Macrocyclic Sulphide Synthesis: Trithia[$n^{n+1,2n+4}$][2n + 1]metacyclophanes †

By **Alfredo Ricci,*** Istituto di Chimica Organica dell'Università, Via G. Capponi 9, 50121 Firenze, Italy
Roberto Danieli and **Sandra Rossini,** Laboratorio dei Composti del Carbonio contenenti Eteroatomi e loro Applicazioni del C.N.R., Ozzano Emilia, Bologna, Italy

The formation of trithiametacyclophanes from the trisodium salt of a tris(mercaptoalkyl)benzene and a trisbromoalkylmethane is described. ^{1}H N.m.r. spectra were used to determine the structures of the products, with the aid of shift reagents.

WE have previously [1] described the preparation of sulphonium and ammonium salts from several new diaza- and dithia-paracyclophanes, and the effects of the bridging system on aromatic reactivity. However, whereas cyclophane systems including only a single polymethylene-type bridge have been extensively investigated,[2] few examples containing a further bridge have been studied.[3] As part of a study of the chemistry of organic molecules containing cavities,[1,4] we now report the synthesis of a series of novel trithiametacyclophanes of this type.

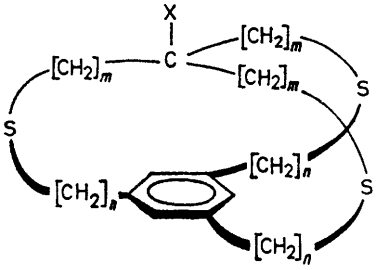
The new compounds (I)—(V) were prepared by the procedure employed in the dithiacyclophane series, by applying the high dilution principle, from aromatic sodium trithiolates and appropriate aliphatic halogenoderivatives (see Scheme) in benzene–ethanol–t-butyl alcohol. However, whereas this procedure was convenient for compounds (I)—(IV), all attempts to prepare (V) in this way led to low yields (*ca.* 3%), probably owing to the low reactivity of 1,1,1-trisbromoethylethane. Compound (V) was prepared conveniently, in satisfactory yield (15%), from 1,1,1-trismercaptomethylethane and 1,3,5-trisbromoethylbenzene. All the cyclisations were carried out by the same procedure the only variation being reaction time required. Even after long reaction times the reaction mixtures always contained starting materials and unindentified high molecular weight products, probably polymers.

† The nomenclature of F. Vögtle and P. Neumann (*Tetrahedron*, 1970, **26**, 5847) is employed. I.U.P.A.C. names for such compounds are of the type: 5,13,18-trithiatricyclo[7.7.5.$1^{3,15}$]docosa-1,3(22),15-triene [for (I)].

[1] A. Ricci, R. Danieli, and J. H. Ridd, *J.C.S. Perkin II*, 1972, 1547, 2107; 1976, 290.

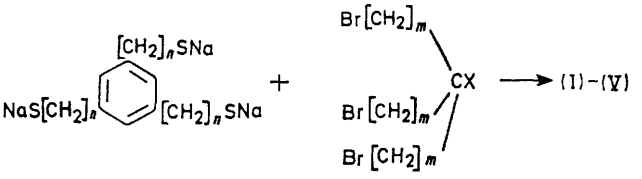
[2] B. H. Smith, 'Bridged Aromatic Compounds,' Academic Press, New York and London, 1964; J. S. Bradshaw and J. Y. K. Hui, *J. Heterocyclic Chem.*, 1974, **11**, 649; F. Vögtle and P. Neumann, *Angew. Chem. Internat. Edn.*, 1972, **11**, 73.

The structures of the new bridged compounds (see Table for yields, analytical data, and m.p.s) were



(I) n = 1, m = 3, X = H
(II) n = 1, m = 2, X = H
(III) n = 2, m = 3, X = H
(IV) n = 2, m = 2, X = H
(V) n = 2, m = 1, X = Me

confirmed by their mass and ^{1}H n.m.r. spectra. With the exception of (V) all the compounds show intense molec-



