Novel Fused Bicyclic Sulphur Compounds

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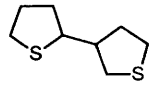
Novel fused (*cis*-octahydrothieno[3,2-*b*]thiepine, *cis*-hexahydrothieno[2,3-*b*]-1,4-oxathiine and *cis*-hexahydrothieno[2,3-*b*]-1,4-dithiine) and spiro (1,4,6-trithiaspiro[4.4]nonane and 1,4,7-trithiaspiro[4.4] nonane) bicyclic compounds containing sulphur have been synthesized and their structures confirmed by NMR spectroscopy. For their synthesis, reactions of nucleophiles, including Grignard reagents, with *trans*-2,3-dichlorotetrahydrothiophene were investigated. Improved methods of forming sulphides from Na_2S and haloalkanes have been developed. 1-Bromo-4-chlorobutane was shown to form the specific Grignard reagent, $Cl[CH_2]_4MgBr$.

Reaction of tetrahydrothiophene with $TiCl_4$ has been shown[1] to produce the dimer **1**. During consideration of possible structures for this dimer, a short synthesis of the fused bicyclic compound **2** (Scheme 1) was undertaken. Previous reported syntheses of such fused bicyclic sulphur heterocycles have involved laborious multi-stage routes. Thus, fused compounds **3** and **4** have been described,[2,3] as has the heteroaromatic system **5**.[4] An attractive two-stage route to fused compounds such as **2** is through reaction of 2,3-dichlorotetrahydrothiophene[5] with nucleophiles at the more reactive 2-position followed by ring closure onto the 3-position. The *cis* or *trans* nature of this cyclisation of sulphur compounds was not reliably predictable but has now been shown to be *cis* through ^1H NMR spectroscopy, including nuclear Overhauser effects.



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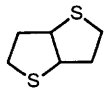

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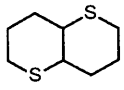

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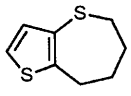

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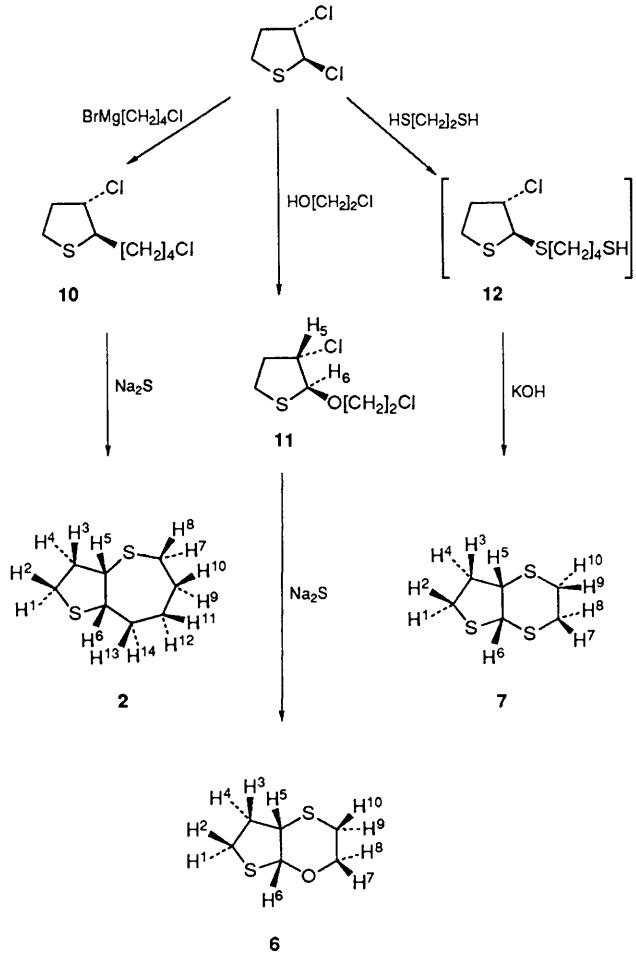
Nucleophilic substitutions at the 2-position of 2-chlorotetrahydrothiophene and 2,3-dichlorotetrahydrothiophene are known[6,7] but there is no information concerning the configuration of the products. In the present work, results from ^1H NMR spectroscopy and spectral simulation are reported and reveal the configurations and coupling constants for some 2-substituted 3-chlorotetrahydrothiophenes.

For the synthesis of bicyclic fused compounds such as **2**, nucleophilic substitution at the 2-position of 2,3-dichlorotetrahydrothiophene by bi-functional Grignard reagents was investigated. As part of this strategy the formation and reactions of the Grignard reagent prepared from 1-bromo-4-chlorobutane were examined.

Although the reaction of sodium sulphide with halogenoalkanes in aqueous ethanol to form sulphides is well known, the highly basic nature of such solutions, due to hydrolysis of Na_2S, leads to competitive dehydrohalogenation which can easily become predominant. It is shown here that use of Na_2S in dimethyl sulphoxide provides a more efficient route to sulphides, particularly cyclic ones such as **2**, **6** and **7**. During the course of these cyclisation studies, two spiro trisulphur heterocycles **8** and **9** (Schemes 2 and 3) were isolated and then synthesised independently.

