9.14
Bicyclic 5-6 Systems: Six and Seven Heteroatoms

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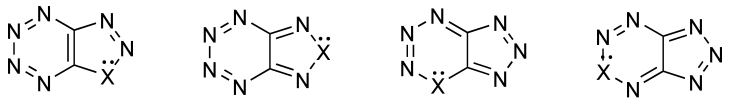
9.14.1 Introduction

This chapter reviews progress since 1994 in the chemistry of bicyclic 5-6 heterosystems that have a total of six or seven ring heteroatoms. Systems with bridgehead heteroatoms are not included and these are covered in Volumes 10 and 11. When this area of chemistry was reviewed in 1994 in Chapter 7.14 of CHEC-II(1996), it was described as being in its infancy <1996CHEC-II(7)513>. Since then, little progress toward maturity has been made.

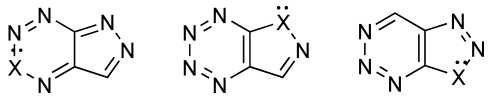
This chapter is structured in the same way as the corresponding chapter in CHEC-II(1996) <1996CHEC-II(7)513>. For a full coverage of the subject, the two chapters must be considered together. In addition to subdivision according to the number of ring heteroatoms (six or seven), these bicyclic 5,6-heterosystems are also conveniently further subdivided according to the number of π-electrons (10, 12, or 14) in the fully-conjugated parent system. Structures **1–4** show the four possible 10π-electron systems with seven heteroatoms (4:3). If the

heteroatoms X are restricted to O, S, or NR, then 12 heterocyclic systems are possible. Replacement of the nitrogen atoms (–N═) by other heteroatoms (e.g. –B═, –HSi═) leads to additional parent systems.



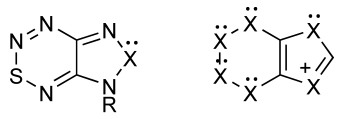
1 **2** **3** **4**

Using a similar analysis, it can be shown that there are 63 possible 10π-electron six-heteroatom systems (4:2 or 3:3) if X is restricted to O, S, or NR. In practice only derivatives of the generalised systems **5–7** have been reported. This number is further increased if –N═ is replace by –B═, –HSi═, etc., and three examples of this type are known (see **Figure 1**).



5 **6** **7**

A large number of parent bicyclic 4:3, 4:2, and 3:3 heterocycles having 12π-electrons are possible but few derivatives have been reported and these are all derived from the generalized system **8**. Finally, one example of a system that can be regarded as being derived from the 14π-electron system **9** is known.



8 **9**

Figure 1 shows the parent structures of all the known compounds that fall within the scope of this chapter together with their systematic names. All compounds are named as derivatives of these parent structures **10–23**.

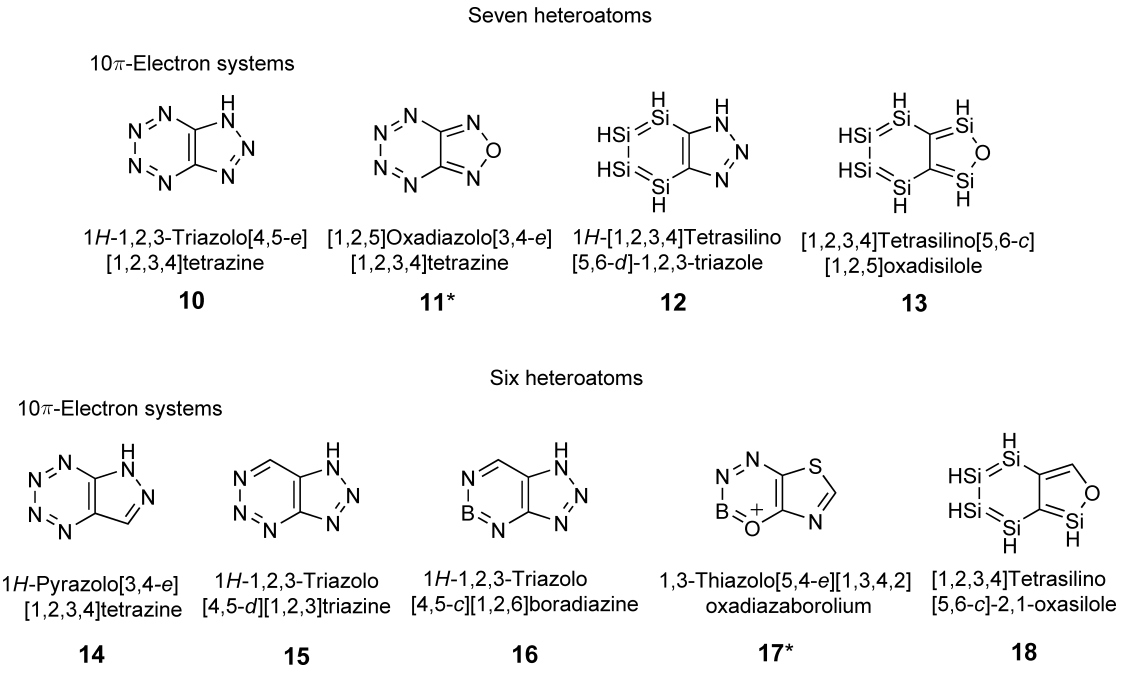
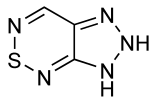


