Heteroatom Chemistry
Volume 1, Number 5, 1990

Synthesis of Mesocyclic and Macrocyclic Polythioethers Using the Cesium Dithiolate Technique[†]

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Received 26 March 1990.

ABSTRACT

The mesocyclic trithioethers, 1,4,7-trithiacyclodecane, 1,4,7-trithiacycloundecane, 1,4,8-trithiacycloundecane, and 1,5,9-trithiacyclododecane; the mesocyclic trithioether ketones, 1,4,7-trithiacyclodecan-9-one; 1,4,8-trithiacycloundecan-6-one, and 1,5,9-trithiacyclododecan-3-one; and the mesocyclic trithioether alcohols, 1,4,7-trithiacyclodecan-9-ol, 1,4,8-trithiacycloundecan-6-ol, and 1,5,9-trithiacyclododecan-3-ol, have been synthesized using the cesium dithiolate technique. In some cases, the corresponding macrocyclic hexathioether was isolated from the reaction mixture in addition to the mesocyclic trithioether; 1,4,7,11,14,17-hexathiacycloeicosane, 1,4,7,11,14,17-hexathiacycloeicosan-9,19-dione, 1,4,7,12,15,18-hexathiacyclodocosane, and 1,5,9,13,17,21-hexathiacyclotetracosane. Single-crystal X-ray structures have been determined for 1,5,9-trithiacyclododecan-3-ol and 1,4,7,12,15,18-hexathiacyclodocosane. For 1,5,9-trithiacyclododecane-3-ol, the compound crystallizes in the monoclinic space group, C2/c, with a = *10.5926(9) Å,* b = *15.582(2) Å,* c = *13.6015(8) Å, β = 98.186(6)°, Z = 8, and* R = *0.038. The macrocycle, 1,4,7,12,15,18-hexathiacyclodocosane, crystallizes in the orthorhombic space group,* Pbca, *with* a = *21.406(5) Å,* b = *9.810(2) Å,* c = *10.225(2) Å, Z = 4, and* R = 0.020.

INTRODUCTION

Mesocyclic (medium-sized-ring) and macrocyclic polythioethers are interesting compounds in terms

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[†] Synthesis and Complexation Studies of Mesocyclic and Macrocyclic Polythioethers V. For Part III, see: W. N. Setzer, E. L. Cacioppo, Q. Guo, G. J. Grant, D. D. Kim, J. L. Hubbard, D. G. VanDerveer, *Inorg. Chem.*, *29*, 1990, 2672; for Part IV, see: W. N. Setzer, Q. Guo, G. J. Grant, J. L. Hubbard, R. S. Glass, D. G. VanDerveer, *Heteroatom Chemistry*, *1*, 1990, 317.

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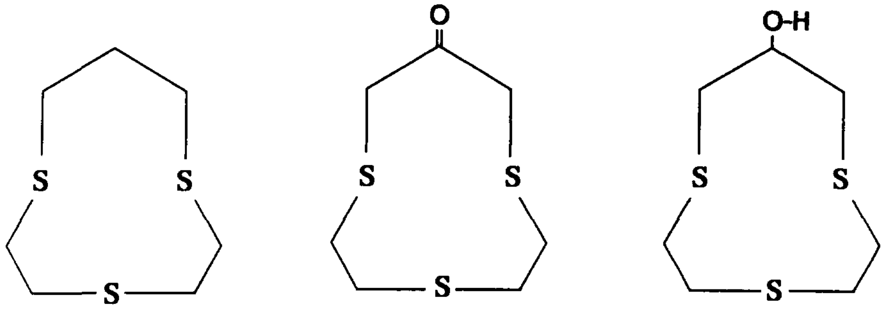
[§] Undergraduate research scholars supported by the Petroleum Research Fund of the American Chemical Society or by Research Corporation.

[||] Undergraduate research scholars supported by the Grote Chemistry Fund; University of Chattanooga Foundation.

1042-7163/90/$3.50 + .25



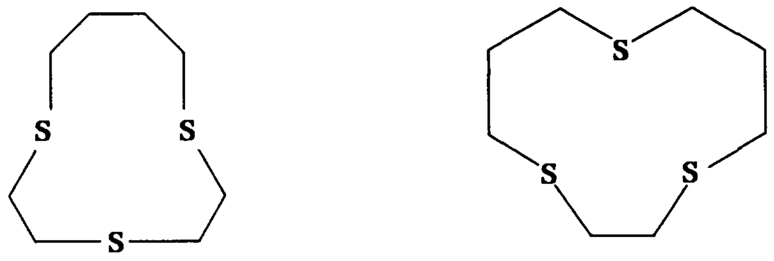
10-ane-S_3 **keto-10-ane-S_3** **hydroxy-10-ane-S_3**

1,4,7-trithiacyclodecane **1,4,7-trithiacyclodecan-9-one** **1,4,7-trithiacyclodecan-9-ol**

SCHEME 1

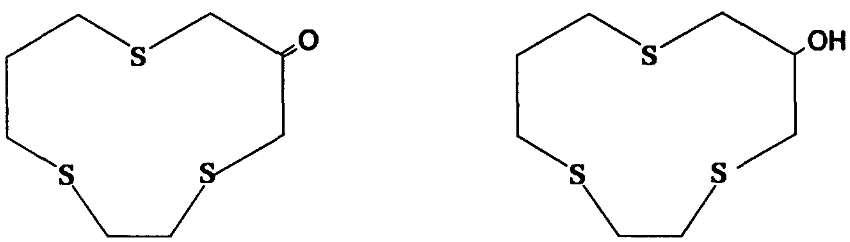
of conformation [1], redox chemistry [2], and transition metal complexation [3]. Until recently, the utility of these heterocyclic materials has been hampered by the generally low yields in their syntheses. The use of cesium salts for the preparation of macrocyclic thioethers, developed by Kellogg and co-workers [4] and extended by Cooper and co-workers to include medium-sized rings as well as macrocycles [5], has vastly improved the yields in the preparation of these compounds.

We have been interested in the effects that structural alterations on mesocyclic and macrocyclic thioether ligands might have on the coordination chemistry of these potential ligands. In addition, our complexation studies required mesocyclic trithioethers and macrocyclic hexathioethers appended with different functional groups. This paper reports the syntheses of a number of mesocyclic and macrocyclic polythioethers using the cesium dithiolate technique [4,5] (Schemes 1–4).