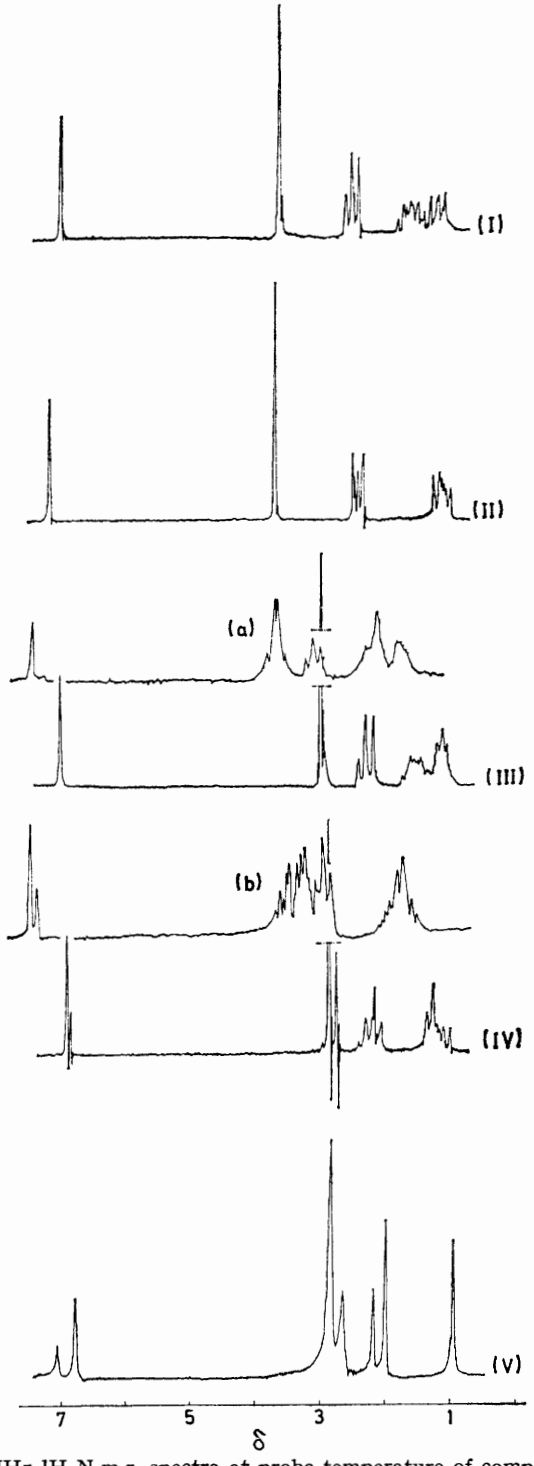
SCHEME

ular ion peaks and a small number of other characteristic peaks. The ^{1}H n.m.r. spectra are shown in the Figure.

[3] F. Vögtle and R. G. Lichtenthaler, *Chem. Ber.*, 1973, **106**, 1319; F. Vögtle and G. Hohner, *Angew. Chem. Internat. Edn.*, 1975, **14**, 497.

[4] A. Ricci, R. Danieli, G. Pirazzini, and S. Rossini, *Gazzetta*, 1975, **105**, 751.

In the series with $n = 1$, the spectral pattern is uncomplicated: the aromatic proton signals appear consistently as singlets at δ 6.9 and 7.2, and the 'inner' methylene groups of the m chain as multiplets centred at δ 2.4 and 1.5, respectively. The benzylic protons give rise to sharp singlets at δ 3.5 and 3.6, implying magnetic equivalence; this suggests either a low energy barrier to conformational interchange or, more likely, the existence of a strongly favoured conformation. Inspection of models coupled with a low-temperature n.m.r. study (−80 °C) supports the presence of a single conformation. The interpretation of the n.m.r. spectra in the $n = 2$ series is less straightforward. For compound (III) the singlet at δ 2.92 (12 protons) appears incompatible with the expected structure. On decreasing m the same spectral pattern is maintained, but further complication occurs in the spectra of (IV) and (V) due to duplication both of the aromatic resonances and of the aliphatic peaks around δ 2.9.



60 MHz ^{1}H N.m.r. spectra at probe temperature of compounds (I)—(V) (*ca.* 0.20M in $CDCl_3$); (a) (III) in the presence of 0.32 mol. equiv. of Eu([$^2H_{10}$]fod)$_3$; (b) (IV) in the presence of 0.54 mol. equiv. of Eu([$^2H_{10}$]fod)$_3$

* Dilution with water followed by extraction with benzene afforded a solid product whose elemental analysis and m.p. agreed perfectly with those of the starting material (IV).

Unequivocal assignment of the resonances was achieved by use of shift reagents.[5] The use of fluorinated shift reagents such as Eu([$^2H_{10}$]fod)$_3$ produces in the spectra of (III) and (IV) the modifications (a) and (b) shown in the Figure. At suitable shift reagent : substrate ratios, each of the anomalous singlets is split into two multiplets; this finding, in analogy with previously observations for diaza- and dithia-cyclophanes,[6] enables the assignment of these resonances to the methylene bridges linking the sulphur atom to the benzene ring.