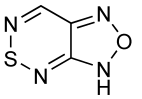
Figure 1 (*Continued*)

12π-Electron systems



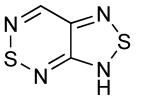
1,2,3-Triazolo[4,5-*c*] [1,2,6]thiadiazine

19



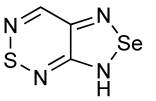
[1,2,5]Oxadiazolo[3,4-*c*] [1,2,6]thiadiazine

20



[1,2,5]Thiadiazolo[3,4-*c*] [1,2,6]thiadiazine

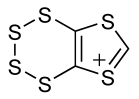
21



[1,2,5]Selenadiazolo[3,4-*c*] [1,2,6]thiadiazine

22*

14π-Electron systems



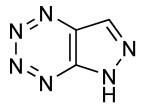
1,3-Dithiolium[4,5-*e*] [1,2,3,4]tetrathiane

23*

Figure 1 Parent fully conjugated ring systems of known compounds. The asterisk indicates systems described since the publication of CHEC-II(1996).

9.14.2 Theoretical Methods

A systematic investigation of the relative energies of azaindazole tautomers including the isomeric pyrazolo[3,4-*e*]-[1,2,3,4]tetrazines **24** and **25** has been reported. Both AM1 and density functional theory (DFT) *ab initio* calculations indicate that the 1*H*-tautomer **24** is more stable: the calculated energy differences are 18.8 (AM1) and 27.8 kJ mol^{-1} (B3LYP/6-31G*) <2005JPO719>. The AM1 calculation appears to underestimate the energy difference and this is attributed to inadequate treatment of the multiple lone pair–lone pair integrals. Previous workers have noted that for calculations on 2-phenyl-1,2,3-triazolo[4,5-*e*][1,2,3,4]tetrazine **26**, the AM1 method underestimates the C–C double bond character <1991AXC590>, and this may be attributed to overestimation of core repulsion energies in multi-nitrogen systems <1992JCS(P1)2779>.



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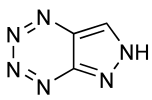

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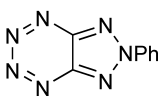
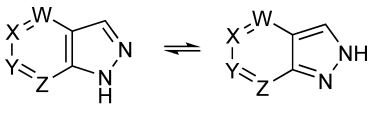


