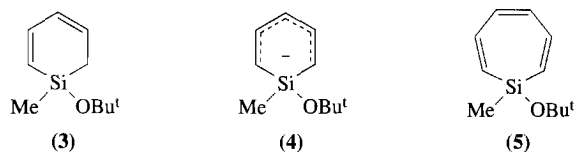
9.36.2.1 Seven-membered Rings

9.36.2.1.1 Monocyclic derivatives

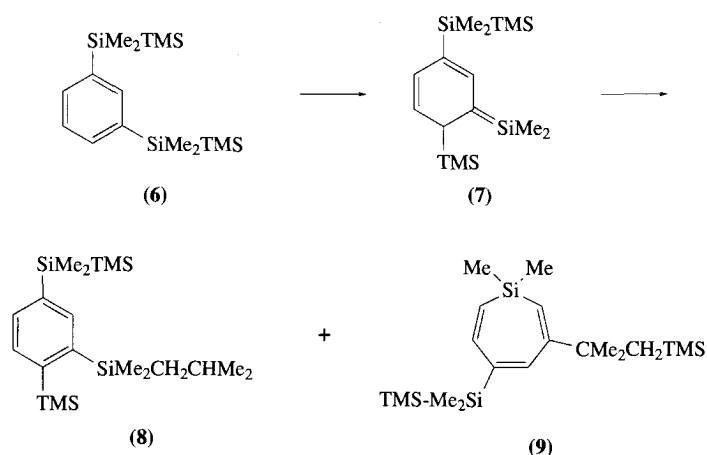
Electron impact ionization of phenylsilane has provided evidence for the silatropylium (**1**) and silabenzyl (**2**) cations <92JA3573>; the relative stabilities of the two cations have been determined by *ab initio* molecular orbital calculations <94JA9769>. The calculations indicated that (**2**) is more stable than (**1**) by 38 kJ mol⁻¹, which is the contrary to the situation for the tropylium and benzyl cations.



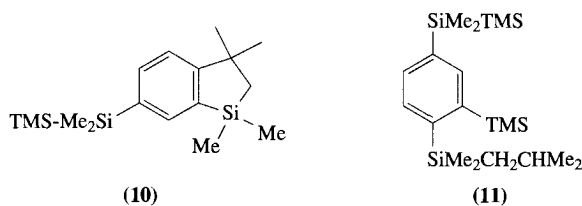
The ring expansion of silacyclohexa-2,4- and -2,5-dienes produces *C*-unsubstituted silepins (silacycloheptatrienes) <91OM435>. Thus, (**3**), when treated with LDA in diethyl ether at 0 °C, afforded a solution of (**4**), which underwent ring expansion when treated with BuⁿLi and dichloromethane to give (**5**) in 32% yield after chromatography. Detailed mechanistic investigations of the above and related reactions were carried out using deuterium labeling. The corresponding 1,1-di-*n*-butylstannepin and 1,1-dimethylgermepin were prepared similarly <92JOM(441)411>.



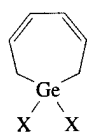
In a remarkably general reaction, the photolysis of (**6**) forms (**7**), which reacts with an excess of isobutene to give a mixture of (**8**) and (**9**) in 70% and 9% yields, respectively (Scheme 1) <89OM2767, 91JOM(418)305>. Heating of (**9**) at 250 °C for 10 h led to (**10**) and (**11**) in 55% and 12% yields, respectively.



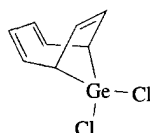
Scheme 1



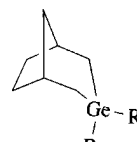
Dichloro- and difluorogermynes exhibit properties analogous to those of carbenes and have been shown to insert into a variety of σ -bonds; with 1,3,5-hexatriene, the seven-membered compounds (**12**; X = Cl, F) are formed by cycloaddition <82BSB1019>. Dichlorogermylene reacts with cyclooctatetraene to give (**13**). The bicyclo compounds (**14**; R = Me, Ph) have been prepared from the appropriate di-Grignard reagent and dichlorodiorganogermynes <90OM1784>.



(12)



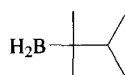
(13)



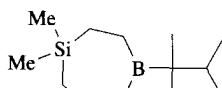
(14)

Certain sila- and germacycloalkanones have been prepared by the hydroboration of dialkenylsilanes and dialkenylgermanes <83JOC1801>. Thus, allyldimethylvinylsilane and hexylborane (**15**) react together to give the borepane (**16**), which was converted into (**17**) by treatment with cyanide (in the presence of trifluoroacetic anhydride), followed by 30% hydrogen peroxide. The sila- and germacyclooctanones (**18**; E = Si, Ge) were prepared similarly. 1,1-Diphenyl-1-silacycloheptan-4-one was obtained in a three-step process from diphenyldivinylsilane in 50% overall yield <95SL111>.

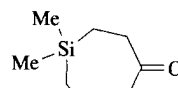
Dichlorodimethylgermane reacts with the appropriate α,ω -di-Grignard reagent to give the germacycloalkanes (**19**; $n = 2, 3$) <82JOM(232)13>. Cyclizations were also achieved by heating the ω -alkenyldimethylgermanes with AIBN.



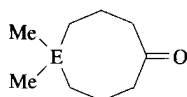
(15)



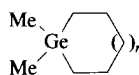
(16)



(17)

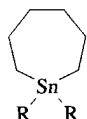


(18)

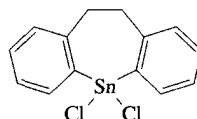


(19)

The stannepanes (**20**; R = Me, Et, Ph, CH_2CMe_3) were isolated in moderate yields as air-stable liquids following reactions of the appropriate diorganotin dichlorides with the di-Grignard reagent of 1,6-dibromohexane <68TL1615>. Heating of the compound (**20**; R = Ph) with chloroacetic acid cleaved both phenyl groups to give an excellent yield of the bis(chloroacetate), which was characterized by x-ray crystallography <93OM4881>. The stannacycloheptane ring adopts an approximately C_2 -symmetric twist-chair conformation with the tin atom lying on the axis. Treatment of the bis(chloroacetate) with sodium hydroxide gave the corresponding tin oxide, for which a polymeric structure was proposed. The dichlorostannacycloheptanes (**20**; R = Cl) and (**21**) react with sodium glycyglycinate to give the corresponding trigonal bipyramidal tin complexes of the deprotonated dipeptide <94MI 936-01>.



(20)

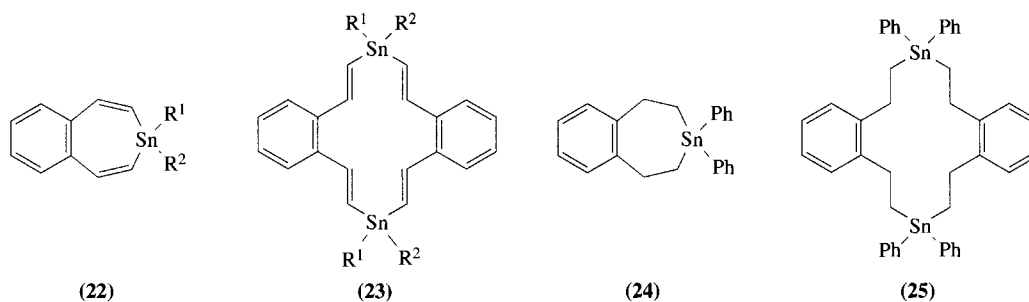


(21)

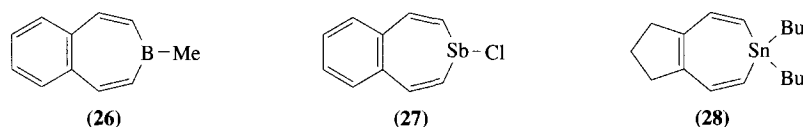
9.36.2.1.2 Fused benzo and dibenzo derivatives

Reactions of 1,2-diethynylbenzene with the appropriate diorganostannanes afforded the benzo [*d*]stannepins (**22**; $\text{R}^1 = \text{R}^2 = \text{Me}$, Et or $\text{R}^1, \text{R}^2 = \text{Et}$, Ph), as well as the dimers (**23**; $\text{R}^1 = \text{R}^2 = \text{Ph}$ or $\text{R}^1, \text{R}^2 = \text{Et}$, Ph) and polymers <64RTC1036>. The proportions of the products depended upon the

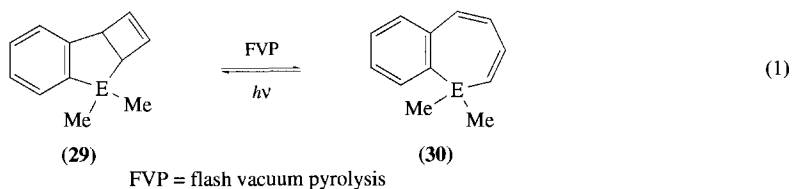
organostannane employed. The reaction between 1,2-divinylbenzene and diphenylstannane in boiling benzene gave (24) and (25) in 16% and 14% yields, respectively, after purification.



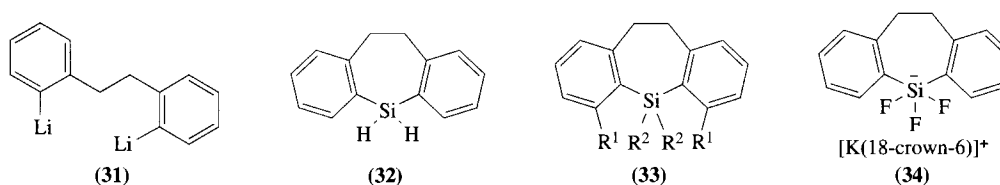
Stannepins are useful precursors of other heteroepins. For example, treatment of (22; $R^1 = R^2 = \text{Bu}^n$) with dibromomethylborane or antimony trichloride led to the benzo[*d*]-borepin (26) <90OM2944> or -stibepin (27) <92AG(E)1642>, respectively. 1-Methyl-4,5-cyclopentanoborepin is similarly accessible from (28) <87JA1879>.



Flash vacuum pyrolysis (FVP) of (29; $E = \text{Si}, \text{Ge}$) affords the compounds (30; $E = \text{Si}, \text{Ge}$) (and naphthalene) (Equation (1)), which readily revert to the starting compounds upon irradiation in benzene <93H(36)2677>. The compounds (30; $E = \text{Si}, \text{Ge}$) are thermally stable, and solutions of them remain largely unchanged when heated at 200°C for 24 h.

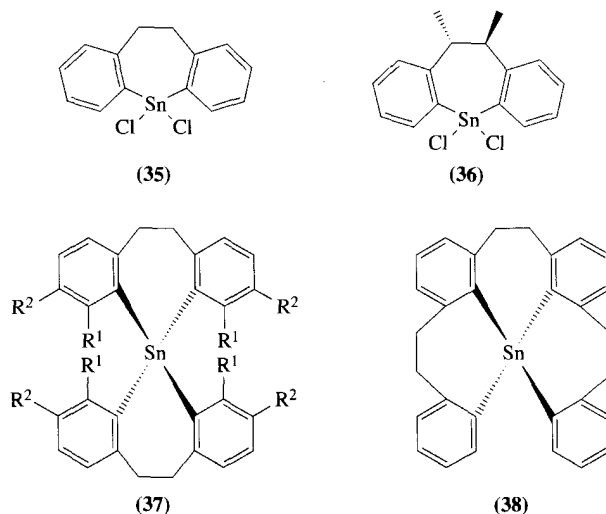


The condensation of (31) with trichlorosilane, followed by reduction of the intermediate with LAH and distillation at 140–160°C (0.01 mm Hg), afforded an almost pure sample of the dibenzo[*b,f*]silepin (32) in 53% yield <86JOM(304)93>. The compounds (33; $R^1 = R^2 = \text{Me}$ or $R^1 = \text{TMS}, R^2 = \text{Me}, \text{H}$) were also prepared from the corresponding aryllithium salts <91OM3189>. Detailed structural investigations were performed on these compounds in the solid state and in solution. Replacement of chlorine in (33; $R^1 = \text{H}, R^2 = \text{Cl}$) by fluorine was effected with copper(II) fluoride; the fluoride was subsequently converted into (34) by treatment with KF/18-crown-6 <89IC3190, 91OM1758>.

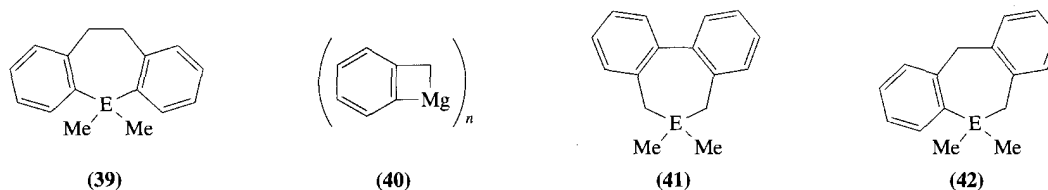


The compound (31), when treated with tin tetrachloride, afforded (35) <58JA3250>, whose structure was determined by x-ray crystallography <90AX(C)2088>. The Lewis acidities of a series of stannepins, including (36) and derivatives with perfluoroaryl rings, were determined by correlating the shifts in the infrared spectra of the triphenylphosphine oxide adducts in the $\nu(\text{P}=\text{O})$ region <93JOC2840>. Stereoisomerism was investigated in a number of spiro derivatives of the type (37); the crystal and molecular structures of (37; $R^1 = \text{Me}, R^2 = \text{H}$) were determined, revealing D_2 -symmetry <93TL657>.

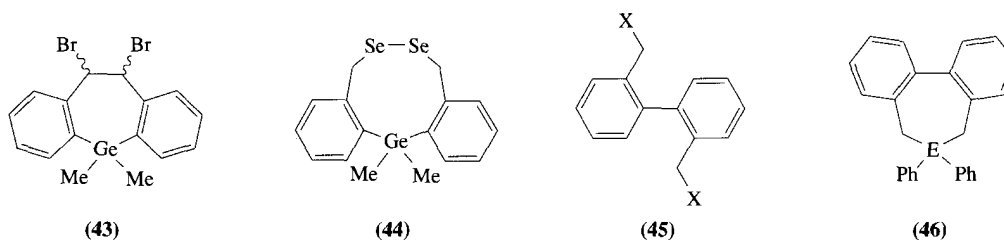
The related compound (38) was found to have approximately C_2 -symmetry in the solid state and was resolved by chiral HPLC <93CL1999>.



The compounds (39; E = Ge, Sn) were prepared from the appropriate di-Grignard reagent and Me_2ECl_2 (E = Ge, Sn) <87JOM(321)291>. When unpurified (40) was used in the attempted synthesis of 1,2-dihydro-1,1-dimethyl-1-germa- and -1-stannabenzocyclobutene, small quantities of (39, 41, 42; E = Ge, Sn) were isolated.

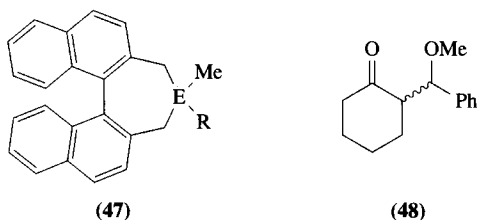


The dibromogermepin (43), when treated with Na_2Se_2 , gave nine-membered (44), which was characterized by x-ray crystallography <86JOM(301)273>. Use of (45; X = Li(TMEDA) or $\text{MgCl}(\text{THF})_n$) in conjunction with diphenyltin dichloride afforded (46; E = Sn) <82JOM(240)C1>. A 90% yield of the silepin (41; E = Si) was obtained from the di-Grignard reagent and SiCl_2Me_2 <84JCS(D)331>. The crystal structure of (46; E = Sn) was determined.

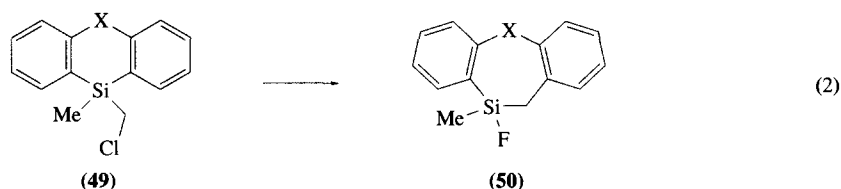


The axially dissymmetric silepin (47; E = Si, R = Me) was obtained in optically pure form by synthesis of the racemate, followed by resolution on a chiral column <82TL2969>. The structure of (R)-(-)-(47; E = Si, R = Me) was determined by x-ray crystallography. In other work, (R)-(-)- and (S)-(+)-(47; E = Si, Sn, R = Me) were prepared from the corresponding dilithium salts of enantiomerically pure deprotonated 2,2'-dimethyl-1,1'-binaphthyl and Me_2ECl_2 (E = Si, Sn) <88JOM(344)277>. The optically active silane (47; E = Si, R = H) reduced various enones and ketones with enantiomeric excesses (*ee*) of 6.2–25.6% <88TL6199>. The cyclohexenyl silyl enol ether (47; E = Si, R = 1-OC₆H₉) reacted with benzaldehyde dimethyl acetal in a Mukayama/Noyori aldol process to give a 4.4:1 mixture of the separable *erythro* and *threo* diastereomers of (48) in 78%

yield; *erythro*-(**48**) had *ee* 17.2%, *threo*-(**48**) had *ee* 35%. The use of chiral organosilicon compounds for asymmetric syntheses has been reviewed <92CRV995>.

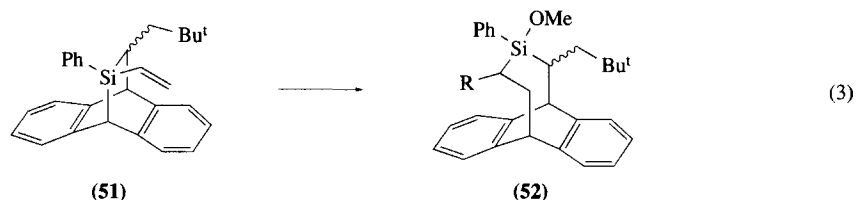


Dibenzosilepins and related compounds of the type (**50**) were prepared by fluoride ion-induced ring expansion of the chloro- or bromomethyl-substituted compounds (**49**; X = CH₂, CH₂CH₂, NMe, O, OCH₂) under heterogeneous and homogeneous conditions (Equation (2)) <84OM1051, 82OM645>.

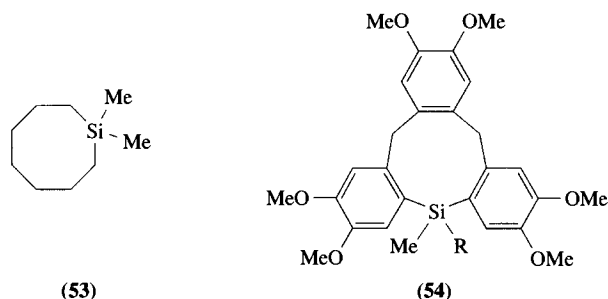


9.36.2.2 Larger Rings

Photolysis of the silabicyclo[2.2.2]octadiene (**51**) in cyclohexane with methanol, methanol-*d*₁, or methoxytrimethylsilane as trapping agents, gave (**52**; R = H, D, TMS) by novel ring-closures of the sila-allylic 1,6-biradicals (Equation (3)) <91OM2529>.

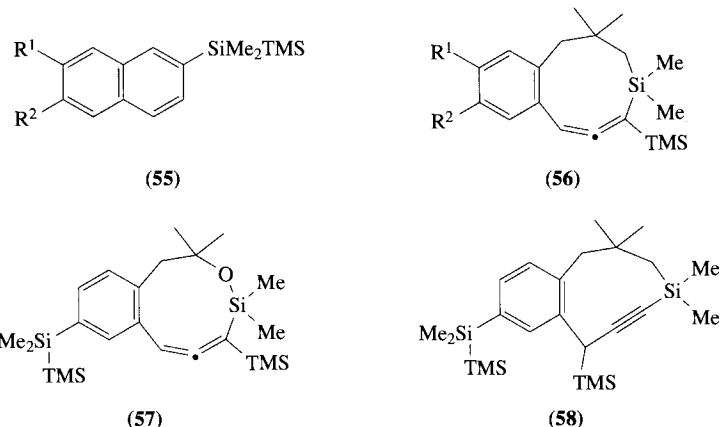


Treatment of the di-Grignard reagent of 1,7-dibromoheptane with Me₂SiCl₂ afforded eight-membered (**53**) as a colorless liquid in 6% yield <88OM38>. Moderate to good yields of the nine-membered rings (**54**; R = Me, CH₂Cl, CH=CH₂, Ph) were obtained from the dilithioaryl precursor with the appropriate dichlorosilane <92H(33)43>.

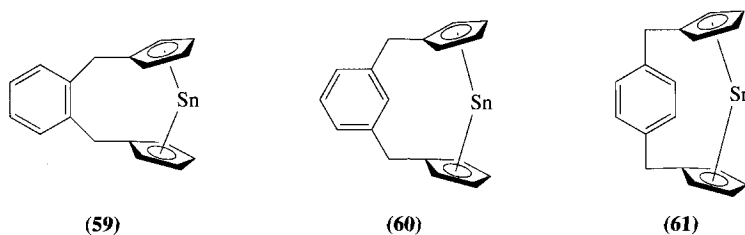


Photolysis of the silyl-substituted naphthalenes (**55**; R¹, R² = H, TMS-Me₂Si, and TMS-Me₂Si, H) in the presence of isobutene affords, among other products, the nine-membered rings (**56**; R¹, R² = H, TMS-Me₂Si, and TMS-Me₂Si, H) in good yields <91OM2685>. The heterocycle (**57**) was obtained in 2% yield when (**55**; R¹, R² = H, TMS-Me₂Si) was photolyzed in the presence of acetone. Compounds (**56**) and (**57**) were isolated by HPLC and characterized by IR, ¹H, and ¹³C NMR

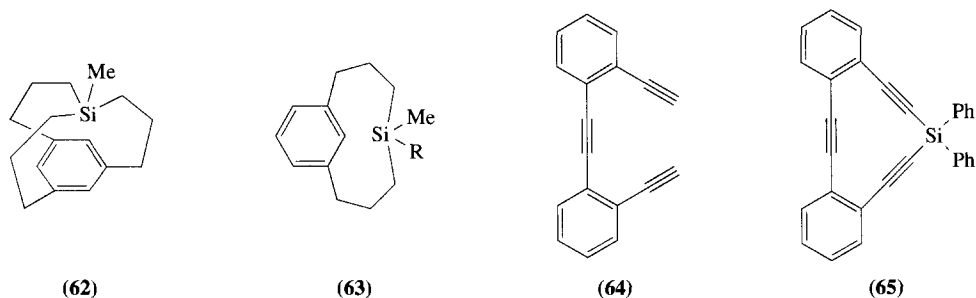
spectroscopy and by mass spectrometry. Attempted isolation of (**56**; $R^1, R^2 = H$, TMS- Me_2Si) by GLC led to the thermal rearrangement product (**58**) in quantitative yield.



The novel stannocenophanes (**59**)–(**61**) were prepared from reactions of the appropriate disodium (phenylenedimethylene)dicyclopentadienides with tin(II) chloride <84JOM(264)295>. The boron trifluoride adduct of the *para* compound was also isolated.

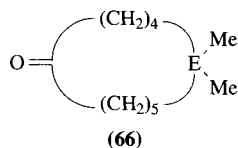


Multiple palladium(0)-catalyzed coupling reactions of silicon-containing boranes and aryl bromides (Suzuki coupling) were employed for the synthesis of silametacyclophane rings <94OM3728>. Thus, treatment of triallylmethylsilane with 9-BBN followed by 1,3,5-tribromobenzene, sodium hydroxide, and the catalyst (e.g., $[Pd(PPh_3)_4]$), gave (**62**) and (**63**; $R = \text{allyl}$, $(CH_2)_3Ph$) after 8–12 h heating at reflux; the products were separated by flash chromatography. A 32% yield of (**63**; $R = Me$) was obtained by coupling the bis-9-BBN adduct of diallyldimethylsilane and 1,3-dibromobenzene under similar conditions. The 11-membered silacyclotriyne (**65**) was prepared from (**64**) by treatment with 2 equiv. of Bu^tLi , followed by addition of dichlorodiphenylsilane <95OM586>. With $[Ni(COD)_2]$, (**65**) formed the planar complex $[Ni \cdot 65]$ where the nickel atom resides in the pocket of the ligand. The crystal and molecular structures of (**65**) and $[Ni \cdot 65]$ were determined.

