

Synthesis and Redox Properties of Substituted 1,4,2-Dithiazines: X-Ray Crystal Structure of 3-(4-Methoxyphenyl)-5,6-dimethyl-1,4,2-dithiazine

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The efficient synthesis of a range of novel 1,4,2-dithiazine derivatives by ring expansion of the corresponding 1,3-dithiolium cations in the presence of iodine and aqueous ammonia is reported; the eight π -electron 1,4,2-dithiazine ring is folded about the S...S axis, as shown by single crystal X-ray analysis, and the heterocycle is electrochemically oxidised to yield, sequentially, the radical cation and dication species.

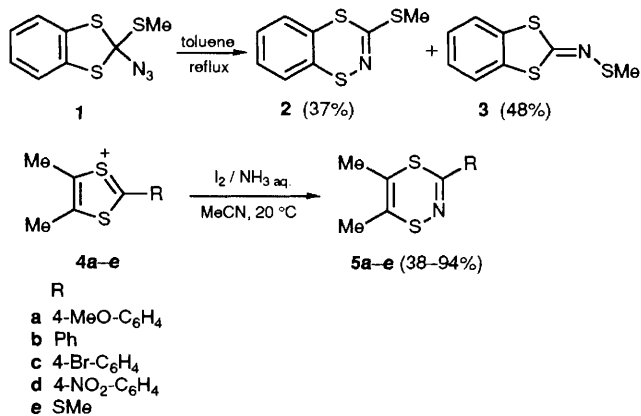
Organic heterocyclothiazines continue to attract much attention owing to the interesting array of chemical, physical and structural properties that results from extensive π -electron delocalisation in these ring systems.¹⁻³ The most widely studied heterocycles of this type are those which are formally heteroaromatic, possessing six or ten π -electrons, either in the neutral or radical ion redox stage. There are notably far fewer reports concerning stable eight π -electron heterocyclothiazines. Herein, we describe a versatile and efficient synthesis of a range of 1,4,2-dithiazine derivatives **5** and **7**; the key step in the formation of this eight π heterocycle is nitrogen insertion into a 1,3-dithiolium cation ring, which occurs readily upon treatment with a mixture of iodine and aqueous ammonia.

A comparable route to 1,4,2-benzodithiazine⁴ and monocyclic 1,4,2-dithiazines substituted with phenyl groups,^{5,6} by reaction of azide ion with dithiolium cations, has been known for some time. However, yields of the dithiazine system under these conditions were generally low, owing primarily to competing reactions of the intermediate nitrene, which yielded imines, sometimes as the major product (*e.g.* the formation of products **2** and **3** from azide **1**).⁴ A further

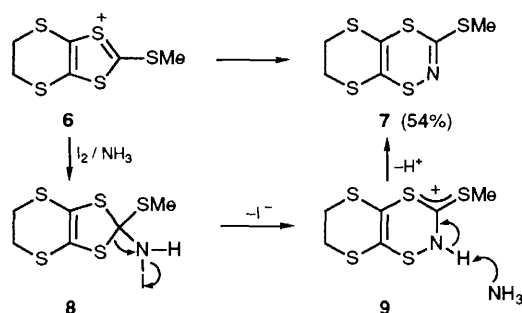
drawback of this azide methodology is that the temperature needed to generate the reactive nitrene intermediate sometimes leads to desulfurisation of the product dithiazine (to afford an isothiazole).⁵ More recently, it has been reported that an equimolar mixture of 1,3-dithiolium cations and iodine, with an excess of ammonia, reacts at 20 °C to yield 1,4,2-dithiazines; all of the derivatives studied carried two, or three, phenyl substituents.⁷

We now describe the use of a mixture of iodine and ammonia (fivefold excess of iodine) for the ring expansion of a range of substituted 1,3-dithiolium cations **4a-4e** and **6**. The product 1,4,2-dithiazines, **5a-5e** and **7**, respectively, are generally formed in good yield (as high as 94% for **5c**) without competing imine formation. Notably, derivative **5e**, which does not bear phenyl substituents, as well as the novel bicyclic ring system **7** are reported.

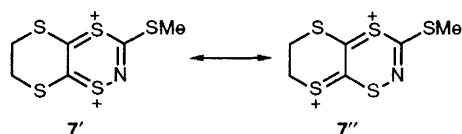
The general synthetic procedure for the ring expansion reaction is as follows: to dithiolium cation salt **4a-4d**,⁸ **4e**⁹ or **6**¹⁰ (1 mol equiv.) and iodine (5 mol equiv.) dissolved in acetonitrile, ammonia solution (33%, 10 mol equiv.) was added dropwise at 20 °C. The mixture was stirred at this temperature for 1.5 h. Aqueous work-up, followed by



Scheme 1



Scheme 2



extraction into dichloromethane and column chromatography (silica, eluent dichloromethane-hexane) yielded the 1,4,2-dithiazine products **5a-5e** or **7**[†] Scheme 1.