26

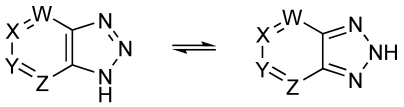
A statistical analysis of the calculated 1*H*- and 2*H*-tautomer energy differences for a series of indazole derivatives reveals that aza substitutions make the following contributions (kJ mol^{-1}) to the energy differences: 4-N (-4.4 ± 1.0); 5-N (-3.3 ± 1.2); 6-N (-5.1 ± 1.1); 7-N ($+9.8 \pm 1.0$) <2005JPO719>. A 7-aza atom favors the 1*H*-tautomer, whereas 4-, 5-, and 6-aza atoms favor the 2*H*-tautomer but the effect is not large enough to shift the equilibrium in favor of the 2*H*-structure. The same analysis indicated that 3-NO_2 and 3-CO_2Me substituents contribute to stabilization of the 2*H*-tautomers (3-NO_2 (-11.4 ± 2.8 kJ mol^{-1}) and 3-CO_2Me (-13.0 ± 2.8 kJ mol^{-1})). This study did not include 3-aza derivatives but an extension of the AM1 study suggests that 3-aza substitution strongly favors the 1*H*-tautomer (3-N ($+24.8$ kJ mol^{-1} (average))) <2006UP1>. **Table 1** shows the calculated AM1 energy differences ($\Delta\Delta E$) for a series of polyazaindazole tautomers **27a**,**b** and **28a**,**b**. In all cases, the 1*H*-tautomer is more stable ($\Delta\Delta E$ positive). However, the relative stability is consistently greater for the 3-aza derivatives **28** and the stabilization attributed to the 3-aza atom (Δ 3-N) is large and consistent, and averages 24.8 kJ mol^{-1} (**Table 1**). This effect is in interesting contrast with the relative destabilizing effect of 3-NO_2 and 3-CO_2Me substituents <2005JPO719>.

As part of an investigation of the binding of adenosine analogues to an active site of mammalian adenosine deaminase, the structure and conformations of 2,8-diazaadenosine **29**, and other isoteric analogs of adenosine **30**, have been modeled using *ab initio* calculations and molecular mechanics (MM+) <2003MI152>.

Table 1 Calculated AM1 energy differences ($\Delta\Delta E$) for polyazaindazole tautomers



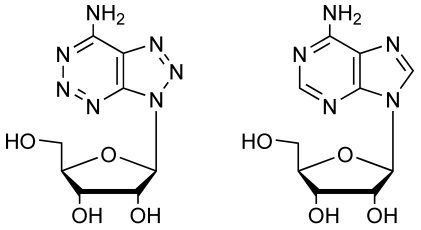
27a **27b**



28a **28b**

W	*X*	*Y*	*Z*	$\Delta\Delta E^{a,b}$	*W*	*X*	*Y*	*Z*	$\Delta\Delta E^{a,c}$	$\Delta 3\text{-}N^{a,c}$
CH	N	N	N	27.91	CH	N	N	N	53.23	25.32
N	CH	N	N	25.36	N	CH	N	N	49.22	23.86
N	N	CH	N	27.53	N	N	CH	N	52.29	24.76
N	N	N	CH	13.35	N	N	N	CH	39.06	25.71
N	N	N	N	18.79	N	N	N	N	43.13	24.34

[a] kJ mol^{-1}.
[b] <2005JPO719>.
[c] <2006UP1>.

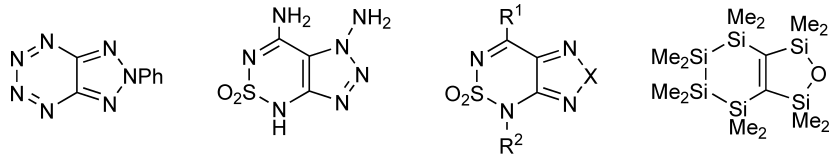


29 **30**

9.14.3 Experimental Structural Methods

9.14.3.1 X-Ray Diffraction

No new structures of compounds belonging to this class have been determined using X-ray crystallography. Previously, the structures of triazolotetrazine **31**, triazolothiadiazine **32**, several bicyclic thiadiazines **33** ($R^1 = NH_2$, O^-K^+; R^2 = H, Me; X = NH, O, S), and the tetrasilinooxadisilole **34** have been reported and are discussed in CHEC-II(1996) <1996CHEC-II(7)513>.