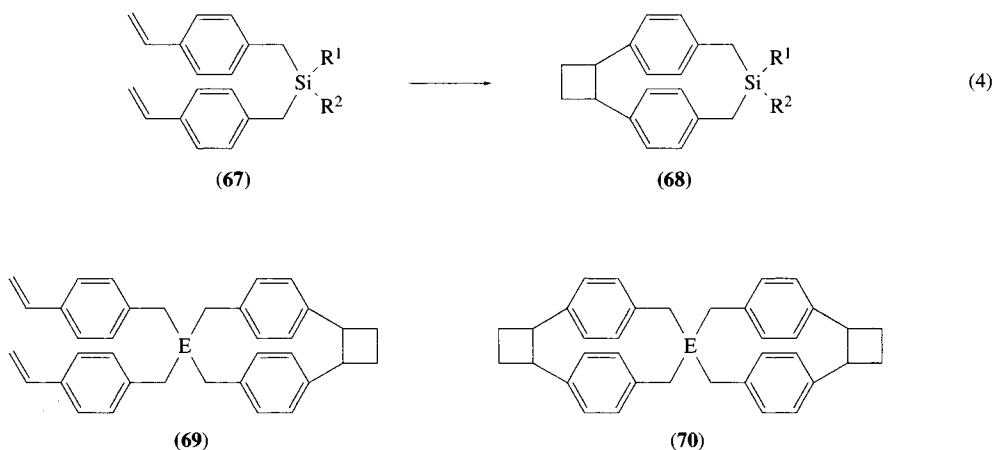


The conformations of (**66**; $E = Si, Ge$) have been investigated by NMR spectroscopy and dipole moment measurements <83JCPB(80)553>. The effect of pressure on the IR spectra of (**66**; $E = Si, Ge$) and related compounds has been investigated <84AJC23>. Evidence was found of reversible

conformational changes under pressure, and of phase transitions in some of the compounds, but not of transannular interactions.



Irradiation of the bis(4-vinylbenzyl)silanes (**67**; $R^1, R^2 = \text{Me, Ph}$ and $R^1 = \text{Me}, R^2 = \text{Ph}$ and $R^1, R^2 = (\text{CH}_2)_4$) in benzene caused efficient intramolecular $[2_\pi + 2_\pi]$ cycloadditions to give the silacyclophanes (**68**; $R^1, R^2 = \text{Me, Ph}$ and $R^1 = \text{Me}, R^2 = \text{Ph}$ and $R^1, R^2 = (\text{CH}_2)_4$) (Equation (4)) $\langle 90\text{JCS(P1)3362} \rangle$. Similar irradiations of tetrakis(4-vinylbenzyl)silane and -germane afforded mixtures of (**69**; $E = \text{Si, Ge}$) and (**70**; $E = \text{Si, Ge}$) in good yields.

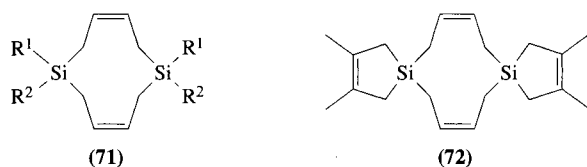


9.36.3 RINGS WITH TWO OR MORE HETEROATOMS

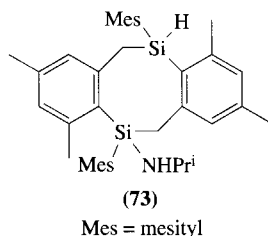
9.36.3.1 Rings Containing E—(CH₂)_n—E and Related Units

The substituted disilacyclodeca-3,8-diene (**71**; $R^1 = \text{Me}, R^2 = \text{vinyl}$) is formed in low yield as a mixture of diastereomers when dichloromethylvinylsilane is reacted with butadienemagnesium and the mixture is subsequently treated with methanol in the presence of triethylamine $\langle 85\text{JOM}(289)45 \rangle$. (The 1,1,6,6-tetramethyl analogue of (**71**) is also known $\langle 68\text{JOC}1975 \rangle$). Silacyclopent-3-enes or dialkylsilicon reagents react with the catalyst $[\text{Mo}(\text{NC}_6\text{H}_3\text{Pr}^i_2-2,6)(\text{CHCMe}_2\text{Ph})\{\text{OCMe}(\text{CF}_3)_2\}_2]$ in benzene to afford the ten-membered disilacyclodeca-3,8-dienes (**71**; $R^1 = R^2 = \text{Me, Ph}$ and $R^1 = \text{Me}, R^2 = \text{Ph}$) $\langle 91\text{CC}1720, 93\text{OM}1780 \rangle$. The crystal and molecular structure of *cis,cis*-(**71**; $R^1 = R^2 = \text{Ph}$) was determined. A 97% yield of (**72**) was obtained in the ring-opening of 2,3-dimethyl-5-sila-spiro[4.4]nona-2,7-diene catalyzed by *n*-butyllithium in HMPA $\langle 90\text{OM}2811 \rangle$. The structure of (**72**) was determined by x-ray crystallography.

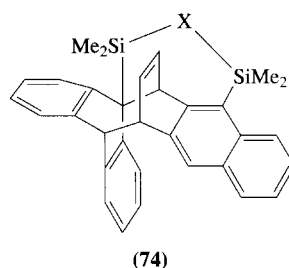
The tetrahydrobenzo[*b,f*][1,5]disilocin (**73**) was isolated in 20% yield from the reaction between



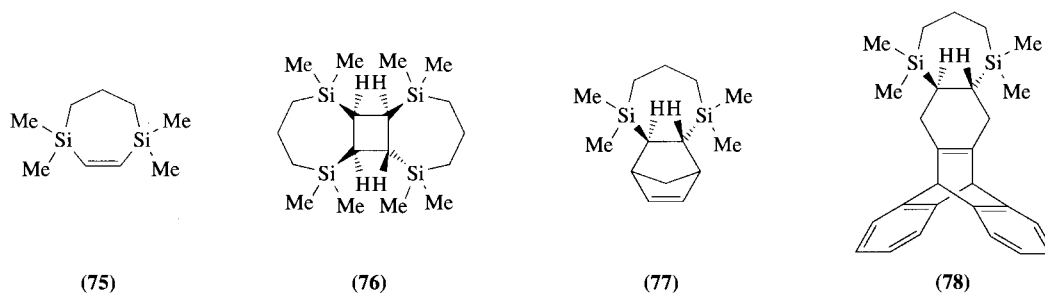
1,2-dichlorotetramesityldisilane and lithium isopropylamide <89CB885>. The crystal structure of (73) was determined.



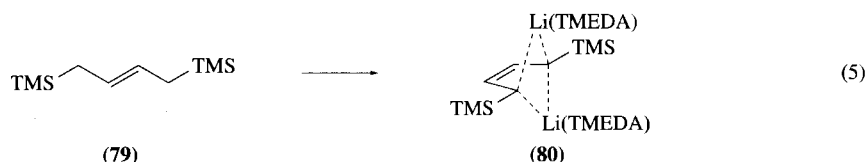
The irradiation of bis(dimethyl-9-anthrylsilyl)methane in benzene or methylcyclohexane at 335 nm gave a quantitative yield of the dissymmetrical product (74; X = CH₂) <89JCR(S)146>. The photocyclodimerization yield of (74; X = CH₂) was small compared with that of the corresponding siloxane (74; X = O) <81CPL(78)446>.

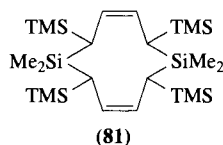


Low-temperature trapping experiments of the photolysis products of disilacycloheptene (75), which was prepared by insertion of ethyne into the Si—Si bond of 1,1,2,2-tetramethyl-1,2-disilacyclopentane <75JA931>, provided evidence for the *trans* isomer of (75) <90JA6601>. GC-MS analyses indicated that, as the decay of *trans*-(75) progressed, a mixture of six dimers of *m/z* 368 was formed. Only one of the dimeric products was successfully isolated in pure form by preparative GC; this dimer was assigned the unsymmetrical *cis,trans*-fused cyclobutene structure (76) on the basis of NMR data. Trapping experiments of metastable *trans*-(75) by Diels–Alder cycloadditions with cyclopentadiene and 9,10-dihydro-11,12-dimethylene-9,10-ethanoanthracene afforded (77) and (78), respectively. The crystal and molecular structures of (78) were determined.

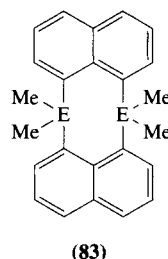
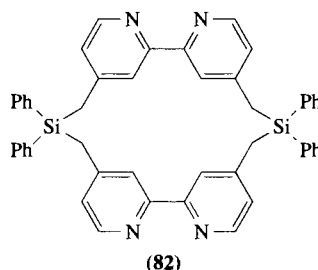


Metalation of (79) with 2 equiv. of BuⁿLi(TMEDA) in *n*-hexane afforded (80) as a red crystalline solid in 80% yield (Equation (5)); the solid was characterized by NMR spectroscopy <91OM3167>. When reacted with dichlorodimethylsilane, (80) gave the ten-membered ring (81) in 10% yield.

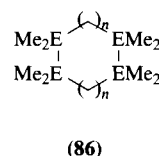
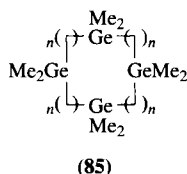
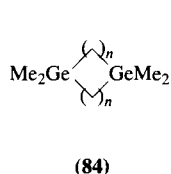




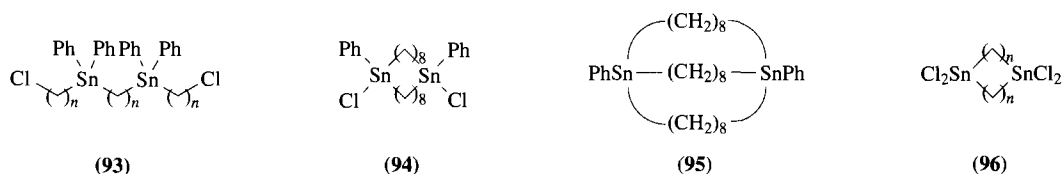
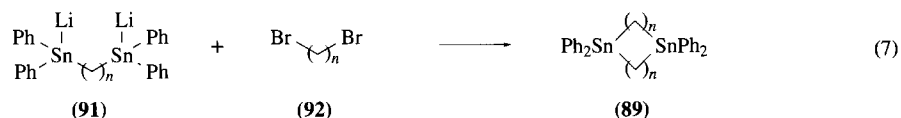
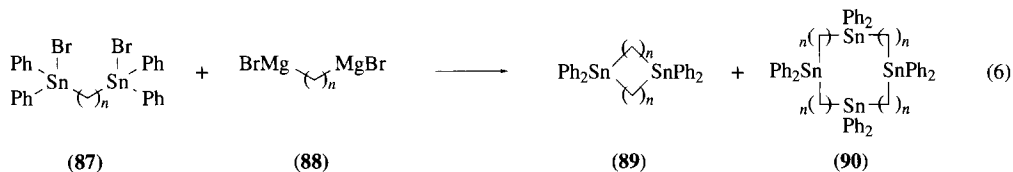
The "one-pot" cyclization of the dilithium salt of deprotonated 4,4'-dimethyl-2,2'-bipyridine with dichlorodiphenylsilane under optimized conditions gave a 2.2% yield of the 18-membered ring (**82**), which was structurally characterized by x-ray crystallography <94TL7233>. The eight-membered ring (**83**; E = Si) was prepared in two steps from 1,8-dilithionaphthalene and 1,1,2,2-tetrachloro-1,2-dimethyldisilane; the analogous germanium and tin compounds were prepared directly from the dilithium reagent and appropriate dimethylgermanium and dimethyltin dichlorides <94JOM(484)137>. The crystal and molecular structure of (**83**; E = Ge) was determined.



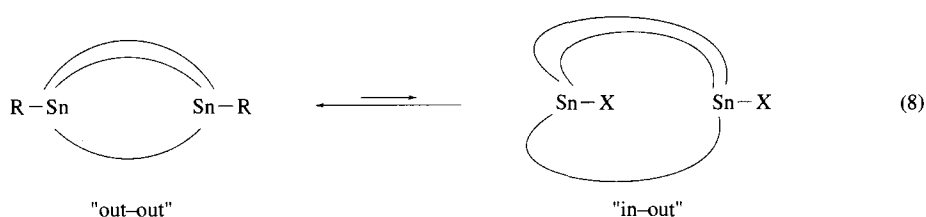
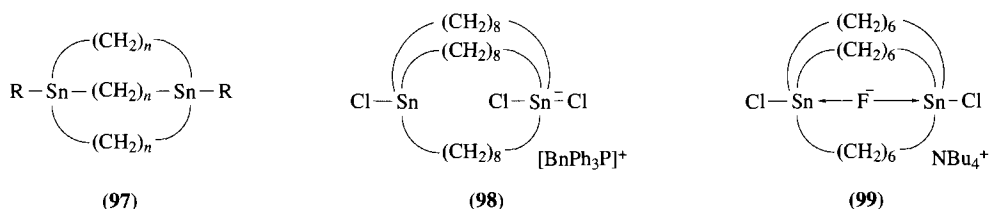
The digermamacrocycles (**84**; $n = 4-6, 8, 10$) and tetragermamacrocycles (**85**; $n = 4-6, 8, 10$) were prepared in low yields by the coupling of α,ω -bis(bromodimethylgermyl)alkanes with di-Grignard reagents <92JCS(P2)2217>. The 1:1 products (**84**) were separated from the dimers (**85**) by chromatography and were characterized by ^{13}C and ^{73}Ge NMR and elemental analyses. Attempts to prepare (**84**; $n = 3$) and (**85**; $n = 3$) by the reaction of 1,3-dibromopropane with 1,3-bis(lithiodimethylgermyl)propane were unsuccessful, yielding (**86**; E = Ge) instead, presumably in a Wurtz-type reaction. Treatment of α,ω -bis(bromodimethylstannyl)alkanes with sodium in liquid ammonia led to the tetrastannacycloalkanes (**86**; E = Sn, $n = 3-6$), which were characterized by multinuclear NMR spectroscopy and mass spectrometry <90MI 936-01>.



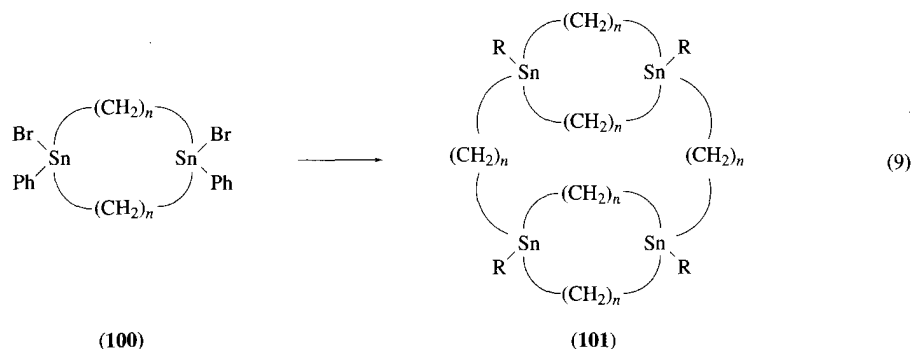
Compounds (**84**; $n = 4, 6$) do not transfer anions. The molecular structure of (**84**; $n = 6$) was determined by x-ray crystallography <93JCS(P2)2389>. The α,ω -bis(bromodiphenylstannyl)alkanes (**87**; $n = 4-6, 8, 10, 12$), which were prepared from the corresponding α,ω -bis(triphenylstannyl)alkanes by treatment with HBr, reacted with the di-Grignard reagents (**88**; $n = 4-6, 8, 10, 12$) to give the mixture of macrocyclic ditin and tetratin compounds (**89**; $n = 4-6, 8, 10, 12$) in moderate and (**90**; $n = 4-6, 8, 10, 12$) in low yields, respectively (Equation (6)) <83OM175, 84OM9>. Better yields of (**89**) were obtained by lithiation of (**87**) to give (**91**; $n = 4-6, 8, 10, 12$), followed by treatment of the lithium salts with α,ω -dibromoalkanes (**92**; $n = 4-6, 8, 10, 12$) (Equation (7)). Good yields of the tetratin macrocycles (**90**; $n = 4-6$) were obtained by treating (**87**; $n = 4-6$) with $\text{Cl}(\text{CH}_2)_n\text{MgBr}$ ($n = 4-6$) to give the dichlorides (**93**; $n = 4-6$) and allowing these to react with (**91**; $n = 4-6$). The macrocycles were purified by preparative reversed-phase chromatography and characterized by NMR spectroscopy, molecular weight determinations, and elemental analyses. Treatment of (**89**; $n = 8$) with HCl yielded the dichloro compound (**94**), which, when reacted with (**88**; $n = 8$), gave 1,10-diphenyl-1,10-distannabicyclo[8.8.8]hexacosane (**95**) in 15% yield <84CC1159>. The molecular structure of the macrobicyclic was determined by x-ray crystallography. Macrocycles (**96**; $n = 8, 10, 12$) were prepared by treatment of (**89**; $n = 8, 10, 12$) with HCl; the chloride binding properties of the macrocycles were investigated by ^{119}Sn NMR spectroscopy <87OM145>.



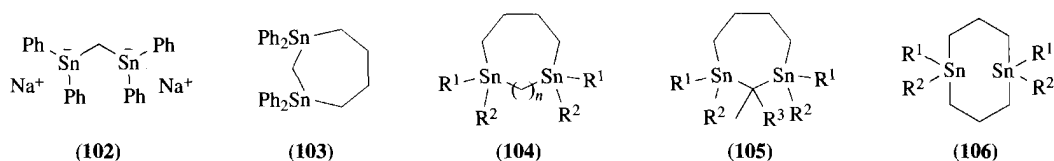
Treatment of the phenyl-substituted macrobicycles (**97**; $n = 6, 8, 10, 12$, $R = Ph$) with HCl in CH_2Cl_2 afforded (**97**; $n = 6, 8, 10, 12$, $R = Cl$) [⟨87JA7878⟩](#). The selectivity of the Lewis-acidic hosts (**97**; $n = 6, 8, 10, 12$, $R = Cl$) for the complexation of chloride was investigated. Compound (**97**; $n = 6$, $R = Cl$) was characterized by x-ray crystallography and was found to bind fluoride strongly and to exclude other halides [⟨88TL4261⟩](#). The molecular structures of the macrobicycles (**97**; $n = 6, 8$ and $R = Cl$) were determined by x-ray crystallography [⟨89JA6294⟩](#). Moreover, the complexes of (**97**; $n = 8$, $R = Cl$) with benzyltriphenylphosphonium chloride, (**98**), and of (**97**; $n = 6$, $R = Cl$) with tetrabutylammonium fluoride, (**99**), were investigated by x-ray crystallography and solid-state ^{119}Sn NMR spectroscopy. In both cases, the halide ions are encrypted within the cavities of the bicyclic hosts. Complex (**98**) is a stannate–stannane species with one strong and one weak interaction between the chloride and the two tin centers; (**99**) is a bis(hemistannate) species in which the Lewis-acidic tin atoms bind the guest fluoride simultaneously. In solution, however, rapid exchange occurs between the fluoride or chloride and the tin atoms. In subsequent work, it was discovered that the smaller members of the macrobicycles (**97**; $n = 6–8$, $R = Cl$) exist in solution as discrete isomers having the “out–out” configuration, but the larger members of the series, (**97**; $n = 10, 12$, $R = Cl$), exist as mixtures of the major “out–out” and minor “in–out” diastereomers (see Equation (8)) [⟨89JOC4626⟩](#). Compounds (**97**; $n = 8, 10, 12$, $R = Br$) were also prepared and their bromide binding properties investigated. Equilibrium constants for the formation of host–guest complexes were measured. The compounds (**97**; $n = 5, 9$, $R = Cl, Ph$) were characterized by x-ray crystallography [⟨91OM1741⟩](#). The structures of the full series of macrobicyclic Lewis-acidic hosts (**97**) were calculated by molecular mechanics.



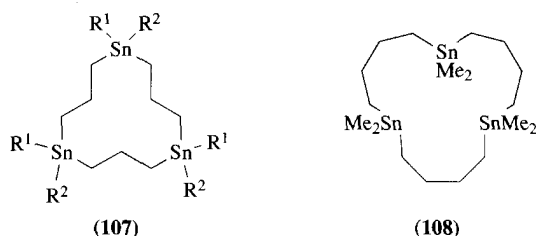
The reaction of the macrocycles (**100**; $n = 4, 5$) with the appropriate di-Grignard reagents resulted in the formation of the macrotricyclic compounds (**101**; $n = 4, 5$, $R = \text{Ph}$; $n = 5$, $R = \text{Cl}$) (Equation (9)) (89TL3501). The chloride binding properties of (**101**; $n = 5$; $R = \text{Cl}$) were investigated by ^{119}Sn NMR spectroscopy.



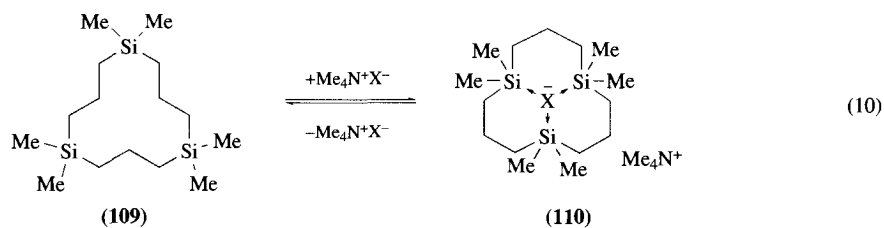
The reaction of (**102**) with 1,4-dichlorobutane in liquid ammonia afforded the 1,3-distannacycloheptane (**103**) (85BSB299). The distannacycloalkanes (**104**; $n = 1-4$, $R^1 = R^2 = \text{Me}$) and (**105**; $R^1 = R^2 = \text{Me}$, $R^3 = \text{H}$, Me) were prepared by reactions of the corresponding 1, n -bis(chlorostannyl)alkanes with the di-Grignard reagent of 1,4-dibromobutane (92JOM(429)311). The alternative coupling, namely reaction of bis(dimethylsodiostannyl)propane with 1,3-dibromopropane, was employed to synthesize the 1,5-distannacyclooctane (**106**; $R^1 = R^2 = \text{Me}$). Compounds (**104**; $n = 1-4$, $R^1 = R^2 = \text{Me}$), (**105**; $R^1 = R^2 = \text{Me}$, $R^3 = \text{H}$, Me), and (**106**; $R^1 = R^2 = \text{Me}$) were converted into the corresponding chlorides, which in turn were converted into the mesylates and triflates.



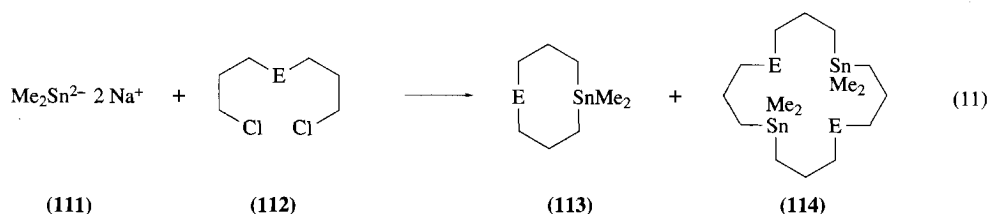
A similar strategy was employed to prepare the tristannacycloalkanes (**107**; $R^1 = R^2 = \text{Me}$) and (**108**) (89OM2755, 90JOM(381)C53) from the disodium salts of the appropriate distannanes and the corresponding bis(ω -chloroalkyl)dimethyltin under high-dilution conditions. Compound (**107**; $R^1 = R^2 = \text{Me}$) is a colorless liquid that can be transformed into the trichloro derivative (**107**; $R^1 = \text{Me}$, $R^2 = \text{Cl}$) or the hexachloro compound (**107**; $R^1 = R^2 = \text{Cl}$) by reaction with the appropriate quantity of mercuric chloride. The complexing behavior of (**107**) and (**108**) towards chloride and bromide was investigated. The x-ray crystal structure of $[(\text{107}; R^1 = R^2 = \text{Cl}) \cdot \text{Cl}]^- [\text{Ph}_3\text{P}=\text{N}=\text{PPh}_3]^+$ revealed that the macrocycle was acting as a bidentate Lewis acid.



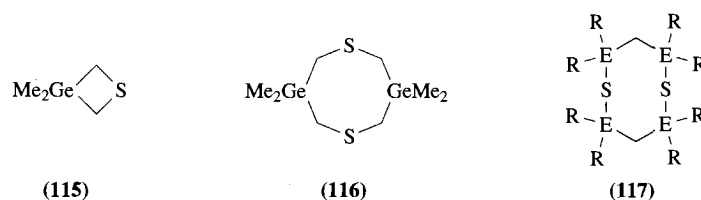
Compounds (**107**; $R^1, R^2 = \text{Me}$) and (**108**) transport chloride and bromide ions from one aqueous solution to another. The cyclotrisilane (**109**), prepared from commercially available 3-chloropropyltrimethoxysilane in nine steps (88TL297), was structurally assigned by mass spectrometry and ^1H and ^{13}C NMR spectroscopy. A solution of (**109**) in dichloromethane transported chloride or bromide ions from one aqueous solution to another, but not fluoride or iodide ions; host-guest complexes of type (**110**) (Equation (10)) were postulated as intermediates in the transport processes.