11-ane-S_3-S(1,4,7)
1,4,7-Trithiacycloundecane

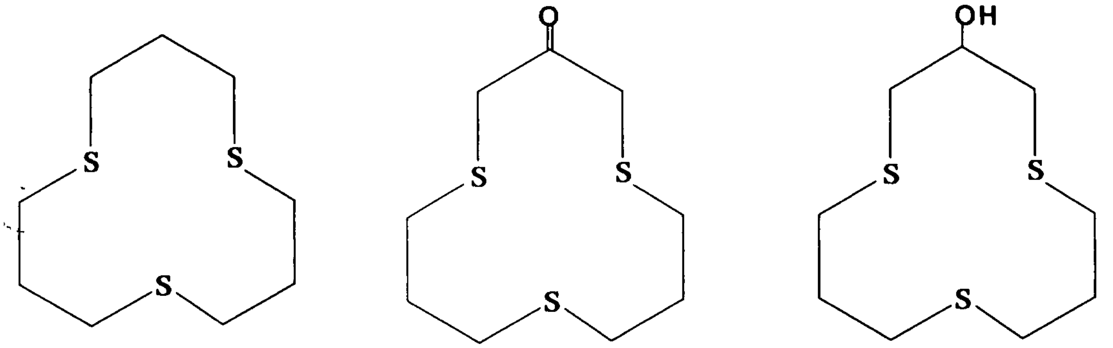
11-ane-S_3-S(1,4,8)
1,4,8-Trithiacycloundecane



keto-11-ane-S_3
1,4,8-Trithiacycloundecan-6-one

hydroxy-11-ane-S_3
1,4,8-Trithiacycloundecan-6-ol

SCHEME 2

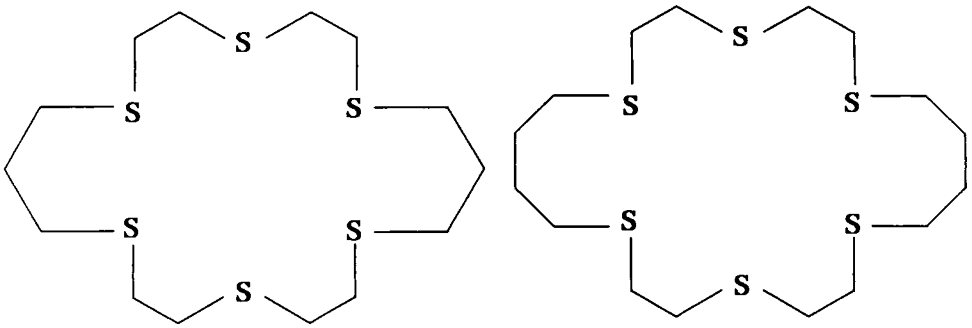


12-ane-S_3
1,5,9-Trithiacyclododecane

keto-12-ane-S_3
1,5,9-Trithiacyclododecan-3-one

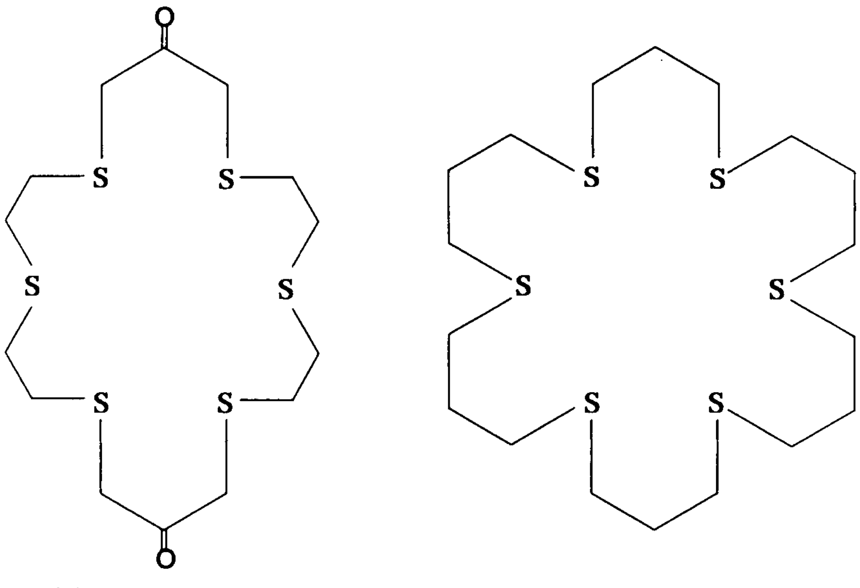
hydroxy-12-ane-S_3
1,5,9-Trithiacyclododecan-3-ol