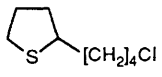


Scheme 1

Results and and Discussion

Syntheses.—Reaction of 1-bromo-4-chlorobutane with magnesium gave a Grignard reagent which reacted with CO_2 to give 5-chloropentanoic acid as the only acidic product, indicating exclusive formation of 4-chlorobutylmagnesium bromide. Treatment of 2-chlorotetrahydrothiophene in benzene[5] with 4-chlorobutylmagnesium bromide afforded a 22% yield of 2-(4-chlorobutyl)tetrahydrothiophene **13**. When a similar reaction was attempted with *trans*-2,3-dichlorotetrahydrothiophene,

prepared in methylene dichloride,[5] none of the expected 2-(4-chlorobutyl)-3-chlorotetrahydrothiophene **10** (Scheme 1) could be isolated; repetition of the reaction in benzene afforded a 14%



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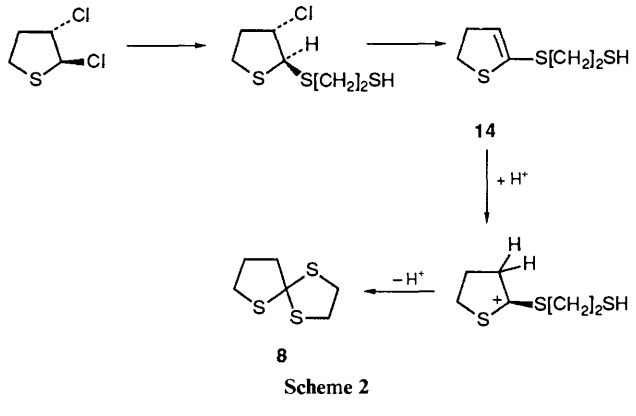
yield of the required dichloride **10**. Reaction of Na_2S with halogenoalkanes to give sulphides is well known,[8] but attempts to cyclise the dichloride **10** to the required bicyclic compound **2** with Na_2S in aqueous ethanol gave a complex mixture of low-boiling products. In dimethyl sulphoxide as solvent, the fused bicyclic compound, octahydrothieno[3,2-*b*]thiepine **2** (Scheme 1) was obtained. ^{1}H NMR and NOE spectroscopic experiments revealed a *cis* arrangement of the bridgehead hydrogens (see below for details).

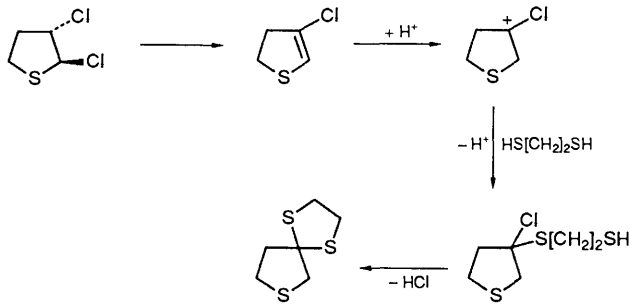
This simple two-stage synthesis prompted the investigation of its generality through short syntheses of other novel sulphur-containing bicyclic compounds. Thus, *trans*-2,3-dichlorotetrahydrothiophene with 2-chloroethanol in the presence of pyridine gave *trans*-2-(2-chloroethoxy)-3-chlorotetrahydrothiophene **11** (Scheme 1). Ring closure of this dichloro compound with Na_2S in dimethyl sulphoxide gave the *cis*-fused bicyclic compound, hexahydrothieno[2,3-*b*]-1,4-oxathiine **6** (Scheme 1; NMR analysis given below) as a white, crystalline solid.

When a similar reaction of 2,3-dichlorotetrahydrothiophene with ethane-1,2-dithiol was undertaken, the expected trisulphur compound **12** (Scheme 1) was isolated as an oil which, unlike its oxygen-containing analogues **11**, spontaneously evolved HCl with time. No attempt was made to fully characterize this oil **12** which was heated at reflux with aqueous ethanolic KOH to give the required bicyclic hexahydrothieno[2,3-*b*]-1,4-dithiine **7** having a *cis*-fused ring junction (see NMR spectroscopic evidence below). Although compound **7** was a major component of this reaction, there was a substantial quantity of a second component **A** having the same molecular weight and subsequently shown to be itself a mixture of two compounds **8** and **9**. Spiro structures for component **A** appeared probable and structures **8** and **9** were synthesised independently by reaction of ethane-1,2-dithiol with, respectively, tetrahydrothiophen-2-one and tetrahydrothiophen-3-one. Comparison of mass and ^{1}H NMR spectra and gas chromatographic retention times of a 1:1 mixture of spiro compounds **8** and **9** with the reaction by-product **A** showed them to be identical. Suggested mechanisms for formation of spiro structures **8** and **9** in the reaction of ethane-1,2-dithiol with 2,3-dichlorotetrahydrothiophene are shown in Schemes 2 and 3. Loss of HCl was observed from



