(13) L. A. Sternson, D. A. Coviello, and R. S. Egan, *J. Amer. Chem. Soc.*, **93**, 6529 (1971).
(14) J. Paasivirta, *Suom. Kemistilehti B*, 364 (1968).
(15) R. H. Cox and S. L. Smith, *J. Phys. Chem.*, **71**, 1809 (1967).
(16) F. A. L. Anet, *J. Amer. Chem. Soc.*, **84**, 747 (1962).
(17) J. B. Lambert, *Accounts Chem. Res.*, **4**, 87 (1971).
(18) C. J. Brown, *Acta Crystallogr.*, **7**, 92 (1954).
(19) R. Ditchfield, J. E. DelBene, and J. A. Pople, *J. Amer. Chem. Soc.*, **94**, 703 (1972).
(20) K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternary, Jr., *J. Amer. Chem. Soc.*, **87**, 1958 (1965).
(21) H. H. Jaffe and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962, pp 491–496.
(22) (a) D. N. Jones, M. J. Green, M. A. Saeed, and R. D. Whitehouse, *J. Chem. Soc. C*, 1362 (1968); (b) D. N. Jones, M. J. Green, and R. D. Whitehouse, *ibid.*, 1166 (1969); (c) D. N. Jones, E. Helmy, and A. C. F. Edmonds, *ibid.*, 833 (1970).
(23) A. H. Haines and C. S. P. Jenkins, *Chem. Commun.*, 350 (1969).
(24) O. Korver, *Tetrahedron*, **26**, 2391 (1970).
(25) Y. Kashman and S. Cherkez, *Tetrahedron*, **28**, 1211 (1972).
(26) R. Nagarajan, B. H. Cholar, and R. M. Dodson, *Chem. Commun.*, 550 (1967).
(27) R. W. Ohline, A. L. Allred, and F. G. Bordwell, *J. Amer. Chem. Soc.*, **86**, 4641 (1964).
(28) C. H. Green and D. G. Hellier, *J. Chem. Soc., Perkin Trans. 2*, 243 (1973).
(29) (a) D. G. Hellier, J. G. Tillett, H. F. van Woerden, and R. F. M. White, *Chem. Ind. (London)*, 1956 (1963); (b) C. Altona, H. J. Geise, and C. Romers, *Recl. Trav. Chim. Pays-Bas*, **85**, 1197 (1966); (c) G. Ecclestone, P. C. Hamblin, R. A. Pethrick, R. F. M. White, and E. Wyn-Jones, *Trans. Faraday Soc.*, **66**, 310 (1970); (d) C. H. Greene and D. G. Hellier, *J. Chem. Soc., Perkin Trans. 2*, 458 (1972).
(30) A suggestion that the similarity of the skew forms of the ring in *cis*- and *trans*-**1c** might be responsible for the similarity in their dichroic absorptions, put forward by the referee, cannot be ruled out.
(31) G. Wood and M. Miskow, *Tetrahedron Lett.*, 1775 (1970).
(32) S. Sarel and Y. Shalon, unpublished results.
(33) Y. Shalon, Y. Yanuka, and S. Sarel, *Tetrahedron Lett.*, 957 (1969).
(34) D. G. Neilson, U. Zakir, and C. M. Scrimgeour, *J. Chem. Soc. C*, 898 (1971).
(35) B. A. Chaudri, D. G. Goodwin, H. R. Hudson, L. Bartlett, and P. M. Scopes, *J. Chem. Soc. C*, 1329 (1970).
(36) R. C. Cookson, G. H. Cooper, and J. Hudec, *J. Chem. Soc. B*, 1004 (1967).
(37) P. Felt, *J. Med. Chem.*, **7**, 14 (1964).
(38) J. Plattner and H. Rappoport, *J. Amer. Chem. Soc.*, **93**, 1758 (1971).
(39) H. A. Staab and G. Walther, *Justus Liebigs Ann. Chem.*, **657**, 98 (1962).
(40) S. Sarel, L. A. Pohoryles, and R. Ben Shoshan, *J. Org. Chem.*, **24**, 1873 (1959).
(41) H. H. Szmant and W. Emerson, *J. Amer. Chem. Soc.*, **78**, 454 (1956).
(42) J. G. Pritchard and P. C. Lauterbur, *J. Amer. Chem. Soc.*, **83**, 2105 (1961).
(43) L. A. Paquette and R. W. Houser, *J. Amer. Chem. Soc.*, **93**, 944 (1971).

Synthesis of Macrocyclic Polythiaethers[1]

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Macrocyclic polythiaethers have been synthesized and some of their properties have been determined. The compounds reported comprise a homologous series containing two, four, or six sulfur atoms in the macrocyclic ring. One example of a five sulfur atom macrocyclic is included. The synthetic methods allow for symmetrical or unsymmetrical bridging of the ring sulfur atoms by ethylene, tri-, tetra-, penta-, and hexamethylene bridges. These methods are contrasted to previously reported methods for macrocyclic polyoxaether and mixed polyoxa–polythiaether synthesis.

The preparation and properties of numerous macrocyclic polyoxaethers have been previously reported.[2] In addition, a limited number of macrocyclic polythiaethers[3,4] and mixed azo-oxa-thia macrocyclic[2b,3a] and macrobicyclic[5] polyethers containing four or more sulfur atoms in the macrocyclic ring have been described.