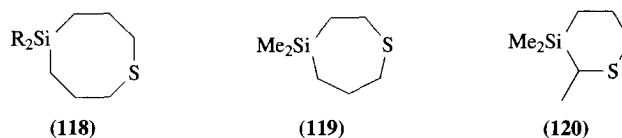
Coupling of (111) with (112; E = S, Se) afforded the 8- and 16-membered products (113; E = S, Se) and (114; E = S, Se) in low yields (Equation (11)), which were purified by column chromatography <94H(39)431>. With 1 or 2 equiv. of methyl triflate, (114; E = Se) was converted into the mono- or bis-methylselenonium salts, respectively.



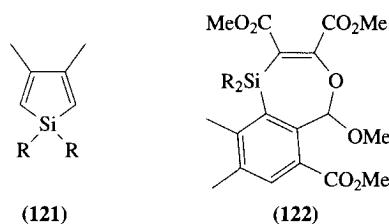
The germathietane (115) dimerizes quantitatively into eight-membered (116) in the presence of sodium sulfide <84SRI21>. The tetrastannadithiacyclooctane (117; E = Sn, R = Ph) was prepared from sodium sulfide and bis(bromodiphenylstannyl)methane and was characterized by ^1H , ^{13}C , and ^{119}Sn NMR spectroscopy <84JOM(273)303>. The germacycle (117; E = Ge, R = Me) was prepared similarly <85JOM(282)315>.



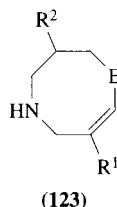
The 1-thia-5-silacyclooctanes (118; R = F, MeO) were prepared by photochemical addition of gaseous hydrogen sulfide to the appropriate diallylsilane <83JGU2168, 84JGU1393>. The thiasilacycloheptane (119) is the only product when allyldimethyl(2-mercaptoethyl)silane is photolyzed <93TL3889>. The isomeric dimethyl(3-thiolpropyl)vinylsilane, however, gives under similar conditions a 1:2 mixture of seven-membered (119) and six-membered (120). The conformational behavior of (dibenzochalcogeno)silocins and -silonins was investigated by ^1H , ^{13}C , and ^{29}Si NMR spectroscopy <88JGU349>.



The reaction of the siloles (121; R, R = $(\text{CH}_3)_2$ or $(\text{CH}_2)_4$) with dimethyl ethynedicarboxylate affords the seven-membered benzo (122; R, R = $(\text{CH}_3)_2$ or $(\text{CH}_2)_4$) <93BCJ2682>.

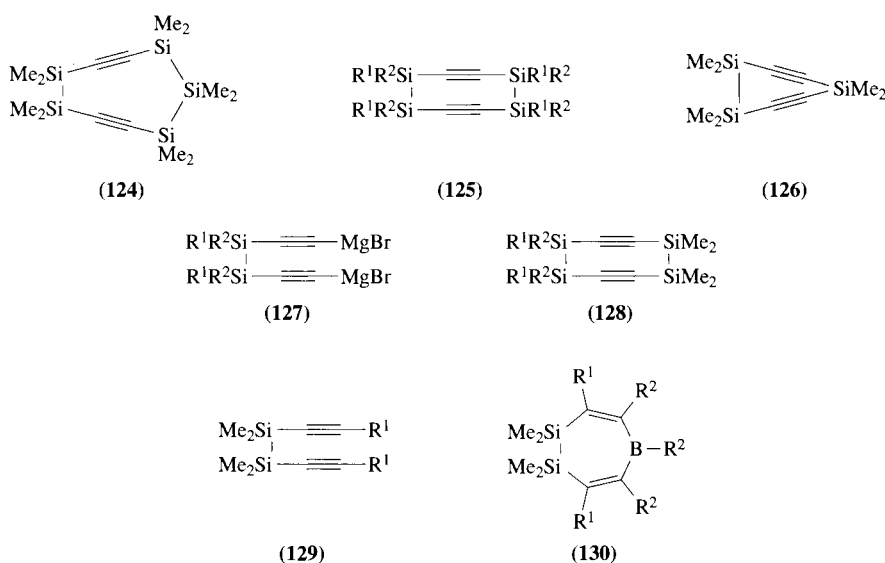


High yields of the azasilocines and azagermocines (**123**; E = SiMe₂, GeEt₂, R¹ = H, Me, R² = Et, Bu) were obtained in one-pot syntheses when the appropriate diallylamine was treated consecutively with three different alkyllithium reagents, followed by the dihalosilane or dihalogermane, respectively <91CC1001>.



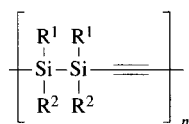
9.36.3.2 Rings Containing E—C≡C—E and Related Units

The nine-membered pentasilacyclodiyne (**124**) was prepared from 1,3-dichlorohexamethyltrisilane by reaction with the appropriate di-Grignard reagent <83JA3359>. Irradiation or FVP of (**124**) resulted in ring contraction and extrusion of dimethylsilylene to give (**125**; R¹ = R² = Me) in 10% or 63% yields, respectively; (**125**; R¹ = R² = Me) was characterized by x-ray crystallography. A 3% yield of the trisilacycloheptadiyne (**126**) was also isolated from the pyrolysis products. Treatment of 1,2-dichlorodisilanes with di-Grignard reagents (**127**; R¹ = R² = Me, Buⁿ) led to the eight-membered rings (**128**; R¹ = R² = Me, Buⁿ) in high yields <88CC954>. Use of dilithium compounds instead of (**127**) led to polymers. Compounds (**129**; R¹ = H, SnMe₃) react with trialkylboranes with cyclization to give (**130**; R¹ = H and R² = Me, Et, R¹ = SnMe₃ and R² = Me, Et, Prⁱ) <88CC1624, 86JOM(303)73>.

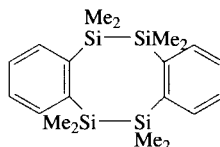


The Grignard approach was also used to prepare the macrocycles (**125**; R¹ = R² = Et, and R¹ = Me, R² = Ph, Et, Buⁿ, Hexⁿ) <92OM1604>. Two isomers of (**125**; R¹ = Me, R² = Ph) were isolated in 20% and 17% yields; x-ray crystal structure analyses revealed that the two isomers had the *cis-trans* and the all-*trans* configurations. Treatment of (**125**) with a catalytic amount (0.5–1 mol%) of BuⁿLi in THF at room temperature caused ring opening to give polymers (**131**) with high molecular weights. Heating of (**125**; R¹ = R² = Me) with 1,3-dienes or their precursors at 400°C for 12 h brought about a Diels–Alder reaction followed by dehydrogenation to give dibenzo products <82CL1971>. For example, (**132**) was obtained from (**125**; R¹ = R² = Me) and α-pyrone. Prolonged heating of (**132**) in bromobenzene at 200°C caused isomerization to the metacyclophane (**133**). The related tetragermacyclooctadiyne (**134**) and the disiladigermacycle (**135**) were prepared in moderate yields by reactions of 1,2-dichlorotetramethyldigermene with the appropriate di-Grignard reagent <94CL1439>. In the presence of TCNE, (**134**) oligomerized into (**136**; E = Ge) and (**137**) in 20% and

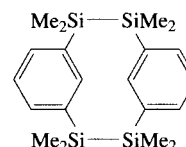
5% yields, respectively, presumably via charge-transfer complexes. With the acceptor ddq, however, (125; $R^1 = R^2 = \text{Me}$), (134), and (135) formed [2 + 6] cycloadducts. For (125; $R^1 = R^2 = \text{Me}$) and (134) only one product is possible, but (135) yields (138) and (139) in 2:1 ratio.



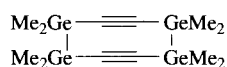
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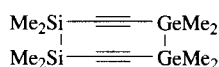
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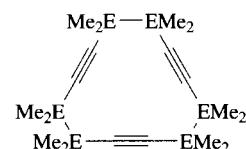
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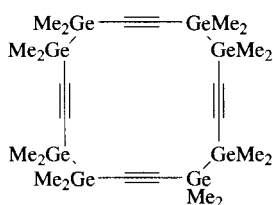
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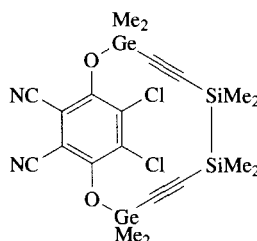
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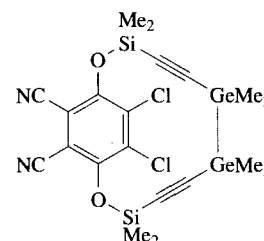
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(137)



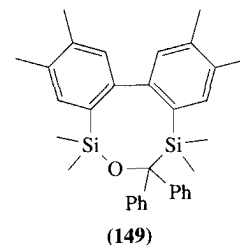
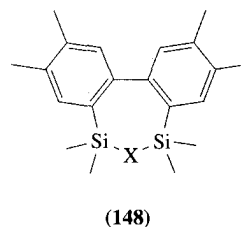
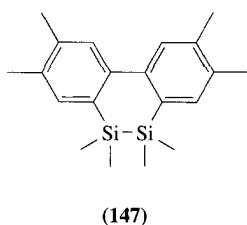
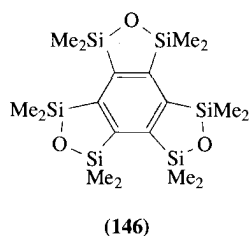
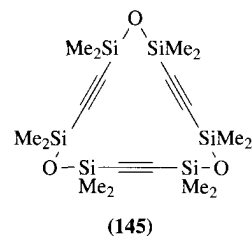
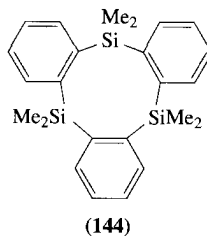
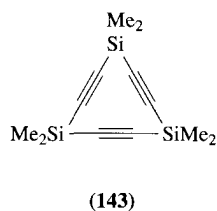
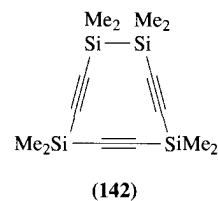
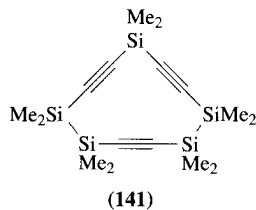
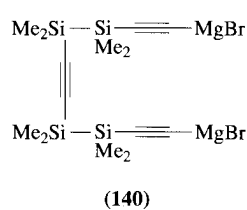
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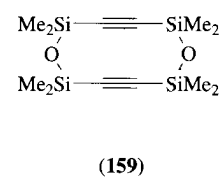
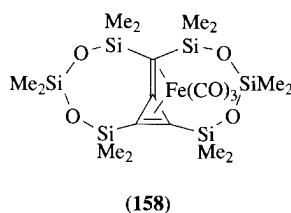
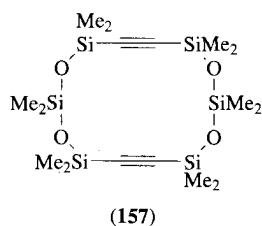
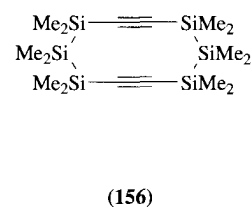
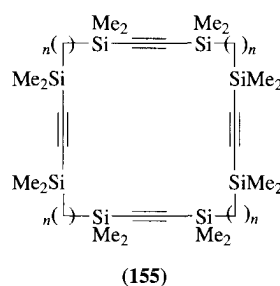
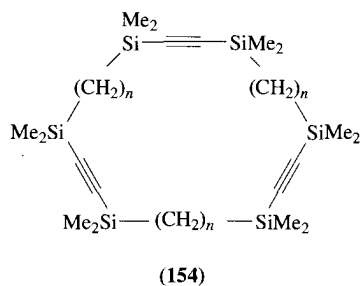
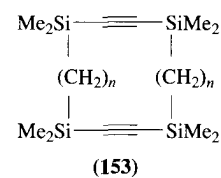
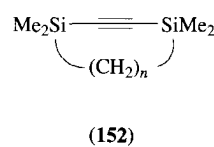
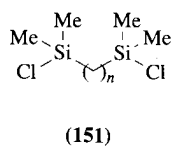
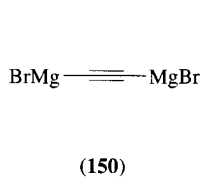
(139)

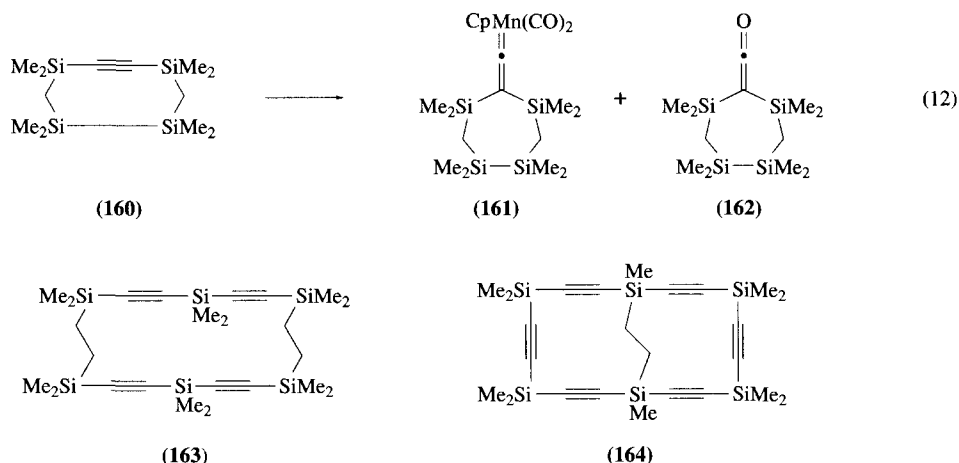
The coupling of (140) with 1,2-dichlorotetramethyldisilane afforded the hexasilacyclododecatriyne (136; $E = \text{Si}$) (84CL595), which, when pyrolyzed at 540°C, gave by stepwise extrusion of dimethylsilylene the cyclic triynes (141), (142), and (143) in 8%, 27%, and 11% yields, respectively. Upon pyrolysis of (136; $E = \text{Si}$) at 690°C, however, (143) was formed as the only product in 68% yield. Cycloaddition of (143) with α -pyrone afforded (144), which was characterized by x-ray crystallography. Selective oxidation of (136; $E = \text{Si}$) with trimethylamine *N*-oxide gave 15-membered (145), which at 710°C slowly underwent an intramolecular [2 + 2 + 2] reaction to produce (146). Compound (146) was also formed among other products when (145) was heated with $[\text{M}(\text{CO})_6]$ ($M = \text{Cr}, \text{W}$) in *n*-octane at 140°C (84JA8315). The photoelectron spectra of (125; $R^1 = R^2 = \text{Me}$), (136; $E = \text{Si}$), and (143) have been recorded and their orbital sequences calculated according to MINDO/3 and MNDO methods (85JA3046). The calculations support strong σ - π interactions in the compounds. A review of reactions controlled by strong σ - π interactions is available (87PAC1637). Treatment of (147) with MCPBA or elemental sulfur afforded quantitative yields of the insertion products (148; $X = \text{O}, \text{S}$) (87CL1075). Compound (148; $X = \text{NH}$) was also formed from (147) in two steps. A 40% yield of (149) was obtained when a benzene solution of (147) was photolyzed in the presence of benzophenone (87CL983).

Reactions of the di-Grignard (150) with α,ω -dichlorodisilanes (151; $n = 0-4$) result in mixtures of [1 + 1], [2 + 2], [3 + 3], and [4 + 4] coupling products (85AG(E)565). Thus, (152; $n = 3, 4$), (153; $n = 0-4$), (154; $n = 0-2$), and (155; $n = 1, 2$) were obtained in low yields from these mixtures. The ten-membered hexasilacyclodiyne (156) gave high yields of (157) upon oxidation with trimethylamine *N*-oxide (87JA6880). Compound (157), when refluxed in toluene for 12 h in the presence of $\text{Fe}_2(\text{CO})_9$, gave complex (158) in 45.5% yield in which a substituted methylenecyclopropene ligand is coordinated in η^4 manner to the $\text{Fe}(\text{CO})_3$. The structure of (158) was established by x-ray diffraction. The related (159) was synthesized as its bis(dicobalt hexacarbonyl) derivative, from which the free ligand was liberated by cerium(IV) oxidation (89OM2779). Compound (159), which has the chair conformation in the solid state (86ACS(B)604), gave with $\text{Fe}_2(\text{CO})_9$ a trimethylenemethane iron complex (88CL485). Photolysis of the cyclic monoethyne (160) in the presence of $\text{CpMn}(\text{CO})_3$ in THF gave the vinylidene complex (161) in 45% yield, together with a small quantity of the ketene

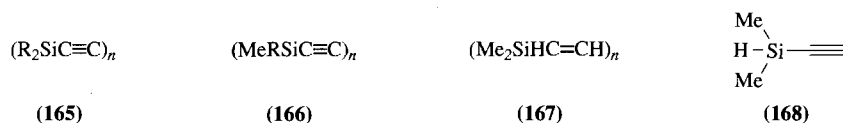


(162) (Equation (12)) <92CL339>. Coupling the appropriate di-Grignard reagent with the appropriate silicon dihalide was also employed to prepare (163) and (164) in 2% and 1% yields, respectively <87JGU1925, 88JGU429>. The crystal and molecular structures have been reported of 18-membered (163) <90JOM(389)1> and similar compounds containing alkenic and alkynic bonds <88MI 936-02, 89MI 936-02>.

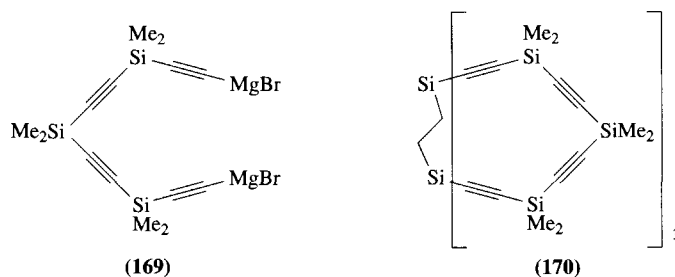




The cyclic silapolyynes (**165**; $n \geq 5$, R = Me, Ph) have been synthesized in high yields by the reactions of the dilithium derivatives of the diorganodiethynylsilanes with the corresponding diorganodichlorosilanes $\langle 88\text{CC}1079 \rangle$. According to an x-ray crystal structure determination of (**165**; $n = 6$, R = Me), the 18-membered macrocycle adopts a chair conformation $\langle 89\text{ICA}137 \rangle$. Compounds (**166**; $n = 4-8$, 10 and R = H, Me, vinyl) are also known $\langle 91\text{MI} 936-01 \rangle$. The related compound (**167**; $n = 6$) was prepared by autohydrosilylation of ethynyldimethylsilane (**168**) $\langle 89\text{MI} 936-03 \rangle$. The crystal and molecular structures of (**167**; $n = 5$) were determined $\langle 91\text{MI} 936-02 \rangle$.



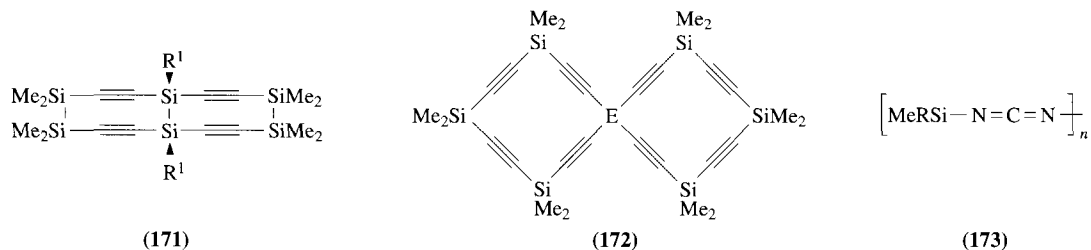
A straightforward method of preparation of macrocycles of the type (**165**) involves the introduction of ethyne into a suspension of K-Na alloy in THF and simultaneous addition of a solution of dimethyl- or diphenyldichlorosilane in the same solvent $\langle 89\text{JOM}(369)\text{C}39 \rangle$. Thus, for example, with dimethyldichlorosilane a mixture of products was obtained that contained macrocycles (**165**, $n = 3-12$, R = Me), according to GC-MS analysis. From this mixture, compounds (**165**; $n = 4, 5$, R = Me) were isolated and characterized by spectroscopic methods, analyses, and x-ray crystallography $\langle 91\text{M}661 \rangle$. Whereas (**165**; $n = 4$, R = Me) contains a symmetrical planar 12-membered ring of D_{4h} symmetry, the 15-membered (**165**; $n = 5$, R = Me) has the envelope conformation. Reaction of the di-Grignard (**169**) with 1,2-bis(trichlorosilyl)ethane under high-dilution conditions afforded macrotricyclic (**170**) in 0.8% yield $\langle 90\text{MI} 936-02 \rangle$.



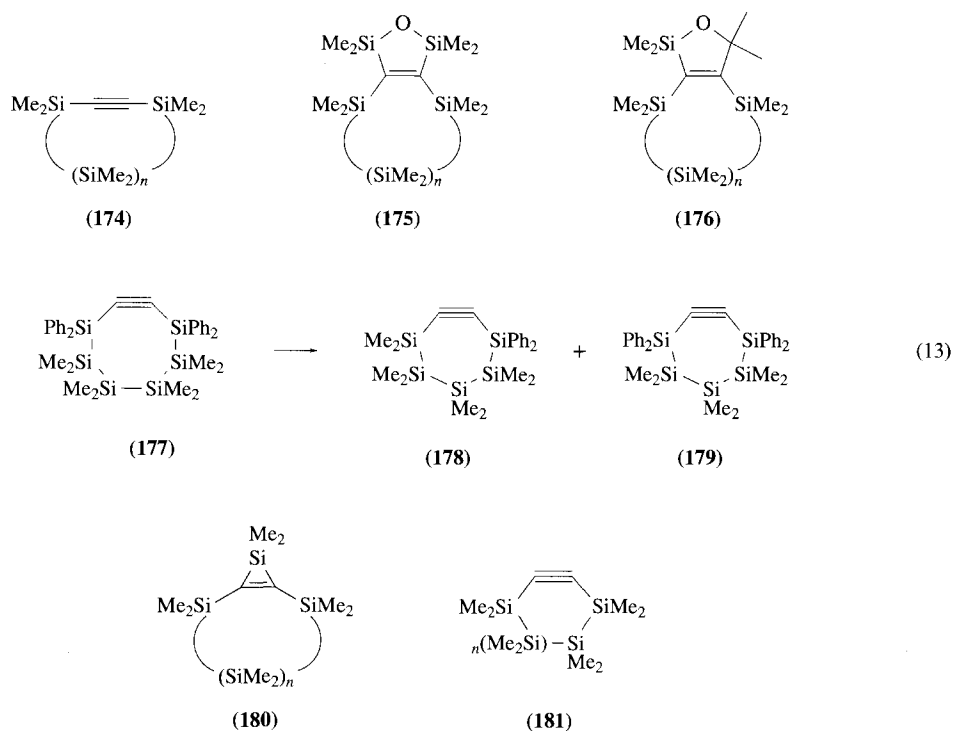
A variety of highly unsaturated macrocyclic and macrobicyclic silahydrocarbons have been synthesized from appropriate di-Grignard precursors and the corresponding dihalosilanes $\langle 90\text{JOM}(389)\text{I} \rangle$, some of which have been characterized by x-ray crystallography $\langle 91\text{MI} 936-02 \rangle$.