Scheme 2

intermediate **12** even when set aside, presumably through loss of the 3-chlorine atom to yield the unsaturated compound **14** (Scheme 2); simple proton catalysed cyclisation would yield



Scheme 3

spiro compound **8**. Similarly, loss of HCl from 2,3-dichlorotetrahydrothiophene and proton catalysed reaction at the 3-position would yield spiro compound **9** (Scheme 3). Free radical addition of thiols to double bonds is well known[9] but addition of thiols under ionic conditions requires Lewis acid catalysis and high temperatures.[10,11]

Stereochemical Features of the Cyclisation of Compounds **10**–**12**.—The *cis*-fused ring junction found in compounds **2**, **6** and **7** (Scheme 1) suggests a different mechanistic displacement of the two chlorines in *trans*-2,3-dichlorotetrahydrothiophene. The 2-chloro atom is more labile,[7] the adjacent S atom being able to stabilize any developing positive charge so that ionisation of the 2-chloroatom is strongly favoured. 3-Chlorotetrahydrothiophene is relatively unreactive towards nucleophilic substitution.[12] Thus, S_N2 substitution at the 2-position by a nucleophile such as 4-chlorobutylmagnesium bromide would give a product in which the 3-chloro atom and the new substituent at the 2-position would be in a *cis*-arrangement. This would hinder formation of the observed *cis*-fused ring junction by S_N2 attack at the 3-position and S_N1 displacement at the 3-position might be expected to produce both *cis* and *trans* ring junctions. Contrariwise, S_N1 displacement of the 2-chlorine atom in *trans*-2,3-dichlorotetrahydrothiophene by a nucleophile (favoured by the adjacent S atom) would probably lead to a *trans* arrangement of the 3-chloro atom and the new substituent at the 2-position for steric reasons; subsequently S_N2 cyclisation to the 3-position would yield the observed *cis* fused ring junction. These considerations suggest that the 2-chloro substituent should react with an incoming nucleophile through an S_N1 mechanism whilst the less ionizable 3-chloro substituent reacts through a predominantly S_N2 mechanism. ^{1}H NMR spectra of reaction products from substitution at the 2-position in *trans*-2,3-dichlorotetrahydrothiophene by oxygen and sulphur nucleophiles in polar solvent indicate only one major *trans* product, in keeping with the above stereochemical argument (see below). GC–MS of 2-alkoxy-3-chlorotetrahydrothiophenes afforded evidence for about 5% or less of an isomer of the *trans* compounds, tentatively identified as the *cis* from its GC retention time and mass spectral fragmentation.

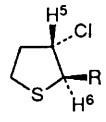
Nuclear Magnetic Resonance Spectroscopic Results on Compounds **2**, **6** *and* **7**.—Chemical shifts, coupling constants and other NMR data on bicyclic compounds **2**, **6** and **7** are given in the Experimental section. For compound **2**, off-resonance decoupled ^{13}C NMR spectroscopy revealed eight separate carbon atoms, which in the ^{13}C-^{1}H coupled spectrum could be separated into six carbons each carrying two hydrogens and two carbons each carrying only one hydrogen. These last two carbons, being furthest downfield were assigned to the bridgehead hydrogens H5 and H6 of compound **2**. A SEFT (JMOD) experiment[13] confirmed this conclusion. Irradiation of either of the quadruplets representing H5 or H6 caused each to

collapse to a triplet and revealed a 6 Hz coupling between them. The collapse to triplets indicated equivalent couplings of H3, H4 to H5 and of H13, H14 to H6. A nuclear Overhauser effect experiment gave a 40% enhancement to H5 on irradiation of H6, together with about a 20% enhancement to H13; similarly, irradiation of H5 gave a 30% enhancement to the signal at H6, a 40% enhancement to H3 and a 25% enhancement to H8 (close spatial proximity of H3, H5 and H8). These results confirm the *cis*-fused ring arrangement of compound **2**. A ^{1}H-^{13}C correlation spectrum[14] revealed the placement of hydrogens on the carbons, as numbered on structure **2** and a ^{1}H-^{1}H correlation (COSY)[15] provided data on couplings between protons. The ^{1}H-^{1}H correlations were confirmed by decoupling experiments at each resonance position. The complete sequence of couplings from the bridghead hydrogens (H5 and H6), together with ^{1}H-^{13}C correlation data provided proof of the *cis*-fused structure **2**, thus confirming the synthesis and revealed no evidence for the presence of any *trans*-fused isomer.