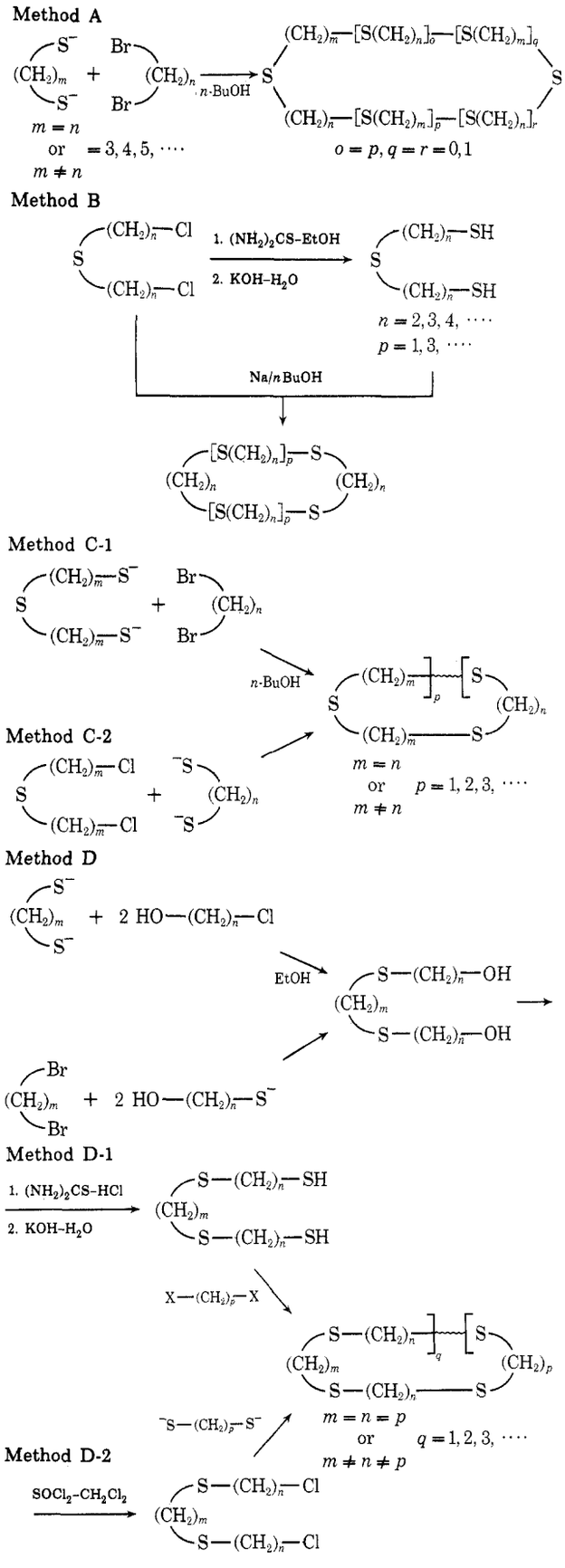
The macrocyclic polyoxaethers have generated particular interest through stable complex formation with cations of the alkali and alkaline earths, ammonium, and silver.[2,6] As model compounds, they have allowed extensive thermodynamic correlations to structurally related macrocyclics, both biological and synthetic in origin, which exhibit varying degrees of biological activity in the processes of active ion transport.[7] Relative to the oxaethers, the thia and mixed oxa–thia macrocyclics exhibit lower selectivity and coordinatability of active metal ions.[2c,6] To date, macrocyclic polythiaethers have not been given consideration as possible ion transport agents owing to their less discriminating coordination chemistry and lack of defined biologically related macrocyclics. However, in the absence of other ring heteroatoms, macrocyclic polythiaethers exhibit substantial coordinatability[3a,5] and selectivity[1,8] toward posttransitional element cations in agreement with hard and soft acids and bases theory.[9] On the basis of the established correlations between biological activity and macrocyclic structure,[7,10] more detailed selectivity and coordinatability studies and chemotherapeutic evaluations of macrocyclic polythiaethers, as related to purging of Hg(II) from test animals, are presently in progress in our laboratories. The scope and purpose of this paper is to report on the convenient preparation of a series of new and some previously reported macrocyclic polythiaethers containing no azo- or oxaether functionality which may be exploited for other than active metal coordination chemistry.

Results and Discussion

A search of the literature has disclosed only several references to macrocyclic polythiaethers containing four or more sulfur atoms. With the exception of thioformaldehyde polymerization,[11] all other methods of thiaether ring closure were based on α-mercaptide displacement of an ω-halide function. The α-mercapto-ω-halopolythiamethylene intermediates are available only by *in situ* generation from condensation of α,ω-dihaloalkanes with active metal sulfide,[4a] α,ω-polymethylene dimercaptides,[4b] or precondensed α,ω-polythiapolymethylene dimercaptides.[3]

Unlike the strong template effect and corresponding high yields of macrocyclic polyoxaethers offered by oxygen coordination of alkali metal ion during cyclization of polyoxa units,[2,12] low sulfur-active metal ion coordination renders template effects of little consequence. Thus, the competition between cyclization and predominant linear polymerization is more statistically defined, entropy constraints of cyclization favoring linear polymerization whereas high dilution favors cyclization kinetically.[13] However, no prior study has elaborated the specific factors effecting relative distribution of cyclic products for the present reaction. By the methods outlined in Scheme

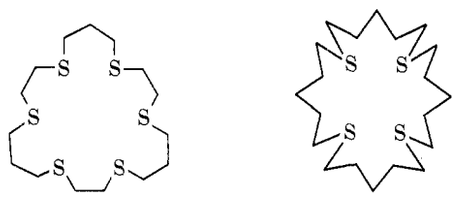
Scheme I



I, we have defined these factors and have refined practical synthetic routes to macrocyclic polythiaethers, particularly those of greater than trimethylene bridges.

