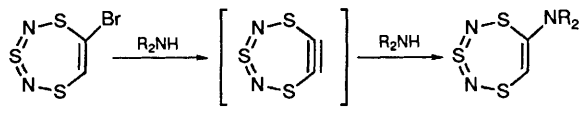
Aminotrithiadiazepines

M. John Plater, Charles W. Rees, Alexandra M. Z. Slawin and David J. Williams

Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW7 2AY, UK

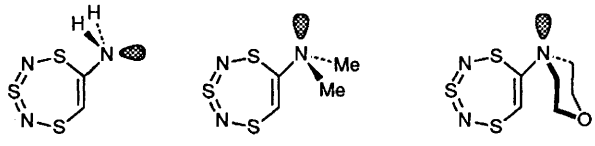
Amino derivatives **3** of the trithiadiazepine ring are moderately stable crystalline solids, readily prepared from 6-bromotrithiadiazepine **1** and ammonia or amines under remarkably mild conditions; unusually for aromatic amines, the amino groups are tetrahedral and are not conjugated with, but are orthogonal to, the 10 π heteroaromatic rings, all of which form infinite overlapping stacks in the crystals.

We have recently described the synthesis and chemistry of 1,3λ⁴δ²,5,2,4-trithiadiazepines as electron-rich, delocalised 10 π aromatic compounds, with a range of electron-withdrawing substituents on carbon.[1] In addition to their novel chemical properties these compounds also have the potential to form π-stacking structures in the solid state. We were anxious to obtain derivatives with strongly electron-releasing substituents, notably NH_2 and OH, because of their key role in synthesis and their interest in having electron-releasing groups on the π-excessive ring. Such groups are commonly introduced by nucleophilic substitution and this process was therefore important, particularly when we failed to reduce the 6-nitro compound to the primary amine.[2] Standard nucleophilic displacement of bromine from the 6-bromo derivative **1** appeared unpromising since the heterocyclic ring is deactivated to nucleophilic attack and is rather unstable to alkaline conditions.[2] However, inspection of the shape of the 7-membered ring with its three large sulphur atoms suggested that an elimination–addition mechanism, *via* the hetaryne **2** might be possible.[3] To test this, 6-bromotrithiadiazepine **1** was treated with lithium diisopropylamide in the presence of furan in tetrahydrofuran (THF) at −78 °C. A slow reaction did occur and whilst none of the aryne–furan cycloadduct was formed, a good yield of 6-diisopropylaminotrithiadiazepine **3a**, the first amine of this ring system, was isolated as a stable, pale yellow crystalline solid. We also observed that this displacement reaction continued *after* quenching the mixture with acetic acid, indicating that the lithio derivative was not essential, and that the amines themselves were sufficiently reactive. Primary and secondary aliphatic amines (5 equiv.) reacted with 6-bromotrithiadiazepine **1** in THF at room temperature to give the corresponding 6-aminotrithiadiazepines **3a–e** in the yields shown (Table 1). Aniline did not react, but its *N*-lithio derivative did to give 6-anilinotrithiadiazepine **3f**. Most remarkable was the reaction with dry ammonia gas at 0 °C to form 6-aminotrithiadiazepine **3b**, which was complete in 20 min. We have since established that the hetaryne **2** is indeed an intermediate in these reactions.[4]

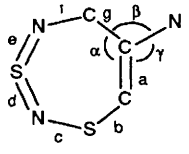


1 **2** **3**

Scheme 1



3b **3c** **3e**



x

Although the primary and particularly the secondary amines are sensitive compounds they have all been fully characterised. They show an IR absorption close to 1150 cm^{-1} and a long wavelength UV absorption around 330 nm, very similar to trithiadiazepine itself. Furthermore, in the NMR spectra the ring protons of the amino derivatives **3a–f** have almost identical chemical shifts (δ_H 7.56–7.90) to that of the parent compound (δ_H 7.76). These spectral similarities suggest that there is little interaction between the amine lone pair of electrons and the delocalised π system of the ring, and this is confirmed by X-ray crystal structures for the amino **3b**, dimethylamino **3c** and morpholinotrithiadiazepine **3e**.†

As in the parent compound[5] the trithiadiazepine ring in all three amino derivatives 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

Table 1 Treatment of 6-bromotrithiadiazepine with amines in THF at room temperature (Scheme 1)

	NR_2	M.p. (*t*/°C)	Yield (%)
3a	NPr^i_2	30–31	70
3b	NH_2	56–57	86
3c	NMe_2	75–76	76
3d	$NHCH_2Ph$	62–63	78
3e	Morpholino	132–133	86
3f	NHPh	94–95	70