SCHEME 3



20-ane-S_6
1,4,7,11,14,17-Hexathiacycloeicosane

22-ane-S_6
1,4,7,12,15,18-Hexathiacyclodocosane



diketo-20-ane-S_6
1,4,7,11,14,17-
Hexathiacycloeicosan-9,19-dione

24-ane-S_6
1,5,9,13,17,21-
Hexathiacyclotetracosane

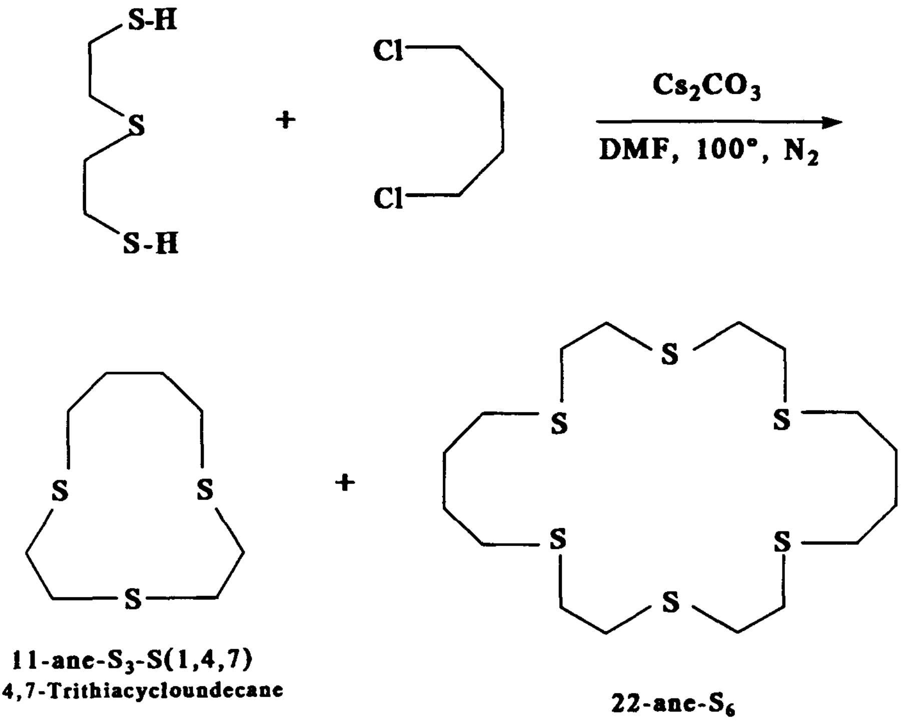
SCHEME 4

RESULTS AND DISCUSSION

The syntheses of the sulfur-containing heterocycles are conveniently carried out under high dilution conditions by slow, simultaneous addition of an alkane dithiol and a dichloroalkane (generally, a dimethylformamide solution containing a 1:1 mixture of the appropriate dithiol and dichloroalkane) to a heated and stirred slurry of cesium carbonate and anhydrous dimethylformamide under dry nitrogen atmosphere (Scheme 5). For cyclizations involving 1,3-dichloroacetone or 1,3-dichloro-2-propanol, it was necessary to add the solution of these dichlorides and the solution of the dithiol separately but simultaneously using a syringe drive pump. Cyclizations involving simple 1,ω-dichloroalkanes can be carried out by mixing the dichloride, the dithiol, and DMF and adding that solution slowly to the Cs_2CO_3/DMF slurry. After the reaction, the cesium chloride is filtered off and the DMF is removed by rotary evaporation. The crude residue is chromatographed on silica gel, generally using MPLC eluting with ethyl acetate/hexane.

We have carried out syntheses of the mesocyclic trithioethers, 1,4,7-trithiacyclodecane (10-ane-S_3) [6], 1,4,7-trithiacycloundecane (11-ane-S_3-S(1,4,7)) [7], 1,4,8-trithiacycloundecane (11-ane-S_3), and 1,5,9-trithiacyclododecane (12-ane-S_3) [8]; the mesocyclic trithioether ketones, 1,4,7-trithiacyclodecan-9-one (keto-10-ane-S_3) [9], 1,4,8-trithiacycloundecan-6-one (keto-11-ane-S_3), and 1,5,9-trithiacyclododecan-3-one (keto-12-ane-S_3); and the mesocyclic trithioether alcohols, 1,4,7-trithiacyclodecan-9-ol (hydroxy-10-ane-S_3) [9], 1,4,8-trithiacycloundecan-6-ol (hydroxy-11-ane-S_3), and 1,5,9-trithiacyclododecane-3-ol (hydroxy-12-ane-S_3). In some cases, the corresponding macrocyclic hexathioether was isolated from the reaction mixture in addition to the mesocyclic trithioether. We have isolated and characterized the following macrocyclic materials: 1,4,7,11,14,17-hexathiacycloeicosane (20-ane-S_6) [10], 1,4,7,11,14,17-hexathiacycloeicosan-9,19-dione (diketo-20-ane-S_6) [11], 1,4,7,12,15,18-hexathiacyclodocosane (22-ane-S_6) [10], and 1,5,9,13,17,21-hexathiacyclotetracosane (24-ane-S_6). The results of these cyclizations are summarized in Table 1.

In the synthesis of 10-ane-S_3/20-ane-S_6, chromatographic purification and separation of the compounds gave only a very small yield of the macrocycle (0.6% yield). Complexation studies with nickel(II) revealed that the majority of the 20-ane-S_6 had adhered to the silica gel adsorbent, and additional amounts of the compound could not be eluted from the column. An alternate means of separation was devised to recover the 20-ane-S_6 in larger quantities. An excess of 1 m*M* $Ni(BF_4)_2$ containing 6 equivalents of acetic anhydride in nitromethane was added to the crude reaction product before



11-ane-S_3-S(1,4,7)
1,4,7-Trithiacycloundecane

22-ane-S_6
1,4,7,12,15,18-Hexathiacylodocosane

+ Higher Molecular Weight S-Macrocycles

SCHEME 5

chromatographing. Both the 10-ane-S_3 and 20-ane-S_6 ligands complexed the nickel(II) under these conditions and were removed in complexed form. After removal and filtration, a stoichiometric excess of water was added to the nickel-complex solution. Due to the instability of the 20-ane-S_6/nickel(II) complex with respect to hydrolysis, the 20-ane-S_6 complex was destroyed, thereby liberating the free 20-ane-S_6 ligand. The ligand was then extracted and isolated in much higher (57%) yield. The 20-ane-S_6 ligand was first prepared in a 30% yield by the reaction of sodium dithiolate salt of bis(2-mercaptoethyl)sulfide and 1,3-dibromopropane [10b]. Our reaction offers two advantages. First, our reaction produces 20-ane-S_6 as a by-product of the synthesis of 10-ane-S_3, thereby eliminating the need of a separate synthesis for the macrocycle. Also, we have improved the yield by almost a factor of two.