Table I summarizes the macrocyclics isolated. Significantly, only two examples of macrocyclic hexathiaethers had been previously reported.[3a,4b] Since many of these polythiaethers have very cumbersome names, the proposed abbreviated nomenclature in Table I is designed to impart some of the salient structural formula features during repeated reference.[14] The terms of the trivial name in Chart I refer, in order, to (1) the number of sulfur atoms contained in the cyclic structure, (2) consecutive sequence of polymethylene bridging between sulfur atoms found as a repeated unit, and (3) total number of atoms comprising the polythiaether ring.

Chart I
Relation of the Trivial Name to Structure



7
S_6-Ethano-Propano-21

15
S_4-Pentano-24

In the absence of template effects, the entropy of cyclization may be considered to parallel the enthalpy of the end product and a relative assessment of these thermodynamic factors is provided by cyclic product distribution obtained by method A, Scheme I. Table II summarizes product ratios of two-sulfur codimerization to four- and six-sulfur copolymerization cyclic products at conditions experimentally optimized to favor cyclization kinetically.

Method A is most suitable for the preparation of tetra- and pentamethylene-bridged macrocyclic tetrathia- and hexathiaethers and may be disregarded as a method for the large ethylene- or trimethylene-bridged rings. The S_4/S_2 product ratios are in agreement with internal ring strain, which is at a minimum for 6, 14, and greater than 17 polymethylene rings.[15] With inclusion of two through four sulfur atoms, internal crowding would minimize ring strain in the 9- through 13-ring atom systems.[16] The entropy constraints of cyclization appear to converge with the kinetics of linear polymerization at macrocyclic polythiaethers of greater than approximately 24 ring atoms.

In order to avoid six- and seven-membered ring formation by method A in the ethylene- and trimethylene-bridged system, and to improve the overall kinetics of cyclization, methods B–E were investigated. Cyclization of the minimum number of precondensed polythia units would exclude two sulfur medium-ring products. Methods B and D should yield rings containing even numbers of sulfur atoms, whereas methods C and E could yield both odd and even sulfur atom numbers.

Method C-1 has been utilized previously for the synthesis of S_6-ethano-18 (3).[3a,4b] We have reinvestigated method C-1 and devised alternative method C-2 with results tabulated in Table III. Although identical products are isolated, total conversion to cyclic products and product distribution differs as a function of halide group leaving ability, bromide (28.9%) *vs.* chloride (15.2%). The unexpected and previously unreported formation of 1 and 2 can be rationalized in terms of cyclic sulfonium ion formation[17] (Scheme II) by means of chain-interior thia displacement of an ω-halo group from the linear intermediates.

Sulfonium ion formation should be more favored in polar media. Accordingly, 1 to 3 product ratios of 2:1 and 5:1 were found respectively in 1-butanol and ethanol media. Parallel leaving group and solvent effects were also

Table I
Code Numbers and Systematic and Trivial Nomenclature of Cyclic Polythiaethers

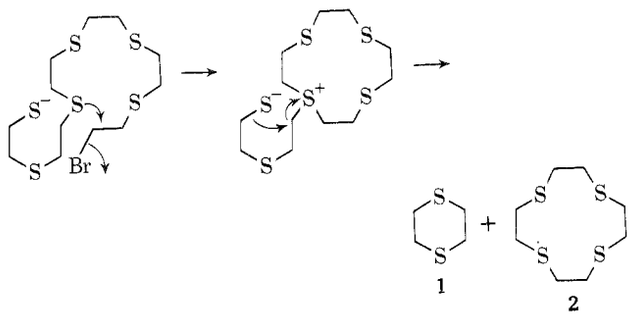
Compd	Systematic name	Trivial name
1	*p*-Dithiane	S_2-Ethano-6
2	1,4,7,10-Tetrathiacyclododecane	S_4-Ethano-12
3	1,4,7,10,13,16-Hexathiacyclooctadecane	S_6-Ethano-18
4	1,4,7,10,13-Pentathiacyclopentadecane	S_5-Ethano-15
5	1,4-Dithiepane	S_2-Ethano-Propano-7
6	1,4,8,11-Tetrathiacyclotetradecane	S_4-Ethano-Propano-14
7	1,4,8,11,15,18-Hexathiacycloheneicosane	S_6-Ethano-Propano-21
8	1,5-Dithiocane	S_2-Propano-8
9	1,5,9,13-Tetrathiacyclohexadecane	S_4-Propano-16
10	1,5,9,13,17,21-Hexathiacyclotetracosane	S_6-Propano-24
11	1,6-Dithiacyclodecane	S_2-Butano-10
12	1,6,11,16-Tetrathiacycloeicosane	S_4-Butano-20
13	1,6,11,16,21,26-Hexathiacyclotriacontane	S_6-Butano-30
14	1,7-Dithiacyclododecane	S_2-Pentano-12
15	1,7,13,19-Tetrathiacyclotetracosane	S_4-Pentano-24
16	1,7,13,19,25,31-Hexathiacyclohexatriacontane	S_6-Pentano-36
17	1,8-Dithiacyclotetradecane	S_2-Hexano-14
18	1,8,15,22-Tetrathiacyclooctacosane	S_4-Hexano-28
19	1,8,15,22,29,36-Hexathiacyclodotetracontane	S_6-Hexano-42

Table II
Product Ratios of Four- and Six-Sulfur to Two-Sulfur Cyclothiaether Products by Method A

Bridge size	Ring size: Compd S_2	Compd S_4	Compd S_6	Product ratios[a,b]: S_6/S_2	S_4/S_2
Ethylene	6	12	18	0.065	0.0069
Ethylene–Trimethylene[c]	7	14	21	0.277	0.284
Trimethylene	8	16	24	0.850	1.19
Tetramethylene	10	20	30	1.05	2.02
Pentamethylene	12	24	36	1.21	7.00
Hexamethylene	14	28	42	1.16	0.867

[a] Based on quantitative separation and recovery, subpreparative scale, utilizing liquid–liquid chromatography. [b] α,ω-Dimercaptide, 0.2 *M* in 1-butanol at room temperature, α,ω-dibromide, 1 *M* in 1-butanol, 3 ml/min addition rate. [c] From ethanedithiol and 1,3-dibromopropane reactants.