The di-Grignard reagent (**127**; $\text{R}^1 = \text{R}^2 = \text{Me}$), when reacted with 0.5 equiv. of 1,2-diisopropyltetrachlorodisilane, gave the bicycle (**171**; $\text{R}^1 = \text{Pr}^i$) in 22% yield, which has the *cis*

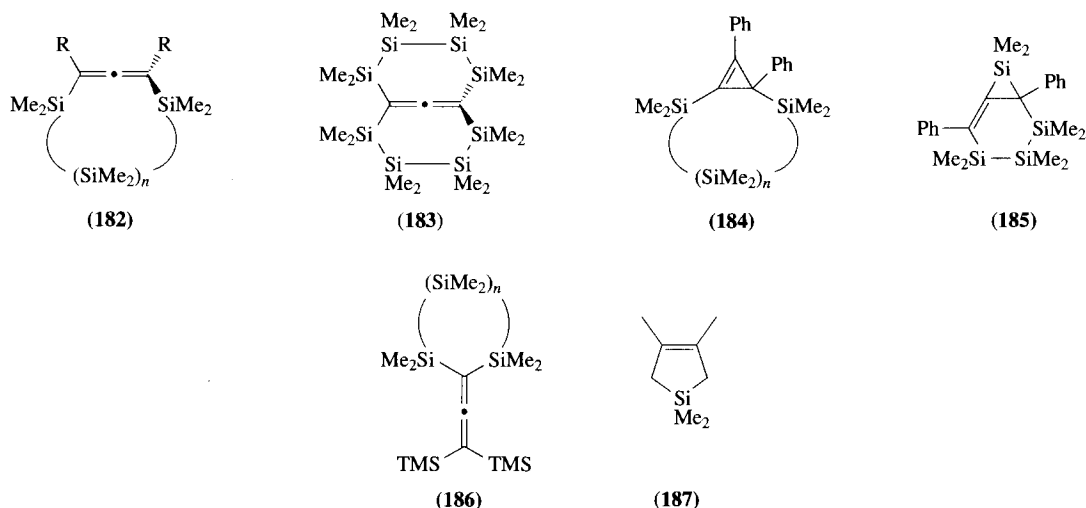
configuration according to NMR data <91CL545>. The corresponding permethyl-substituted compound (**171**; $R^1 = \text{Me}$) is also known <91CL549>. Treatment of tetrachlorosilane or tetrachlorogermane with 2 equiv. of (**169**) gave the macrocyclic spiro compounds (**172**; $E = \text{Si, Ge}$) in 2.5% and 2% yields, respectively <91MI 936-03>. The macrocycles (**173**; $R = \text{H, Me, vinyl}$) with carbodiimide bridges between the silicon centers were prepared by reactions of the respective dichlorosilanes with cyanamide <93CB2569>. The crystal and molecular structures of (**173**; $n = 4$, $R = \text{Me}$) were determined by x-ray crystallography.



The hexasilacyclooctyne (**174**; $n = 4$) was obtained in 46% yield as a colorless liquid by reaction of the ethyne di-Grignard reagent (**150**) with 1,6-dichlorododecamethylhexasilane <90TL3597>. Photolysis in the presence of triethylsilane and thermolysis (at 550°C) of (**174**; $n = 4$) effected ring contraction and formation of the pentasilacycloheptyne (**174**; $n = 3$) in 22% and 18% yields, respectively. The molecular structure of (**174**; $n = 3$) was determined by x-ray diffraction. In the above-mentioned photolytic synthesis of (**174**; $n = 3$), compounds (**175**; $n = 2, 3$) were also formed in low yields <93OM803>. When the photolysis was carried out in the presence of a large excess of acetone, compounds (**176**; $n = 2, 3$) were formed in low yields, together with (**174**; $n = 3$) as the main product. Compound (**174**; $n = 3$) in *n*-hexane undergoes further photolytic ring contraction to give octamethyltetrasilacyclohexyne in 20% yield. Moderate yields of the hexasilacyclooctyne (**177**) were obtained when bis(chlorodiphenylsilyl)ethyne was treated with 1,4-dichlorooctamethyltetrasilane in the presence of magnesium in THF <93T6359>. Compound (**177**) when irradiated in cyclohexane afforded the cycloheptynes (**178**) and (**179**) in 16% and 14% yields, respectively (Equation (13)). The reaction of polysilacycloalkynes (**174**; $n = 2-4$) with dimesitylsilylene (generated from photolysis of 2,2-dimesitylhexamethyltrisilane) gave the bicyclic products (**180**; $n = 2-4$) in moderate yields. Photolysis of (**180**; $n = 2$) yielded (**181**; $n = 2$) along with (**174**; $n = 2$). Compound (**180**; $n = 4$) gave under the same conditions ring-expanded (**181**; $n = 4$) along with (**181**; $n = 3$) and some (**174**; $n = 4$).

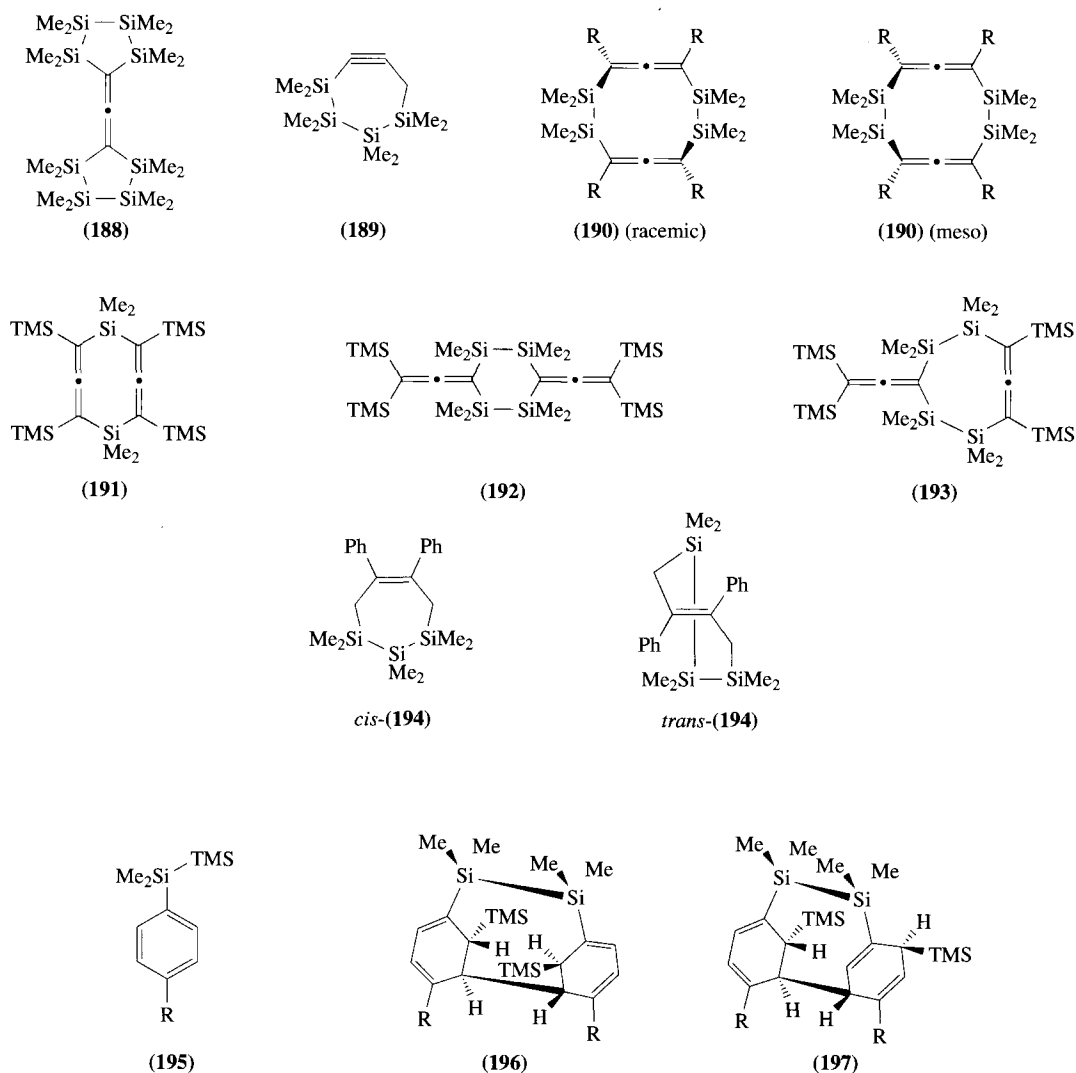


The 1,3-diphenylallene dianion, prepared from 1,3-diphenylallene and 2 equiv. Bu^nLi , reacted with the appropriate α,ω -dichloropermethyilsilanes to afford the polysila-bridged allenes (**182**; $n = 1, 2, 4$, $\text{R} = \text{Ph}$) in 11%, 72%, and 24% yields, respectively ($\langle 93\text{JA}3111 \rangle$). The reaction of hexachloropropene and 1,4-dichlorooctamethyltetrasilane in the presence of magnesium in THF gave octasila[4.4]betweenallene (**183**) in 34% yield. The molecular structures of (**182**; $n = 1, 2$, $\text{R} = \text{Ph}$) and (**183**) were determined by x-ray crystallography. Semiempirical PM3 calculations for the smaller polysilacyclic allenes and betweenallenes were carried out. Irradiation of (**182**; $n = 2$, $\text{R} = \text{Ph}$) in *n*-hexane gave (**184**; $n = 2$) and (**185**) in 45% and 20% yields, respectively ($\langle 94\text{OM}3402 \rangle$). Irradiation of (**182**; $n = 4$, $\text{R} = \text{Ph}$) under the same conditions gave (**184**; $n = 4$), (**182**; $n = 3$, $\text{R} = \text{Ph}$), and (**184**; $n = 3$) in 59%, 14%, and 23% yields. These photoreactions proceed via vinylcarbene intermediates. For the synthesis of the compounds (**182**; $n = 1-3$, $\text{R} = \text{TMS}$), a similar strategy was employed ($\langle 93\text{JA}2534 \rangle$); seven-membered (**182**; $n = 2$, $\text{R} = \text{TMS}$) was characterized by x-ray crystallography. Gas-phase flow copyrolysis of (**182**; $n = 3$, $\text{R} = \text{TMS}$) with excess 2,3-dimethylbutadiene gave isomeric (**186**; $n = 3$), together with small amounts of ring-contracted (**186**; $n = 2$) and the dihydrosilole (**187**). Gas-phase flow pyrolysis of (**182**; $n = 2$, $\text{R} = \text{TMS}$) resulted in the formation of isomerized compound (**186**; $n = 2$) and a small amount of (**182**; $n = 1$, $\text{R} = \text{TMS}$).



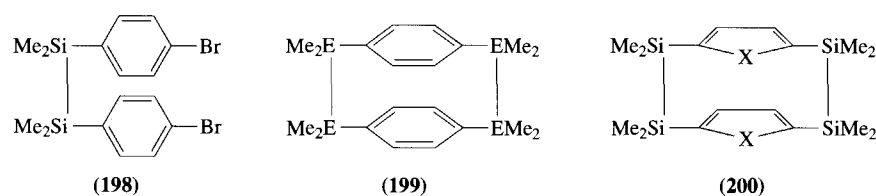
Reaction of allene with Bu^nLi followed by 1,4-dichlorooctamethyltetrasilane gave a 26% yield of a $\sim 1:1$ mixture of (**183**) and (**188**) ($\langle 93\text{JA}1591 \rangle$). Sequential metalation of propargyl bromide with magnesium and Bu^nLi followed by quenching with 1,4-dichlorooctamethyltetrasilane afforded the tetrasilacycloheptyne (**189**) in 81% yield. Reaction of (**189**) with 2 equiv. Bu^nLi followed by quenching with the dichlorosilane produced the betweenallene (**183**) in 20% yield and its molecular structure was again determined by x-ray crystallography. Gas-phase flow pyrolysis of (**183**) at 520°C gave a remarkably clean conversion into (**188**) (83% yield). The 1,3-diphenylallene dianion, when reacted with 1,2-dichlorotetramethyldisilane, gave the racemic and meso diastereomers of the ten-membered diallene (**190**; $\text{R} = \text{Ph}$) in 2% and 6% yields, respectively ($\langle 93\text{CL}1171 \rangle$). X-ray crystallographic analyses of both diastereomers of (**190**; $\text{R} = \text{Ph}$) showed the allenic *sp*-carbons to be bent by an average of 4° . Similarly, the diallene (**190**; $\text{R} = \text{TMS}$) was obtained in 57% yield as a 1:1 mixture of racemic and meso diastereomers; the latter was isolated by fractional crystallization and structurally characterized by x-ray diffraction ($\langle 93\text{JA}3794 \rangle$). The eight-membered diallene (**191**) was prepared in 33% yield from 1,3-bis(trimethylsilyl)propyne by treatment with 2 equiv. Bu^nLi in THF followed by the addition of dichlorodimethylsilane. The molecular structure of (**191**) was determined by x-ray crystallography. Photolysis of racemic or meso (**190**; $\text{R} = \text{TMS}$) effected configurational isomerization and after 24 h a 14% yield of the constitutional isomer (**192**) was isolated. In the gas-phase flow pyrolysis of diastereomeric mixtures of (**190**; $\text{R} = \text{TMS}$), a significant amount of (**193**) was produced, together with unreacted starting material and (**192**).

Diastereomer *cis*-(**194**), which was prepared from 2,3-diphenylbutadiene and 1,3-dichlorohexamethyltrisilane in the presence of magnesium, affords a 19% yield of *trans*-(**194**) when irradiated in *n*-hexane ($\langle 91\text{JA}354 \rangle$). The molecular structure of *trans*-(**194**) was established by x-ray crystallography. Photolysis of (**195**; $\text{R} = \text{TMS}$, $\text{SiMe}_2\text{-TMS}$) in *n*-hexane or cyclohexane affords mixtures of (**196**; $\text{R} = \text{TMS}$, $\text{SiMe}_2\text{-TMS}$) and (**197**; $\text{R} = \text{TMS}$, $\text{SiMe}_2\text{-TMS}$) ($\langle 93\text{JOM}(443)\text{C}3$, $\langle 93\text{OM}3474 \rangle$). The molecular structure of (**197**; $\text{R} = \text{TMS}$) was determined by x-ray crystallography.

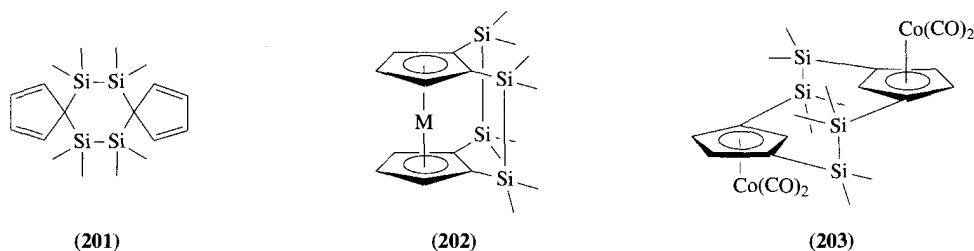


9.36.3.3 Cyclophanes and Related Compounds

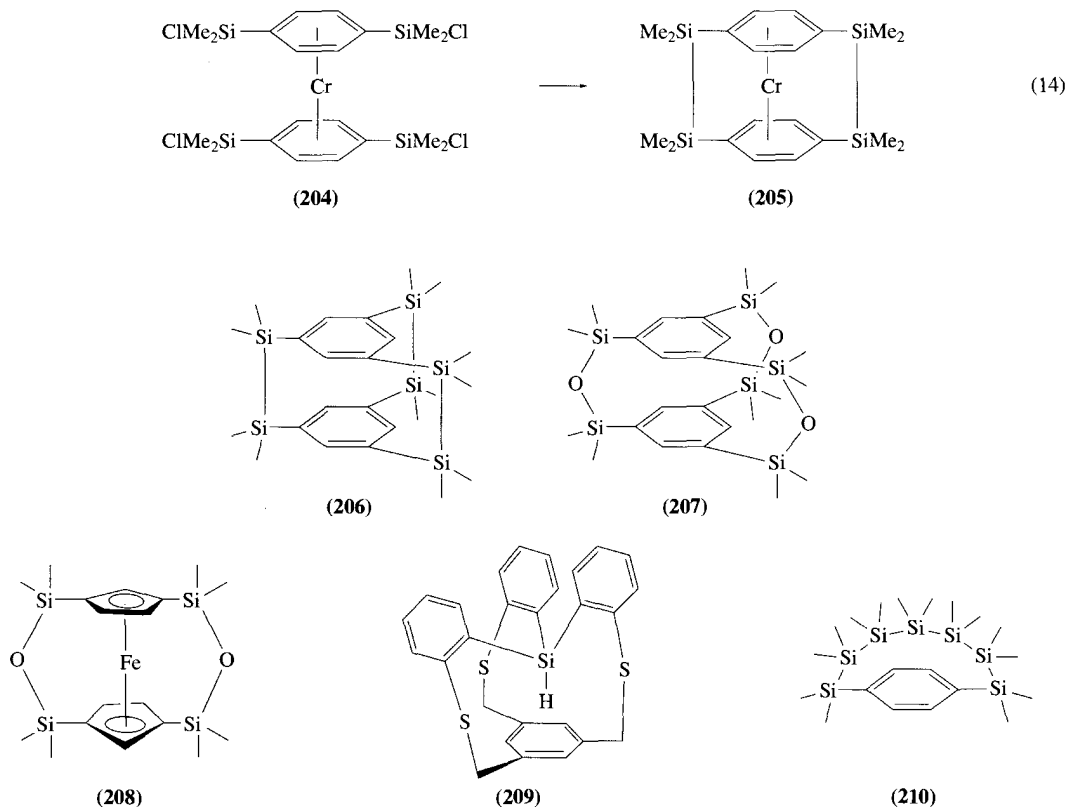
The tetrasil[2.2]paracyclophane (**199**; E = Si) was prepared in 1.6% yield by treatment of (**198**) with magnesium in THF and addition of 1,2-dichlorotetramethyldisilane $\langle 86\text{CL1781} \rangle$. The molecular structure of (**199**; E = Si) was determined by x-ray crystallography. The physical and chemical properties of (**199**; E = Si) were compared with those of the corresponding tetrasil[2.2]meta- and -orthocyclophanes (see (**132**) and (**133**) in Section 9.36.3.2). The reductive coupling of 1,4-bis(chlorodimethylgermyl)benzene with molten sodium in boiling toluene in the presence of [18]-crown-6 afforded colorless crystals of the tetragerma[2.2]paracyclophane (**199**; E = Ge) in 2.6% yield $\langle 90\text{JOM}(390)\text{C27} \rangle$. The molecular structure of (**199**; E = Ge) was determined by x-ray crystallography. The Ge—Ge bonds in (**199**; E = Ge) are inert to trimethylamine *N*-oxide and sulfur in boiling benzene. The photoelectron spectra of (**199**; E = Si) and the thiophenophane and furanophane (**200**; X = S, O) have been recorded $\langle 88\text{JA4117} \rangle$.



Compound **(201)**, when reacted with 1 or 2 equiv. of Bu^nLi , afforded the corresponding mono- and dicyclopentadienide anions, which were used to prepare sandwich complexes $\langle 91\text{CB}2391 \rangle$. Thus, for example, the metallocenes **(202)**; $\text{M} = \text{Fe}, \text{Ge}, \text{Sn}, \text{Pb}$ were obtained in good yields. Unlike the metallocenes **(202)**, where the 1,2-positions of the disilane bridges were retained, reaction of **(201)** with $\text{Co}_2(\text{CO})_8$ afforded the dinuclear complex **(203)** having the disilane bridges in 1,3-positions. The molecular structures of **(202)**; $\text{M} = \text{Fe}$ and **(203)** were determined by x-ray crystallography.

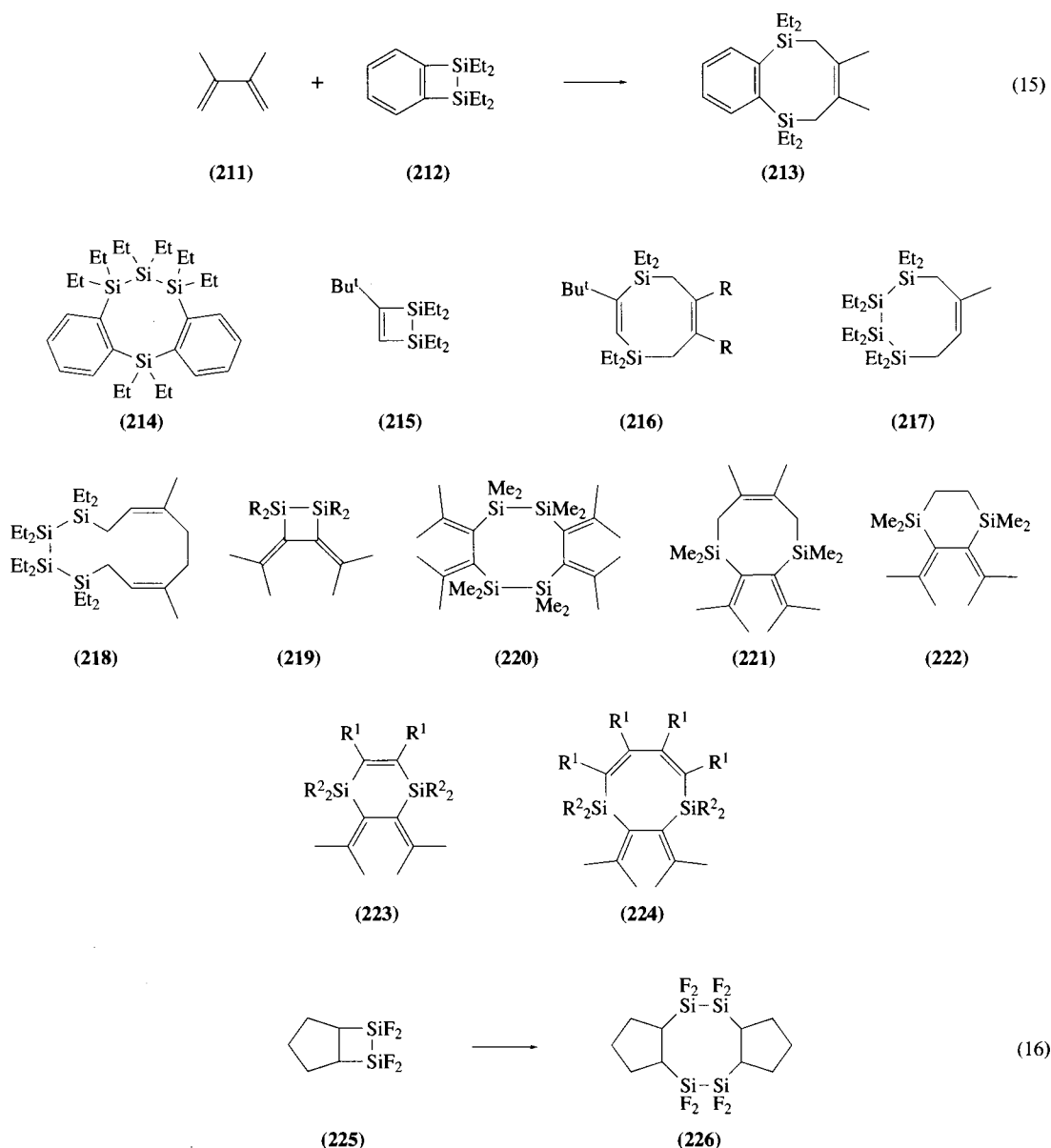


Compound **(204)** was obtained by metal-atom ligand-vapor cocondensation. Dechlorinative coupling of **(204)** with lithium-naphthalene in DME led to **(205)** in 3.5% yield ($\langle 88\text{AG(E)}684 \rangle$), whose molecular structure was determined by x-ray crystallography. Reductive coupling of 1,3,5-tris(chlorodimethylsilyl)benzene with sodium in toluene in the presence of [18]-crown-6 afforded the hexasila[2.2.2]cyclophane **(206)** in 0.22% yield ($\langle 89\text{AG(E)}757 \rangle$). Compound **(206)**, which was characterized by x-ray crystallography, is readily oxidized by trimethylamine *N*-oxide to the cyclophane **(207)** with Si—O—Si bonds. The ferrocenophane **(208)** was also characterized by x-ray crystallography $\langle 93\text{CB}1311 \rangle$. The reaction of tris(2-thiolphenyl)silane with 1,3,5-tris(bromomethyl)benzene in the presence of potassium hydroxide afforded the silaphane **(209)** in ~1% yield $\langle 91\text{JA}2672 \rangle$. According to the x-ray crystal structural investigation of **(209)**, the silane-H is directed towards the basal aromatic ring. The heptasila[7]paracyclophane **(210)** was prepared in 1.2% yield $\langle 90\text{AG(E)}778 \rangle$ and was structurally characterized by x-ray crystallography.