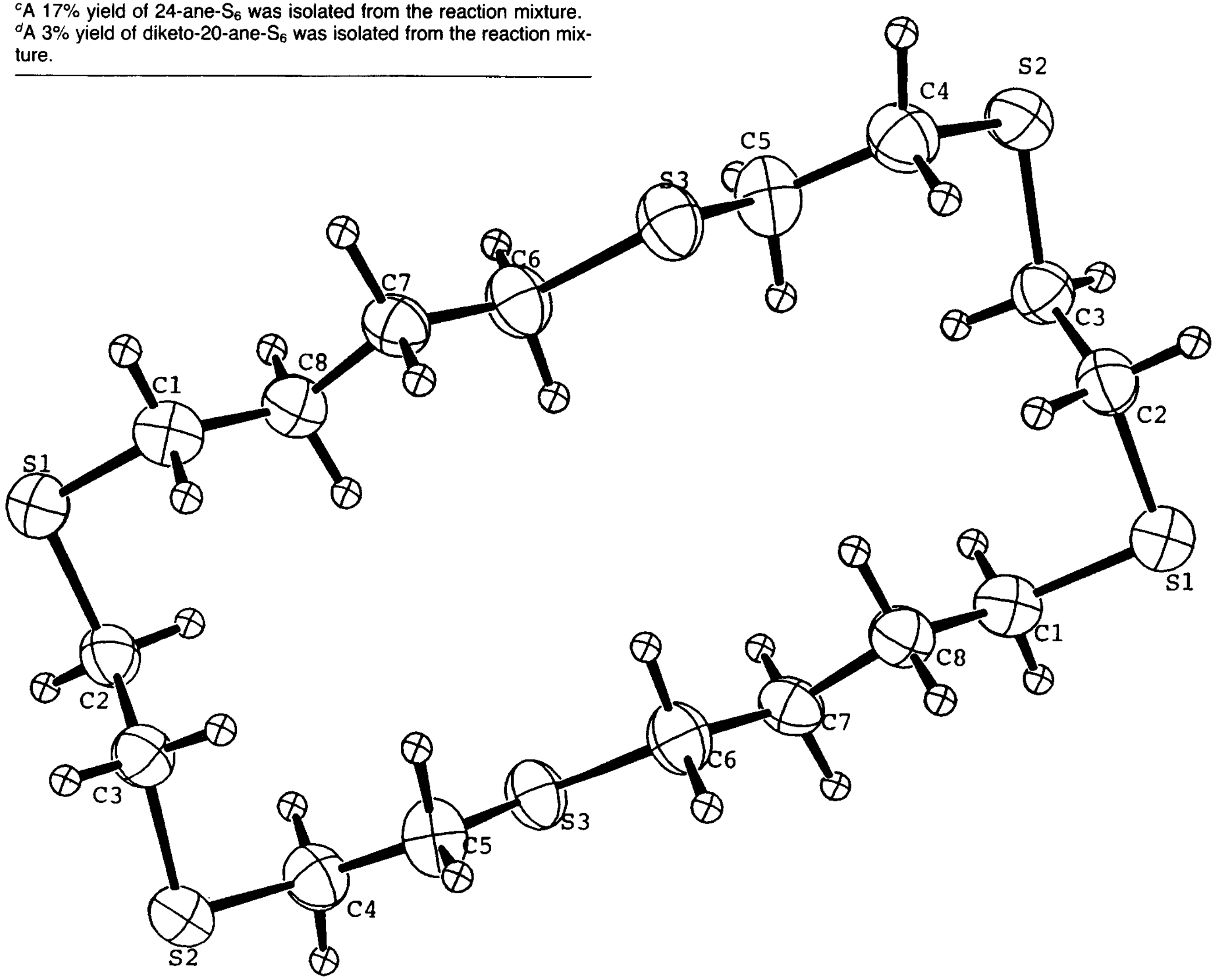
TABLE 1 Synthesis of Mesocyclic and Macrocyclic Polythioethers

Mesocycle	*Mercaptan*	*Dihalide*	*%Yield*
10-ane-S_3	MES	DCP	18%[a]
11-ane-S_3	MPS	DCE	30%
	DMTH	DCP	11%
11-ane-S_3-S(1,4,7)	MES	DCB	13%[b]
12-ane-S_3	MPS	DCP	33%[c]
keto-10-ane-S_3	MES	DCA	18%[d]
keto-11-ane-S_3	DMTH	DCA	6%
keto-12-ane-S_3	MPS	DCA	4%
hydroxy-10-ane-S_3	MES	DCPOH	23%
hydroxy-11-ane-S_3	DMTH	DCPOH	11%
hydroxy-12-ane-S_3	MPS	DCPOH	20%

MES = bis(2-mercaptoethyl)sulfide
MPS = bis(3-mercaptopropyl)sulfide
DMTH = 1,6-dimercapto-3-thiahexane
DCP = 1,3-dichloropropane
DCE = 1,2-dichloroethane
DCB = 1,4-dichlorobutane
DCA = 1,3-dichloroacetone
DCPOH = 1,3-dichloro-2-propanol

[a] A 57% yield of 20-ane-S_6 was isolated from the reaction mixture.
[b] A 4% yield of 22-ane-S_6 was isolated from the reaction mixture.
[c] A 17% yield of 24-ane-S_6 was isolated from the reaction mixture.
[d] A 3% yield of diketo-20-ane-S_6 was isolated from the reaction mixture.

FIGURE 1 ORTEP Perspective Drawing of 22-ane-S_6.



X-ray Crystal Structures of 22-ane-S_6 and Hydroxy-12-ane-S_3

ORTEP perspective drawings of 22-ane-S_6 and hydroxy-12-ane-S_3, along with their labeling schemes, are shown in Figures 1 and 2, respectively. The crystallographic data for the compounds are listed in Table 2. Atomic coordinates for the non-hydrogen atoms appear in Tables 3 and 4. Bond lengths and bond angles for the compounds are given in Tables 5 and 6, respectively.

The twelve-membered ring, hydroxy-12-ane-S_3, adopts a square conformation in the crystalline state, similar to that of cyclododecane and 1,5,9-trithiacyclododecane (12-ane-S_3) [8(b)]. As in the structure of 12-ane-S_3, two sulfur atoms occupy side positions and one sulfur occupies a corner. The hydroxy group occupies an exodentate disposition with respect to the ring.

The potentially hexadentate thioether, 22-ane-S_6, represents the third macrocyclic hexathioether and the first crown thioether ligand containing tetramethylene bridges to be structurally characterized. The structure of 22-ane-S_6 generally resembles those obtained for other macrocyclic thioether ligands [3(a), 11]. All six sulfur atoms in the 22-ane-S_6 are arranged in exodentate fashion, as they are in diketo-20-ane-S_6, in contrast to 18-ane-S_6, which has two sulfur atoms endodentate [5(b)]. This preferred conformation of 22-ane-S_6 will likely have important implications for its complexation properties since the ligand will have to undergo significant conformational changes in order to complex in an octahedral fashion. Four of the six sulfur at-

TABLE 2 Crystal Data for 22-ane-S_6 and Hydroxy-12-ane-S_3

Compound	22-ane-S_6	Hydroxy-12-ane-S_3
Molecular formula	$C_{16}H_{32}S_6$	$C_9H_{18}S_3O$
Molecular weight	416.79	238.42
Crystal system	Orthorhombic	Monoclinic
Space group	*Pbca*	*C*2/*c*
Cell dimensions		
a, Å	21.406(5)	10.5926(9)
b, Å	9.810(2)	16.582(2)
c, Å	10.225(2)	13.6015(8)
β, deg	90.0	98.186(6)
V, Å^3	2147.1(8)	2364.8(3)
Z	4	8
No. of obsd. data	1517	1502
No. of variables	116	118
Absorption coeff., cm^{-1}	5.71	53.58
F(000)	896	1024