Scheme II
Intrachain Cyclization



observed *via* method D for the mixed ethylene–trimethylene rings: **5** was isolated in 13.6% yield in addition to 12.6% of **6**. Consistent with lesser nucleophilic character of the oxa relative to the thia function, and further nucleophilic deactivation of the former by alkali metal ion coordination and resulting template effects, intrachain cyclization does not appear to intervene in macrocyclic polyoxaether synthesis.[2] Since the anticipated yield[3a] of **3** could not be attained even at extreme dilution by method C, method F, Scheme III, was devised.

Method F minimizes intrachain cyclization by appropriate choice of chloride leaving group and solvent polarity, thus yielding **3** as the smallest ring product from normal cyclization of reactants **21** and **23**. The method offers

Table III
Product Distribution for Ethylene-Bridged Cyclopolythiaethers *via* C Methods[a]

Product[b]	Yield, %: Method C-1	Method C-2
1	16.0	8.1
2	4.8	1.2
3	8.1[c,d]	5.9
Linear polymer and larger rings	64.0	78.0

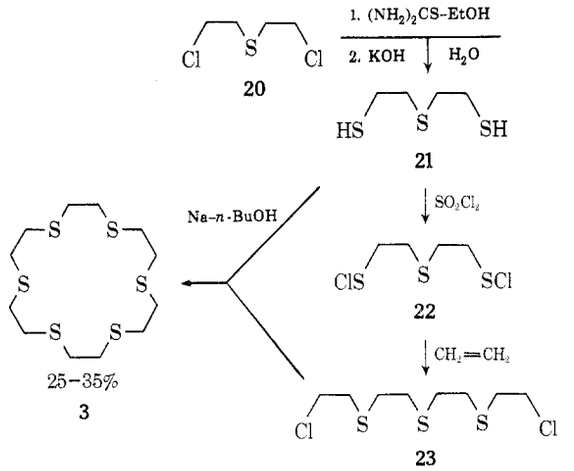
[a] Based on liquid–liquid chromatography isolation. [b] No 1,4,7-trithiacyclononane was observed by methods C-1 or C-2. [c] A 31% yield reported under identical conditions.[3a] [d] A 1.7% yield reported in ethanol media.[4b]

greatly simplified bulk isolation of **3** by liquid–liquid chromatography owing to virtual elimination of smaller ring products. However, the commercially unavailable intermediates, **21**, **22**, and **23**, are *potent vesicants* which require extreme care in handling.

Scheme III

Method F

$SCl_2 + CH_2{=}CH_2 \longrightarrow$



Some optimized yields of macrocyclic polythiaethers synthesized by the methods outlined in Schemes I and II are summarized in Table IV. Only representative examples are cited. All methods of Scheme III are of general utility by adapting procedures outlined in the Experimental Section.

Table IV
Macrocyclic Polythiaethers Isolated by Liquid–Liquid Chromatography

Compd[a]	Mp, °C[b]	Method	Elution solvent[c]	Yield, %[d]
2	224–225	B	Methylene chloride	6.3[e]
3	91–93	A	10:90 ethyl acetate–hexane	0.8
		C-1		8.1[f]
		C-2		21.7
		F		35.0
4	97.5–99	E (B + D-2)	20:80 ethyl acetate–hexane	11.0
5	47–49	A	5:95 ethyl acetate–hexane	16.2[g]
6	121–122.5	A		4.6
		D-2		22.1[h]
7	64–65	A	5:95 ethyl acetate–hexane	0.5
		D (D-1 + D-2)		9.7
8	bp 86–87 (1 Torr)	A	5:95 ethyl acetate–hexane	5.2[g]
9	57.5–59	A	5:95 ethyl acetate–hexane	6.2
		D-2		19.5
10	29–30	A	5:95 ethyl acetate–hexane	7.3
		C-2		15.1
11	94–95.5	A	1:99 ethyl acetate–hexane	1.9[g]
12	31–32	A	1:99 ethyl acetate–hexane	3.9[i]
13	67–70	A	Hexane	1.7
14	81–82.5	A	Pentane	0.8
15	33–33.5	A	50:50 pentane–hexane	5.3
		D-1		3.6
16	36.5–38	A	50:50 pentane–hexane	6.8
17	77–78	A	Pentane	1.4[g]
18	30–32	A	Pentane	3.9
19	56–59.5	A	Pentane	3.2

[a] Proof of structure based on acceptable elemental analysis and molecular weight measurements in solution, and consistent nmr and infrared spectra. [b] Uncorrected Thomas-Hoover capillary melting point values. [c] Volume ratios. [d] Based on the polymerization process, representing in hand-multigram quantities of analytical grade material. [e] Reference 3c reported 4% yield. [f] Reference 3a reported 31% yield. [g] By-product of S_4 and S_8 macrocyclics *via* method A. [h] Reference 3d reported 7.5% yield. [i] A 19.7% yield was obtained on a small reaction scale by simultaneous addition of reactants to a bulk diluting solution; effective concentration of reactants below *ca.* 10^{-3} *M*.

