522. *Cyclic Trisulphides from Bunte Salts*

By B. Milligan and J. M. Swan

Two cyclic trisulphides, 1,2,3-trithian (II) and 2,3,4-benzotrithiepin (III) have been prepared from the bifunctional Bunte salts (I) and (IV), respectively, by reaction with sodium sulphide in the presence of formaldehyde. The reaction failed in a number of other cases, the products being almost entirely polymers.

Oxidation of the benzotrithiepin (III) with monoperphthalic acid yielded the 2-oxide, containing the unsymmetrical grouping, $\cdot CH_2S(O)\cdot S\cdot SCH_2$. This appears to be the first example of a trisulphide monoxide.

We have previously shown[1] that dialkyl trisulphides may be obtained by reaction of sodium *S*-alkyl thiosulphates (Bunte salts) with sodium sulphide at pH 8, according to the following equations:

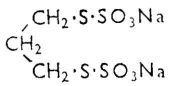
$$S^{2-} + RS\cdot SO_3^- \rightleftharpoons RS\cdot S^- + SO_3^{2-}$$

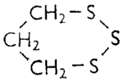
$$RS\cdot S^- + RS\cdot SO_3^- \rightleftharpoons RS\cdot S\cdot SR + SO_3^{2-}$$

The purity of the products was improved by adding formaldehyde to the reaction mixture; this combines with the liberated sulphite and thus minimises subsequent conversion of trisulphide into disulphide.[2] We have now applied this method to the synthesis of several cyclic trisulphides, from bifunctional Bunte salts.

Reaction of disodium trimethylene di(thiosulphate)[3] (I) with sodium sulphide in the presence of formaldehyde gave 1,2,3-trithian (II), which was separated from polymeric material by vacuum sublimation. The product was shown by gas–liquid chromatography (g.l.c.) to contain traces of two impurities believed from their retention volumes to be the corresponding cyclic di- and tetra-sulphides. The crystalline product was insoluble in most organic solvents, although readily soluble in carbon disulphide. Its structure was established as (II) by elemental analysis, molecular weight determination, and proton magnetic resonance (p.m.r.) spectroscopy.

Several complex examples of this ring system have been prepared earlier by reaction of sodium tetrasulphide with pentaerythrityl tetrabromide[4,5] or 1,3-dibromo-2,2-dimethylpropane,[5,6] but an attempt to prepare the trithian (II) by this approach was unsuccessful.[5] We were also unable to prepare it by reaction of propane-1,3-dithiol and sulphur dichloride in anhydrous ether, only polymer being obtained.


(I)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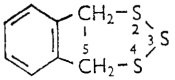
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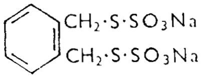
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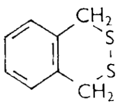
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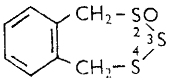
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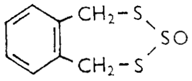
(VII)

Our attempts to prepare other monocyclic trisulphides from Bunte salts were less successful. Reaction of disodium 3-oxapentamethylene di(thiosulphate) with sodium sulphide in the presence of formaldehyde gave an oily mixture which, from g.l.c. examination, appeared to contain the corresponding cyclic di-, tri-, and tetra-sulphides in the molar

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[1] B. Milligan, B. Saville, and J. M. Swan, *J.*, 1961, **4850**.
[2] B. Milligan, B. Saville, and J. M. Swan, *J.*, 1963, **3608**.
[3] Y. G. Mazover, *J. Gen. Chem.* (*U.S.S.R.*), 1949, **19**, 829.
[4] H. J. Backer and N. Evenhuis, *Rec. Trav. chim.*, 1937, **56**, 174.
[5] L. Schotte, *Arkiv. für Kemi*, 1956, **9**, 361.
[6] H. J. Backer and A. F. Tasma, *Rec. Trav. chim.*, 1938, **57**, 1183.

ratios 16 : 72 : 12. However, reaction of the di(thiosulphate) with thiourea in acid [7] yielded the cyclic disulphide 1-oxa-4,5-dithiepan, prepared earlier by Affleck and Dougherty [8] by steam distillation of the di(thiosulphate) with cupric chloride. Disodium pentamethylene di(thiosulphate) and disodium hexamethylene di(thiosulphate) both reacted very slowly with sodium sulphide in the presence of formaldehyde, giving polymer only. Disodium 2-oxotrimethylene di(thiosulphate) and disodium ethylene di(thiosulphate) reacted rapidly, but the products were almost entirely polymers.