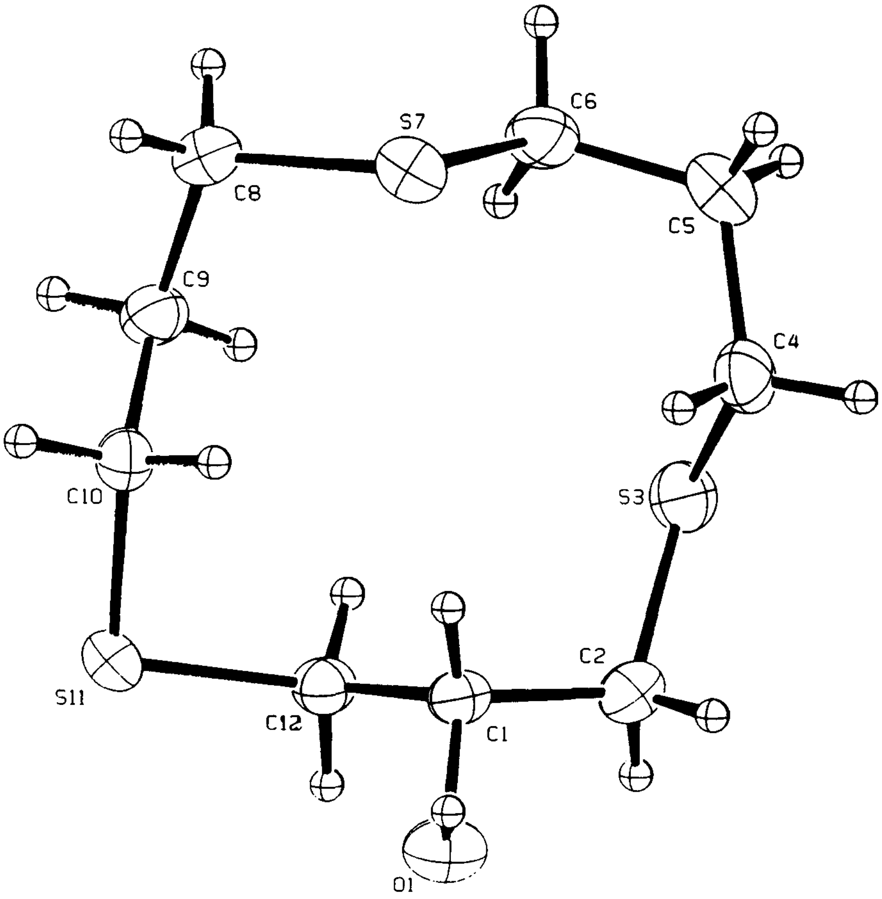


FIGURE 2 ORTEP Perspective Drawing of Hydroxy-12-ane-S_3.

TABLE 3 Final Atomic Parameters for 22-ane-S_6

Atom	*x*	*y*	*z*	U_{iso}(Å^2)[a]
C1	−0.2028(2)	−0.1092(4)	0.3772(4)	0.047
C2	−0.1955(2)	0.1132(4)	0.2024(6)	0.046
C3	−0.1582(2)	0.0307(4)	0.1046(4)	0.042
C4	−0.0605(2)	0.2238(4)	0.0973(4)	0.049
C5	−0.0152(2)	0.1324(4)	0.1674(4)	0.051
C6	0.0761(2)	0.0994(4)	0.3548(4)	0.049
C7	0.1244(2)	0.1569(4)	0.4483(4)	0.042
C8	0.1566(2)	0.0479(4)	0.5291(4)	0.044
S1	−0.25195(5)	0.0106(1)	0.2902(1)	0.0572
S2	−0.11322(4)	0.1327(1)	−0.0104(1)	0.0486
S3	0.03457(5)	0.2348(1)	0.2726(1)	0.0483

[a] U_{iso} is the mean of the principal axes of the thermal ellipsoid.

TABLE 4 Final Atomic Parameters for Hydroxy-12-ane-S_3

Atom	*x*	*y*	*z*	B_{iso}(Å^2)[a]
S(3)	0.55713(8)	0.06425(5)	0.11793(6)	4.19(4)
S(11)	0.87672(8)	−0.00705(5)	0.39682(6)	3.80(4)
S(7)	0.81785(8)	0.24251(5)	0.21567(7)	4.12(4)
O(1)	0.8595(2)	−0.0858(1)	0.1745(2)	4.9(1)
C(10)	0.9130(3)	0.0978(2)	0.3771(2)	3.5(1)
C(9)	0.8098(3)	0.1574(2)	0.3936(2)	4.0(1)
C(1)	0.7797(3)	−0.0190(2)	0.1931(2)	3.3(1)
C(12)	0.7462(3)	−0.0247(2)	0.2979(2)	3.4(1)
C(8)	0.8342(4)	0.2404(2)	0.3500(3)	4.2(2)
C(2)	0.6597(3)	−0.0226(2)	0.1166(2)	4.1(1)
C(6)	0.6457(3)	0.2438(2)	0.1856(3)	4.4(2)
C(4)	0.6359(3)	0.1369(2)	0.0489(2)	4.3(2)
C(5)	0.6029(4)	0.2226(2)	0.0779(3)	4.7(2)

[a] B_{iso} is the mean of the principal axes of the thermal ellipsoid.