Conclusions

The use of chloro leaving groups and low solvent polarity favored larger rings within total cyclic product. However, cyclic to linear product conversion was more favorable with a bromo leaving group. Under the former conditions, a number of eight-sulfur macrocyclics were isolated by methods C and D, although no quantitative or optimization attempts were made to isolate rings of greater than six sulfurs. For ring systems containing larger than propane bridging, formation of two-sulfur cyclic products is less favored than larger cyclic products owing to ring constraints. Thus, methods of greater synthetic complexity than method A would not generally justify the slightly improved yields of cyclic product. However, method A gives rise to complications during attempted isolation of pure products owing to similarity in physical properties of mixture components. Moreover, odd sulfur atom numbered rings are available only by method E.

Experimental Section

General. Nuclear magnetic resonance (nmr) spectra were obtained on a Varian Associates T-60 spectrometer with tetramethylsilane as internal reference. Infrared (ir) spectra were recorded on either a Beckman IR-8 or a Perkin-Elmer 727. Molecular weights were determined with a Hitachi Perkin-Elmer 115 vapor pressure osmometer and compared to values obtained by manual cryoscopic determinations based on colligative freezing point depression of purified solvents. Optimum chromatographic solvents were established on microanalytical air-dried tlc plates prepared by immersion coating in a chloroform suspension of Merck silica gel H (neutral). Iodine vapor was used for spot development. Preparative column chromatography was carried out on Baker Analyzed silica gel (60–200 mesh). Crystallization and chromatographic elution solvent mixtures are volume ratios.

Intermediate Reactants. When not obtained from commercial sources, α,ω-dibromoalkanes were prepared from the corresponding α,ω-dihydroxyalkanes by reaction with 48% hydrobromic acid according to a modification of the procedure by Kamm and Marvel.[18]

Generation of α,ω-bisisothiuronium bromides from the corresponding α,ω-dibromoalkanes and subsequent hydrolysis by a modification of the procedure as described by Speziole[19] yielded simple α,ω-dimercaptoalkanes. Hydrolysis of α,ω-bisisothiuronium chlorides prepared in like fashion from α,ω-dichloroalkyl sulfides (**20**) yielded α,ω-dimercaptoalkyl sulfides (**21**). Alternatively, α,ω-dihydroxyalkyl sulfides (3,7-dithianonane-1,9-diol) were converted directly to the dithiols by *in situ* generation and hydrolysis of α,ω-bisisothiuronium chlorides according to the procedure described by Rosen and Busch.[3b] All three methods are of general utility, affording preparative yields of α,ω-dimercaptoalkanes in excess of 50%.

Simple α,ω-disulfenyl chlorides, as well as α,ω-dichlorosulfenylalkyl sulfides (**22**), were prepared from the corresponding dithiols by a modification of the procedure according to Mueller and Dines.[20]

α,ω-Dichloroalkyl sulfides were prepared by two general methods. β-Chloroethyl sulfides (**23**) were prepared by reaction of the α,ω-disulfenyl chlorides with ethylene by a modification of the procedure according to Brintzinger, *et al.*[21] The preparation of 1,5-dichloro-3-thiapentane (**20**) from ethylene and sulfur dichloride is an extension of this procedure.[22] The alternative method involves reaction of α,ω-dihydroxyalkyl sulfides with thionyl chloride by a modification of the procedure according to Bennett and Whincap.[23] Extreme vesicant properties were observed for all halo sulfides prepared.

Preparation of 1,4,7,10-Tetrathiacyclododecane (2). Method B. To a sodium butoxide solution, generated and maintained under a nitrogen atmosphere by dissolving sodium (2.2 mol) in 2 l. of 1-butanol, was added 154 g (1 mol) of 3-thiapentane-1,5-dithiol (**21**). The solution was equilibrated for 1 hr and cooled to 5° and 168 g (1 mol) of 1,5-dichloro-3-thiapentane was added all at once. The reaction was stirred below 10° for the first 2 hr, then at room temperature for an additional 16 hr. The solution was filtered, the filtrate was concentrated, and the oil residue was taken up in 1 l. of chloroform, washed with 0.5 l. of water, and dried with magnesium sulfate. The filter cake was vigorously stirred with 3 l. of water to dissolve salts. Insoluble solids were recovered by filtration, air dried, and combined with the chloroform solution of filtrate residue. The chloroform mixture was refluxed for 2 hr and filtered hot and insolubles were discarded. The solvent was vacuum evaporated and the residue was leached under reflux

with 5 × 100 ml of 5:95 ethyl acetate–hexane. The leachings contained traces of **1**, **4**, and higher polymers. The residue containing **2** was refluxed for 1 hr with 130 ml of methylene chloride. From the cooled methylene chloride filtrate was recovered 15.1 g (6.3%) of **2** (S_4-Ethano-12) as a fine, white, granular product.