A possible mechanism for the ring expansion reaction is presented for compound **6** (Scheme 2). Nucleophilic attack at C(2) of a 1,3-dithiolium ring is known to be a facile reaction;¹¹ hence intermediate **8**, containing an electron-deficient nitrogen centre, could readily form under these reaction conditions. Sulfur-nitrogen bond formation, with concomitant loss of iodide ion, followed by deprotonation of the resulting cationic intermediate **9**, would yield the 1,4,2-dithiazine derivative **7** (*cf.* a nitrenium ion intermediate considered previously⁷). Products arising from insertion of nitrogen into the exocyclic S-C bond of **8** (or the C-C bond of analogous intermediates formed from **4**) were not observed. Consistent with this, PM3 molecular orbital calculations performed on the model compounds **10** and **11** gave heats of formation of 130 and 179 kJ mol⁻¹, respectively, indicating that dithiazine **10**, is, thermodynamically, the more stable isomer.

[†] All the 1,4,2-dithiazines **5** and **7** are previously unreported compounds; satisfactory microanalyses, mass spectra and NMR spectra were obtained. Melting points and yields are as follows: **5a**, yellow crystals, 56-58 °C, 56%; **5b**, orange oil, 87%; **5c**, yellow solid, 58-59 °C, 94%; **5d**, orange solid, 128-129 °C, 61%; **5e**, orange solid, 42-44 °C, 38%; **7**, yellow oil, 54%.

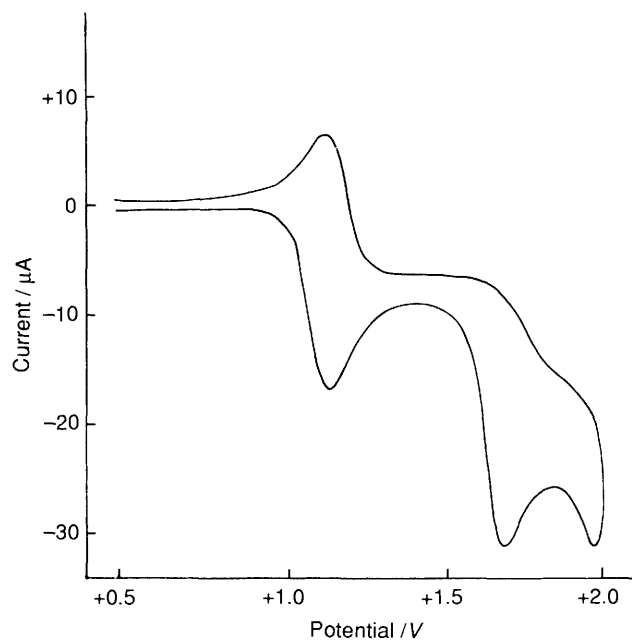
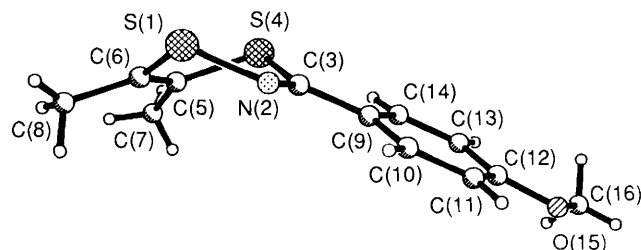
Fig. 1 Cyclic voltammogram of 1,4,2-dithiazine derivative **5c**

Fig. 2 X-Ray crystal structure of 1,4,2-dithiazine derivative **5a**. Bond lengths (Å) and bond angles (°) within the heterocycle are: S(1)-N(2) 1.709(2), S(1)-C(6) 1.752(2), N(2)-C(3) 1.274(3), C(3)-S(4) 1.785(2), S(4)-C(5) 1.762(2), C(5)-C(6) 1.336(3); N(2)-S(1)-C(6) 105.1(1), S(1)-N(2)-C(3) 119.2(2), N(2)-C(3)-S(4) 122.9(2), C(3)-S(4)-C(5) 100.5(1), S(4)-C(5)-C(6) 119.9(2), C(5)-C(6)-S(1) 119.5(2).