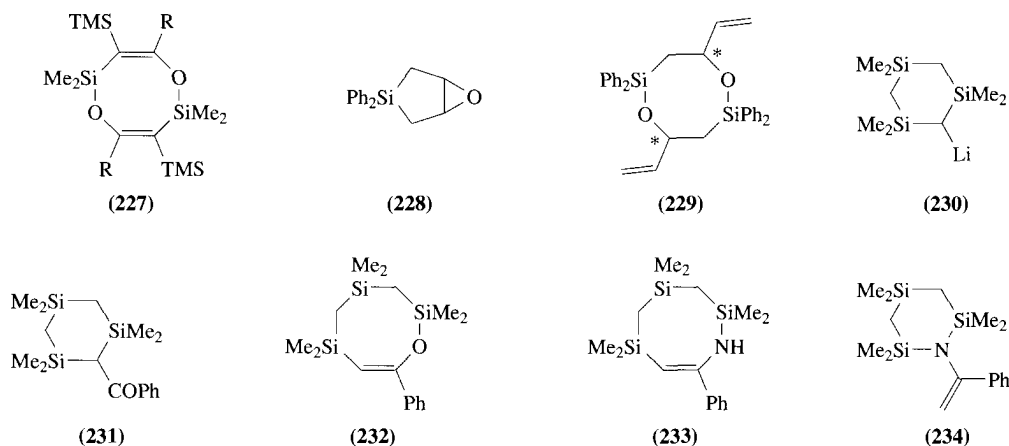
9.36.3.4 Insertions into Si—Si Bonds

A 30% yield of **(213)** was obtained from the nickel(0)-catalyzed insertion of the diene **(211)** into the Si—Si bond of **(212)** (Equation (15)) <95OM114>. Thermolysis of **(212)** at 250°C in a sealed degassed tube for 24 h gave **(214)** in 72% yield <91OM3173>. Thermal reactions of the disilacyclobutene **(215)** with 1,3-butadiene and 2,3-dimethylbutadiene **(211)** afford **(216; R = H, Me)** in high yields <87OM1882>, which isomerized in the presence of $\text{Fe}(\text{CO})_5$. A variety of similar insertion products were prepared by the $\text{Cp}(\text{CO})_2\text{Co}$ -mediated cycloaddition of **(215)** with dienes <88OM1271>. It was found that $\text{Ni}(\text{CO})_4$ is also capable of mediating these cycloadditions <88OM1265>. Octaethylcyclotetrasilane reacts with isoprene in the presence of $[\text{PdCl}_2(\text{PPh}_3)_2]$ to give the mono and double insertion products **(217)** and **(218)** in low yields <83OM1801>. In the presence of $[\text{Pd}(\text{PPh}_3)_4]$ as catalyst, disilacyclobutene **(219; R = Me)** dimerizes into **(220)**, which exists as a 1 : 1 mixture of stable twist and chair conformational isomers; the latter was characterized by x-ray crystallography <93CL985>. Under $\text{Pt}(0)$ catalysis, **(219; R = Me)** reacts with 2,3-dimethylbutadiene to give **(221)** and **(222)**. With alkynes, **(219; R = Me, Et)** undergo insertions in the presence of palladium catalysts to afford mixtures of **(223)** and **(224)**, respectively. Co-condensation of difluorosilylene with cyclopentene gives a variety of products, including **(225)**, which at room temperature dimerizes into **(226)** (Equation (16)) <82JOM(226)21>.

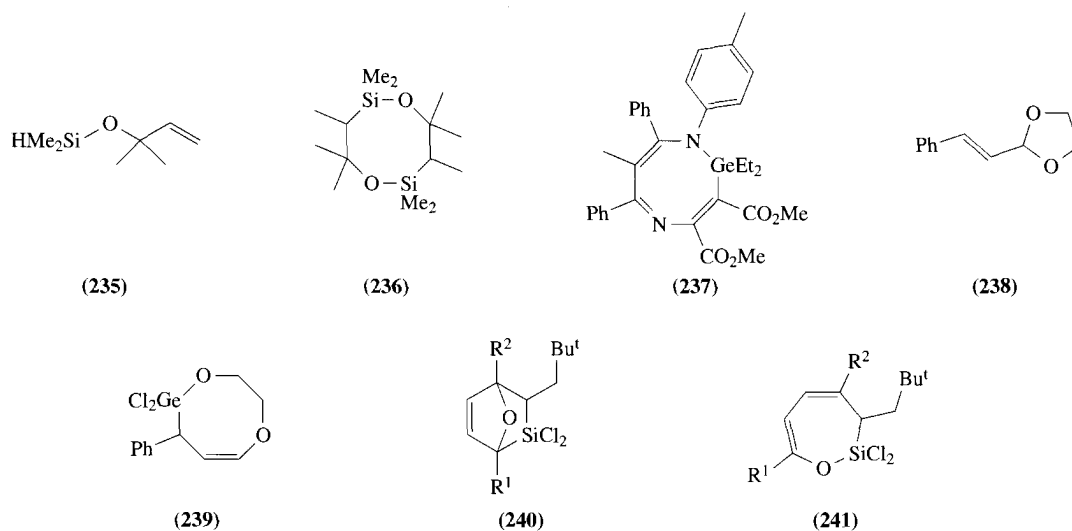


9.36.3.5 C—E—O and C—E—N Rings

UV irradiation of compounds of the type TMS-SiMe₂C(N₂)COR in benzene furnishes the eight-membered heterocycles (**227**), which were isolated as stable crystalline solids <90CB589>. Bromide ion-catalyzed dimerization of (**228**) yields racemic- and meso-(**229**) <91OM1586>. The structure of the *trans* (racemic) compound was determined by NMR spectroscopy and x-ray crystallography. The reaction of (**230**) with benzyl chloride resulted in the formation of the stable β -ketosilane (**231**), which was isolated and fully characterized; when heated under argon at 140 °C, (**231**) underwent quantitative ring expansion into the enoxysilane (**232**) <92OM3464>. The lithium reagent (**230**), upon reaction with benzonitrile at -78 °C followed by methanol, gave a mixture of (**233**) and (**234**).

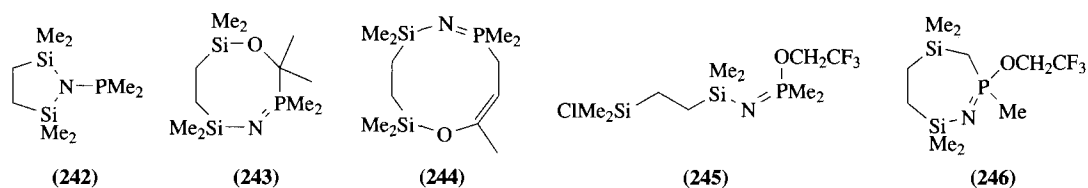


The platinum-catalyzed cyclohydrosilylation of (**235**) gave (**236**) and 2,2,5,5-tetramethyl-1-oxa-2-silacyclopentane in 70% combined yield <93JOM(446)183>. The eight-membered ring underwent β -elimination during chromatography to give a six-membered ring. 1,3,2-Diazagermines react with dimethyl ethynedicarboxylate with insertion to give 1,5,2-diazagermocines in quantitative yields <92OM2348>. The molecular structure of (**237**) was determined by x-ray crystallography. The germanium(II) chloride-dioxane complex reacts with the acetal (**238**) to give the eight-membered alkoxygermane (**239**) in 95% yield <92JOC5281>. Thermolysis of (**240**; R¹ = R² = H, Me and R¹ = H, R² = Me) gave the oxasilacycloheptadienes (**241**; R¹ = R² = H, Me and R¹ = H, R² = Me) in good yields <93CB575>.

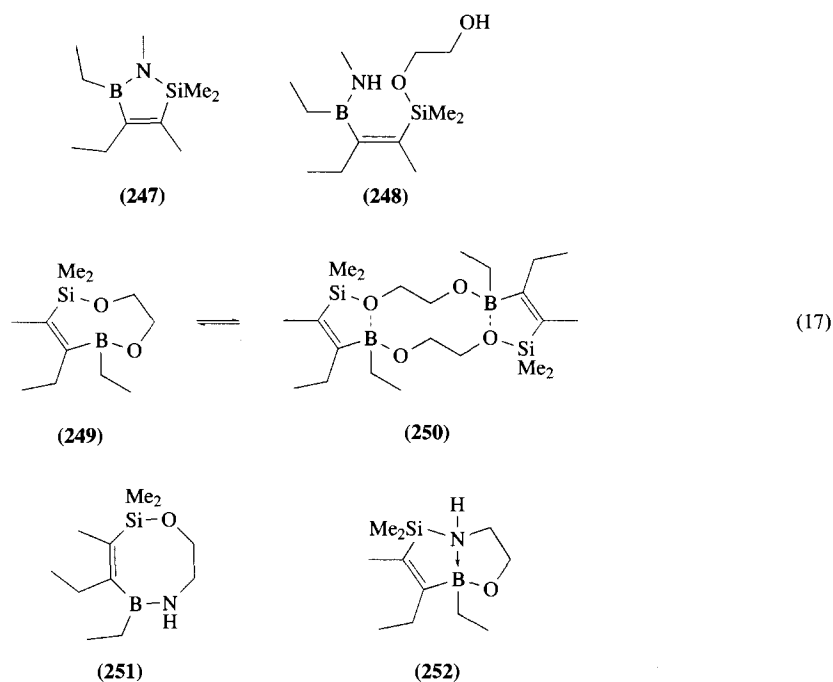


Treatment of the (disilylamino)phosphine (**242**) with acetone afforded the ring-expanded eight-membered phosphinimine (**243**) <82OM289>; the colorless solid, when heated above 65 °C, cleanly reverted to the starting materials. With methyl vinyl ketone, (**242**) gave first the (*Z*)-isomer of (**244**),

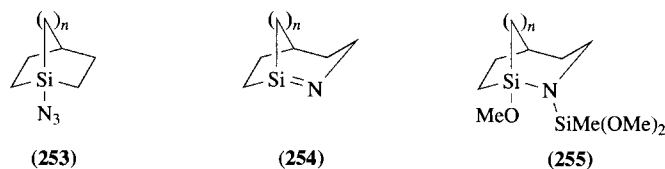
which slowly isomerized into the (*E*)-isomer. The related compound (**246**) was obtained when (**245**) was reacted with methyllithium at -78°C <87IC929>.



Compound (**247**) reacts with ethylene glycol to give the ring-opened adduct (**248**), which, when heated above 100°C , loses methylamine to give eight-membered (**249**) <90CB1013>. Compound (**249**) is in equilibrium with the dimer (**250**) (Equation (17)); the latter was characterized by x-ray crystallography. With 2-aminoethanol, (**247**) gave a mixture of (**251**) and (**252**) <90CB2287>.



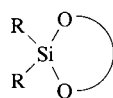
The bridgehead silaneimines (**254**; $n = 1, 2$) were prepared by matrix isolation by UV irradiation of the silylazide precursors (**253**; $n = 1, 2$) and were characterized as the derivatives (**255**; $n = 1, 2$), which were obtained by trapping with trimethoxymethylsilane <93JA8401>. The IR spectra of the ^{14}N and ^{15}N species and the $n \rightarrow \pi^*$ transition in the UV spectra of (**254**; $n = 1, 2$) were in good agreement with *ab initio* calculations.



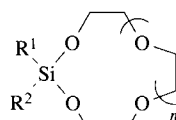
9.36.3.6 Silacrown Ethers and Related Compounds

Reactions of diorganodichlorosilanes, -dialkoxysilanes, -diacetoxysilanes, -dicyanosilanes, -bis(dialkylamino)silanes, -bis(pentafluorophenyl)silanes, and related compounds with diols afford a variety of 1,3,2-dioxasilane heterocycles (**256**) <84JOM(267)1, 85JOM(289)23>. A review is available of bidentate oxygen donor chelates of silicon, germanium, and tin <94CCR175>. Most of the rings

contain six or seven members, with larger rings being considerably more difficult to obtain. The heterocycles have generally high thermal stabilities and hydrolyze upon exposure to moist air. Investigations of ^{29}Si NMR shifts for a series of 2,2-diphenyl-1,3,2-dioxasilacycloalkanes revealed a clear dependence of the chemical shift on the ring size for rings of 5–14 atoms $\langle 85\text{JOM}(291)153 \rangle$. There is also a relationship between the steric structure and internal movements in molecules of this type as determined by variable-temperature ^1H NMR spectroscopy $\langle 85\text{MI } 936-01, 90\text{JST}(218)21 \rangle$. The synthesis of the silacrowns (**257**) and their use for the solubility enhancement of alkali metal salts and the phase transfer catalysis of acetate, azide, cyanide, fluoride, and nitrate ions in displacement reactions, have been reported $\langle 83\text{OM}454 \rangle$. Compounds of type (**257**; $n = 0$) are also known $\langle 88\text{JGU}473 \rangle$. Alkali metal ions can facilitate the synthesis of silacrown ethers $\langle 93\text{TL}7413 \rangle$. The electrochemistry of the $(\eta^6\text{-arene})\text{chromium tricarbonyl}$ adduct of (**257**; $n = 2$ $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Ph}$) in acetonitrile in the presence of alkali metal ions has been investigated $\langle 91\text{ICA}33 \rangle$.

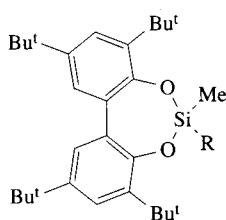


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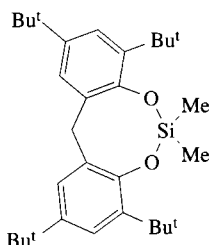


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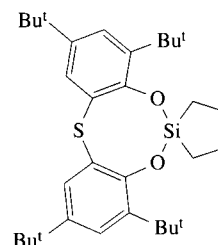
The synthesis and NMR conformational analysis of the dioxasilepin (**258**; $\text{R} = \text{Ph}$), which was prepared in 77% yield from dichloromethylphenylsilane and the tetrasubstituted biphenyl-2,2'-diol using triethylamine as the proton scavenger, have been reported $\langle 84\text{JOC}1297 \rangle$. A variety of related seven- and eight-membered compounds were prepared similarly. The addition of fused benzene rings to the heterocyclic rings decreases their mobilities, as found previously for dibenzodioxaphosphocin and its boron analogue. The x-ray crystal structure of (**259**; $\text{R} = \text{Me}$) showed that the eight-membered heterocycle adopts a boat–boat conformation in the solid state $\langle 93\text{HCA}1476 \rangle$. The syntheses of (**260**)–(**262**) have been reported $\langle 94\text{JA}7026, 94\text{OM}1285 \rangle$ and the crystal and molecular structures of (**261**) have been determined.



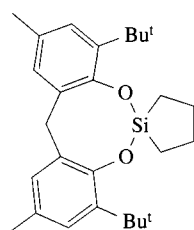
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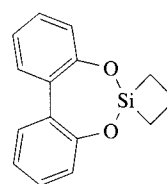
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(260)



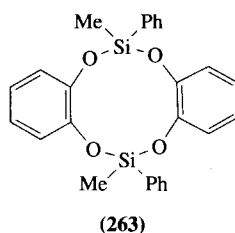
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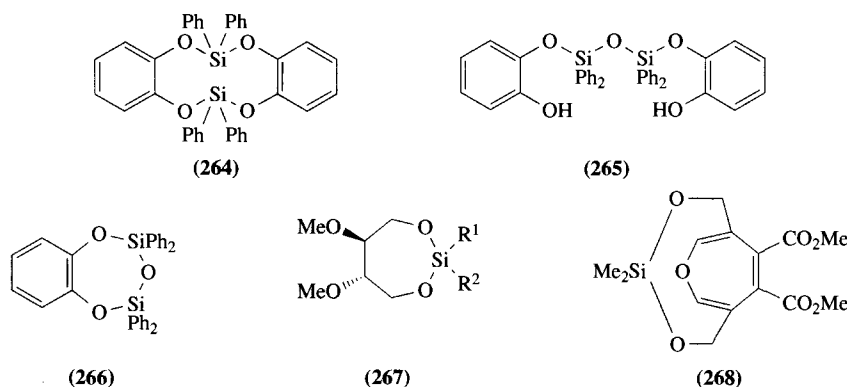
(262)

Colorless crystals of (**263**) were obtained in 59% yield from the condensation of dichloromethylphenylsilane with catechol in the presence of pyridine $\langle 84\text{JOM}(270)25 \rangle$. Detailed investigations of the ^1H , ^{13}C , and ^{29}Si NMR spectra of (**263**) and related compounds indicated reversible dissociation between monomeric five-membered and dimeric ten-membered forms of the compounds at elevated temperatures. Large cavitands containing cylindrical wells of variable depths have been synthesized with use of similar synthetic strategies $\langle 85\text{JA}2574 \rangle$. The limited diameters of the cavities deny occupancy to all but slim linear guests, such as carbon disulfide, propyne, and dioxygen.

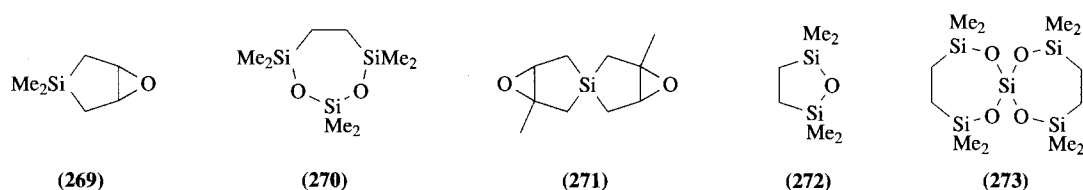
The facile acid-catalyzed reaction of (**264**) with water gave the dihydroxy derivative (**265**), which, in turn, decomposed by a base-catalyzed path into (**266**) and catechol $\langle 86\text{CJC}1450 \rangle$. The crystal



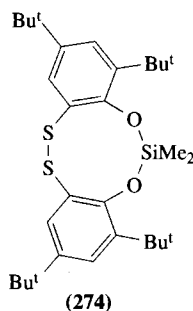
structures of (266) and related compounds, including a siloxatrane <93NJC787>, were determined. The optically active compounds (267), which were prepared from (*S,S*)-2,3-dimethoxy-1,4-butanediol and prochiral dialkyldichlorosilanes in the presence of ammonia, react with organometallic reagents followed by LAH to give mostly high yields of optically active silanes with small enantiomeric excesses <87CL101>. The shortest bridge to be found in a (3,6)oxepin occurs in the [5](3,6)oxepinophane (268) <85JCS(P1)2119>, which was obtained in five steps from diethyl furan-3,4-dicarboxylate.



When (269) and a catalytic amount of *N*-benzyltriphenylphosphinimine were melted together with a threefold excess of $[\text{Me}_2\text{Si}=\text{O}]$, the oxasilaheptane (270) was formed <87CL237>. A 20% yield of (273) was obtained when (271) and (272) were copolyolyzed <86OM1818>.

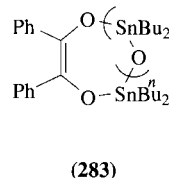
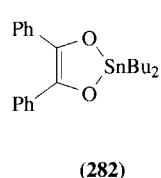
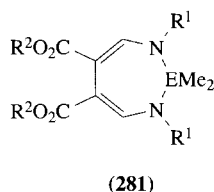
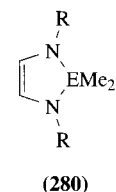
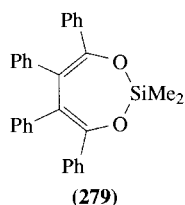
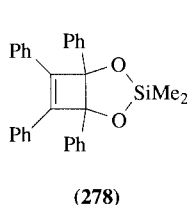
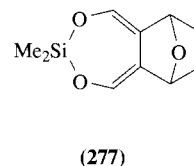
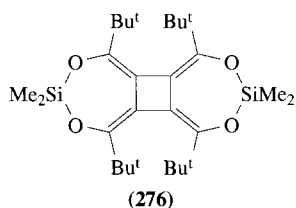
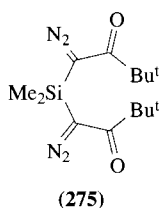


The first example of the dibenzo[*d,h*][1,3,6,7,2]dioxadithiasilone ring was reported in 1988 <88JHC681>. Compound (274) was prepared in four steps from 2,4-di-*t*-butylphenol; variable-temperature ^1H NMR spectra of (274) and related compounds were recorded.

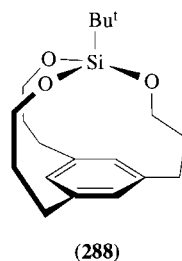
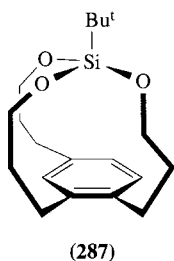
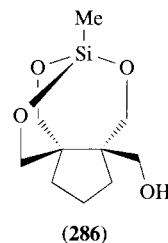
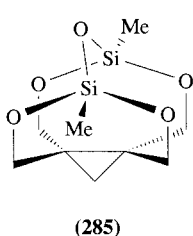
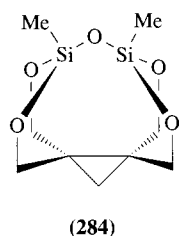


The bisdiaz compound (275), which is unstable as a pure substance, affords the [4]radialene (276) in 38% yield upon catalytic decomposition with copper(I) triflate in cyclohexane <89AG(E)1663>.

93CB523). A similar yield of **(276)** was obtained with use of palladium(II) acetate as the catalyst, but the reaction was appreciably slower; when the palladium(II) acetate-catalyzed decomposition was carried out in the presence of an excess of furan, the tricyclic compound **(277)** was obtained in 18% yield together with **(276)** in 6% yield. Thermolysis of **(278)** at 190°C gives the valence isomer **(279)** (83CL209). The reaction of **(280)**; E = Si, R = Bu^t, 2,4-C₆H₃Me₂) with dialkyl ethynedicarboxylates produces **(281)**; E = Si, R = Bu^t, 2,4-C₆H₃Me₂) (87CB795). A similar germanium compound has also been prepared (89TL6669). Benzoin readily reacts with di-*n*-butyltin oxide to give the 1,3,2-dioxastannole **(282)** and thence the stannoxane oligomers **(283)**; *n* = 0–9 (82JOM(224)C37). The melting points of the oligomers for *n* = 0, 1, 3, 4, 5, and 9 are given in that article.

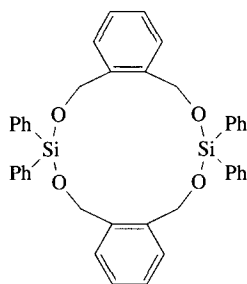


The tetraols (HOCH₂)₂C(CH₂)_nC(CH₂OH)₂ (*n* = 1 or 3) react with MeSi(OMe)₃ in the presence of base to give the stable tetracyclic isomers **(284)** and **(285)**; *n* = 1 and **(286)**; *n* = 3 (90IC1065, 93IC2796). The structures of the three compounds were determined by x-ray crystallography. The cyclophanes **(287)** and **(288)** have been synthesized by the Bu^t₃Al–TiCl₄-catalyzed cyclotrimerization of Bu^tSi(OCH₂CH₂CH₂C≡CH)₃ and characterized by x-ray crystallography (91OM3962).



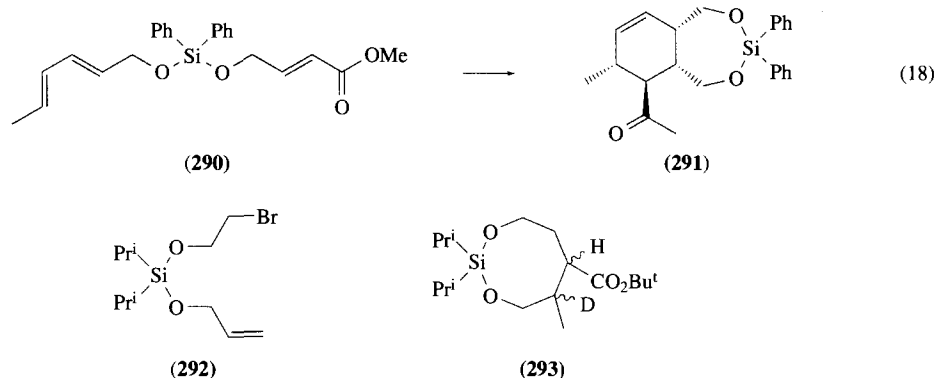
Reactions of [Co₂{μ-(HOCH₂C≡CCH₂OH)}(CO)₆] with diorganodichlorosilanes in the presence of triethylamine afford hexacarbonyldicobalt-complexed 1,3-dioxa-2-silacycloalkynes (90CC993, 91JCS(D)137). The structures of the complexes parallel that of **(289)** (86CJC1450), indicating the similarities between the geometries of the coordinated alkynes and the benzene-1,2-dimethanol.

The triene **(290)** undergoes a regiospecific and highly stereoselective intramolecular Diels–Alder reaction in toluene at 160°C to give **(291)** (Equation (18)) (90TL6585, 92TL4073). Intramolecular radical cyclizations of substrates possessing a silaketal tether proceed predominantly via an endo mode to give, in moderate to good yields, seven-, eight-, and nine-membered heterocycles (91TL573).