Preparation of 1,4,7,10,13,16-Hexathiacyclooctadecane (3). Method C-1. Dimercaptide **21** (61.7 g, 0.40 mol) was converted to the disodium salt in the usual fashion in 0.5 l. of 1-butanol. This solution was added simultaneously over 2.5 hr, with the dropwise addition of ethylene bromide (75.2 g, 0.4 mol) in 0.5 l. of 1-butanol, to 2 l. of 1-butanol under nitrogen. The reaction was maintained below 10° for the first 10 hr, then stirred at room temperature for 36 hr. The solution was filtered and the filtrate was concentrated under vacuum while the filter cake was treated with 2 l. of water. The filtrate residue and air-dried, salt-free solids were extracted with 6 × 400 ml of refluxing pentane. The combined extracts were concentrated, and the residue was taken up in 0.5 l. of methylene chloride, washed with 300 ml of 5% potassium hydroxide, dried with magnesium sulfate, and reconcentrated to a thick, oily mass of 53.8 g. The mixture was eluted through a silica gel column with 30:70 ethyl acetate–hexane to remove immobile polymers and reconcentrated to 32.2 g of residue. The residue was rechromatographed on silica gel. Elution with 280 ml of pentane yielded 7.65 g (16%) of **1**, followed by elution of **3** with 600 ml of 10:90 ethyl acetate–hexane. Crude **3** was recrystallized from 5:95 ethyl acetate–hexane, yielding 5.78 g (8.1%) of **3** (S_6-Ethano-18) as a single crop of white crystals. From the pentane extraction residue was recovered 4.60 g (4.8%) of **2** according to the procedure for **2**, method B.

Method C-2. Solutions of **20** (58.9 g, 0.37 mol) dissolved in 0.5 l. of 1-butanol and the disodium salt of 1,2-ethanedithiol, 34.8 g (0.37 mol) of dimercaptan treated with butoxide in 0.5 l. of 1-butanol in the usual fashion, were simultaneously added dropwise to 2 l. of 1-butanol under nitrogen over 2.5 hr below 10°. After stirring at room temperature for an additional 36 hr, products were isolated in identical fashion with method C-1. The final chromatographic elution yielded 3.60 g (8.1%) of crude **1** and 14.43 g (21.7%) of **3** after recrystallization of the crude elution product, and 1.15 g (1.2%) of **2** was recovered from extraction residues.

Method F. Dimercaptan **21** (30.8 g, 0.2 mol) was converted to the disodium salt in 2 l. of 1-butanol in the usual fashion. To the solution was added all at once 45.8 g (0.2 mol) dichloride **23** and the reaction mixture was stirred below 25° for 48 hr. Products were separated according to the procedures in method C-1. Only 0.15 g (0.6%) of crude **1** was isolated, while recrystallization of the crude column concentrates of **3** yielded 11.7 g (32.8%) of analytical product.

Preparation of 1,4,7,10,13-Pentathiacyclopentadecane (4). Method E (B + D-2). 1,8-Dichloro-3,6-dithiaoctane (50.4 g, 0.23 mol), prepared in 83% yield from the reaction of ethylene with 1,2-ethanedisulfenyl chloride[21] or in 96% yield from 3,6-dithiaoctane-1,8-diol reaction with thionyl chloride,[23] was dissolved in 400 ml of 50:50 ether–1-butanol. Dimercaptan **21** (35.5 g, 0.23 ml) was converted to the disodium salt in 400 ml of 1-butanol in the usual fashion. The two solutions were simultaneously added dropwise over 2.5 hr to 2.2 l. of 1-butanol at 60° under nitrogen. The reaction mixture was stirred for an additional 15 hr at 60° and cooled and solids were separated by filtration. The filtrate was concentrated under vacuum, while the filter cake was treated with 2 l. of water to dissolve salts. The combined residues were extracted with 5 × 300 ml of refluxing hexane. The combined extracts were concentrated, taken up in 300 ml of methylene chloride, washed with 5% potassium hydroxide, dried with magnesium sulfate, and reconcentrated. The oily residue was eluted through a silica gel column to remove immobile polymers with 50:50 ethyl acetate–hexane, then rechromatographed with 20:80 ethyl acetate–hexane to yield traces of **1** and **2** and a concentrated band of **4**. The crude **4** (S_5-Ethano-15), recrystallized from 10:90 ethyl acetate–hexane, yielded 7.59 g (11%) of fine white crystals in a single analytical batch.

Preparation of 1,4,8,11-Tetrathiacyclotetradecane (6). Method D-2. 1,9-Dichloro-3,7-dithianonane was prepared from 3,7-dithianonane-1,9-diol[3b] by the general method previously described.[23] The dichloride (69.9 g, 0.3 mol) was dissolved in 400 ml of anhydrous ether and added simultaneously with a 400-ml 1-butanol solution of 1,3-propanediol disodium salt (0.3 mol) to 0.5 l. of 1-butanol under nitrogen over 6 hr at room temperature. After 12 hr, the reaction mixture was filtered, the filtrate was concentrated, and the filter cake was treated with water. The salt-free filter cake residues were extracted with 300 ml of cold ethylene chloride and the extracts were combined with the original filtrate residue. The solution was washed with two 200-ml portions of 5% sodium hydroxide, dried with anhydrous sodium sulfate, and reconcentrated to yield 34.1 g of paste residue. The residue was eluted with ethyl acetate through a silica gel column to remove immobile polymers, then rechromatographed with 5:95 ethyl acetate–hexane to yield a trace (0.08 g) of **5** as the first eluent. Recrystallization from 10:80 ether–hexane of subsequent crude column concentrates yielded 17.8 g (22.1%) of **6** (S_4-Ethano-Propano-14) as a single crop of white crystals.