TABLE 5 Selected Geometrical Parameters for 22-ane-S_6

Selected Bond Lengths (Å)			
C1–S1	1.810(4)	C2–C3	1.514(5)
C2–S1	1.811(4)	C3–S2	1.820(4)
C4–C5	1.505(6)	C4–S2	1.812(4)
C5–S3	1.817(4)	C6–C7	1.518(5)
C6–S3	1.806(4)	C7–C8	1.516(5)
C1–C8	1.503(5)		
Selected Bond Angles (*deg*)			
S1–C2–C3	112.5(3)	S2–C3–C2	114.3(3)
S2–C4–C5	113.4(4)	S3–C5–C4	109.3(3)
S3–C6–C7	110.8(3)	C8–C7–C6	113.0(3)
C2–S1–C1	102.5(2)	C4–S2–C3	102.0(2)
C6–S3–C5	99.0(2)		

TABLE 6 Selected Geometrical Parameters for Hydroxy-12-ane-S_3

Selected Bond Lengths (Å)			
S3–C4	1.803(4)	S3–C2	1.806(4)
S11–C10	1.808(3)	S11–C12	1.810(3)
S7–C8	1.811(4)	S7–C6	1.811(4)
C9–C10	1.514(5)	C8–C9	1.536(5)
C1–C12	1.520(4)	C1–C2	1.526(4)
C5–C6	1.513(5)	C4–C5	1.528(5)
O1–C1	1.437(4)		
Selected Bond Angles (*deg*)			
C2–S3–C4	101.8(2)	C10–S11–C12	101.6(1)
C6–S7–C8	100.1(2)	C9–C10–S11	115.6(2)
C8–C9–C10	111.3(3)	C1–C12–S11	115.5(2)
O1–C1–C12	109.8(3)	O1–C1–C2	107.7(3)
C12–C1–C2	110.7(3)	S7–C8–C9	114.2(2)
C1–C2–S3	114.0(2)	C5–C6–S7	111.7(3)
S3–C4–C5	110.3(2)	C4–C5–C6	114.7(3)

oms are arranged approximately in the corners of a rectangle, and the S–C–C–S bond linkages are approximately linear (the conformations about S–C–C–S are anti) as is generally observed [3(b), 11]. Since they are located at the corners of the rectangular structure, the torsion angles about the sulfurs, C–S–C–C, are gauche, whereas for the two sulfurs not located on corners, the C–S–C–C are anti. Another interesting contrast between this structure and other crown thioethers are the carbon–carbon bond lengths; these are longer and much less varied in 22-ane-S_6 than in the other reported structures [5(b), 11].

EXPERIMENTAL

Materials

Dimethylformamide (DMF) and tetrahydrofuran (THF) were dried using common methods. Lithium aluminum hydride ($LiAlH_4$), thiodi-3,3′-propionic acid, bis(2-mercaptoethyl)sulfide, 1,3-dichloropropane, 1,4-dichlorobutane, 1,3-dichloroacetone, and cesium carbonate were purchased from Aldrich Chemical Company and used as received. Thiourea and 1,3-dichloro-2-propanol were used as received from Eastman Organic Chemicals.

Measurements

Elemental analyses were performed by Atlantic Microlab, Inc. of Atlanta, Georgia, or by Galbraith Laboratories, Inc. of Knoxville, Tennessee. Infrared spectra were obtained using a Perkin-Elmer 1330 infrared spectrophotometer. Fourier transform infrared spectra were obtained using a Beckman FT 1100 infrared spectrophotometer. Proton NMR spectra were obtained at either 60 MHz on a JEOL JNM-PMX60 NMR spectrometer or at 200 MHz on a Bruker AF 200 spectrometer using TMS as an internal standard. Reported melting points are uncorrected.

Preparation of 1,4,7-Trithiacyclodecane (10-ane-S_3)

We have recently reported the synthesis of this compound [6]. The method used was based upon the Cooper synthesis of 1,4,7-trithiacyclononane [5(a)]. A 1000-mL three-necked round bottom flask, equipped with 125-mL pressure equalizing dropping funnel, magnetic stir bar, thermometer, and nitrogen inlet-outlet, was charged with a slurry of DMF (250 mL) and cesium carbonate (13.03 g, 40.00 mmol). In the funnel a solution of bis(2-mercaptoethyl)sulfide (4.70 mL, 5.56 g, 36.0 mmol), 1,3-dichloropropane (3.42 mL, 4.07 g, 36.0 mmol), and 150 mL DMF was prepared. The solution was added to the rapidly stirred and heated (100°C) DMF/Cs_2CO_3 slurry at a rate of about 3 mL/h. After completion of the addition (48 h), the mixture was cooled to room temperature and stirred for an additional 24 h. A yellow supernatant solution and a white precipitate of CsCl had formed. The CsCl was filtered off, and the solvent was removed in vacuo leaving a brown sticky solid. The brown solid was taken up in 100 mL of CH_2Cl_2, and the mixture filtered. The CH_2Cl_2 solution was washed with 100 mL water, 2 × 100 mL 0.1 *M* NaOH, 2 × 100 mL water, and dried over anhydrous $MgSO_4$. The drying agent was filtered off, and the CH_2Cl_2 was removed in vacuo. The brown sticky residue was chromatographed on a silica gel gravity column (3 cm diameter × 50 cm length), and was eluted with 10% ethyl acetate/hexane to give 1.24 g (17.7% yield) of 10-ane-S_3 as a colorless, viscous oil; IR (thin film) 2926, 1419, 1337, 1252, 1193, 1139, 1084, 833, 694, 681, 643 cm^{-1}; ^1H NMR ($CDCl_3$) 2.77 (s, 8 H, SCH_2CH_2S), 2.67 (t, 4 H, $SCH_2CH_2CH_2S$), 1.93 (p, 2 H, $SCH_2CH_2CH_2S$). Anal. Calcd. for $C_7H_{14}S_3$: C, 43.27; H, 7.25; S, 49.49. Found: C, 43.33; H, 7.11; S, 49.56.

Preparation of 1,4,7,11,14,17-Hexathiacycloeicosane (20-ane-S_6)

The compound 20-ane-S_6 is obtained as a second product using the above procedure for the preparation of 10-ane-S_3. The 20-ane-S_6 eluted much later than did the 10-ane-S_3 (R_f for 10-ane-S_3 was approximately 3× larger than that for 20-ane-S_6). A yield of 41 mg (0.6% yield) was obtained from the column: mp 78–80°C; IR (KBr) 2950, 2924, 1418, 1380, 1260, 1192, 1039, 1033, 925, 715, 685, 642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.77 (s, 8 H, SCH_2CH_2S), 2.67 (t, 4 H, $SCH_2CH_2CH_2S$), 1.93 (p, 2 H, $SCH_2CH_2CH_2S$). Anal. Calcd. for $C_{14}H_{28}S_6$: C, 43.27; H. 7.25; S. 49.49. Found: C, 43.11; H, 7.48; S, 49.33.