† *Crystal data*: **3b**, $C_2H_3N_3S_3$, M = 165.3, monoclinic, a = 6.997(1), b = 24.529(7), c = 7.107(1) Å, β = 102.78(1)°, V = 1189 $Å^3$, space group $P2_1/a$, Z = 8 (2 crystallographically independent molecules), D_c = 1.85 g cm^{-3}, μ = 104 cm^{-1}. **3c**, $C_4H_7N_3S_3$, M = 193.3, monoclinic, a = 6.798(1), b = 6.965(2), c = 9.096(2) Å, β = 103.41(2)°, V = 419 $Å^3$, space group $P2_1/m$, Z = 2 (the molecule is disposed about a mirror plane), D_c = 1.53 g cm^{-3}, μ = 75 cm^{-1}. **3e**, $C_6H_9N_3OS_3$, M = 235.3, monoclinic, a = 20.341(4), b = 6.922(1), c = 7.443(1) Å, β = 111.21(2)°, V = 977 $Å^3$, space group $C2/m$, Z = 4 (the molecule is disposed about a mirror plane), D_c = 1.60 g cm^{-3}, μ = 66 cm^{-1}. Data for all three compounds were measured on a Nicolet R3m diffractometer with Cu-Kα radiation (graphite monochromator) using ω-scans. The structures were solved by direct methods and refined anisotropically using absorption corrected data to give for **3b** R = 0.040, R_w = 0.040, for **3c** R = 0.035, R_w = 0.043, and for **3e** R = 0.054, R_w = 0.062 for 1363, 605 and 704 independent observed reflections respectively [$|F_o| > 3\sigma(|F_o|)$, $2\theta \leq 116°$]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

Table 2 Comparative bond lengths (Å) and angles (°); see structure **X**

Dimension	Trithiadiazepine	**3bi**[a]	**3bii**[a]	**3c**	**3e**
a	1.346(9)	1.367(6)	1.356(6)	1.356(4)	1.350(6)
b	1.684(6)	1.690(4)	1.687(5)	1.701(3)	1.695(5)
c	1.599(5)	1.623(4)	1.616(4)	1.605(4)	1.601(4)
d	1.542(5)	1.551(4)	1.548(4)	1.554(4)	1.559(4)
e	1.559(5)	1.567(4)	1.556(4)	1.564(4)	1.572(5)
f	1.599(5)	1.601(4)	1.617(4)	1.604(4)	1.609(5)
g	1.696(7)	1.720(4)	1.721(4)	1.705(3)	1.708(4)
α	135.6(5)	131.6(3)	131.8(4)	133.9(3)	134.4(4)
β	—	110.4(3)	109.4(3)	102.2(2)	103.3(3)
γ	—	117.9(4)	118.8(4)	121.9(3)	122.3(3)

[a] **3bi** and **3bii** are the two crystallographically independent molecules in the crystals of **3b**

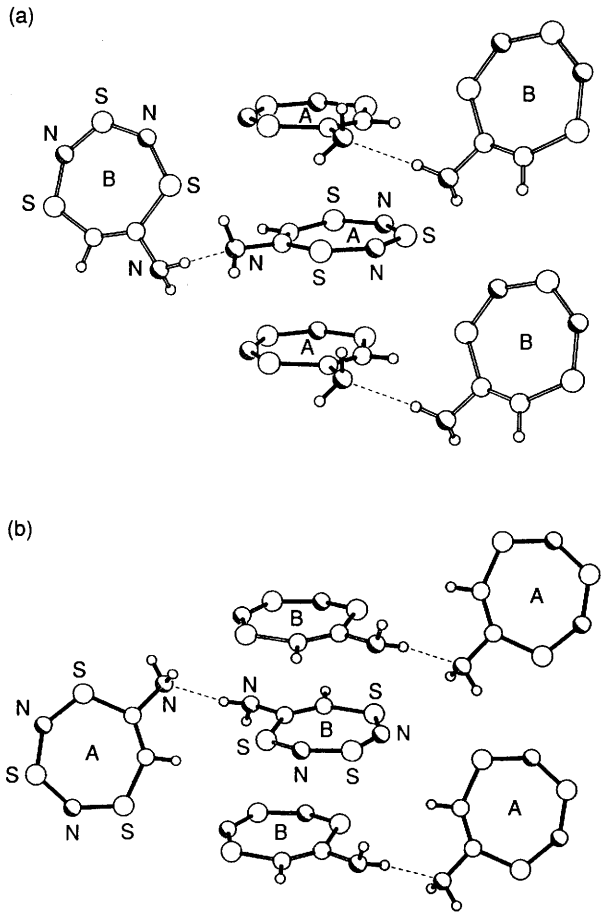


Fig. 1 Stacking arrangements of the two crystallographically independent molecules A, B of **3b**. The interplanar separations are 3.48 and 3.50 Å in the A stack and 3.44 and 3.56 Å in the B stack

the π system.‡ This is rare for sterically unencumbered aromatic amines. For the dimethylamino **3c** and morpholino **3e** compounds the amine nitrogen lone pair is antiperiplanar to the less polarisable carbon–carbon bond. Hence the bond lengths of the trithiadiazepine ring are undistorted and identical with those of the parent compound (Table 2). The lone pair on the primary amino group in **3b** is antiperiplanar to the more polarisable carbon–sulphur bond, and overlap

‡ In the dimethylamino **3c** and morpholino **3e** compounds this orthogonal geometry is exact as both molecules have crystallographic C_s symmetry.