The 10 hydrogens in the ^{1}H NMR spectrum of the fused bicyclic compound **6** separated into a 6-spin and a 4-spin set. Hydrogen H6 was readily distinguishable from its chemical shift and irradiation of this proton affected only the resonance at δ 2.98, thereby identifying H5. Similar results from decoupling experiments identified H1–H4. Of the four remaining hydrogens, two (H7 and H8) were well downfield as expected from their proximity to oxygen and the remaining two were identified as H9 and H10 from decoupling experiments. Using these chemical shift data, a PANIC simulation spectrum[16] proved to be identical with that observed with coupling constants as given in the Experimental section. The *cis* arrangement of hydrogens at the ring junction was deduced from NOE experiments. Irradiation at δ 4.25 revealed a 3-spin NOE system which was evaluated through use of the equation, $(r_{ax}/r_{am}) = [f_A(m)/f_A(x)]^{1/6}$, where the distances, r_{ax}/r_{am}, of two spins (x,m) from the third (a) were measured from Dreiding models and the percentage enhancements, $f_A(m)$, $f_A(x)$, were taken from the observed NOE enhancements.[17] Initially, assuming a chair conformation for the oxathia ring in structure **6**, the NOE results for irradiation at δ 4.25 indicated relative distances to two other spins H10 and H7 (δ 2.98, 3.81) of 1.3:1. Measurements from unstrained Dreiding models indicated an expected distance ratio of 1.4:1 for the arrangement shown in structure **6**. Similarly, irradiation at δ 3.81 (H7) also revealed a strong enhancement of a 3-spin system, with a measured ratio of 1.17:1 for the relative distances to two spins at δ 5.11 and 4.25 (H6 and H8). Dreiding models for structure **6** suggest an expected distance ratio of 1.14:1. Thus, the two 3-spin systems are consistent with the arrangement shown in structure **6** and with the coupling constants from the PANIC simulation. Irradiation at δ 2.9 enhances H6 (δ 5.11) by 12% and *vice versa*, indicating a *cis* relationship for H6 and H5. Although these enhancements are very much greater than could be expected for a *trans* relationship for H6 and H5, they are relatively modest; the H5 proton appears to form part of a 3-spin system in which the relative positions of H4, H5 and H6 could be expected to lead to a reduced NOE.[17]

For the bicyclic compound **7**, a SEFT correlation showed that two carbons (δ 43.8, 48.2; C-3, C-4) were each connected to one proton, the remainder being attached to two protons, as required by the structure. From a ^{1}H-^{13}C correlation, carbon C-3 is connected to H5 (δ 3.33) and C-4 to H6 (δ 4.52). Since H6, lying between two sulphur atoms would be expected to have the largest downfield shift, these data fix the carbons and hydrogens at the bridgehead. Irradiation at H6 affects only H5 and reveals a 4 Hz coupling between them. The remaining assignments in structure **7** were obtained through decoupling experiments which revealed a six spin system (H1–H6) and a four-spin system (H7–H10). In NOE experiments, irradiation at H6 gave a 64% enhancement at H5, proving the *cis* relationship between them; similar irradiation at H5 produced an 85% enhancement to H6 and an approximate 50% enhancement at H3. These results attest to the *cis* relationship of the three spins (H3, H5 and H6). Irradiation at H3 caused strong enhancement at H4 and H5 as expected and some 30% enhancement of H2, indicating the close proximity of H3 and H2. These results provide excellent proof of the *cis*-fused ring junction in compound **7**.

Nuclear Magnetic Resonance Spectroscopic Results on Compounds **15**.—Compounds **15** resulted from nucleophilic substitution of chlorine at the 2-position in *trans*-2,3-dichlorotetrahydrothiophene by a variety of alcohols (see Experimental section). Chemical shifts and coupling patterns of the tetrahydrothiophene ring protons in all of these compounds were almost identical in position and appearance. Thus, in 2-(2-chloroethoxy)-3-chlorotetrahydrothiophene **15** (R = OCH_2CH_2Cl) the H6 proton at δ 5.18 was coupled to H5 by about 1 Hz, H5 appeared as a broad, ill-resolved multiplet at δ 4.24, whilst H1 and H2 were clearly resolved into triplets of doublets centred at δ 3.09 and 2.96. The H3, H4 protons, centred near δ 2.35, gave a very complex multiplet due to their close chemical shifts. PANIC simulation spectra were consistent with the couplings and shifts given in the Experimental section. Most significant were the large couplings (*J* 10.0, 6.6 and 7.2 Hz) between, respectively, H1 and H3, H4 and H2 with H3 and the very small coupling between H5 and H6. The results suggest that the five-membered tetrahydrothiophene ring in all of these compounds **15** has a similar, relatively fixed conformation. The vicinal



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coupling between H5 and H6 might be expected to be 5–8 Hz for *cis* or *trans* arrangements if there was complete pseudo rotation through conformations of similar energy.[7c] The observed small coupling requires a highly favoured conformation with a torsional angle of near 90°. This would only be allowed for *trans*-diaxial substitution. For all alkoxy compounds **15** (R = *O*-alkyl), the hydrogens adjacent to the oxygen were well separated from each other in chemical shift, indicating very restricted rotation about the first two carbon atoms in the alkoxy group, R, nearest to the oxygen.