A crystalline bicyclic trisulphide, 2,3,4-benzotrithiepin (III) was obtained in 48% yield from the corresponding Bunte salt (IV). The analogous cyclic disulphide,[9] 2,3-benzodithiin (V), was also prepared from the same Bunte salt by reaction with thiourea in hot dilute hydrochloric acid.[7] The p.m.r. spectrum of the benzodithiin (V) shows all four methylene protons to be equivalent, by virtue of rapid conformational interchange.[10] In contrast, the four methylene protons of the larger trisulphide ring in the benzotrithiepin (III) appeared in the p.m.r. spectrum as an AB quartet, indicating a higher degree of rigidity of the conformational isomers. In chloroform solution at 40°, the frequency difference between the chemical shifts of the two protons on each methylene carbon was 41 c./sec., so that the frequency of interconversion of the conformers at 40° is less than 41 sec.^{-1}.

Oxidation of the benzotrithiepin (III) with an equimolecular amount of monoperphthalic acid gave a monosulphoxide, which we formulate as the 2-oxide (VI) rather than the 3-oxide (VII). Feher *et al.*[11] have shown that oxidation of linear trisulphides with excess of peroxide gives symmetrical disulphonyl sulphides, which suggests that the central sulphur atom is least prone to attack. The p.m.r. spectrum, measured at 60 Mc./sec., showed a pair of overlapping AB quartets of equal intensity (see Experimental section), the central point of one being some 9 c./sec. from the central point of the other. This small difference in chemical shift between the two sets of protons, $CH_2{\cdot}S(O){\cdot}S$ and $CH_2{\cdot}S{\cdot}S$ (formula VI), would be expected on the basis of the very small difference in chemical shift (2—3 c/sec. at 60 Mc./sec.) reported for the two different methylene groups in dibenzyl disulphide monoxide.[12] The fact that each methylene group in the trisulphide monoxide appears as a quartet would again be ascribed to a degree of conformational rigidity of the cyclic seven-membered ring system. It may be noted that the monosulphoxide (VI) is theoretically resolvable into two enantiomers. It is unlikely that any conformational rigidity in the alternative structure (VII) would give rise to a pair of quartets of equal area in the proton magnetic resonance spectrum, and we therefore conclude that the structure (VI) is correct.

EXPERIMENTAL

Synthesis of Bifunctional Bunte Salts.—Bifunctional Bunte salts were prepared by heating a solution of the appropriate dihalide and sodium thiosulphate pentahydrate (2 equiv.) in 50% ethanol under reflux. The reaction mixture was then evaporated to dryness *in vacuo*, and the residue was extracted with boiling 90% ethanol, from which the product separated on cooling.

The starting materials and reaction times required for *ca.* 90% consumption of thiosulphate are given in the annexed Table, together with the formulæ of the Bunte salts obtained, yields, and analytical results obtained after several recrystallisations from the solvents shown; samples were dried at 80°/20 mm. for 3 hr. before analysis.

Attempts to prepare Bunte salts from 1,4-dibromobutane, bischloromethyl ether, 1,3-dibromopropan-2-ol, and 1,3-dichloroprop-2-yl acetate were unsuccessful. The reaction mixtures became acidic, resulting in decomposition of the thiosulphate, but no Bunte salts were obtained, even when the mixtures were buffered with sodium acetate. The reactions of 1,3-dibromo-2,2-dimethylpropane, pentaerithritol tetrabromide and 2,2-bischloromethyl-1,3-dioxolan with sodium thiosulphate were extremely slow, and no Bunte salts were obtained in these cases.

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[7] B. Milligan and J. M. Swan, *J.*, 1962, 2172.
[8] J. G. Affleck and G. Dougherty, *J. Org. Chem.*, 1950, **15**, 865.
[9] A. Lüttringhaus and K. Hägele, *Angew. Chem.*, 1955, **67**, 304.
[10] A. Lüttringhaus, S. Kabuss, W. Maier, and H. Friebolin, *Z. Naturforsch.*, 1961, **16***b*, 761.
[11] F. Feher, K. H. Schäfer, and W. Becher, *Z. Naturforsch.*, 1962, **17***b*, 847.
[12] P. Allen, P. J. Berner, and E. R. Malinowski, *Chem. and Ind.*, 1963, 208.