Complexation studies with nickel(II) revealed that the majority of the 20-ane-S_6 had adhered to the silica gel column, and additional amounts of the compound could not be eluted. An alternate means of separation was devised to recover the 20-ane-S_6 in larger quantities. An excess of 1 m*M* $Ni(BF_4)_2$ (greater than one nickel per six sulfurs) containing 6 equivalents of acetic anhydride (to react with the water of hydration of the nickel(II) salt) in nitromethane was added to the crude reaction product before chromatographing. Both the 10-ane-S_3 and 20-ane-S_6 ligands complexed the nickel(II) under these conditions and were removed in complexed form. After removal and filtration, a stoichiometric excess of water (greater than six equivalents of water per nickel) was added to the nickel-complex solution. Due to the instability of the 20-ane-S_6/nickel(II) complex with respect to hydrolysis, the 20-ane-S_6 complex was destroyed, liberating the free 20-ane-S_6 ligand. The ligand was extracted into CH_2Cl_2, the solution was dried ($MgSO_4$), and the solvent was removed by evaporation to give 3.97 g (56.7% yield) 20-ane-S_6.

Preparation of 1,4,7-Trithiacycloundecane {11-ane-S_3-S(1,4,7)} [7]

A 1000-mL three-necked round bottom flask, equipped with 125-mL pressure equalizing dropping funnel, magnetic stir bar, thermometer, and nitrogen inlet-outlet, was charged with a slurry of DMF (275 mL) and cesium carbonate (19.46 g, 55.00 mmol). In the funnel a solution of bis(2-mercaptoethyl)sulfide (6.53 mL, 7.72 g, 50.0 mmol), 1,4-dichlorobutane (5.47 mL, 6.35 g, 50.0 mmol), and 200 mL DMF was prepared. The solution was added to the rapidly stirred and heated (100°C) DMF/Cs_2CO_3 slurry at a rate of about 1 drop/15 sec. After completion of the addition (48 h), the mixture was cooled to room temperature and stirred for an additional 24 h. A yellow supernatant solution and a white precipitate of CsCl had formed. The CsCl was filtered off, and the solvent was removed in vacuo leaving a brown oily liquid. The brown residue was taken up in 100 mL of CH_2Cl_2, and the mixture filtered. The CH_2Cl_2 solution was washed with 100 mL water, 2 × 100 mL 0.1 *M* NaOH, 2 × 100 mL water, and dried over anhydrous $MgSO_4$. The drying agent was filtered off, and the CH_2Cl_2 was removed in vacuo leaving a yellow oily liquid. The yellow oily residue was chromatographed on a silica gel gravity column (3 cm diameter × 50 cm length), and was eluted with 10% ethyl acetate/hexane to give 1.53 g (4.13% yield) of 11-ane-S_3-S(1,4,7) as a colorless, crystalline solid: mp 42–44°C; IR (KBr) 2926, 1421, 1283, 1221, 1137, 1083, 1038, 790, 635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.85 (s, 8 H, SCH_2CH_2S), 2.68 (t, 4 H, $SCH_2CH_2CH_2CH_2S$), 1.84 (m, 4 H, $SCH_2CH_2CH_2CH_2S$). Anal. Calcd. for $C_8H_{16}S_3$: C, 46.11; H, 7.74; S, 46.15. Found: C, 46.22; H, 7.73; S, 46.05.

Preparation of 1,4,7,12,15,18-Hexathiacyclodocosane (22-ane-S_6) [7]

The compound 22-ane-S_6 is obtained as a second product in the above procedure for the preparation of 11-ane-S_3. The 22-ane-S_6 eluted later than did the 11-ane-S_3 (R_f for 11-ane-S_3-S(1,4,7) was 1.2× larger than that for 22-ane-S_6). After eluting with 10% ethyl acetate/hexane, a mass of 0.45 g (4.3% yield) of 22-ane-S_6 as a colorless, crystalline solid was obtained: mp 61–63°C; IR(KBr) 2965, 1423, 1285, 1223, 1139, 1040, 656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.97 (s, 8 H, SCH_2CH_2S), 2.78 (t, 4 H, $SCH_2CH_2CH_2CH_2S$), 1.92 (m, 4 H, $SCH_2CH_2CH_2CH_2S$); mass spectrum, m/e 416 (M^+). Anal. Calcd. for $C_{16}H_{32}S_6$: C, 46.11; H, 7.74; S, 46.15. Found: C, 46.15; H, 7.77; S, 46.14.

X-ray Single Crystal Structure Study of 22-ane-S_6 [12]

A clear colorless crystal suitable for X-ray diffraction and having approximate dimensions 0.51 × 0.31 × 0.27 mm was mounted on a Syntex $P2_1$ auto diffractometer equipped with a scintillation counter, and graphite-monochromated MoKα radiation (λ = 0.71069 Å). The automatic centering, indexing, and least-squares routines were carried out on 15 independent reflections in the range of 17.4° $\leq 2\theta \leq$ 33.7° to obtain the unit cell dimensions that are given in Table 2. The ω-scan technique over the range 4° $\leq 2\theta \leq$ 50° was used to collect the data of which those with $F \geq 3\sigma(F)$ were considered observed. No correction was made for absorption.

The structure was solved by direct methods. The atoms were located by structure factor calculations and difference electron density maps. The structure was refined by full-matrix least-squares techniques. The hydrogen atoms were located by difference maps and were isotropically refined (positional parameters were not refined). All non-hydrogen atoms were refined anisotropically, converging at $R = 0.020$, $R_w = 0.023$, and GOF = 1.698. The final atomic parameters for 22-ane-S_6 with their standard deviations are given in Table 3. Selected bond distances and bond angles are given in Table 5.