Conclusion

The fused bicyclic sulphur compound **2** was synthesised in two steps from 2,3-dichlorotetrahydrothiophene. Reaction of a Grignard reagent with the 2-chlorine atom was shown to proceed in benzene–ether as a solvent but not in the presence of methylene dichloride. Improved yields of cyclic sulphides were obtained by using Na_2S in dimethyl sulphoxide as solvent rather than the commonly used aqueous ethanol. Synthesis of other heterocyclic compounds **6** and **7** was achieved but, in the case of the trisulphur compound **7**, considerable quantities of the thioacetal or spiro compounds **8** and **9** were isolated also. ^{1}H NMR coupling constants in some 2,3-disubstituted tetrahydrothiophenes indicate a common *trans*-diaxial, fixed conformation.

Experimental

NMR spectroscopy was carried out with $CDCl_3$ as solvent on a variety of instruments. Routine ^{1}H NMR spectra were obtained on a Perkin-Elmer R34 220 MHz instrument, NOE, ^{1}H-^{1}H correlation data and ^{1}H-decoupling experiments were

acquired on a Bruker WH 360 MHz spectrometer and ^1H-^{13}C correlations were obtained on a General Electric QE-300. Mass spectra were recorded on an AEI MS12 or MS902 mass spectrometer at 70 eV and GC–MS results were acquired from a VG 7070 mass spectrometer.

Preparation of 2-*Chlorotetrahydrothiophene*.—A solution of 2-chlorotetrahydrothiophene in benzene was prepared[5] by the action of *N*-chlorosuccinimide (1 mol) on tetrahydrothiophene (2 mol) at 20–25 °C and used immediately.

Preparation of 2,3-*Dichlorotetrahydrothiophene*.—This was prepared[5] by the action of *N*-chlorosuccinimide (1 mol) on tetrahydrothiophene (1 mol) in methylene dichloride at 20–25 °C and distilled immediately before use.

Reaction of 1-*Bromo*-4-*chlorobutane with Magnesium*.—To a stirred mixture of Mg (turnings; 0.48 g, 0.02 mol) and diethyl ether (30 ml) was added a crystal of I_2 followed by a little 1-bromo-4-chlorobutane (0.5 g). Formation of Grignard reagent commenced on warming the mixture slightly. The remainder of the 1-bromo-4-chlorobutane (3.0 g total amount used; 0.02 mol) was added dropwise at such a rate as to maintain gentle reflux. When addition of halide was complete, the resulting solution was cooled to about room temperature and an excess of dry, solid CO_2 was added. The mixture was set aside for 1 h, and then poured into dilute HCl. After separation, the ether layer was extracted with dilute NaOH to give 5-chloropentanoic acid (0.64 g, 23% yield) as the only acidic material: δ_H 9.55 (s, 1 H, CO_2H; disappears in D_2O), 3.57 (t, 2 H, CH_2Cl), 2.41 (t, 2 H, CH_2CO) and 1.83 (m, 4 H).

Reaction of 2-*Chlorotetrahydrothiophene with* 4-*Chlorobutyl magnesium Bromide*.—To an ice-cooled solution of 4-chlorobutylmagnesium bromide [*ca.* 0.09 mol, prepared as above from Mg (2.15 g) and 1-bromo-4-chlorobutane (15.4 g) in diethyl ether (100 ml)] was added dropwise, with stirring, a solution of 2-chlorotetrahydrothiophene (*ca.* 0.09 mol) in dry benzene (130 ml) at such a rate that the temperature was maintained at 10–15 °C. After the addition, the resulting mixture was stirred at room temperature for 24 h and then poured onto a mixture of ice and 20% aqueous H_2SO_4. The organic layer was dried ($MgSO_4$) and the solvent evaporated to yield an oil which was fractionally distilled to give: (i), 1-bromo-4-chlorobutane (1.42 g), b.p., 30–35 °C at 0.5 mmHg and (ii) an oil (3.77 g), b.p., 70–90 °C at 0.5 mmHg. This latter oil was chromatographed on silica gel, eluting with pentane–benzene (4:1), to give 2-(4-chlorobutyl)tetrahydrothiophene **13** (2.95 g, 22% yield), b.p., 76–79 °C at 0.5 mmHg; *m/z* 180, 178 ($M^{\bullet+}$; Cl); δ 3.51 (t, *J*/Hz 6.8, 2 H), 3.31 (m, 2 H), and 2.15–1.40 (complex m, 10 H) (Found: C, 54.0; H, 8.7. $C_8H_{15}ClS$ requires C, 53.8; H, 8.4%).