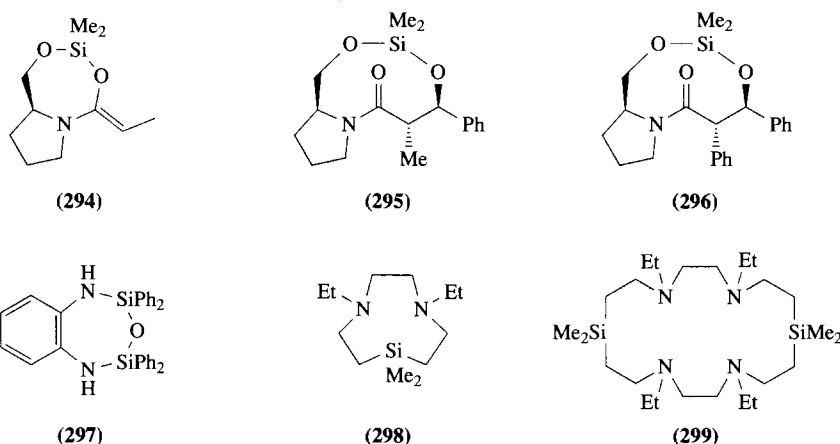


(289)

For example, the addition of Bu^n_3SnD and AIBN over 16 h to a boiling solution of (292) gave eight-membered (293) in 57% yield.



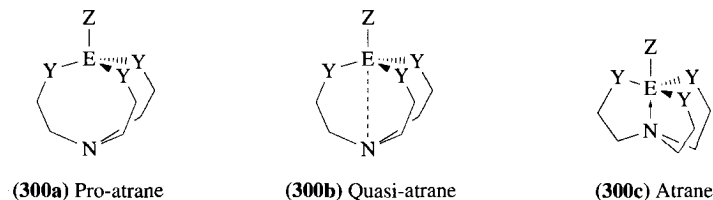
Siloxane (294) undergoes efficient and highly diastereoselective condensations with aldehydes <90JA9672>. With benzaldehyde, for example, the nine-membered products (295) and (296) are formed in the ratio 39:1. The yellow siloxazane (297) is formed quantitatively in the reaction between $(\text{ClPh}_2\text{Si})_2\text{O}$ and 1,2- $\text{C}_6\text{H}_4(\text{NH}_2)_2$ and is readily isolated by crystallization <94IC1778>. The polyamine macrocycles (298) and (299) have been prepared from dimethyldivinylsilane and *N,N'*-diethylethylenediamine <93CL1825>.



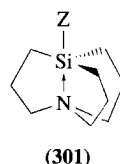
9.36.3.7 Atranes and Related Compounds

Depending on the degree of transannular interaction, these compounds have been classified as pro-atranes, quasi-atranes, and atranes (300a-c; E = Si, Ge, Sn and Y = CH_2 , NR, O, S). A

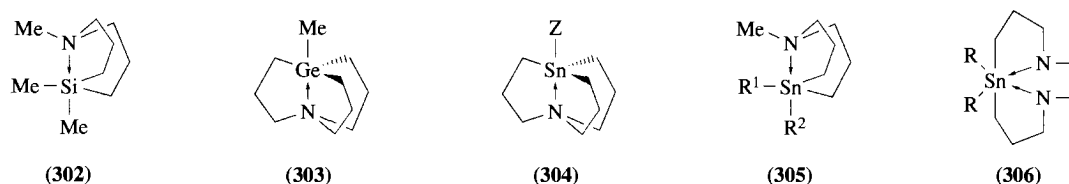
comprehensive review entitled "Main group atranes: chemical and structural features" has been published <94CCR233>. Detailed earlier reviews are available on the chemistry of silatranes <82JOM(233)1> and metallatranes, including germanium, tin, and lead compounds <82JOM(239)199>.



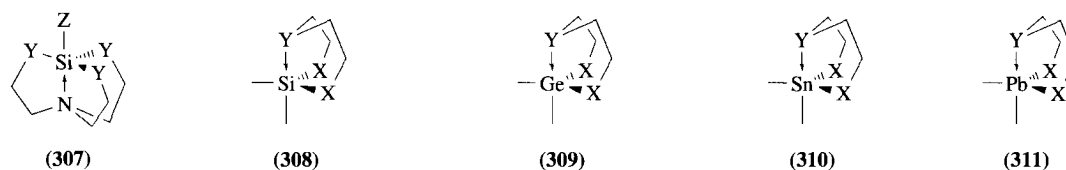
The carbasilatranes (**301**; $Z = \text{Me, Cl, } 0.5\text{O, Ph, } p\text{-MeC}_6\text{H}_4$) are known; transannular interactions in (**301**; $Z = 0.5\text{O, Ph, } p\text{-MeC}_6\text{H}_4$) have been confirmed by x-ray crystallography <85JOM(287)C1, 85JOM(293)185, 86JOM(317)145, 86PAC639, 88RTC170, 89MI 936-04>. Compound (**301**; $Z = \text{Me}$) was prepared from the tri-Grignard reagent of tris(3-chloropropyl)amine and trichloromethylsilane. Treatment of (**301**; $Z = \text{Me}$) with dichlorodimethylstannane gave (**301**; $Z = \text{Cl}$) in 90% yield.



The Grignard approach was also used to synthesize (**302**). The carbagermatrane (**303**) was structurally characterized by x-ray diffraction <81MI 936-01>. The carbastannatranes (**304**; $Z = \text{Me, Cl, Br, I, OH, SPh, Bu}^t, 2\text{-C}_4\text{H}_9, \text{CH}_2\text{OCH}_2\text{OCH}_3, \text{CH}_2\text{TMS}$) have been prepared <84JOM(272)C13, 88ZAAC(567)122, 92JA6556>. X-ray crystal structures have been determined for (**304**; $Z = \text{Cl, Me}$) <86JOM(315)45>. Methyl-substituted (**304**; $Z = \text{Me}$) was obtained when the chloro compound (**304**; $Z = \text{Cl}$) (prepared by Grignard coupling with SnCl_4) was reacted with methyl lithium. The variable-temperature NMR spectra of (**304**; $Z = \text{Cl}$) were interpreted in terms of an equilibrium between the atrane and the corresponding pro-carbastannatrane <86PAC639>. The activation enthalpies for the racemization of the bicyclo[3.3.3] skeleton in these compounds were estimated to be $37 \pm 1 \text{ kJ mol}^{-1}$ <88ZAAC(567)122>. The related compounds (**305**; $\text{R}^1 = \text{R}^2 = \text{Cl, Me, Bu}^t$ and $\text{R}^1 = \text{Me, R}^2 = \text{Cl}$) were prepared similarly and for (**305**; $\text{R}^1 = \text{R}^2 = \text{Cl}$) the transannular bond was confirmed in the x-ray crystal structure <84JOM(272)C13, 86PAC639, 88OM38, 88OM593, 90JST(218)189, 90M615>. A number of the related hexacoordinated tin compounds of the type (**306**) are also known <88JOM(347)41, 88BSB1075>.

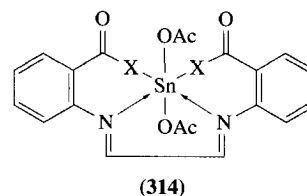
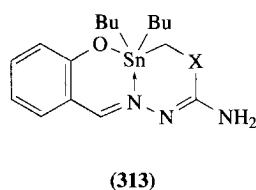
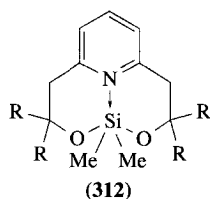


For references to the field of silatrane chemistry, viz. (**307**; $\text{Y} = \text{O}$), azasilatranes (**307**; $\text{Y} = \text{NR}$), and thiasilatranes (**307**; $\text{Y} = \text{S}$), and their germanium and tin congeners, the reader is referred to the following reviews: <81MI 936-02, 82JOM(233)1, 82JOM(239)199, 83MI 936-02, 86TCC99, 93ACR483, 93CRV1371, 94OM4164, 95JA141>.



Transannular interactions were also found in the heterocycles (**308**; $\text{X} = \text{NR}$ and $\text{Y} = \text{NR}$, $\text{X} = \text{O}$ and $\text{Y} = \text{NR}$) <90JOM(399)221, 91JA944, 92JGU285>, (**309**; $\text{X} = \text{O}$ and $\text{Y} = \text{NR}$, $\text{X} = \text{S}$ and $\text{Y} = \text{O, S}$) <83JGU1067, 90MI 963-03, 93ICA99>, (**310**; $\text{X} = \text{NR}$ and $\text{Y} = \text{NR}$, $\text{X} = \text{O}$ and $\text{Y} = \text{NR, PR}$, $\text{X} = \text{S}$ and

Y = NR, O, PR, S) <81MI 936-02, 82ZAAC(488)45, 83MI 936-02, 85ZAAC(523)21, 88ZAAC(556)161, 90JA7408, 91AOC(33)171, 91BSB743, 93MI 936-01, 94IC4522, 94OM4413>, and the lead compounds (**311**; X = S and Y = O, S) <85ZAAC(522)48, 86SA(A)1255>. A similar transannular interaction occurs in ten-membered (**312**; R,R = 2-adamantylidin), which was characterized by x-ray crystallography <94JOM(464)127>. In compounds of the type (**313**; X = O, S) or (**314**; X = O, S), dative bonds from the imino-N centers increase the coordination numbers at tin from 4 to 5 or 6, respectively <84POL681, 85ZN(B)1173>.



9.37

Rings containing Boron

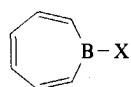
GARY W. MORROW
University of Dayton, OH, USA

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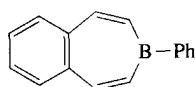
9.37.1 INTRODUCTION

Much of the available information of interest related to large-ring boron heterocycles is devoted to the preparation and study of the seven-membered ring borepins (1), the benzoborepins (2), and their various derivatives; thus, most of this chapter focuses on these unusual boracycles. The nomenclature for these compounds can be somewhat confusing, as different ring numbering schemes have been in use over the years by various groups. For clarity and consistency with the naming of certain dihydro derivatives, the ring atom numbering scheme shown in (3) is employed throughout, wherein (3) is named 1-phenyl-4,5-cyclopentenoborepin (by IUPAC rules, (3) is named 3,6,7,8-tetrahydro-3-phenylcyclopenta[*d*]borepin). Note that the prefix "bora-" denotes replacement of CH by B (as in borabenzene), while the prefix "borata-" indicates replacement of CH by BH⁻ (or BR⁻). Thus, certain borepin complexes are referred to as the corresponding boratepins (the a of "borata-" is dropped here).

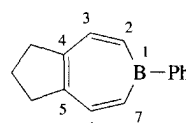
Partially or totally saturated large-ring boracycles, such as the borepanes, are dealt with only



(1)



(2)



(3)

briefly, as these and related cyclic organoboranes have been the subject of numerous reviews [B-73MI 937-01, B-75MI 937-01, 82COMC-I(1)311, 90JOM(392)1]. For similar reasons and for the sake of focus and economy, 9-borabicyclononane (9-BBN-H) and related bicyclic organoboranes are not treated here, nor are ring systems containing heteroatoms in addition to boron. A few examples of other large-ring boracycles or larger rings with more than one boron atom are briefly introduced primarily from a synthetic standpoint, as little information is available beyond their preparative chemistry.

9.37.2 THEORETICAL METHODS AS APPLIED TO BOREPINS

From a theoretical standpoint, borepins (**1**) are of considerable interest as they are 6 π -electron systems that are isoelectronic with the tropylium cation (**4**) and therefore should have at least some "aromatic" character. Initial *ab initio* calculations using the STO-3G basis set indicated that 1*H*-borepin (**5**), the boron analogue of (**7**), should be planar, and it was calculated to be about 37 kcal mol⁻¹ (155 kJ mol⁻¹) more stable than boranorcaradiene (**6**) [82JA3785, 83TL1863, 84JA7696].

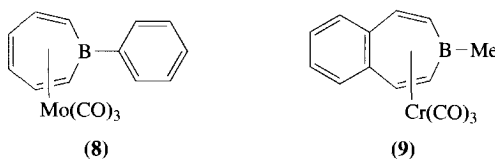


Such theoretical studies imply at least some π conjugation involving boron, although only about 35% of the π conjugation reported for tropylium cation [82JA3785]. Theoretical dipole moments for (**5**) were calculated to be 1.9–2.0 D (1 D = 3.336×10^{-30} C m) depending on the basis set employed [84JA7696]. The aromatic character of (**5**) was also assessed through the use of so-called empirical resonance energies (EREs) calculated from *ab initio* 6-31G* SCF energies [89OM733]. This basis set has also been used for comparison of a calculated structure versus an x-ray structure for 1-chloroborepin, where good agreement was found [93AG(E)1065]. Additional evidence supporting the aromaticity of borepins is also found in their NMR chemical shifts and UV spectra (see Section 9.37.3.2).

9.37.3 EXPERIMENTAL STRUCTURAL METHODS AS APPLIED TO BOREPINS

9.37.3.1 X-ray Analysis

Until the early 1990s, x-ray analysis of the borepin ring system geometry had been confined to examination of stable metal complexes such as Mo(CO)₃ complex (**8**) and Cr(CO)₃ complex (**9**) [90OM2944, 92AG(E)1255].



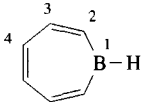
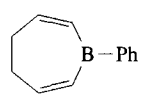
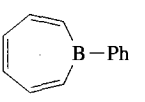
In both cases, x-ray structures showed the metal coordinated to the borepin ring rather than to the benzene moiety. The borepin ring was found to be essentially planar and served as an η^7 -ligand to the metal. The planarity of the borepin ring was confirmed through a direct x-ray analysis of crystals (m.p. -37°C) of highly air- and moisture-sensitive 1-chloroborepin [93AG(E)1065]. The C—C bond lengths (1.37–1.42) found for this compound were comparable to those of naphthalene (1.36–1.42) but smaller than those of cycloheptatriene (1.33–1.46) again consistent with a ring with aromatic character.

9.37.3.2 NMR and UV Studies

Spectroscopic data for certain benzoborepins and ring-substituted borepins were reported over two decades ago in the mid-1970s [67TL1263, 75JA4436], but ¹H, ¹¹B, and ¹³C NMR data for

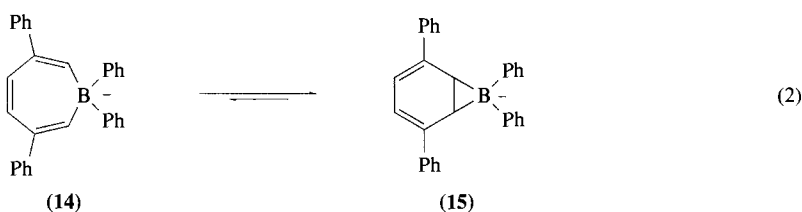
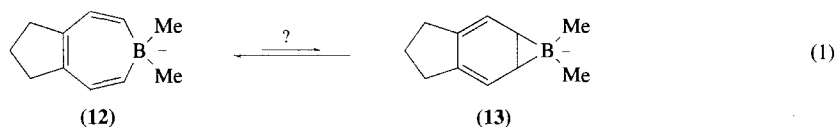
C-unsubstituted borepins has only become available since the mid-1970s. Table 1 compares some of this data with that of a related nonconjugated system. The low-field ^1H NMR shifts observed for (5) and (11), as well as other borepins have been taken as evidence of a diamagnetic ring current. For (5), the observed H(3)–H(4) vicinal coupling constant of 8.3 Hz is very close to a calculated value from the Karplus torsion angle–coupling constant relationship. A comparison of the UV spectrum of 1-methyl-4,5-cyclopentenoborepin (λ_{max} 223, 315 nm) with that of tropone (λ_{max} 225, 312 nm) offers further support for conjugation of the boron atom with the triene system $\langle 87\text{JA}1879 \rangle$.

Table 1 ^1H , ^{11}B , and ^{13}C NMR shifts (ppm) of borepins versus dihydroborepin (10).

Nucleus			
	(5)	(10)	(11)
H-2(7)	8.09	6.75	8.10
H-3(6)	7.60	7.18	7.62
H-4(5)	6.89		6.85
B	48.0	54.6	48.8
C-2(7)	152.0	135.9	149.5
C-3(6)	149.2	156.7	148.2
C-4(5)	136.4	132.7	135.4
Reference	92AG(E)1255	77CB760	92AG(E)1255

9.37.4 THERMODYNAMIC ASPECTS OF BOREPINS

Ab initio MO calculations suggest that a boranorcaradiene structure should be highly disfavored relative to the “aromatic” borepin structure, although this may be due in part to a more favorable C—B—C bond angle for trigonal boron in the borepin form. Nevertheless, although experimental evidence supporting a borepin–boranorcaradiene equilibrium is somewhat ambiguous and limited to certain heptaaryl-substituted systems $\langle 75\text{JA}4436 \rangle$, boratepin systems, in which the borepin boron atom is coordinated to a ligand (such systems should be nonaromatic), show behavior analogous to the cycloheptatriene–norcaradiene system. Thus, while boratepin (12) showed no evidence for formation of the corresponding boratanorcaradiene (13) (Equation (1)) $\langle 90\text{PAC}513 \rangle$, boratepin (14) was found to be disfavored relative to (15) (Equation (2)) $\langle 88\text{JA}7569 \rangle$.



Given their aromatic character, many borepin systems are more thermally and chemically stable than might otherwise be expected, although most exhibit the tendency toward air oxidation which is characteristic of other organoboron compounds $\langle 67\text{TL}1263 \rangle$. Benzo- $\langle 67\text{TL}1263 \rangle$, dibenzo- $\langle 60\text{TL}14 \rangle$, and C-substituted borepins $\langle 75\text{JA}4436 \rangle$ are generally recrystallizable solids or distillable oils and appear to be more stable both thermally and oxidatively than the corresponding C-unsubstituted derivatives which, while often pot-to-pot distillable, are most conveniently handled

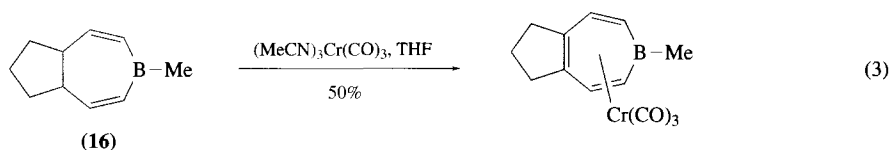
using Schlenk techniques $\langle 87\text{CL}1451, 92\text{AG}(\text{E})1255 \rangle$. Beyond the reported solubility of various borepins in benzene, THF, and the usual NMR solvents, detailed data on their solubility characteristics are lacking. The borepin precursor to (12) is reportedly a colorless, air-sensitive oil (m.p. $10\text{--}12^\circ\text{C}$) that is stable to 150°C in dilute solutions $\langle 87\text{JA}1879 \rangle$. 1-Methylborepin was reportedly heated to 150°C in degassed carbon tetrachloride for 1.5 h without decomposition, although it underwent gradual decomposition to benzene even at -20°C when dissolved in degassed chloroform- d , a transformation ascribed to trace amounts of acid in the solvent $\langle 87\text{CL}1451 \rangle$.

9.37.5 REACTIONS OF THE BOREPIN RING SYSTEM

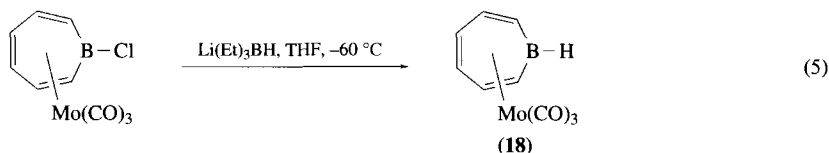
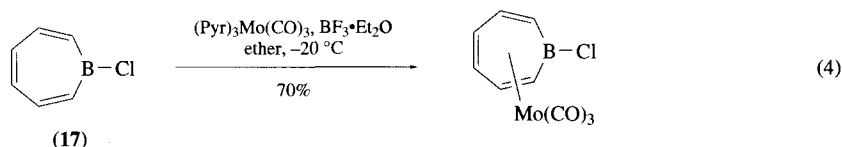
Since most efforts related to the chemistry of borepins have focused on the development of synthetic approaches, the body of information related to transformations of these ring systems is rather limited. The following brief sections serve as an overview of this chemistry.

9.37.5.1 Reactions of the Ring with Organometallics

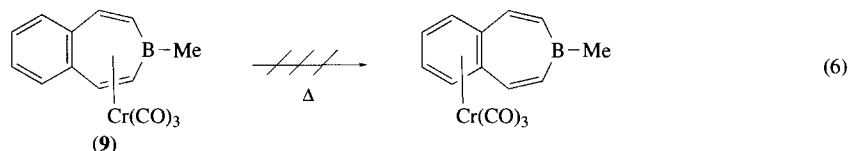
As indicated in Section 9.37.3.1, borepins react with certain organometallics to form complexes in which the borepin ring serves as an η^7 -ligand to the metal. Thus, borepin (16) reacts with tris(acetonitrile)chromium tricarbonyl in refluxing THF to afford the corresponding chromium complex in 50% yield as yellow crystals, m.p. $56\text{--}60^\circ\text{C}$ (Equation (3)) $\langle 87\text{JA}1879 \rangle$.



1-Chloroborepin (17) is readily converted to the corresponding Mo(CO)_3 complex (Equation (4)) by reaction with tricarbonyl-tris(pyridine)molybdenum and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in ether. This Mo(CO)_3 derivative is smoothly converted to the corresponding 1*H*-borepin-molybdenum complex (18) by reduction with lithium triethylborohydride (Super-Hydride) in THF (Equation (5)). This is noteworthy as (18) cannot be prepared directly from the highly labile 1*H*-borepin itself $\langle 93\text{AG}(\text{E})1065 \rangle$.



Benzoborepin- Cr(CO)_3 complex (9) is readily formed and shows no tendency toward haptotropic migration from the borepin ring to the benzene moiety (Equation (6)) $\langle 90\text{OM}2944 \rangle$.

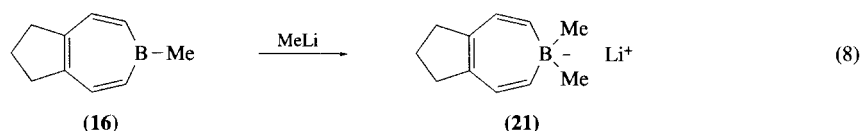
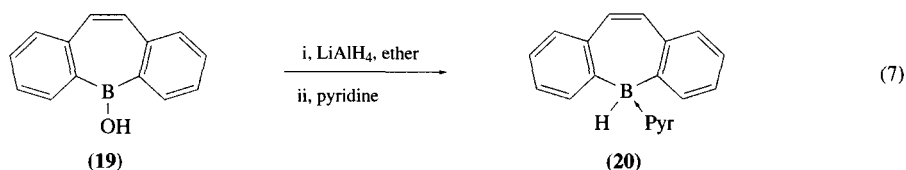


9.37.5.2 Reactions at Boron

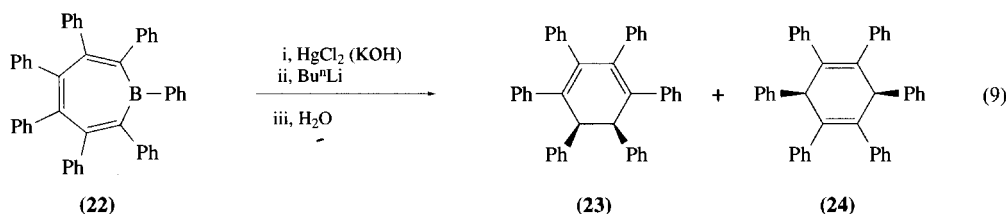
Although there is little data comparing the relative reactivity of borepins with corresponding nonaromatic derivatives, the unusual air-stability of benzoborepin (**2**) compared to that of dihydroborepin (**10**) has been attributed to resonance stabilization <67TL1263>.

As expected, the boron atom in borepins reacts with nucleophiles. In early work, certain labile borepins were characterized by preparation and isolation of their corresponding Lewis base adducts. Benzoborepin (**2**) formed a stable complex with dimethyl amine which showed the expected loss of characteristic UV absorption bands <67TL1263>. Dibenzoborepin (**19**) was originally isolated and characterized as the corresponding ethanolamine derivative. Reduction of crude (**19**) with LiAlH_4 , followed by addition of pyridine (Equation (7)), gave the low-melting pyridine complex (**20**) <60TL14>.

Reaction of borepin (**16**) with methyllithium (Equation (8)) reportedly gave the corresponding boratepin (**21**) <90PAC513>.