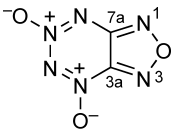
31 **32** **33** **34**

9.14.3.2 NMR Spectroscopy

^{15}N and ^{13}C chemical shifts have previously been reported for the derivatives **32** and **33** and are tabulated in CHEC-II(1996) <1996CHEC-II(7)513>.

The ^{13}C, ^{14}N, ^{15}N, and ^{17}O nuclear magnetic resonance (NMR) spectra of the oxadiazolotetrazine 4,6-di-*N*-oxide **35** have been reported <1995MC227>. The ^{13}C signals at δ 143.5 (C-3a) and 155.8 (C-7a) are comparable to those reported for the triazolotetrazine **31** (δ 145.7 (C-3a) and 145.7 (C-7a)) <1996CHEC-II(7)513>. The ^{15}N signals in the di-*N*-oxide **35** occur at δ 35.0 (N-1), 38.2 (N-3), 8.0 (N-5), −43.9 (N-6), −52.8 (N-4), and −106.0 (N-7). A study of

^{15}N-enriched samples of compound **35** in combination with the natural isotope spectrum enabled the unambiguous assignment of the structure.



35

9.14.3.3 Mass Spectrometry

Nothing of special significance has been reported since the publication of CHEC-II(1996).

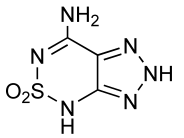
9.14.3.4 IR and UV Spectroscopy

Ultraviolet (UV) spectra of the derivatives **32** and **33** and two triazolotriazine derivatives have been reported and are tabulated in CHEC-II(1996) <1996CHEC-II(7)513>. No new UV spectra have been reported.

A detailed study, including the use of isotopic substitution, of the infrared (IR) and Raman spectra of the triazolotetrazine-4,6-di-*N*-oxide **35** has been reported <1995MC100, 1995IZV2187>, and characteristic vibration frequencies of the tetrazine dioxide fragment have been identified.

9.14.3.5 Dipole Moments

No experimental dipole moments have been reported for the compounds covered by this chapter. Previously, on the basis of calculations, the greater stability of the tautomers **36**, relative to isomers **37**, has been ascribed to the significantly larger dipole moments (calc. 5.08 D vs. 2.97 D) which leads to greater solvation <1996CHEC-II(7)513>. More recently *ab initio* calculations (B3LYP/6-31G*) indicate a similar difference in the calculated dipole moments of the tautomers **38** and **39** ($\Delta\mu$ 2.84 D), suggesting that polar solvents would favor the tautomer **38** <2005JPO719>.



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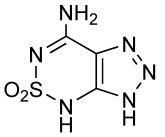

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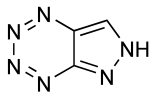

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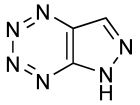


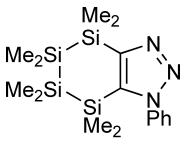
39

9.14.4 Thermodynamic Aspects

There is nothing new to report in this area. Some pK_a values of compounds with structures **33** ($R^1 = NH_2$; $R^2 = H$; X = O, S, NR) have been measured and these were tabulated in CHEC-II(1996) <1996CHEC-II(7)513>.

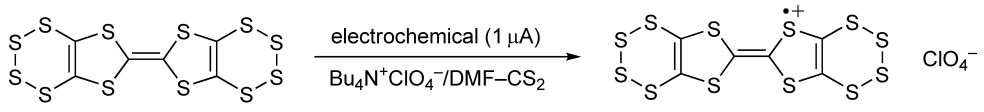
9.14.5 Reactivity of Fully Conjugated Rings

Previously there have been limited studies on: (1) the thermal decomposition of compounds **31** and **40**; (2) N-alkylation of the five-membered ring of the amine **33** (X = O; $R^1 = NH_2$; $R^2 = H$) and N-amination of the amine **33** (X = NH; $R^1 = NH_2$; $R^2 = H$); and (3) reduction of the derivatives of the amine **33** (X = O) to 3,4,5-triamino-1,2,6-thiadiazine-1,1-dioxides. A full discussion of these transformations can be found in CHEC-II(1996) <1996CHEC-II(7)513>.