Preparation of trans-2-(4-*Chlorobutyl*)-3-*chlorotetrahydrothiophene* **10**.—When the following reaction was attempted with crude 2,3-dichlorotetrahydrothiophene, prepared[5] in methylene dichloride, no coupled product **10** was isolated and it was necessary to freshly distil the dichloro compound. To an ice-cooled solution of 4-chlorobutylmagnesium bromide [*ca.* 0.15 mol, prepared from magnesium (36 g) and 1-bromo-4-chlorobutane (25.7 g) as above] in deithyl ether (200 ml) was added dropwise a solution of 2,3-dichlorotetrahydrothiophene (15.7 g, 0.1 mol) in dry benzene (150 ml) at such a rate that the temperature of the reaction was maintained at 10–15 °C. The resulting mixture was stirred at room temperature for 24 h and then poured onto a mixture of ice and 20% aqueous H_2SO_4. The organic layer was dried ($MgSO_4$) and the solvent evaporated to give an oil which was fractionally distilled to yield: (i), 1-bromo-4-chlorobutane (4.1 g), b.p., 30–35 °C at 0.5 mmHg; (ii), 1,8-dichlorooctane (5.2 g), b.p., 60–70 °C at 0.5 mmHg and (iii), 2-(4-chlorobutyl)-3-chlorotetrahydrothiophene **10** (3.9 g, 14.6% yield), b.p., 90–105 °C at 0.5 mmHg; *m/z* 216, 214 and 212 (M^+; 2 Cl); δ 4.05 (m, 1 H), 3.52 (t, *J*/Hz 6.7, 2 H), 3.39 (m, 1 H), 2.92 (m, 2 H) and 1.75 (complex m, 6 H). The sample was used without further purification.

Preparation of cis-*Octahydrothieno*[3,2-b]*thiepine* **2**.—The above crude dichloro compound **10** (3.3 g) in dimethyl sulphoxide (10 ml) was added dropwise, with stirring, to a mixture of powdered sodium sulphide trihydrate (4.0 g) and dimethyl sulphoxide (30 ml) which had been warmed to 95–100 °C. The mixture was heated for 3 h after addition had been completed and then cooled and poured into water (50 ml). The product was extracted with diethyl ether (3 × 50 ml) and the combined extracts were washed with water and dried ($MgSO_4$). Evaporation of the solvent gave an oil (2.5 g) which was chromatographed on silica gel, eluting with pentane–benzene (4:1), to afford *cis*-octahydrothieno[3,2-*b*]thiepine **2**, b.p., 90–92 °C at 0.4 mmHg, (0.31 g, 12% yield); *m/z* 174 (100% abundance, $M^{\bullet+}$), 141 (35%), 127 (16), 119 (25), 114 (24), 113 (52), 101 (31), 99 (27), 87 (48), 86, (53), 85 (52), 67 (42), 45 (55) and 41 (40); δ_H (for H atom numbering, see structure **2**), 3.62 (q, H6), 3.48 (q, H5), 2.93 (oct., H1), 2.78 (m, H2), 2.74 (m, H7), 2.50 (oct., H8), 2.23 (oct., H3), 2.16 (oct., H4), 2.01 (m, H10), 1.97 (m, H13, H14), 1.83 (m, H12), 1.61 (m, H9) and 1.28 (m, H11); ^1H-^{13}C correlation: δ 31.0(C1)–2.93(H1), 2.78(H2); 38.4(C2)–2.23(H3), 2.16(H4); 53.8(C3)–3.62(H6; 53.6(C4)–3.48(H5); 33.2-(C5)–2.74(H7), 2.50(H8); 32.9(C6)–2.01(H10), 1.61(H9); 26.7-(C7)–1.28(H11), 1.83(H12); and 33.9(C8)–1.97(H13), H14). ^1H-^1H correlations: δ 3.62(H6)–3.48(H5); 3.48(H5)–3.62(H6), 2.23(H3), 2.16(H4); 2.93(H1)–2.78(H2), 2.23(H3), 2.16(H4); 2.75(H2, H7)–2.93(H1), 2.50(H8), 2.23(H3), 2.16(H4), 1.95-(H10), 1.61(H9); 2.50(H8)–2.74(H7), 1.95(H10), 1.61(H9); 2.17-(H3, H4)–3.48(H5), 2.93(H1), 2.78(H2); 1.95(H10, H13, H14)–3.62(H6), 2.74(H7), 2.50(H8), 1.61(H9), 1.28(H11); 1.61(H9)–2.74(H7), 2.50(H8), 1.95(H10); 1.28(H11)–1.83(H12) and 1.95-(H10, H13, H14); (Found: C, 55.2; H, 8.1. $C_8H_{14}S_2$ requires C, 55.1; H, 8.0%). GC (column, 1.5 m × 2 mm; OV 351, 10% on Celite; 240 °C) confirmed that only one isomer had been obtained.