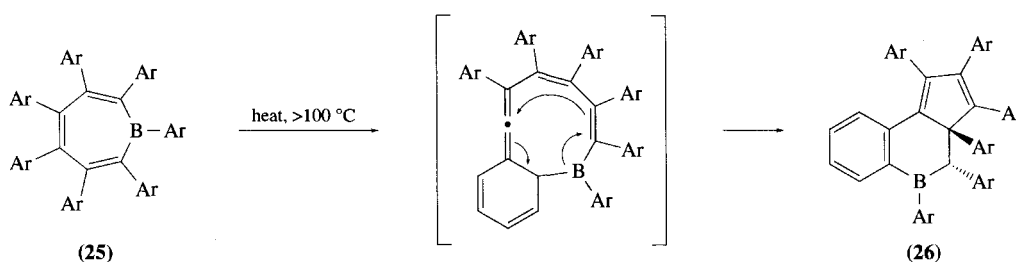


Fluorescent, greenish yellow heptaphenyl borepin (**22**) reportedly formed a colorless complex with pyridine that dissociated in warm toluene solution. Mercurideborination of (**22**) and treatment of the crude organomercury product with *n*-butyllithium, followed by hydrolysis (Equation (9)), afforded hexaphenyldihydrobenzenes (**23**) and (**24**), along with some hexaphenylbenzene <75JA4436>.



9.37.5.3 Reactions of Substituents Attached to Carbon

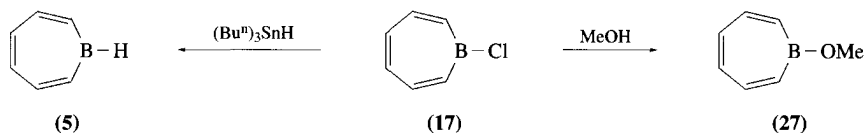
Little is known about how the reactivity profile of a given substituent is affected by attachment to a borepin ring carbon, although it has been shown that heptaarylborepins (**25**) undergo a thermal isomerization above 100°C involving an aryl group attached to the carbon adjacent to boron (Scheme 1), giving rearrangement products (**26**) <90OM2342>.



Scheme 1

9.37.5.4 Reactions of Substituents Attached to Boron

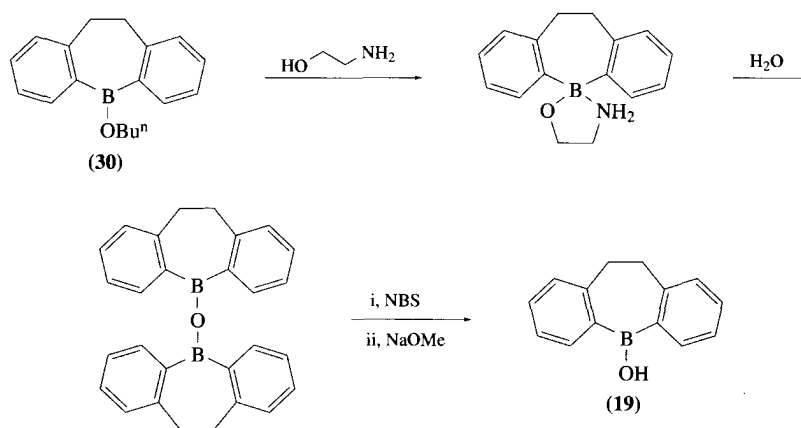
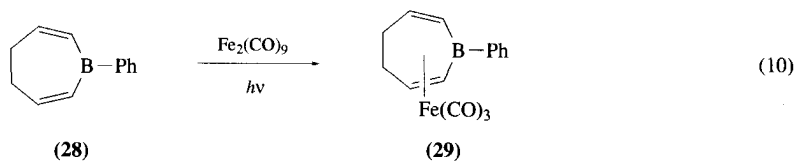
Reaction of 1-chloroborepin (**17**) with methanol or tri-*n*-butyltin hydride (Scheme 2) afforded the corresponding 1-methoxyborepin (**27**) or 1*H*-borepin (**5**) <92AG(E)1255>. The Mo(CO)₃ complex of (**17**) undergoes replacement of Cl by hydride using LiEt₃BH, as a reducing agent <93AG(E)1065>.



Scheme 2

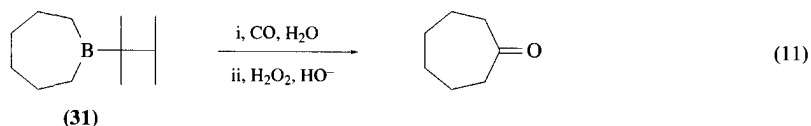
9.37.5.5 Reactions of Nonconjugated Derivatives

1-Phenyl-4,5-dihydroborepin (**28**) <67TL1263> reportedly undergoes photochemical conversion to the corresponding Fe(CO)₃ complex (**29**) (Equation (10)) <77CB760>. The analogous dibenzo derivative (**30**), one of the earliest boron heterocycles studied <55JA5176>, undergoes the sequence of reactions shown in Scheme 3, culminating in a synthesis of dibenzoborepin (**19**) <60TL14>.



Scheme 3

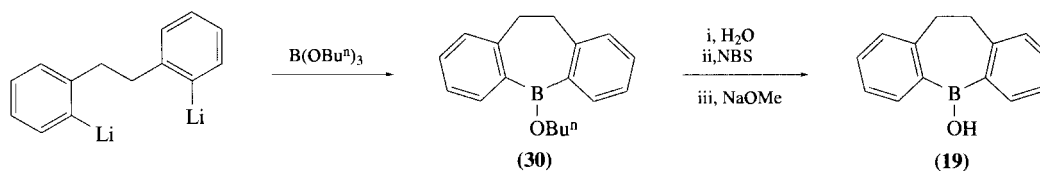
One of the major transformations of interest for the corresponding hexahydro derivatives (borepanes) and similar cyclic organoboranes is conversion to cyclic ketones, as in the conversion of (**31**) to cycloheptanone (Equation (11)) <67JA5477>. 1*H*-Borepanes have also been used in the monohydroboration of terminal alkynes <82JOC1792>.



9.37.6 SYNTHETIC ASPECTS OF BOREPINS AND RELATED BORACYCLES

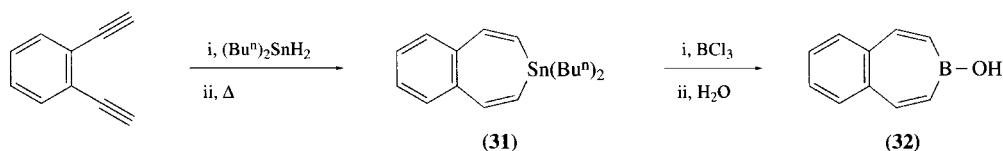
9.37.6.1 Synthesis of Borepins and Benzoborepins

One of the earliest examples of an approach to the borepin ring system was synthesis of (19) from (30) <60TL14>, which was prepared from *o,o'*-dilithiobibenzyl as shown in Scheme 4 <55JA5176>.



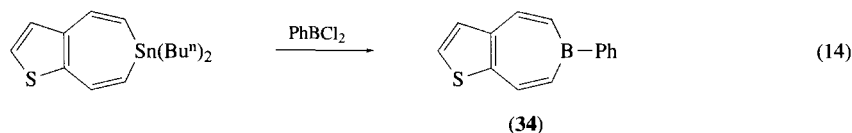
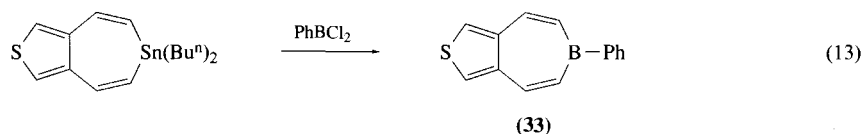
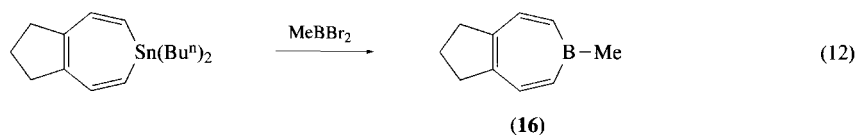
Scheme 4

A more general approach to borepins (Scheme 5) involves reaction of dialkynes with di-*n*-butyltin dihydride to give stannepins, which react with boron compounds such as BCl_3 , for example, benzoborepin (32) from stannepin (31) <71CC291>. Other benzoborepins have been prepared by this basic method using PhBCl_2 , PhBBr_2 , and MeBBr_2 <67TL1263, 90OM2944>.

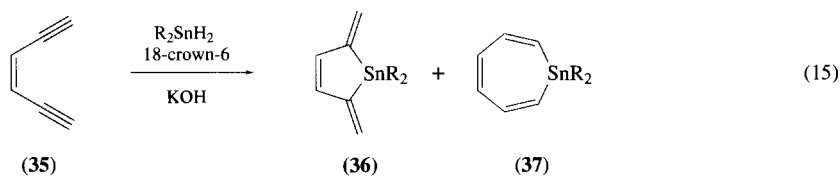


Scheme 5

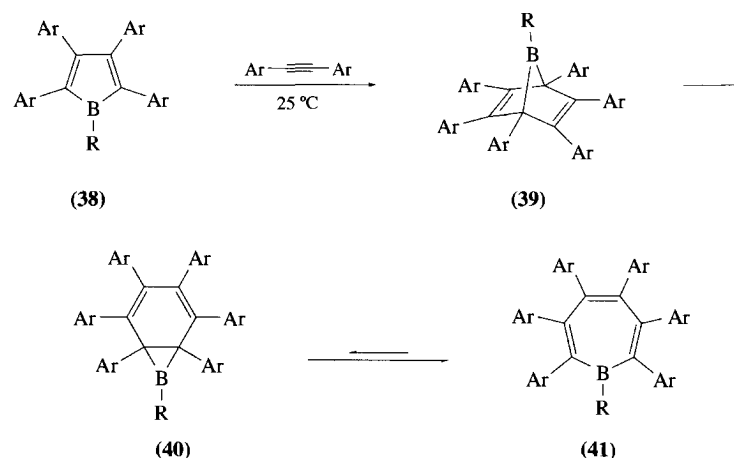
Cyclopentenoborepin (16) and thienoborepins (33) and (34) have also been prepared by modifications of this basic approach (Equations (12)–(14)) <87JA1879, 92JA1479, 93CL933>.



One limitation of this methodology for the preparation of *C*-unsubstituted borepins is illustrated. Thus, hydrostannation of enediyne (35) under the usual conditions affords mostly (36), accompanied by only minor amounts of the desired stannepin (37) (Equation (15)) <90PAC513>.



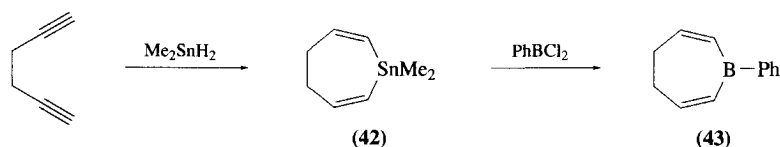
A remarkable, albeit less general, approach to the borepin ring system (Scheme 6) involves [4 + 2] cycloaddition of alkynes to boroles (38) to give Diels–Alder adducts (39), which undergo sigmatropic rearrangement and electrocyclic ring opening of the intermediate boranorcaradienes (40) to give borepins (41) (75JA4436, 90OM2342).



Scheme 6

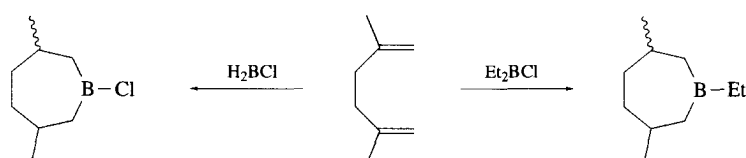
9.37.6.2 Synthesis of Dihydroborepins and Borepanes

In contrast to the difficulties encountered in application of the dialkyne hydrostannation approach to the synthesis of simple C-unsubstituted borepins (90PAC513), C-unsubstituted 4,5-dihydroborepins are accessible by this method. Thus, hydrostannation of 1,5-hexadiyne gives stannepin (42) as the major product, which is readily converted to dihydroborepin (43) (Scheme 7) (67TL1263, 77CB760).

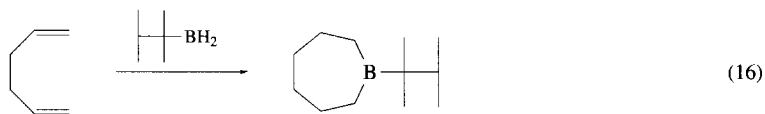


Scheme 7

The fully saturated borepanes are most readily prepared via hydroboration of 1,5-dienes. The earliest efforts gave low yields of what were apparently mixtures of oligomeric and polymeric compounds (60JA2081, 62JA183), but later work, in the 1970s, in which stoichiometry was optimized, has led to greatly improved yields. Some selected examples are shown in Scheme 8 and Equation (16) (73JA3654, 76JA4917).

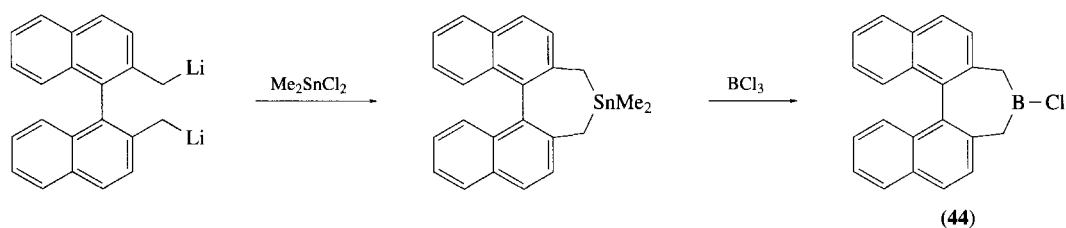


Scheme 8



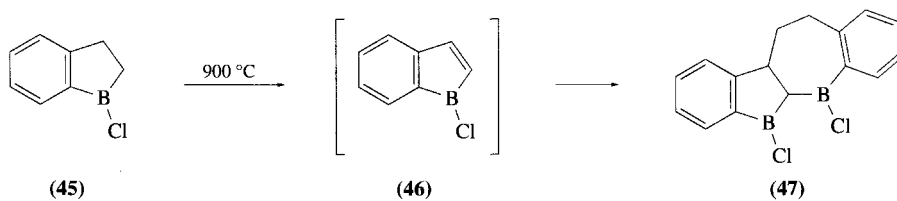
9.37.6.3 Synthesis of Related Large-ring Boracycles

Efforts related to the development of novel asymmetric Lewis acid catalysts led to the synthesis of the (*S*)-binaphthylboracycle (**44**), as shown in Scheme 9 <88JOM(344)277>.



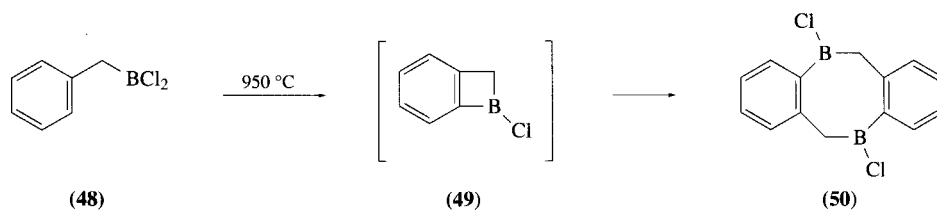
Scheme 9

Pyrolysis of 1-chloro-1-boraindane (**45**) led to formation of the dimeric boracycle (**47**) (Scheme 10), apparently via the intermediate benzoborole (**46**) <87AG(E)665>.



Scheme 10

Similarly, diboracycle (**50**) is isolated after pyrolysis of tolylboron dichloride (**48**) (Scheme 11) via the intermediate benzodihydroborote (**49**) <87CB1331>. Analogous compounds have also been obtained in alternate approaches to *B*-alkylated derivatives of (**49**) <88JOM(339)33>.



Scheme 11

9.38

Rings containing Other Elements

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Reilly Industries, Inc., Indianapolis, IN, USA

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9.38.1 INTRODUCTION

Since the mid-1970s, syntheses of new heteromacrocyclic systems with atoms other than oxygen have increased tremendously. A systematic account of synthesis, structure and physical properties, and reactions of three- to seven-membered metallocycloalka(e)nes, with and without additional heteroatoms, has been reviewed (85JA5027, 86AHC(39)237). General overviews of eight-membered and larger ring heterocycles are available (B-89MI 938-01, 89PHC317, 90PHC277, 91PHC319, 92PHC279, 93PHC322, 94PHC321) in addition to those in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) (84CHEC-I(7)709). Metallomacrocycles, which exhibit electrical, optical, and magnetic properties, are called “organic metals” or “synthetic metals” or “molecular metals.” The impact of “organic metals” has increased as shown in the increases in research and related publications. The design, synthesis, characterization, and theory of new molecular and macromolecular substances with electrical properties have been reviewed (90AG(E)857). A general review of current strategies for, approaches to, and problems of electrically conductive metallomacrocycles is available (85SCI881). The versatile nature of the tailorability of electrically conductive metallomacrocycles has been discussed (83JA677, 83JA1539, 83JA1551, 83MI 938-01, 83MI 938-02, 84IC4325, 84MI 938-01, 85JA7224, 86JA7595, 86JPC4917, 86SM115, 88JA3326). Such metallomacrocyclic complexes are thus not considered here.

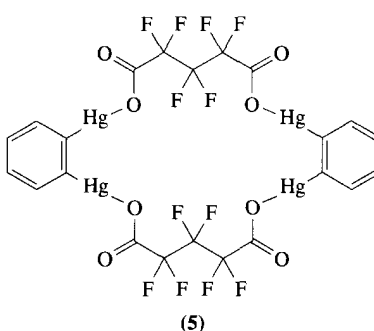
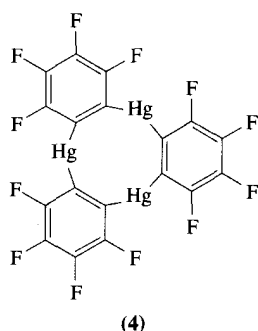
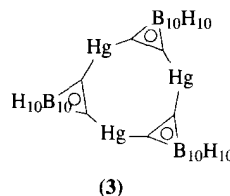
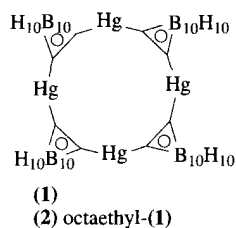
This chapter addresses the rather special and rare species of heterocycles with seven atoms or more, including one or more heteroatom other than nitrogen, oxygen, sulfur, selenium, tellurium, phosphorus, arsenic, antimony, bismuth, silicon, germanium, tin, lead, and boron. Other heteroatoms are lithium (group 1), beryllium, magnesium, strontium, barium, zinc, cadmium, mercury (groups 2 and 12), aluminum, gallium, indium, tantalum (group 13) and transition metals. By virtue of the nature of these elements, the compounds containing these elements are of four types, based on the type of bond(s): (i) ionic, (ii) metal–carbon σ , (iii) metal–carbon π , and (iv) their combinations with and without heteroatoms. Metallomacrocycles with seven or more atoms in the ring with

M—C σ bonds are very few. In this chapter more precisely, larger metallomacrocycles with at least one M—C σ bond with or without additional heteroatoms are reviewed. Unlike in other chapters, here the compounds are reviewed on the basis of the metal atom that is present in the ring, since the generalization of the synthesis, structure elucidation, and physical and chemical properties of all titled metallomacrocycles is rather intricate. Hence the chapter is framed to focus on two classes of metallomacrocycles: (i) with mercury atoms, and (ii) with platinum and/or palladium atoms.

9.38.2 METALLOMACROCYCLES WITH MERCURY ATOMS

Supramolecular chemistry—the chemistry beyond the molecule—is the chemistry of the intermolecular bond, just as molecular chemistry is that of the covalent bond (90AG(E)1304). The concept of “supramolecular chemistry,” or “host–guest chemistry” has increased the interest in the synthesis of host heteromacrocycles for specific affinity for cationic guest molecules. Numerous reviews and articles reveal the host–guest chemistry, scope and perspectives of supramolecular chemistry (88AG(E)89), ligand design for selective complexation of metal ions in aqueous solution (89CRV1875), macrocyclic Lewis-acidic hosts (89JA6294), new heterotropic host molecules (91AG(E)1472, 91AG(E)1474), heteromacrocycles with a mimic enzyme binding site (87JA3456), selective transport of polyfunctional cations (89JOC1000), and co-complexation of neutral guests and electrophilic metal cations (88JA4994). The success of selective complexation of cationic guest molecules in biological processes as well as in organic synthesis opened up a quest for the synthesis of host heteromacrocycles for the complexation of selective anion guest molecules (94AG(E)1832).

A new class of carborane-supported, macrocyclic and multidentate Lewis acid-containing mercury atoms has been synthesized for complexing specifically anions. The tetradentate [12]mercurocarborand-4 (1), a charge-reversed analogue of the well-known [12]crown-4 macrocycle, is the first member of these (91AG(E)1507). The octaethyl derivative (2) of (1) (93JA4904), tridentate [9]mercurocarborand-3 (3) (93JA193), mercuraperfluoroorophenyl-3 (4) (93JA193), and macrocyclic tetradentate organomercuric perfluoroglutarate (5) (87JA4714) are the only known compounds.



9.38.2.1 Carborane-supported Mercuriomacrocycles

9.38.2.1.1 Synthesis

Syntheses (Scheme 1) of carborane-supported cyclic multidentate Lewis acid derivatives are based on the lithiation of icosahedral carborane 1,2- $C_2B_{10}H_{12}$ (6) or its octaethyl derivative (7) and on

The reaction scheme illustrates the synthesis of cyclobutadiene (1) from octaethylcyclobutadiene (6). The starting material (6) is an octaethylcyclobutadiene derivative. It can be converted to cyclobutadiene (1) via two main pathways:

- Top Pathway:**
 - (6) reacts with $2 \text{ Bu}^n\text{Li}$ to form a lithium-substituted intermediate (7) octaethyl-(6).
 - (7) reacts with $\text{Hg}(\text{OAc})_2$ (65% yield) to form Cyclootrimer (3).
 - Cyclootrimer (3) reacts with LiCl to form Cyclootrimer•ClLi (10).
 - (10) reacts with $[\text{As}(\text{C}_6\text{H}_4)_4]\text{Cl}$ to form Cyclobutadiene•I₂[As(C₆H₄)₄]₂ (14).
- Bottom Pathway:**
 - (6) reacts with $2 \text{ Bu}^n\text{Li}$ to form a lithium-substituted intermediate (7) octaethyl-(6).
 - (7) reacts with HgI_2 (70% yield) to form Cyclobutadiene•ILi (9).
 - (9) reacts with LiCl (80% yield) to form Cyclobutadiene•I₂Li₂ (11).
 - (11) reacts with $[\text{As}(\text{C}_6\text{H}_4)_4]\text{Cl}$ to form Cyclobutadiene•I₂[As(C₆H₄)₄]₂ (14).

Intermediate (14) is a dimeric complex that can further react with LiCl to form Cyclobutadiene•Cl₂Li₂ (12) or with HgCl_2 to form Cyclobutadiene•ClLi (8).

Scheme 1

All of these complexes were characterized by multinuclear NMR (^1H , ^{13}C , ^{11}B , ^{199}Hg) and fast atom bombardment mass spectrometry (FAB/MS). Monoanion complexes (**8**) and (**9**) form dianion complexes (**11**) and (**12**), respectively, on further treatment with the respective halides ($\langle 92\text{JA}380 \rangle$). Both monoanion and dianion complexes can undergo metathesis with $[\text{As}(\text{C}_6\text{H}_4)_4]\text{Cl}$ to form products (**13**) and (**14**), respectively ($\langle 91\text{AG}(\text{E})1507, 92\text{JA}380 \rangle$). Uncomplexed cyclotetramer (**1**) was extracted from its iodide ion complexes (**8**) and (**11**) by $\text{Ag}(\text{OAc})$ in ethanol. The same reaction from bromide and iodide complexes resulted in incomplete extraction of host tetramer ($\langle 92\text{AG}(\text{E})893 \rangle$). Uncomplexed host macrocycles (**1**) and (**3**) were characterized by ^1H , ^{13}C , and ^{11}B NMR ($\langle 92\text{AG}(\text{E})893, 93\text{JA}193 \rangle$).