However for compound (V) no splitting but a broadening of the aliphatic peaks (not shown in the Figure) was observed, even at high shift reagent : substrate ratios. The adventitious degeneracy which gives rise to coincident peaks from formally non-equivalent protons thus appears a general feature of the spectra of the compounds with $n = 2$, regardless of the number of bridges involved. Inspection of models in the $n = 2$ series suggests a reduction in conformational randomness as a consequence of increased steric crowding with decreasing values of m, and the duplication of the signals in the n.m.r. spectra of (IV) and (V) is in accord with the presence of two conformers at equilibrium. A variable temperature n.m.r. study was used to test this hypothesis: heating a sample of (IV) in $(CD_3)_2SO$ at 130 °C for several hours substantially modified the original spectral pattern; in the doublets the contribution of the less intense aromatic and aliphatic peaks increased up to a 1 : 1 ratio.* Under the same conditions only small changes were noticed for (V), as one would expect from the much more strained conformation of this bridged system. A noteworthy feature in the n.m.r. spectrum of (V) is the high-field resonance of the apical methyl group (δ 0.80) in comparison with that of 1,1,1-trismethylthiomethylethane (δ 1.1). The upfield shift of 0.3 p.p.m. is a strong indication of an effective ring current,[7] which in this

[5] J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, 1971, **93**, 641.

[6] A. Ricci, R. Danieli, R. A. Phillips, and J. H. Ridd, *J. Heterocyclic Chem.*, 1974, 551.

[7] J. A. Pople, W. G. Schneider and H. J. Bernstein, 'High Resolution Nuclear Magnetic Resonance,' McGraw-Hill, New York, 1959, p. 180; F. A. Bovey, 'Nuclear Magnetic Resonance Spectroscopy,' Academic Press, New York and London, 1969, p. 64.

molecule is likely to contribute significantly owing to the proximity of the aromatic π-cloud to the upper framework of the molecule.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded with a JEOL C-60 HL instrument and mass spectra with a Varian MAT-111 spectrometer. M.p.s were determined with a Kofler micro-hot-stage apparatus.

1,3,5-Tris-(2-mercaptoethyl)benzene.— 1,3,5-Trisbromoethylbenzene [8] (6.9 g, 20 mmol) and thiourea (3.9 g, 60 mmol) were dissolved in dry ethanol (30 ml) and heated under reflux for 30 min. The solvent was removed *in vacuo* and the residual oil refluxed with 10% sodium hydroxide (100 ml) for 2 h. After cooling, the mixture was acidified with dilute sulphuric acid and the aqueous layer extracted twice with chloroform. Evaporation of the extracts and distillation of the residual oil under high vacuum afforded *1,3,5-tris-(2-mercaptoethyl)benzene* (2.7 g, 60%) as a pale yellow oil, b.p. 189—191° at 0.8 mmHg (Found: C, 55.9; H, 6.8; S, 37.2. $C_{12}H_{18}S_3$ requires C, 55.7; H, 7.0; S, 37.2).

1,3,5-Trismercaptomethylbenzene, prepared from 1,3,5-trisbromomethylbenzene [8] and thiourea by a similar procedure, in 20% yield, had b.p. 177° at 1 mmHg (Found: C, 49.75; H, 5.7; S, 44.1. $C_9H_{12}S_3$ requires C, 49.95; H, 5.6; S, 44.4%).

1,1,1-Tris(methylthiomethyl)ethane.—This *trisulphide* was synthesized by methylation of the corresponding thiol [9] with dimethyl sulphate in 10% sodium hydroxide; b.p. 129° at 25 mmHg (Found: C, 45.4; H, 8.2; S, 45.9. $C_8H_{18}S_3$ requires C, 45.7; H, 8.6; S, 45.7%).