Preparation of 1,4,8,11,15,18-Hexathiacycloheneicosane (7). Method D (D-1 + D-2). Condensation intermediates, 3,7-dithianonane-1,9-dithiol and 1,10-dichloro-4,7-dithiadecane, were prepared from the corresponding diols as previously illustrated. The α,ω-dichloro precursor was prepared from 1,2-ethanedithiol disodium salt and 3-chloropropanol (Aldrich). In identical fashion with the preparation of **6** (method D-2), 400-ml solutions of 68.4 g (0.3 mol) of dithiol disodium salt and 73.8 g (0.3 mol) of dichloride were simultaneously added to 0.5 l. of 1-butanol. Following 16 hr of reaction, crude product was concentrated according to the procedure for **6**. This residue (95.4 g) was eluted with 30:70 ethyl acetate–hexane through a silica gel column to remove immobile polymers, then rechromatographed with 5:95 ethyl acetate–hexane. In order were recovered a small amount (0.34 g) of **5**, a trace (0.02 g) of **6**, and 11.7 g (9.7%) of **7** (S_6-Ethano-Propano-21) as a single crop of white crystals, the latter by crystallization of elution concentrates from 5:95 ether–hexane.

Preparation of 1,6,11,16-Tetrathiacycloeicosane (12) and Isolation of By-products 11 and 13. Method A. In 3.5 l. of 50:50 ethanol–1-butanol, 161 g (1.32 mol) of 1,4-butanedithiol was converted to the disodium salt. To the cooled solution was added all at once 282 g (1.32 mol) of 1,4-dibromobutane under nitrogen. The reaction mixture was stirred for 3 hr below 15°, then for an additional 14 hr at 50°. Products of interest (**11**, **12**, and **13**) were concentrated by combining filtrate oil residue with four 500-ml ether extracts of the filter cake residue. This solution was washed with three 500-ml portions of 10% potassium hydroxide, dried with sodium sulfate, and reconcentrated to 42.6 g of paste. Higher polymers were removed by elution through a silica gel column with 10:90 ether–hexane. Complete separation of components in order of ring size, **11** first, was achieved by rechromatographing with 1:99 ethyl acetate–hexane. Recrystallization of aliquot concentrates yielded 4.50 g (1.9%) of **11** (S_2-Butano-10) and 6.00 g (1.7%) of **13** (S_6-Butano-30) from hexane, and 8.99 g (3.9%) of **12** (S_4-Butano-20) from pentane. Products **11** and **12** were isolated as fine white needles, and **13** as a white powder.

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Registry No.—**1**, 505-29-3; **2**, 25423-56-7; **3**, 296-41-3; **4**, 36338-04-2; **5**, 6008-55-5; **6**, 24194-61-4; **7**, 51540-11-5; **8**, 6572-95-8; **9**, 295-91-0; **10**, 51472-63-0; **11**, 51472-64-1; **12**, 51472-65-2; **13**, 51472-66-3; **14**, 51472-67-4; **15**, 51472-68-5; **16**, 51472-69-6; **17**, 295-32-9; **18**, 51472-70-9; **19**, 51472-71-0; **20**, 505-60-2; **21**, 3570-55-6; **22**, 51472-72-1; **23**, 51472-73-2.

Supplementary Material Available. Tables V and VI, listing literature references to physical constants, elemental analysis and molecular weight data, and more detailed experimental, chromatographic, intermediate, and duplicate synthesis examples, will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2079.

References and Notes

(1) (a) Taken in part from the M.S. Thesis of J. D. Michna, University of Wisconsin—Eau Claire, 1972. (b) Supported in part by the Research Corporation, Cottrell Award to L. A. Ochrymowycz, 1971–1973.

(2) (a) C. J. Pedersen, *J. Amer. Chem. Soc.*, **89**, 2495, 7017 (1967); **92**, 386, 391 (1970); (b) C. J. Pedersen, *Fed. Proc., Fed. Amer.*