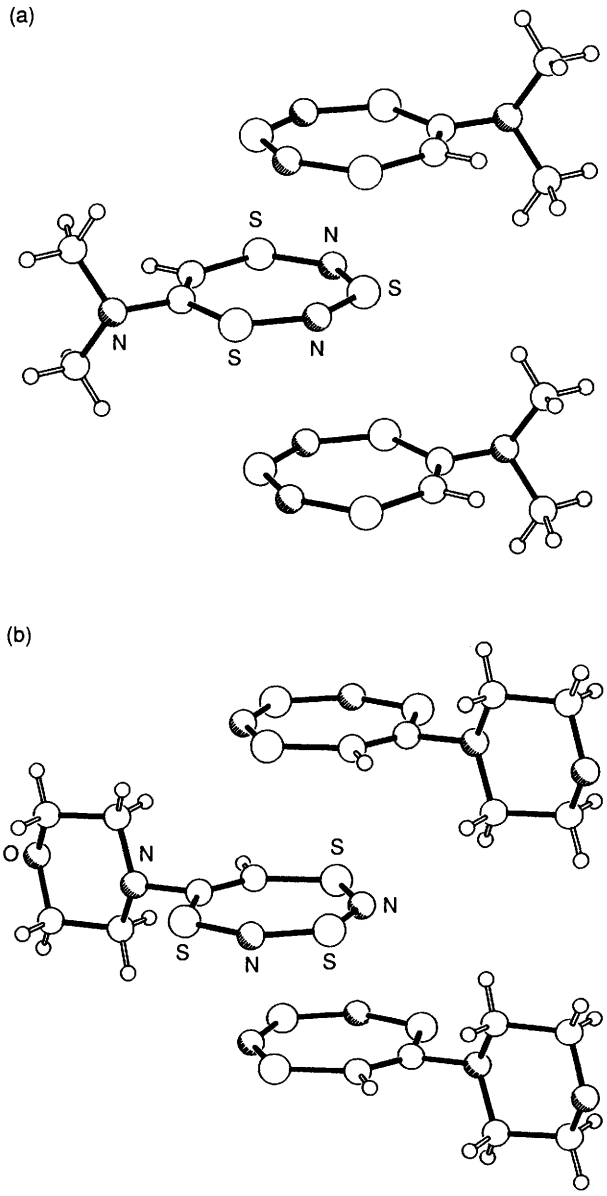


Fig. 2 Stacking of molecules of (a) the dimethylamino compound **3c** and (b) of the morpholino compound **3e** in the crystal. The interplanar separations between the trithiadiazepine rings are 3.48 Å in **3c** and 3.46 Å in **3e**

between the nitrogen lone pair and the σ* antibonding orbital of the carbon–sulphur bond should elongate the carbon–sulphur bond slightly. This ground-state stereoelectronic effect is observed with a slight lengthening of this bond in both independent molecules (g in Table 2) and with some distortion of the ring bond angles, though these differences are at the margin of significance of the data. Presumably the electron-rich nature of the ring π-system disfavours interaction with the amine lone pair, and the exocyclic nitrogen is acting simply as an inductively electron-withdrawing group.

A possible alternative explanation for the difference in orientation of the amino group in **3b** compared to **3c** and **3e** may be found from a study of the packing of the molecules of **3b** in the crystal. Both crystallographically independent molecules, A and B, form infinite π–π overlapping stacks (Fig. 1), 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 almost exactly towards the lone pair of the nitrogen of an adjacent molecule in the 'A' stack forming a series of weak inter-stack N–H···N hydrogen bonds (N···N 3.17, N···H 2.22 Å, N–H···N angle 170°). This interaction is accompanied by rotations of the lone pairs out of the plane of their associated trithiadiazepine rings, by *ca.* 23 and 40° for molecules A and B respectively. Molecules of both the dimethylamino **3c** and morpholino **3e** compounds also form infinite π–π overlapping stacks in the crystals (Fig. 2).

6-Aminotrithiadiazepine **3b** is best stored in a cold dilute dichloromethane solution, with removal of the solvent *in vacuo* at room temperature prior to use; heating causes decomposition of the amine. It is acid sensitive, although the hydrochloride, m.p. 118–120 °C (decomp.), could be formed by precipitation from ether under anhydrous conditions. The *N*-acetyl derivative, m.p. 138–139 °C, and the benzaldehyde imine, m.p. 120–121 °C, were readily formed in high yield as stable crystalline solids. Diazotisation proved difficult, as might be expected from the non-conjugated nature of the amine, and pentyl nitrite and hydrochloric acid in THF gave only a 15% yield of 6-chlorotrithiadiazepine, presumably *via* the unstable diazonium salt.

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