40

The only new chemistry concerns electrochemical oxidation of the tetrathiafulvene derivative **41** to the radical cation perchlorate **42** (Equation 1) <2005MCL575>. The salt **42** was formed electrochemically as a dense thin film on the electrode surface and shown to be a conducting cation-radical salt that behaves like an organic metal. The electrical conductivity shows an interesting variation with temperature which may be related to a phase transition at 102 K <2005MCL575>.



41 **42** (1)

9.14.6 Reactivity of Nonconjugated Rings

Earlier studies have described N-alkylations of the six-membered rings of the derivatives **33** ($R^2 = H$) and reaction of the derivatives **33** ($R^1 = NH_2$; $R^2 = H$) with amines resulting in either transamination or ring opening to furazans <1996CHEC-II(7)513>.

No new reactions have been reported since 1996.

9.14.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Apart from a simple N-formylation of the oxadiazolothiadiazine derivative **33** ($R^1 = NHMe$; $R^2 = Me$; $X = O$) <1996CHEC-II(7)513>, reactions of substituents have not been studies and there are no new results.

9.14.8 Reactivity of Substituents Attached to Ring Heteroatoms

No reactions in which the heterocyclic system plays an influential role in determining the product have been reported.

9.14.9 Ring Synthesis from Two Components

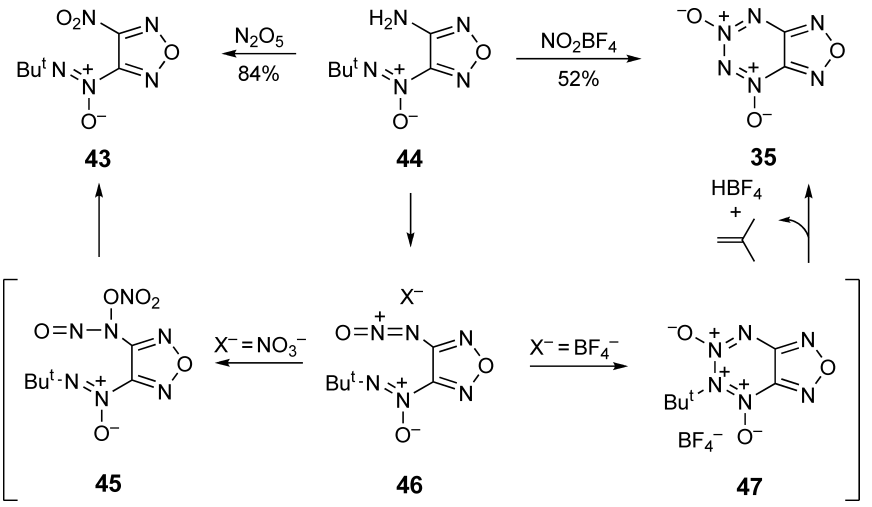
The synthesis of the diverse systems covered by this chapter are discussed in the same order as their parent structures are presented in **Figure 1** (see Section 9.14.1). Only systems for which preparative studies have been reported since 1994 are included in this section. All earlier work is described in CHEC-II(1996) <1996CHEC-II(7)513>.

9.14.9.1 Seven Heteroatoms (10π)

9.14.9.1.1 Oxadiazolo[3,4-*e*][1,2,3,4]tetrazines **11**

Oxadiazolo[3,4-*e*][1,2,3,4]tetrazine 4,6-di-*N*-oxide **35** is obtained as a yellow crystalline compound (m.p. 110–112 °C (decomp.)) by reaction of the amine **44** with excess nitronium tetrafluoroborate in acetonitrile at −20 °C (**Scheme 1**). Compound **35** is very sensitive to shock and, although it can be stored for long periods at 0 °C, it should be handled with care. The authors propose the mechanism shown in **Scheme 1** to account for the formation of compound **35**. When the counterion is tetrafluoroborate, the intermediate **46** cyclizes to the bicyclic cation **47**, which liberates

isobutene and HBF_4. Interestingly, treatment of the amine **44** with dinitrogen pentoxide gives the nitro derivative **43** and it is proposed that under these conditions the intermediate **46** reacts with nitrate ion leading to the nitrofurazan *via* the intermediate **45** <1995MC102, 1995MC227>.