Details of preparation and analyses of cyclic trisulphides

Starting material	Re-action time (hr.)	Product	Yield (%)	Solvent for recryst.	Analysis
$Br\cdot[CH_2]_5\cdot Br$	0·5	$(NaO_3S\cdot S\cdot CH_2\cdot CH_2)_2CH_2$	33	95% ethanol	Found: C, 16·3; H, 3·8; S, 34·8. $C_5H_{10}O_6S_4Na_2,2H_2O$ requires C, 16·0; H, 3·7; S, 34·1%
$Br\cdot[CH_2]_6\cdot Br$	1·5	$(NaO_3S\cdot S\cdot CH_2\cdot CH_2\cdot CH_2)_2$	49	95% ethanol	Found: C, 18·7; H, 4·3; S, 33·0. $C_6H_{12}O_6S_4Na_2,2H_2O$ requires C, 18·5; H, 4·1; S, 32·8%
$ClCH_2\cdot CH{:}CH\cdot CH_2Cl$	2	$(NaO_3S\cdot S\cdot CH_2\cdot CH)_2$	58	95% ethanol	Found: C, 14·3; H, 2·6; S, 38·4. $C_4H_6O_6S_4Na_2,H_2O$ requires C, 14·0; H, 2·3; S, 37·5%
$ClCH_2\cdot CO\cdot CH_2Cl$	0·1	$(NaO_3S\cdot S\cdot CH_2)_2CO$	68	90% ethanol	Found: C, 10·4; H, 2·2; S, 34·8. $C_3H_4O_7S_4Na_2,2H_2O$ requires C, 9·9; H, 2·2; S, 35·4%
$ClCH_2\cdot CH_2\cdot O\cdot CH_2\cdot CH_2Cl$	6	$(NaO_3S\cdot S\cdot CH_2\cdot CH_2)_2O$	34	90% ethanol	Found: C, 13·6; H, 3·0; S, 36·1. $C_4H_8O_7S_4Na_2,H_2O$ requires C, 13·7; H, 2·9; S, 36·6%
$C_6H_4(CH_2Br)_2$-*o*	2	$C_6H_4(CH_2\cdot S\cdot SO_3Na)_2$-*o*	37	80% ethanol	Found: C, 24·2; H, 3·0; S, 31·7. $C_8H_8O_6S_4Na_2,1\frac{1}{2}H_2O$ requires C, 23·9; H, 2·8; S, 32·0%

1,2,3-*Trithian*.—A solution of sodium sulphide nonahydrate (5·2 g.) in water (50 ml.) was added dropwise over 1 hr. to a solution of disodium trimethylene di(thiosulphate) [3] (6·6 g.) in 0·25M-phosphate buffer (pH 8; 200 ml.) containing formaldehyde (35% w/v; 5 ml.) at room temperature. The pH of the reaction mixture was maintained at 8 by addition of hydrochloric acid. After 3 hr. the crude product (1·4 g.) was filtered off, and purified by sublimation at 50°/0·1 mm. The product (0·68 g., 23%) had m. p. 44° [Found: C, 26·6; H, 4·7; S, 69·8%; *M* (ebulliometry in benzene; 134. $C_3H_6S_3$ requires C, 26·1; H, 4·3; S, 69·6%; *M*, 138]; purity by g.l.c. (silicone-gum rubber–Chromosorb P) [2] was >99%; ultraviolet $\lambda_{max.}$ (in MeOH) 264 mμ, ε 1500. The p.m.r. spectrum (CS_2 solution) showed a complex multiplet in the range 115—145 c./sec. due to the methylene group at position 5 and an unsymmetrical triplet (δ 3·13 p.p.m.) due to the equivalent methylene groups at positions 4 and 6.

In the absence of formaldehyde the product was a yellow oil, shown by g.l.c. to contain roughly equal proportions of 1,2,3-trithian, and a product which, from its retention volume and the method of synthesis, was believed to be 1,2-dithiolan.