Soc. Exp. Biol., 27, 1305 (1968); (c) C. J. Pedersen, J. Org. Chem., 36, 254, 1690 (1971); N. S. Poonia, J. Amer. Chem. Soc., 96, 1012 (1974).
(3) (a) D. St. C. Black and I. A. McLean, Tetrahedron Lett., 3961 (1969); (b) W. Rosen and D. H. Busch, J. Amer. Chem. Soc., 91, 4694 (1969); (c) W. Rosen and D. H. Busch, Inorg. Chem., 9, 262 (1970); (d) L. F. Linday and D. H. Busch, J. Amer. Chem. Soc., 91, 4690 (1969).
(4) (a) N. B. Tucker and E. E. Reid, J. Amer. Chem. Soc., 55, 775 (1933); (b) S. R. Meadow and E. E. Reid, ibid., 56, 2177 (1934).
(5) (a) B. Dietrich, J. M. Lehn, and J. P. Sauvage, Chem. Commun., 1055 (1970); 440 (1971); (b) Tetrahedron Lett., 2990 (1969).
(6) H. K. Freusdorff, J. Amer. Chem. Soc., 93, 600 (1971).
(7) (a) R. M. Izatt, J. H. Rytting, D. P. Nelson, B. L. Haymore, and J. J. Christensen, Science, 164, 44 (1969); (b) G. Eisenman, S. M. Ciani, and G. Szobo, Fed. Proc., Fed. Amer. Soc. Exp. Biol., 27, 1289 (1968); (c) B. C. Pressman, ibid., 27, 1283 (1968); (d) L. Lardy, ibid., 27, 1278 (1968); (e) A. Thore, D. L. Keister, N. Shani, and A. San Pietro, Biochemistry, 7, 3499 (1968).
(8) L. A. Ochrymowycz and J. M. Michna, unpublished results.
(9) R. G. Pearson, J. Amer. Chem. Soc., 85, 3533 (1963); 89, 1827 (1967).
(10) (a) B. T. Kilbourn, J. D. Dussitz, L. A. R. Pioda, and W. Simon, J. Mol. Biol., 30, 559 (1967); (b) V. T. Ivanov, I. A. Laine, N. D. Abduleav, L. B. Senyavina, E. M. Popov, Y. A. Ovchinnikov, and M. M. Shemyakin, Biochem. Biophys. Res. Commun., 38, 803 (1969).
(11) M. Russo, L. Mortillaro, L. Credali, and C. de Checchi, Polym. Lett., 3, 455 (1965).
(12) J. L. Down, J. Lewis, B. Moore, and G. Wilkinson, J. Chem. Soc., 3767 (1959).
(13) W. H. Carothers, J. Amer. Chem. Soc., 51, 2548, 2560, (1929); 52, 314, 711, 3292 (1930); 54, 1559, 1566, 1569, 1579 (1932); 55, 5023, 5031 (1933); Chem. Rev., 8, 353 (1931).
(14) The proposed nomenclature supplements the abbreviated nomenclature introduced by Rosen and Busch[3] and Pedersen's "oxycrown" nomenclature.[2a]
(15) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 188.
(16) (a) E. L. Eliel, N. L. Albinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965; (b) H. R. Allcock, "Heteroatom Ring Systems and Polymers," Academic Press, New York, N. Y., 1967, Appendix II; (c) G. W. Frank, P. J. Degen, and F. A. L. Anet, J. Amer. Chem. Soc., 94, 4792 (1972).
(17) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 572, and references cited therein.
(18) O. Kamm and C. S. Marvel, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 25.
(19) A. S. Speziole, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 401.
(20) W. H. Mueller and M. Dines, J. Heterocycl. Chem., 6, 627 (1969).
(21) H. Brintzinger, M. Langheck, and H. Ellwanger, Chem. Ber., 87, 320 (1954).
(22) R. C. Fuson, C. C. Price, R. A. Bauman, O. H. Bullitt, W. R. Hatehard, and E. W. Maynert, J. Org. Chem., 11, 469 (1946).
(23) G. M. Bennett and E. M. Whincap, J. Chem. Soc., 1860 (1921).

Intramolecular Aromatic and Aliphatic Ullmann Reactions[1]

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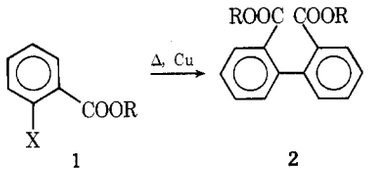
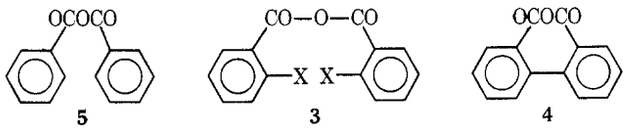
Intramolecular Ullmann cyclizations of several *o*-halobenzoic anhydrides have been shown to take place in high yields at temperatures near 60–70° in tetramethylethylenediamine (TMEDA), dimethylformamide (DMF), *N*-methylpyrrolidone (NMP), hexamethylphosphoramide (HMPA), and pyridine. In all cases except that of pyridine, appreciable (10–30%) to large (50–82%) amounts of reduction products accompany the coupling product. The coupling of aliphatic α-bromo-unsaturated anhydrides under comparable conditions has also been demonstrated.

The Ullmann coupling of 2-halo esters, **1**, to dialkyl diphenates, **2**, has often been effected.[3] In general the reaction has been carried out by long heating with copper at temperatures over 200°. We wished to find out if this type of reaction could be carried out under milder conditions than usual by changing the reaction from an intermolecular to an intramolecular type. In one case tried here earlier the synthesis of 6,6′-diethyldiphenic acid was markedly better when 3-ethyl-2-iodobenzoic anhydride was used instead of methyl 3-ethyl-2-iodobenzoate.[4] A few isolated cases in which intramolecular Ullmann reactions were tried are mentioned[3] but little study of this type of ring closure has been made. We had hoped that the synthesis of unsymmetrical diphenic acids might be improved by the use of unsymmetrical halo anhydrides, but this hope was not fully realized (see later, below).



1 2

We have found out that Ullmann reactions are carried out much more easily if anhydrides are used instead of halo esters. Two general types of reactions have been studied: method A, in which the 2-halobenzoic acid anhydrides, **3**, are cyclized to diphenic anhydrides, **4**, in a variety of nitrogenous solvents by heating with copper powder at 60–70°; and method B, in which the anhydrides, **3**, are heated with copper powder in benzene containing catalytic amounts of nitrogenous complexing agents. The complexing agents were chosen with the thought that they might complex with any hypothetical organocopper intermediate which might be involved in the reaction.[5-7] For analysis of the results of most experiments the reaction mixtures were treated with methanol and with diazomethane to convert anhydrides into the corresponding methyl esters.



5 3 4

The choice of solvent is important because the ratio of ring-closed product, a diphenic anhydride, **4**, to reduced product, a benzoic anhydride, **5**, is markedly solvent dependent.

The experiments (method A) which illustrate these points are listed in Table I. In our experience, the best solvent for this type of reaction is pyridine. In 1 hr at 60–70° not only is the starting anhydride almost completely reacted but the ratio of diphenic anhydride to benzoic anhydride formed is greatest (see expt 5, 11, and 17 in Table I). Surprisingly, appreciable to large amounts of reduction product were obtained in all of the other solvents studied.[8] That reduction occurs prior to, and not on, quenching of the reaction mixture with water was shown in the case of 2-bromobenzoic anhydride in tetramethylethylenediamine (TMEDA) by quenching with D_2SO_4 in D_2O.