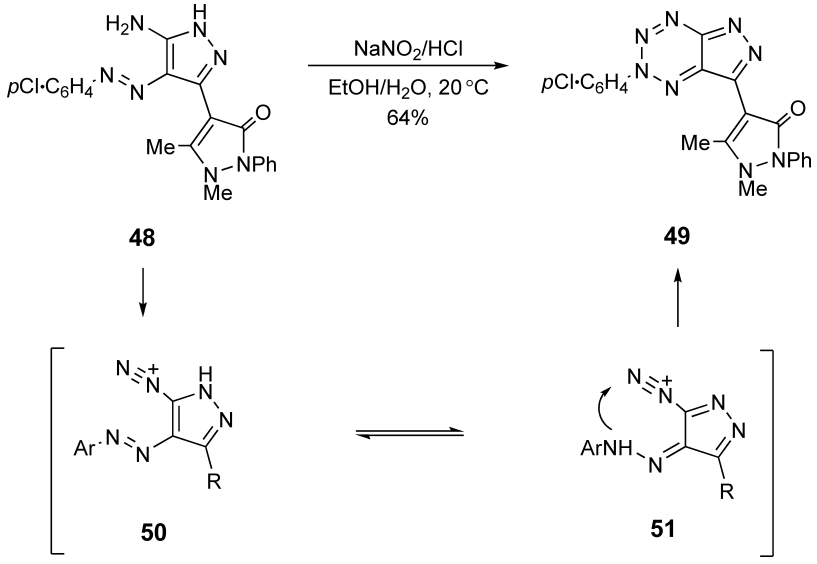


Scheme 1

9.14.9.2 Six Heteroatoms (10π)

9.14.9.2.1 Pyrazolo[3,4-*e*][1,2,3,4]tetrazines **14**

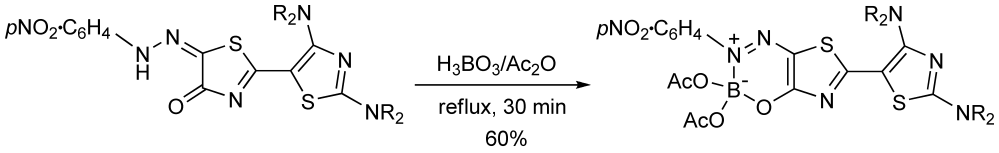
The pyrazolo[3,4-*e*][1,2,3,4]tetrazine derivative **49** has been reported to be formed by treatment of the hydrochloride salt of the amine **48** with sodium nitrite in aqueous ethanol at room temperature. Only a single example was described. Compound **49** was obtained as red crystals (m.p. > 300 °C). The product is presumed to form from the diazonium cation **50** which cyclizes via the hydrazone tautomer **51** (**Scheme 2**) <1998MI11>.



Scheme 2

9.14.9.2.2 1,3-Thiazolo[5,4-*e*][1,3,4,2]oxadiazaborolium **17**

The derivative **53** (m.p. 297–300 °C) has been prepared by heating the hydrazone **52** with 1 equiv of boric acid in hot acetic anhydride (Equation 2). No other derivatives were described <2003HCA1949>.



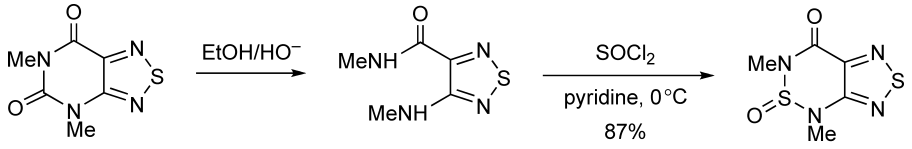
52 **53**

R_2N = morpholinyl (2)

9.14.9.3 Six Heteroatoms (12π)

9.14.9.3.1 1,2,5-Thiadiazolo[3,4-*c*][1,2,6]thiadiazines **21**

The novel derivative **56** (m.p. 127–128 °C) has been prepared in high yield by reaction of the 1,2,5-thiadiazole **55** with thionyl chloride (**Scheme 3**) <2000JHC1269>. The intermediate **55** is made by alkaline hydrolysis of 4,6-dimethyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione **54** <2000JHC1269>.