9.38.2.1.2 Structure elucidation

(i) *Mercuriromacrocyclic-solvent aggregate*

Using x-ray diffraction, the molecular structures of the macrocycles **(1)** and **(2)** without the complexing anion were elucidated in the form of their crystallizing solvent aggregates $\langle 92\text{AG(E)893, 93JA193} \rangle$. Tridendate macrocycle **(3)** forms two types of aggregates in acetonitrile: one with three molecules of acetonitrile and one with five molecules of acetonitrile. Both aggregates are nearly planar, similar to the structure of the trimer of *o*-phenylmercury **(4)** $\langle 80\text{ICAL193} \rangle$. The unusual binding ability of the tridendate macrocycle **(3)** towards acetonitrile extend to other nitrogen-containing bases including some of biological interest, such as purines and pyrimidines. The tetra-dendate macrocycle **(1)** formed the aggregate **(1)**(THF)₄·2H₂O in crystallizing solvents THF and hexane. The aggregate showed *S*₄ symmetry and the four mercury atoms are approximately in a butterfly configuration. The two water molecules reside in the cavity even though there is no significant interaction between the water molecules and **(1)**. It is also noteworthy that the mercury atoms are bent away from the cavity, in contrast to the anionic complexes. This flexibility allows the framework of **(1)** to bind with the donor solvent located outside the cavity, through the Lewis acid mercury atoms.

This phenomenon was also evidenced in the behavior of (1) in $[D_6]$ acetone at 25°C elucidated by ^{199}Hg NMR spectroscopy ($\langle 92\text{AG}(\text{E})893, 93\text{JA}193 \rangle$). Macrocycle (3) and its two adducts in acetonitrile are nearly planar ($\langle 93\text{JA}193 \rangle$); in contrast, the THF adduct of the tetramer is nonplanar. However,

the halide ion complexes of this tetramer have planar structures $\langle 91\text{AG(E)1507, 92JA380} \rangle$. ^1H , ^{13}C , ^{11}B , and ^{199}Hg NMR results also supported the structures of the trimer, the tetramer, and their solvent aggregates.

(ii) Mercurumacrocycle–anion complex

Among the known anion co-complexes with the carborane-supported macrocycles, x-ray diffraction studies have been reported for the following: $(\mathbf{1}) \cdot \text{ClLi}$ (**8**) $\langle 91\text{AG(E)1507} \rangle$; $(\mathbf{1}) \cdot \text{I}_2\text{Li}_2$ (**11**) $\langle 92\text{JA380} \rangle$; $(\mathbf{1}) \cdot (\text{closo-B}_{10}\text{H}_{10})^{2-}$ (**15**); and octaethyl derivative of $(\mathbf{1}) \cdot (\text{closo-B}_{10}\text{H}_{10})^{2-}$ (**16**) $\langle 93\text{JA4904} \rangle$. The co-complex (**8**) possessed C_{4h} symmetry consisting of four bivalent 1,2- $\text{C}_2\text{B}_{10}\text{H}_{10}$ cages linked by four mercury atoms in cyclic tetramer with a chloride ion located in the center of the array. Consequently, the mercury atoms are positioned toward the cavity of the ring, which maximizes the bonding between the chloride ion and the four mercury atoms. In this cooperative interaction, the four empty orbitals of mercury and two filled p -orbitals of the chloride ion are involved, and all these orbitals are within the plane of the macrocycle. Thus, the chloride ion is bound to the host molecule by a pair of three-orbital two-electron bonds $\langle 91\text{AG(E)1507} \rangle$. The molecular structure of (**11**) has the similar framework to (**8**). Formation of the co-complex is due to the interaction of the filled p_x - and p_y -orbitals of both I^- ions, with a total of eight empty mercury p -orbitals with four directed 45° above and four below the plane of the host macrocycle $\langle 92\text{JA380} \rangle$. The molecular structures of (**15**) and (**16**) consist of similar structural parameters $\langle 93\text{JA4904} \rangle$. ^1H , ^{13}C , ^{11}B , and ^{199}Hg NMR and FAB/MS results also supported the structures of the trimer, the tetramer, and their aggregates.

9.38.2.1.3 Physical properties

They are readily soluble in polar organic solvents such as diethyl ether, tetrahydrofuran, methylene chloride, and acetonitrile, but not in aliphatic hydrocarbons. It was found that (**8**) decomposed upon prolonged heating at 300°C or during UV irradiation to form mercury, icosahedral carborane, and carborane-containing polymers.

9.38.2.1.4 Chemical properties

The tetramer (**8**) is a more effective Lewis acid than the corresponding trimer. The formation of supramolecules with complex nucleophiles, such as polyhedral borane anions, has been explored $\langle 93\text{JA4904} \rangle$. The intermolecular interaction of the tetramer (**1**) and its octyl derivative (**2**) with $\text{closo-B}_{10}\text{H}_{10}^{2-}$ (**17**) was studied in organic solvents such as acetone, methylene chloride, and acetonitrile, using ^{11}B and ^{199}Hg NMR. The dianion (**17**) does not bind with (**1**) and (**2**) simultaneously to form a sandwich aggregate; and it cannot bind with two molecules of either host simultaneously. Neither host molecule interacts with $\text{closo-B}_{12}\text{H}_{12}^{2-}$ (**18**) and $\text{nido-7,8-C}_2\text{B}_9\text{H}_{12}^{1-}$ (**19**) as revealed by ^{11}B NMR studies. Dianion (**18**) is less nucleophilic than (**17**) and also sterically incompatible. Consequently, both electronic and geometrical factors control the interaction of the nucleophiles (**18**) and (**19**) with host molecules (**1**) and/or (**2**). However, the host molecules (**1**) and (**2**) bind with two fragments of nucleophile, $\text{B}_{10}\text{H}_9^{2-}$ (**20**) to form 1 : 1 and 1 : 2 sandwich aggregates $\langle 93\text{JA4904} \rangle$.

Unlike crown ethers and cryptands, this new class of compounds ((**1**) and derivatives) has a planar preorganized host with a cavity in the uncomplexed state. The electron-withdrawing ability of the carborane cages greatly enhances the electrophilicity of the four Hg(II) atoms. Thus, these metallomacrocycles are excellent electrophilic hosts for the complexation of anions or nucleophilic organic substrates.

9.38.2.2 Noncarborane Mercurumacrocycles

9.38.2.2.1 Synthesis

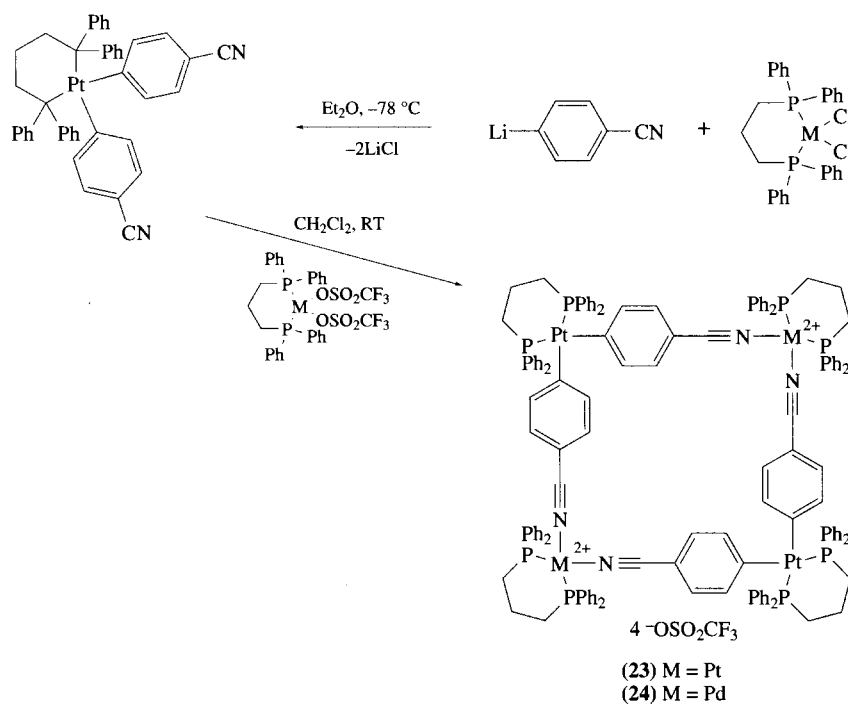
Treatment of 1,2-phenylenedichlorodimercury (**21**) with aqueous NaOH produces 1,2-phenylene- $(\mu\text{-oxo})$ dimercury (**22**), and the subsequent reaction with an equimolar amount of perfluoroglutaric acid produced a crystalline THF complex of tetradentate macrocycle (**5**) $\langle 87\text{JA4714} \rangle$.

9.38.2.2.2 Structure elucidation

X-ray crystallographic study of the macrocyclic 22-membered ring of perfluoroglutarate (**5**) revealed that it is approximately planar. Two molecules of THF interact symmetrically with the mercury atoms of a phenylenedimercury unit, with one molecule of THF bound above and the other below the plane of the cavity $\langle 87JA4714 \rangle$.

9.38.3 METALLOMACROCYCLES WITH PLATINUM AND PALLADIUM ATOMS

Very few compounds are known with tetranuclear, macrocyclic ring systems, possessing approximately 90° bond angles and concomitant rigidity. Even the compounds reported $\langle 94OM3776 \rangle$ do not possess an $M-C$ σ -bond. The first examples of neutral-charged homonuclear $Pt^{II}-Pt^{II}$ (**23**) and heteronuclear $Pt^{II}-Pd^{II}$ (**24**) tetranuclear macrocycles possessing approximately 90° bond angles and with $M-C$ σ -bonds have been reported $\langle 94OM3776 \rangle$. Compounds (**23**) and (**24**) were synthesized (Scheme 2) via self-assembly from the easily available precursors, dppp-chelated $Pt(II)$ dichloride and 4-cyanophenyllithium, and were characterized by multinuclear (^1H , ^{13}C , ^{31}P , ^{19}F) NMR, IR, melting point, and elemental analysis. Compounds (**23**) and (**24**) are very stable, and highly soluble in organic solvents. They add a unique new dimension to supramolecular chemistry.



Scheme 2

References

EXPLANATION OF THE REFERENCE SYSTEM

Throughout this work, references are designated by a number–lettering coding of which the first two numbers denote tens and units of the year of publication, the next one to three letters denote the journal, and the final numbers denote the page. This code appears in the text each time a reference is quoted; the advantages of this system are outlined in the Introduction. The system has been used previously in the first edition of *Comprehensive Heterocyclic Chemistry*, eds A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984 and is based on that used in the following two monographs: (a) A. R. Katritzky and J. M. Lagowski, “Chemistry of the Heterocyclic N-Oxides,” Academic Press, New York, 1971; (b) J. Elguero, C. Marzin, A. R. Katritzky and P. Linda, “The Tautomerism of Heterocycles,” in “Advances in Heterocyclic Chemistry,” Supplement 1, Academic Press, New York, 1976.

The following additional notes apply:

1. A list of journal codes in alphabetical order, together with the journals to which they refer, is given immediately following these notes. Journal names are abbreviated throughout using the CASSI (Chemical Abstracts Service Source Index) system.
2. Each volume contains all the references cited *in that volume*; no separate lists are given for individual chapters.
3. The list of references is arranged in order of (a) year, (b) journal in alphabetical order of journal code, (c) part letter or number if relevant, (d) volume number if relevant, (e) page number.
4. In the reference list the code is followed by (a) the complete literature citation in the conventional manner and (b) the number(s) of the page(s) on which the reference appears, whether in the text or in tables, schemes, etc.
5. For nontwentieth-century references the year is given in full in the code.
6. For journals which are published in separate parts, the part letter or number is given (when necessary) in parentheses immediately after the journal code letters.
7. Journal volume numbers are *not* included in the code numbers unless more than one volume was published in the year in question, in which case the volume number is included in parentheses immediately after the journal code letters.
8. Patents are assigned appropriate three-letter codes.
9. Frequently cited books are assigned codes.
10. Less common journals and books are given the code “MI” for miscellaneous with the whole code for books prefixed by the letter “B-”.
11. Where journals have changed names, the same code is used throughout, e.g. CB refers to both *Chem. Ber.* and to *Ber. Dtsch. Chem. Ges.*

Journal Codes

AAC	Antimicrob. Agents Chemother.
ABC	Agric. Biol. Chem.
AC	Appl. Catal.
AC(P)	Ann. Chim. (Paris)
AC(R)	Ann. Chim. (Rome)
ACH	Acta Chim. Acad. Sci. Hung.

ACR	Acc. Chem. Res.
ACS	Acta Chem. Scand.
ACS(A)	Acta Chem. Scand., Ser. A
ACS(B)	Acta Chem. Scand., Ser. B
AF	Arzneim.-Forsch.
AFC	Adv. Fluorine Chem.
AG	Angew. Chem.
AG(E)	Angew. Chem., Int. Ed. Engl.
AHC	Adv. Heterocycl. Chem.
AHCS	Adv. Heterocycl. Chem. Supplement
AI	Anal. Instrum.
AJC	Aust. J. Chem.
AK	Ark. Kemi
AKZ	Arm. Khim. Zh.
AM	Adv. Mater. (Weinheim, Ger.)
AMLS	Adv. Mol. Spectrosc.
AMS	Adv. Mass. Spectrom.
ANC	Anal. Chem.
ANL	Accad. Naz. Lincei
ANY	Ann. N. Y. Acad. Sci.
AOC	Adv. Organomet. Chem.
AP	Arch. Pharm. (Weinheim, Ger.)
APO	Adv. Phys. Org. Chem.
AQ	An. Quim.
AR	Annu. Rep. Prog. Chem.
AR(A)	Annu. Rep. Prog. Chem., Sect. A
AR(B)	Annu. Rep. Prog. Chem., Sect. B
ARP	Annu. Rev. Phys. Chem.
ASI	Acta Chim. Sin. Engl. Ed.
ASIN	Acta Chim. Sin.
AX	Acta Crystallogr.
AX(A)	Acta Crystallogr., Part A
AX(B)	Acta Crystallogr., Part B
B	Biochemistry
BAP	Bull. Acad. Pol. Sci., Ser. Sci. Chim.
BAU	Bull. Acad. Sci. USSR, Div. Chim. Sci.
BBA	Biochim. Biophys. Acta
BBR	Biochim. Biophys. Res. Commun.
BCJ	Bull. Chem. Soc. Jpn.
BEP	Belg. Pat.
BJ	Biochem. J.
BJP	Br. J. Pharmacol.
BMC	Bioorg. Med. Chem. Lett.
BP	Biochem. Biopharmacol.
BPJ	Br. Polym. J.
BRP	Br. Pat.
BSB	Bull. Soc. Chim. Belg.
BSF	Bull. Soc. Chim. Fr.
BSF(2)	Bull. Soc. Chim. Fr., Part 2
C	Chimia
CA	Chem. Abstr.
CAN	Cancer
CAR	Carbohydr. Res.
CAT	Chim. Acta Turc.
CB	Chem. Ber.

CBR	Chem. Br.
CC	J. Chem. Soc., Chem. Commun.
CCA	Croat. Chem. Acta
CCC	Collect. Czech. Chem. Commun.
CCR	Coord. Chem. Rev.
CE	Chem. Express
CEN	Chem. Eng. News
CHE	Chem. Heterocycl. Compd. (Engl. Transl.)
CHEC-I	Comp. Heterocycl. Chem., 1st edn.
CI(L)	Chem. Ind. (London)
CI(M)	Chem. Ind. (Milan)
CJC	Can. J. Chem.
CJS	Can. J. Spectrosc.
CL	Chem. Lett.
CLY	Chem. Listy
CM	Chem. Mater.
CMC	Comp. Med. Chem.
COC	Comp. Org. Chem.
COMC-I	Comp. Organomet. Chem., 1st edn.
COS	Comp. Org. Synth.
CP	Can. Pat.
CPB	Chem. Pharm. Bull.
CPH	Chem. Phys.
CPL	Chem. Phys. Lett.
CR	C. R. Hebd. Seances Acad. Sci.
CR(A)	C. R. Hebd. Seances Acad. Sci., Ser. A
CR(B)	C. R. Hebd. Seances Acad. Sci., Ser. B
CR(C)	C. R. Hebd. Seances Acad. Sci., Ser. C
CRAC	Crit. Rev. Anal. Chem.
CRV	Chem. Rev.
CS	Chem. Scr.
CSC	Cryst. Struct. Commun.
CSR	Chem. Soc. Rev.
CT	Chem. Tech.
CZ	Chem.-Ztg.
CZP	Czech. Pat.
DIS	Diss. Abstr.
DIS(B)	Diss. Abstr. Int. B.
DOK	Dokl. Akad. Nauk SSSR
DP	Dyes Pigm.
E	Experientia
EC	Educ. Chem.
EF	Energy Fuels
EGP	Ger. (East) Pat.
EJM	Eur. J. Med. Chem.
EUP	Eur. Pat.
FCF	Forstchr. Chem. Forsch.
FCR	Fluorine Chem. Rev.
FES	Farmaco Ed. Sci.
FOR	Fortschr. Chem. Org. Naturst.
FRP	Fr. Pat.
G	Gazz. Chim. Ital.
GAK	Gummi Asbest Kunstst.
GEP	Ger. Pat.
GEP(O)	Ger. Pat. Offen.

GSM	Gen. Synth. Methods
H	Heterocycles
HAC	Heteroatom Chem.
HC	Chem. Heterocycl. Compd.
HCA	Helv. Chim. Acta
HOU	Methoden Org. Chem. (Houben-Weyl)
HP	Hydrocarbon Process
IC	Inorg. Chem.
ICA	Inorg. Chim. Acta
IEC	Ind. Eng. Chem. Res.
IJ	Isr. J. Chem.
IJC	Indian J. Chem.
IJC(A)	Indian J. Chem., Sect. A
IJC(B)	Indian J. Chem., Sect. B
IJM	Int. J. Mass Spectrom. Ion Phys.
IJQ	Int. J. Quantum Chem.
IJS	Int. J. Sulfur Chem.
IJS(A)	Int. J. Sulfur Chem., Part A
IJS(B)	Int. J. Sulfur Chem., Part B
IS	Inorg. Synth.
IZV	Izv. Akad. Nauk SSSR, Ser. Khim.
JA	J. Am. Chem. Soc.
JAN	J. Antibiot.
JAP	Jpn. Pat.
JAP(K)	Jpn. Kokai
JBC	J. Biol. Chem.
JC	J. Chromatogr.
JCC	J. Coord. Chem.
JCE	J. Chem. Ed.
JCED	J. Chem. Eng. Data
JCI	J. Chem. Inf. Comput. Sci.
JCP	J. Chem. Phys.
JCPB	J. Chim. Phys. Physico-Chim. Biol.
JCR(M)	J. Chem. Res. (M)
JCR(S)	J. Chem. Res. (S)
JCS	J. Chem. Soc.
JCS(A)	J. Chem. Soc. (A)
JCS(B)	J. Chem. Soc. (B)
JCS(C)	J. Chem. Soc. (C)
JCS(D)	J. Chem. Soc., Dalton Trans.
JCS(F1)	J. Chem. Soc., Faraday Trans. 1
JCS(F2)	J. Chem. Soc., Faraday Trans. 2
JCS(P1)	J. Chem. Soc., Perkin Trans. 1
JCS(P2)	J. Chem. Soc., Perkin Trans. 2
JCS(S2)	J. Chem. Soc. (Suppl. 2)
JEC	J. Electroanal. Chem. Interfacial Electrochem.
JEM	J. Energ. Mater.
JES	J. Electron. Spectrosc.
JFA	J. Sci. Food. Agri.
JFC	J. Fluorine Chem.
JGU	J. Gen. Chem. USSR (Engl. Transl.)
JHC	J. Heterocycl. Chem.
JIC	J. Indian Chem. Soc.
JINC	J. Inorg. Nucl. Chem.
JLC	J. Liq. Chromatogr.

JMAS	J. Mat. Sci.
JMC	J. Med. Chem.
JMOC	J. Mol. Catal.
JMR	J. Magn. Reson.
JMS	J. Mol. Sci.
JOC	J. Org. Chem.
JOM	J. Organomet. Chem.
JOU	J. Org. Chem. USSR (Engl. Transl.)
JPC	J. Phys. Chem.
JPJ	J. Pharm. Soc. Jpn.
JPO	J. Phys. Org. Chem.
JPP	J. Pharm. Pharmacol.
JPR	J. Prakt. Chem.
JPS	J. Pharm. Sci.
JPS(A)	J. Polym. Sci., Polym. Chem., Part A
JPU	J. Phys. Chem. USSR (Engl. Transl.)
JSC	J. Serbochem. Soc.
JSP	J. Mol. Spectrosc.
JST	J. Mol. Struct.
K	Kristallografiya
KFZ	Khim. Farm. Zh.
KGS	Khim. Geterotsikl. Soedin.
KO	Kirk-Othmer Encyc.
KPS	Khim. Prir. Soedin.
L	Langmuir
LA	Liebigs Ann. Chem.
LC	Liq. Cryst.
LS	Life Sci.
M	Monatsh. Chem.
MAC	Macromol. Chem.
MC	Mendeleev Chem. J. (Engl. Transl.)
MCLC	Mol. Cryst. Liq. Cryst.
MI	Miscellaneous [book/journal]
MIP	Miscellaneous Pat.
MM	Macromolecules
MP	Mol. Phys.
MRC	Magn. Reson. Chem.
N	Naturwissenschaften
NAT	Nature
NEP	Neth. Pat.
NJC	Nouv. J. Chim.
NKK	Nippon Kagaku Kaishi (J. Chem. Soc. Jpn.)
NKZ	Nippon Kagaku Zasshi
NZJ	N. Z. J. Sci. Technol.
OCS	Organomet. Synth.
OM	Organometallics
OMR	Org. Magn. Reson.
OMS	Org. Mass Spectrom.
OPP	Org. Prep. Proced. Int.
OR	Org. React.
OS	Org. Synth.
OSC	Org. Synth., Coll. Vol.
P	Phytochemistry
PA	Polym. Age
PAC	Pure Appl. Chem.

PAS	Pol. Acad. Sci.
PB	Polym. Bull.
PC	Personal Communication
PCS	Proc. Chem. Soc.
PHA	Pharmazi
PHC	Prog. Heterocycl. Chem.
PIA	Proc. Indian Acad. Sci.
PIA(A)	Proc. Indian Acad. Sci., Sect. A
PJC	Pol. J. Chem.
PJS	Pak. J. Sci. Ind. Res.
PMH	Phys. Methods Heterocycl. Chem.
PNA	Proc. Natl. Acad. Sci. USA
POL	Polyhedron
PP	Polym. Prepr.
PRS	Proceed. Roy. Soc.
PS	Phosphorus Sulfur
QR	Q. Rev., Chem. Soc.
QRS	Quart. Rep. Sulfur. Chem.
QSAR	Quant. Struct. Act. Relat. Pharmacol. Chem. Biol.
RC	Rubber Chem. Technol.
RCM	Rapid Commun. Mass Spectrom.
RCP	Rec. Chem. Prog.
RCR	Russ. Chem. Rev. (Engl. Transl.)
RHA	Rev. Heteroatom Chem.
RJ	Rubber J.
RP	Rev. Polarogr.
RRC	Rev. Roum. Chim.
RS	Ric. Sci.
RTC	Recl. Trav. Chim. Pays-Bas
RZC	Rocz. Chem.
S	Synthesis
SA	Spectrochim. Acta
SA(A)	Spectrochim. Acta, Part A
SAP	S. Afr. Pat.
SC	Synth. Commun.
SCI	Science
SL	Synlett
SM	Synth. Met.
SR	Sulfur Reports
SRI	Synth. React. Inorg. Metal-Org. Chem.
SS	Sch. Sci. Rev.
SST	Org. Compd. Sulphur, Selenium, Tellurium [R. Soc. Chem. series]
SUL	Sulfur Letters
SZP	Swiss Pat.
T	Tetrahedron
T(S)	Tetrahedron, Suppl.
TA	Tetrahedron Asymmetry
TAL	Talanta
TCA	Theor. Chim. Acta
TCC	Top. Curr. Chem.
TCM	Tetrahedron, Comp. Method.
TFS	Trans. Faraday Soc.
TH	Thesis
TL	Tetrahedron Lett.
TS	Top. Stereochem.

UK	Usp. Khim.
UKZ	Ukr. Khim. Zh. (Russ. Ed.)
UP	Unpublished Results
URP	USSR Pat.
USP	US Pat.
WCH	Wiadom. Chem.
YGK	Yuki Gosei Kagaku Kyokaishi
YZ	Yakugaku Zasshi (J. Pharm. Soc. Jpn.)
ZAAC	Z. Anorg. Allg. Chem.
ZAK	Zh. Anal. Khim.
ZC	Z. Chem.
ZN	Z. Naturforsch.
ZN(A)	Z. Naturforsch., Teil A
ZN(B)	Z. Naturforsch., Teil B
ZOB	Zh. Obshch. Khim.
ZOR	Zh. Org. Khim.
ZPC	Hoppe-Seyler's Z. Physiol. Chem.
ZPK	Zh. Prikl. Khim.

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