Tris-(3-bromopropyl)methane.—A solution of tris-(2-bromoethyl)methane [10] (10.1 g, 30 mmol) in dimethyl sulphoxide (20 ml) was added dropwise to a solution of sodium cyanide (4.5 g, 90 mmol) in dimethyl sulphoxide (50 ml) warmed at 60 °C. The mixture was heated at 130 °C for 5 h, poured on crushed ice, and extracted with chloroform. Evaporation of the extract yielded a solid which was recrystallized from ethanol to give *tris-(2-cyanoethyl)methane* (4.2 g, 85%), m.p. 79—81° (Found: C, 68.45; H, 7.4; N, 23.8. $C_{10}H_{13}N_3$ requires C, 68.5; H, 7.5; N, 24.0%). A suspension of the product (8 g, 45.6 mmol) in ethanol (80 ml) was saturated with dry hydrochloric acid. The mixture was refluxed for 6 h, then evaporated, and water (150 ml) was added. Extraction with chloroform and evaporation afforded an oil which was distilled to give *tris-(2-carboxyethyl)methane* (10 g, 87%), b.p. 158—160° at 0.4 mmHg (Found: C, 60.0; H, 8.4. $C_{16}H_{28}O_6$ requires C, 60.75; H, 8.9%). A suspension of lithium aluminium hydride (4 g) in dry ether (50 ml) was added dropwise to a solution of the foregoing ester (5.3 g, 16.75 mmol) in dry ether (50 ml). The mixture was refluxed overnight and decomposed cautiously with 10% sodium hydroxide. The solid was filtered off and extracted (Soxhlet) with ethanol for 12 h. After saturation with CO_2 the solution was filtered and evaporated and the crude tris-(3-hydroxypropyl)methane was used without further purification. The crude alcohol (3 g) in acetic acid (50 ml) saturated with hydrogen bromide was heated in a Carius tube at 110 °C for 4 h. The solution was then poured on crushed ice and extracted with chloroform. The extract was washed with sodium hydrogen carbonate, dried, and evaporated. Distillation of the residual oil gave *tris-(3-bromopropyl)methane* (3.8 g, 45%), b.p. 165—167° at 2.5 mmHg (Found: C, 31.5; H, 5.25; Br, 63.2. $C_{10}H_{19}Br_3$ requires C, 31.7; H, 5.05; Br, 63.3%).

Cyclization Experiments.—The synthesis and isolation procedures for all the bridged compounds were similar except that the sulphide (V) required a longer reaction time and higher dilution. The general procedure is outlined for compound (I).

M.p.s and analytical data for compounds (I)—(V)

Compound	Yield (%)	M.p. (°C)	Formula	Found (%)			Required (%)		
				C	H	S	C	H	S
(I)	44	215—216	$C_{19}H_{28}S_3$	64.7	7.95	27.2	64.7	8.0	27.3
(II)	17	176	$C_{16}H_{22}S_3$	61.85	7.02	30.7	61.9	7.15	31.0
(III)	23	92—94	$C_{22}H_{34}S_3$	67.2	8.45	23.9	66.9	8.7	24.4
(IV)	40	123—124	$C_{19}H_{28}S_3$	64.8	8.05	26.9	64.7	8.0	27.3
(V)	15	>290	$C_{17}H_{24}S_3$	63.2	7.3	28.8	62.9	7.45	29.6

2,10,19-Trithia[5^{6,14}][11]metacyclophane (I).—Tris-(3-bromopropyl)methane (7.58 g, 20 mmol) and 1,3,5-trismercaptomethylbenzene (4.36 g, 20 mmol) in benzene (400 ml), and sodium hydroxide (2.4 g, 60 mmol) in ethanol (400 ml), were added simultaneously with vigorous stirring and at a constant rate over 6 h, from two calibrated dropping funnels to boiling t-butyl alcohol (2 l) under a stream of nitrogen. The mixture was then refluxed for a further 15 h, and evaporated. The solid residue, taken up in benzene, was chromatographed on silica gel (elution with benzene). The first solid product was crystallized from n-hexane or light petroleum, to give the white crystalline *product* (I) (see Table).

2,8,17-Trithia[4^{5,12}][9]metacyclophane (II) was similarly prepared from tris-(2-bromoethyl)methane [10] and 1,3,5-trismercaptomethylbenzene.

3,11,22-Trithia[6^{7,16}][13]metacyclophane (III) was prepared from tris-(3-bromopropyl)methane and 1,3,5-tris-(2-mercaptoethyl)benzene. The waxy product obtained from chromatography was further purified by crystallization from n-hexane.

3,9,20-Trithia[5^{6,14}][11]metacyclophane (IV) was obtained from tris-(2-bromoethyl)methane and 1,3,5-tris-(2-mercaptoethyl)benzene and recrystallized from ligroin.

5-Methyl-3,7,18-trithia[4^{5,12}][9]metacyclophane (V) was obtained from 1,1,1-trismercaptomethylethane [8] and 1,3,5-trisbromoethylbenzene, by employing higher dilution (3 l of t-butyl alcohol) and a longer reaction time (30 h). After column chromatography the solid residue was washed with benzene and crystallized from dimethyl sulphoxide.

The technical assistance of Mr. A. Benassi of the C.N.R. is gratefully acknowledged.

[6/016 *Received*, 5*th January*, 1976]

[8] W. P. Cochrane, P. L. Pauson, and T. Stevens, *J. Chem. Soc.* (*C*), 1968, 630.

[9] G. R. Franzen and G. Binsch, *J. Amer. Chem. Soc.*, 1973, **95**, 175.

[10] R. Lukes, O. Strouf, M. Ferles, *Chem. listy*, 1956, **50**, 1624; R. Lukes and K. Syhora, *ibid.*, 1952, **46**, 731.