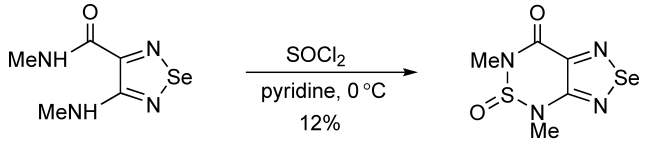


54 **55** **56**

Scheme 3

9.14.9.3.2 1,2,5-Selenadiazolo[3,4-*c*][1,2,6]thiadiazines **22**

Reaction of a pyridine solution of the 1,2,5-selenadiazole **57** with thionyl chloride at 0 °C gave a low yield of the novel selenadiazolo[3,4-*c*][1,2,6]thiadiazine **58** (m.p. 208–210 °C) (Equation 3). The precursor **57** was prepared from the corresponding selenadiazolo[3,4-*d*]pyrimidine, in a similar procedure to that used for compound **55** <2000JHC1269>.

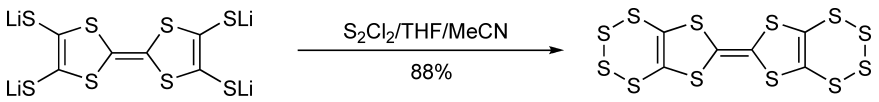


57 **58** (3)

9.14.9.4 Six Heteroatoms (14π)

9.14.9.4.1 1,3-Dithiolium[4,5-*e*][1,2,3,4]tetrathiane **23**

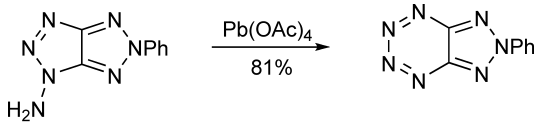
The compound **60** (C_6S_{12}) has been reported to be formed by reaction of the tetralithium salt **59** with sulfur monochloride at room temperature (Equation 4). In an alternative procedure, the tetrasodium salt was used. Similar procedures gave the C_6S_{10} and C_6S_{14} analogues. Products were obtained as solvates and were not recrystallized <2005MCL575>.



59 60 (4)

9.14.10 Ring Synthesis by Transformation of Another Ring

The only ring synthesis in this category is formation of the triazolotetrazine **26** by oxidation of the 1-aminotriazolotriazole **61** (Equation 5), and this was discussed in CHEC-II(1996) <1996CHEC-II(7)513>.



61 26 (5)

9.14.11 Important Compounds and Applications

A number of the compounds described in this chapter and the corresponding chapter in CHEC-II(1996) <1996CHEC-II(7)513> have been made because of their structural relationship to purines. Although some biological activities have been reported no useful applications have emerged. Some of the polyaza derivatives are of potential interest as explosives and high-energy oxidizing agents <1992MI1109, 1995MC100, 2004MI75>. More recently, there has been some preliminary interest in polysulfur derivatives as organic metals <2005MCL575>.

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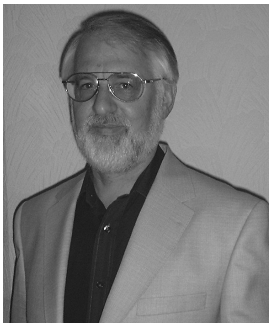
Biographical Sketch



Chris Ramsden was born in Manchester, UK in 1946. He is a graduate of Sheffield University and received his PhD (W. D. Ollis) in 1970 and DSc in 1990. After post-doctoral work at the University of Texas (M. J. S. Dewar)(1971–73) and University of East Anglia (A. R. Katritzky)(1973–76), he worked in the pharmaceutical industry. He moved to Keele University as Professor of Organic Chemistry in 1992. His research interests are heterocycles and three-center bonds and applications of their chemistry to biological problems.