1-*Oxa*-4,5-*dithiepan*.—A solution of disodium 3-oxapentamethylene di(thiosulphate) monohydrate (30 g.) and thiourea (7·0 g.) in 1N-hydrochloric acid (300 ml.) was heated at 100° for 1 hr. The product was extracted with carbon disulphide. Distillation gave the disulphide (3·2 g., 28%), b. p. 42—43°/0·2 mm., lit.,[7] 55—56°/3 mm.), n_D^{20} 1·5817 (Found: C, 35·2; H, 6·1; S, 46·3. Calc. for $C_4H_8OS_2$: C, 35·3; H, 5·9; S, 47·1%). A viscous residue (4·4 g.) remained in the distilling flask. The product was shown by g.l.c. to be more than 99·9% pure.

2,3,4-*Benzotrithiepin*.—Disodium *o*-phenylene di(thiosulphate) was treated with sodium sulphide (1 equiv.) and formaldehyde at pH 8 as described above. The crude product (98%) was filtered off, and the trisulphide separated from polymer by extraction with boiling light petroleum (b. p. 60—90°). When the extract was cooled, the product (48%) separated as plates, m. p. 101—102° [Found: C, 47·6; H, 4·3; S, 47·5%; *M* (ebulliometry, in benzene), 184; *M* (vapour pressure osmometer, 38° in chloroform), 191. $C_8H_8S_3$ requires C, 48·0; H, 4·0; S, 48·0%; *M*, 200]. An attempt at gas–liquid chromatography caused the trisulphide to decompose. The p.m.r. spectrum in deuterochloroform (with tetramethylsilane as an internal reference, δ 0·00 p.p.m.) showed an AB quartet; δ_A 4·80, δ_B 4·12, J_{AB} 15 c./sec., and the four aromatic protons as a sharp singlet, δ 7·10. A minor impurity was responsible for peaks at δ 4·08 and 7·27. The amount of this polymeric material was considerably increased by heating the compound with an equal weight of sulphur in benzene solution.

2,3,4-*Benzotrithiepin* 2-*Oxide*.—An ethereal solution of monoperphthalic acid (1 equiv.) was added dropwise to a solution of the above trisulphide (4·0 g.) in ether (150 ml.), giving a white precipitate. After 2 days the precipitate (2·3 g.) was filtered off and crystallised from ethyl acetate, giving the monoxide (1·7 g., 40%), as yellow prisms, m. p. 133° [Found: C, 44·3; H, 3·7; S, 44·6%; *M* (vapour pressure osmometer, chloroform, 38°): 216. $C_8H_8OS_3$ requires C, 44·4; H, 3·7; S, 44·5%; *M*, 216]. The p.m.r. spectrum showed a set of 8 lines between 240 and 290 c./sec., corresponding to two overlapping AB quartets of equal intensity, δ_A 4·68,

δ_B 4·29, J_{AB} 13 c.p.s., assigned to CH_2·SO and $\delta_{A'}$ 4·51, $\delta_{B'}$ 4·16, $J_{A'B'}$ 12 c.p.s. assigned to CH_2·S. The infrared spectrum (carbon disulphide solution) showed bands at 1065m and 1096s cm.$^{-1}$. In a potassium bromide disc, the bands were found at 1065 and 1085 cm.$^{-1}$, and were more nearly equal in intensity. The band at the higher wave number can be ascribed to the S=O stretching frequency, since shifts of 10—20 cm.$^{-1}$ generally occur on passing from the solid state to solution.[13]

2,3-*Benzodithiin*.—Disodium *o*-phenylene di(thiosulphate) (1·9 g.) and thiourea (0·8 g.) were heated in 1N-hydrochloric acid (50 ml.) at 100° for 30 min. A dark oil separated, and solidified on cooling. Sublimation of this crude material at 50°/0·1 mm. gave the disulphide (0·51 g., 64%), which crystallised from methanol as needles, m. p. 77—78° (lit.,[9] m. p. 80°) (Found: S, 37·5. Calc. for $C_8H_8S_2$: S, 38·1%). The p.m.r. spectrum (in deuterochloroform) (cf.[10]) showed two peaks of equal area, δ 4·07 (CH_2) and 7·13 (approx.) (aromatic protons). The spectrum remained unchanged when the solution was cooled to −60°.

(B. M.) DIVISION OF PROTEIN CHEMISTRY.
(J. M. S.) DIVISION OF ORGANIC CHEMISTRY, C.S.I.R.O.,
MELBOURNE, AUSTRALIA.

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[13] L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen & Co., London, 1958, p. 358.