The redox properties of the eight- π 1,4,2-dithiazine ring have been studied by cyclic voltammetry; the data for compounds **5a-5e** and **7** are collated in Table 1 and the cyclic voltammogram of compound **5c** is shown in Fig. 1. Each member of the series undergoes a single-electron oxidation to form the radical cation at a half-wave potential, $E_1^{\frac{1}{2}}$ of *ca.* 1.1 V. This is a reversible process, except for 3-methylthio derivative **5e**, for which the corresponding cathodic reduction peak is not observed. A trend in the variation of the peak potential for E_1 is clearly seen in the 3-phenyl series, **5a-5d**: the heterocycle is harder to oxidise (increased value of E_1) when an electron-withdrawing substituent is present on the phenyl ring. This is consistent with the solid-state conformation of compound **5a** (discussed below) and the variation in λ_{max} values in the UV spectra (Table 1), both of which point to conjugation between the phenyl ring and the heterocycle. A second oxidation, E_2^{ox} , to form the six- π electron dication is seen for derivatives **5a-5c** and **7**, but not for derivatives **5d** and **5e**. This is an irreversible redox wave and scanning to 2.0 V (*i.e.* beyond the potential of E_2^{ox}) has no effect on the reversibility of E_1 ; this implies that the dication does not decompose in a chemical reaction (*e.g.* with solvent or with oxygen) but rather a coprotonation reaction occurs, with electron transfer from neutral to dication species, thereby generating radical cations. The difference, ΔE , between the

first and second oxidation peaks is a measure of the coulombic repulsion in the dication redox stage, and it is notable that this value is significantly greater for the monocyclic derivatives **5** than for the bicyclic derivative **7**, where the extra sulfur substituents can assist in charge delocalisation (e.g. see canonical structures **7'** and **7''** for the dication).

Crystals of the title compound **5a**, obtained by slow evaporation of a hexane-dichloromethane solution (1:1 v/v), have provided the first X-ray crystal structure of the 1,4,2-dithiazine ring system.[‡] The heterocycle adopts an envelope conformation folded along the N(2)⋯C(6) and C(3)⋯C(5) axes by 35.1 and 36.4°, respectively. The N(2), C(3), C(5) and C(6) atoms are coplanar within ±0.01 Å, and S(1) and S(4) are displaced from their mean plane by 0.60 and 0.67 Å, respectively. The methoxyphenyl group is essentially coplanar with the best plane formed by S(1), N(2), C(3) and S(4), (dihedral angle 2.9°) thereby maximising the conjugation between the methoxy substituent and the dithiazine ring; this is in accord with the solution UV and cyclic voltammetric data (Table 1).

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Table 1 Cyclic voltammetric data for 1,4,2-dithiazine derivatives^a

Compound	$E_1^{1/2}/V^b$	E_2^{ox}/V	$\Delta E/V^c$	λ_{max}/nm^d
5a	1.04	1.70	0.66	382
5b	1.14	1.72	0.59	389
5c	1.15	1.72	0.57	393
5d	1.20	^e		432
5e	1.03 ^f	^e		304, 360
7	1.17	1.58	0.41	291, 312 (shoulder)

^a Compound ca. 10^{-3} mol dm⁻³, in dichloromethane, electrolyte tetrabutylammonium hexafluorophosphate ca. 10^{-2} mol dm⁻³, Pt electrode, vs. Ag/AgCl, 20°C, using a BAS 100 electrochemical analyser. ^b $E_1^{1/2}$ is the average of the anodic and cathodic peak potentials. ^c $\Delta E = E_2^{ox} - E_1^{1/2}$. ^d Solvent: CH₂Cl₂-hexane (1:1 v/v). ^e Peak not observed. ^f This is the value of E_1^{ox} ; the accompanying reduction peak was not observed.

Chemistry, Bristol University, for access to X-ray data collection facilities.

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[‡] Crystal data for **5a**: C₁₂H₁₃NOS₂, $M = 251.4$, monoclinic space group $P2_1/c$, $a = 14.226(2)$, $b = 10.896(2)$, $c = 8.142(2)$ Å, $\beta = 104.44(2)^\circ$, $U = 1222.1(3)$ Å³, $Z = 4$, $D_c = 1.37$ g cm⁻³, $\mu(\text{Mo-K}\alpha) = 4.13$ cm⁻¹, crystal dimensions $0.2 \times 0.8 \times 0.6$ mm. The intensities of 2133 independent absorption corrected (numerical method) reflections with $2\theta < 50^\circ$ were measured by Wyckoff (limited ω scan), of which 1899 reflections with $I > 2\sigma(I)$ were used in the final calculations. The structure was solved by direct methods and refined by least-squares analysis (anisotropic displacement parameters for non-hydrogen atoms, isotropic displacement parameters for hydrogen atoms) to $R = 0.047$ ($R_w = 0.066$). The data were collected on a Siemens R3mV four-circle diffractometer using graphite-monochromated Mo-K α radiation ($\lambda = 0.71073$ Å) at room temperature. All calculations were performed using the SHELXTL PLUS programs¹² on a DEC microVAX II computer.

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.