Preparation of cis-*Hexahydrothieno*[2,3-b]-1,4-*oxathiine* **6**.—To a stirred solution of 2,3-dichlorotetrahydrothiophene (7.85 g, 0.05 mol) in CH_2Cl_2 (150 ml) was added 2-chloroethanol (4.8 g, 0.06 mol) and pyridine (4.75 g, 0.06 mol) in small portions. The mixture was allowed to stand at room temperature for 24 h and then washed with 10% aqueous HCl and water and dried ($MgSO_4$) to yield 2-(2-chloroethoxy)-3-chlorotetrahydrothiophene **11** (6.57 g, 65% yield) as a yellow oil, b.p., 80–82 °C at 0.2 mmHg (lit.,[7a] b.p., 71 °C at 0.1 mmHg); *m/z* 204, 202 and 200 ($M^{\bullet+}$; 2 Cl); δ_H 5.18 (d, *J*/Hz 1.5, H6), 4.54 (t d., *J*/Hz 1, H5), 3.55 (m, 4 H), 3.15 (m, 1 H), 3.02 (m, 1 H) and 2.38 (complex m, 2 H). This dichloro compound **11** (6.5 g, 0.03 mol) in dimethyl sulphoxide (10 ml) was added dropwise, with stirring, to a mixture of powdered $Na_2S{\cdot}3H_2O$ (6.0 g, 0.045 mol) and dimethyl sulphoxide (30 ml) at 95–100 °C. After addition, the reaction mixture was heated at about 100 °C for a further 3 h. Work-up as above for the thiepine **2** gave *cis*-hexahydrothieno[2,3-*b*]-1,4-oxathiine **6** (1.87 g, 36% yield), b.p., 79–81 °C at 0.2 mmHg, m.p., 53–55 °C (from pentane); *m/z* 162 (99%; $M^{\bullet+}$), 115 (56%), 105(26), 102(42), 89(46), 86(36), 85(41), 73(30), 61(28), 60(36), 59(34) and 45(100); δ_H (for H atom numbering, see structure **6**) 2.17 (d t, H9), 2.28 (m, H3), 2.45 (m, H4), 2.9 (m, H2, H5), 2.98 (m, H5, H10), 3.11 (m, H1), 3.81 (t of d, H7), 4.25 (d t, H8) and 5.11 (d, H6); ^1H-^1H correlations: H6–H5; H8–H7, H9, H10; H7–H8, H9, H10; H1–H2, H3, H4; H4–H1, H2, H3, H5; H3–H1, H2, H4, H5; and H9–H7, H8, H10; PANIC

simulation H-H couplings (*J*/Hz): 1,2(−10.2); 1,3(1.6); 1,4(8.4); 1.5(0); 1,6(0); 2,3(6.9); 2,4(10.5); 2,5(0); 2,6(0); 3,4(−12.6); 3,5(5.5); 3,6(0); 4,5(12.8); 4,6(0); 5,6(3.1); 7,8(−11.8); 7,9(2.2); 7,10(11.6); 8,9(2.6); 8,10(3.1); and 9,10(−13.6) (Found: C, 44.4; H, 6.2. $C_6H_{10}OS_2$ requires C, 44.4; H, 6.2%).

Preparation of 1,4,6-*trithiaspiro*[4.4]*nonane* **8**.—A mixture of tetrahydrothiophen-2-one (2.0 g, 0.2 mol), ethane-1,2-dithiol (2.8 g, 0.03 mol) and toluene-*p*-sulphonic acid (0.3 g) in benzene (80 ml) was heated at reflux for 48 h, the water produced being removed by means of a Dean-Stark apparatus. The cooled reaction mixture was diluted with diethyl ether (50 ml) and washed with dilute NaOH and water and dried ($MgSO_4$). After evaporation of the solvent, the residue was distilled to give 1,4-t-trithiaspiro[4.4]nonane **8** (2.44 g, 70% yield), b.p. 90–91 °C at 0.25 mmHg, m.p. 43–45 °C (from pentane); *m*/*z* 178 (81%, $M^{\bullet+}$), 150 (49%), 131(44), 118(37), 85(40), 76(17), 71(31), 58(33) and 45(100); δ_H 3.51–3.23 (complex m, H4), 3.05 (t, *J*/Hz 6.5, H2), 2.46 (m, H2) and 2.19 (m, H2); (Found: C, 40.4; H, 5.7. $C_6H_{10}S_3$ requires C, 40.4; H, 5.6%).

Preparation of 1,4,7-*Trithiaspiro*[4.4]*nonane* **9**.—A mixture of tetrahydrothiophen-3-one [19] (2.0 g, 0.02 mol), ethane-1,2-dithiol (2.8 g, 0.03 mol) and toluene-*p*-sulphonic acid (0.1 g) in benzene (80 ml) was treated and worked-up as for the spirononane **8** above to afford 1,4,7-trithiaspiro[4.4]nonane **9** (3.1 g, 89% yield) as a colourless oil, b.p., 89–91 °C at 0.15 mmHg, (lit.,[20] b.p. 128 °C at 4 mmHg); *m*/*z* 178 (80%; $M^{\bullet+}$), 150(52%), 131(45), 118(38), 104(49), 85(30), 76(16), 71(28), 58(21) and 45(100); δ_H 3.35 (s, 4 H), 3.21 (s, 2 H), 2.98 (t, *J*/Hz 6.5, 2 H) and 2.37 (t, *J*/Hz 6.6, 2 H) (Found: C, 40.4; H, 5.8. Calc. for $C_6H_{10}S_3$: C, 40.4; H, 5.6%).

Reaction of 2,3-*Dichlorotetrahydrothiophene with Ethane*-1,2-*dithiol*.—To a solution of 2,3-dichlorotetrahydrothiophene (7.9 g, 0.05 mmol) in CH_2Cl_2 (150 ml) was added ethane-1,2-dithiol (5.7 g, 0.06 mol) and pyridine (4.8 g, 0.06 mol) in small portions. The mixture was allowed to stand at room temperature for 24 h and then washed successively with dilute HCl and water and dried ($MgSO_4$). On evaporation of the solvent, the residual oil, which spontaneously evolved HCl with time, was heated at reflux for 1 h with a 10% aqueous KOH (2.8 g, 0.05 mol) in EtOH–H_2O (1:1). The organic products were extracted into CH_2Cl_2 which was then washed with water and dried ($MgSO_4$). Evaporation of the solvent gave an oil, b.p., 105–115 °C at 0.5 mmHg (1.77 g) which was separated by preparative scale GC on a column of OV 351 (10% on Celite) into two components (ratio 27:63). The first component was a mixture (1:1) of the two spirononanes **8** and **9**; *m*/*z* 178 (77%, $M^{\bullet+}$), 150(41%), 131(54), 118(44), 104(36), 85(51), 76(26), 71(46), 58(31) and 45(100); δ_H 3.45–3.23 (m), 3.32 (s), 3.20 (s), 3.02 (t), 2.95 (t), 2.43 (m), 2.34 (t) and 2.16 (m). The second component was redistilled to give *cis*-hexahydrothieno[2,3-*b*]-1,4-dithiine **7** as a pale yellow oil, b.p., 110–112 °C at 0.15 mmHg; *m*/*z* 178 (53%, $M^{\bullet+}$), 92(48%), 86(100), 85(62), 45(68); δ_H (for H atom numbering, see structure **7**) 2.21 (m, H3), 2.58 (m, H4), 2.66 (m, H10), 2.87 (complex m, H7, H8, H9 and H2), 3.15 (m, H1), 3.33 (m, H5) and 4.52 (d, *J*/Hz 4.1, H6); ^1H–^{13}C correlations: δ 24.3(C6)–2.66(H10), 2.87(H9); 29.3(C5)–2.87(H7,H8); 29.5(C1)–2.87(H2), 3.15(H1); 32.1(C2)–2.21(H3), 258(H4); 43.8(C3)–3.33(H5); and 48.2(C4)–4.52(H6); JMOD δ 43.8(C3) and 48.2(C4), invert (CH) (Found: C, 40.2; H, 5.7. $C_6H_{10}S_3$ requires C, 40.4; H, 5.6%).

trans-2-*Alkoxy*-3-*chlorotetrahydrothiophenes* **15**.—These compounds **15** were prepared by a similar method to that described above for 2-(2-chloroethoxy)-3-chlorotetrahydrothiophene **11**. R = CH_3CH_2O, b.p. 40–42 °C at 0.3 mmHg, 69% yield; (Found: C, 43.2; H, 6.8. $C_6H_{11}ClOS$ requires, C, 43.2; H, 6.6%); *m*/*z* 166 and 168 (3:1); δ_H 1.16 (t, CH_3), 2.35 (m, H3, H4), 3.0 (t d, H2), 3.13 (t d, H1), 3.33 (m, OCH_2, 1 H), 3.65 (m, OCH_2, 1 H), 4.48 (m, H5), 5.13 (d, *J*/Hz 1, H6). R = $CH_3CH_2CH_2O$, b.p. 56–60 °C at 0.45 mmHg, 66% yield (Found: C, 46.4; H, 7.3. $C_7H_{13}ClOS$ requires, C, 46.5; H, 7.3%); *m*/*z* 180 and 182; δ 0.87 (t, CH_3), 1.55 (m, CH_2, 2H), 2.36 (m, H3, H4), 3.0 (t d, H2), 3.12 (t d, H1), 3.23 (m, OCH_2, 1 H), 3.55 (m, OCH_2, 1 H), 4.49 (m, H5) and 5.12 (d, H6). R = CH_3-$CH_2CH_2CH_2O$, b.p., 65–68 °C at 0.27 mmHg, 72% yield (Found: C, 49.6; H, 8.0. $C_8H_{15}ClOS$ requires C, 49.3; H, 7.8%); *m*/*z* 194 and 196; δ_H (0.87, CH_3), 1.32 (m, CH_2), 1.52 (m, CH_2), 2.35 (m, H3, H4), 2.99 (t d, H2), 3.12 (t d, H1), 3.27 (m, OCH_2, 1 H), 3.59 (m, OCH_2, 1 H), 4.48 (m, H5) and 5.12 (d, H6). R = $ClCH_2CH_2CH_2O$, b.p. 92–96 °C at 0.25 mmHg, 44% yield (Found: C 44.5; H, 5.7. $C_7H_{12}Cl_2OS$ requires C, 44.6; H, 5.6%); *m*/*z* 214, 216, 218; δ_H 1.97 (quint, CH_2), 2.35 (m, H3, H4), 3.0 (t d, H2), 3.14 (t d, H1), 3.57 (m, OCH_2, $ClCH_2$, 4 H), 4.49 (m, H5) and 5.13 (d, *J*/Hz 1, H6).

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