Preparation of 1,4,7-Trithiacyclodecan-9-one (Keto-10-ane-S_3) [9] *and 1,4,7,11,14,17-Hexathiacycloeicosan-9,19-dione (Diketo-20-ane-S_6)* [11]

A 1-L three-necked round-bottom flask, equipped with syringe drive pump, magnetic stir bar, heating mantle, and a nirogen inlet-outlet, was charged with freshly distilled dimethylformamide (DMF, 250 mL) and cesium carbonate (32.6 g, 100 mmol). Into one syringe was added a solution of bis(2-mercaptoethyl) sulfide (14.5 mL, 17.1 g, 100 mmol) and sufficient anhydrous DMF to dilute to 50 mL. Into the other syringe was added a solution of 1,3-dichloroacetone (9.7 mL, 13.4 g, 100 mmol) and sufficient anhydrous DMF to dilute to 50 mL. The two solutions were added simultaneously to the rapidly stirred and heated (held at 52°C) DMF/Cs_2CO_3 mixture at a rate of about 5.5 mL/h. Upon completion of the addition (9 h), the reaction mixture was stirred for 36 h. The heating was discontinued after the first 12 h. The reaction mixture was vacuum filtered and the DMF was removed by rotary evaporation. The crude material was chromatographed using MPLC on a silica gel column (51 mm diameter × 45 cm length) in 2-g portions, eluting with 20% ethyl acetate in hexane to give 604 mg (2.9% yield) of diketo-20-ane-S_6, a colorless, parallelepiped crystal, and 3.71 g (17.8% yield) of keto-10-ane-S_3, a colorless, needle-like crystal. For diketo-20-ane-S_6: mp 107–108°C; IR (KBr) 2910, 1675, 1390, 1250, 1190, 1140, 1075, 940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.72 (s, 8 H, —SCH_2CH_2S—), 3.53 (s, 4 H, —$SCH_2C(O)$—); mass spectrum (CI, methane) m/e (relative intensity), 417(100%, M+1), 268.9(41%), 208.9(32%), 149(28%), 121(35%), 89(24%), 61(25%). Anal. Calcd. for $C_{14}H_{24}S_6O_2$: C, 40.37; H, 5.81; S, 46.13. Found: C, 40,34; H, 5.85; S, 46.20. For keto-10-ane-S_3: mp 102–104°C; IR (KBr) 2910, 1960, 1390, 1275, 1220, 1140, 1075, 950, 925, 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.72 (s, 8 H, —SCH_2CH_2S—), 3.53 (s, 4 H, —$SCH_2C(O)$—); mass spectrum, (CI, methane) m/e (relative intensity) 209(75%, M+1), 181(23%), 149(100%), 121(30%), 89(15%), 61(24%). Anal. Calcd. for $C_7H_{12}S_3O$: C, 40.37; H, 5.81; S, 46.13. Found: C, 40.36; H, 5.86; S, 46.22.

Preparation of 1,4,7-Trithiacyclodecan-9-ol (Hydroxy-10-ane-S_3) [9]

A 1-L three-necked round-bottom flask, equipped with matching calibrated 200-mL addition funnels, magnetic stir bar, heating mantle, and a nitrogen inlet-outlet, was charged with freshly distilled dimethylformamide (DMF, 300 mL) and cesium carbonate (32.6 g, 100 mmol). Into one funnel were added 2-mercaptoethyl sulfide (13.7 mL, 16.2 g, 100 mmol) and sufficient anhydrous DMF to dilute to 200 mL. Into the other funnel were added 1,3-dichloro-2-propanol (9.5 mL, 12.9 g, 100 mmol) and sufficient anhydrous DMF to dilute to 200 mL. The two solutions were added simultaneously to the rapidly stirred and heated (held at 65°C) DMF/Cs_2CO_3 mixture at a rate of about 15 drops/min. Upon completion of the addition (5 h), the reaction mixture was stirred for 36 h. The heating was discontinued after the first 12 h. The reaction mixture was vacuum filtered and the DMF was removed by rotary evaporation to give 34.29 g of a light brown solid residue. A 15.89-g sample of the crude product was recrystallized three times from ethanol to give 2.260 g (23.2% yield) hydroxy-10-ane-S_3 as a colorless, microcrystalline solid: mp 74–79°C; IR (KBr) 3600-3100 (s,b, O—H), 2950, 1418, 1190, 1133, 1060, 1032, 992, 716, 677 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.81 (m, 4 H, —$SCH_2CH(OH)$—), 2.93 (s, 8 H, —SCH_2CH_2S), 4.47 (m, 1 H —$CH(OH)$—); mass spectrum (CI, methane) m/e (relative intensity) 210(1%, M+), 209(1%), 149(12%), 121(14%), 117(15%), 105(32%), 87(37%), 73(42%), 61(100%). Anal. Calcd. for $C_7H_{14}S_3O$: C, 39.96; H, 6.71; S, 45.72. Found: C, 39.87; H, 6.71; S, 45.65.

Preparation of 3-Thia-1,6-hexanediol

Mercaptoethanol (54.5 g, 0.683 mol) was slowly added to a stirred solution of sodium ethoxide in ethanol (prepared by dissolving 15.7 g Na in 300 mL anhydrous ethanol). 3-Bromo-1-propanol (100 g, 0.683 mol) was then slowly added with stirring. The reaction mixture was heated and allowed to reflux gently overnight. The sodium bromide was filtered off, the ethanol was removed from the filtrate by rotary evaporation, and the residue was distilled under vacuum (bp 114–120°C, 0.4 mm Hg) to give 62.9 g (67.6% yield) 3-thia-1,6-hexanediol as a clear colorless liquid: IR (thin film) 3450-3250 (s, b, O—H), 2930, 2880, 1640, 1466, 1423, 1378, 1350, 1285, 1265, 1218, 1160, 1050 (s), 1010, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84 (p, 2 H $SCH_2CH_2CH_2OH$), 2.63–2.78 (m, 4 H, CH_2SCH_2), 3.34 (s, 2 H, OH), 3.47–3.76 (m, 4 H, CH_2OH).

Preparation of 3-Thia-1,6-hexanedithiol

A solution of 62.9 g 3-thia-1,6-hexanediol (0.462 mol), thiourea (76.1 g, 1.00 mol) and concentrated hydrochloric acid (244 mL) was refluxed for 25 h. The resulting solution was cooled in an ice bath and a solution of potassium hydroxide (174.5 g, 3.11 mol) in water (400 mL) was slowly added. The reaction mixture was refluxed for 4 h and the two-phase mixture allowed to cool to room temperature. The upper aqueous phase was separated from the oily organic layer. The aqueous phase was acidified with diluted hydrochloric acid and extracted with ether (3 × 100 mL). The ethereal extracts were combined with the organic layer and the solution was dried over anhydrous magnesium sulfate. The solution was filtered, the ether was removed by rotary evaporation, and the residue was distilled under vacuum (bp 87°C, 0.4 mm Hg) to give 42.8 g (55.1% yield) 3-thia-1,6-hexanedithiol as a clear, pale yellow liquid: IR (thin film) 2920 (s, C—H), 2840, 2540 (s, S—H), 1424 (s), 1344, 1240 (sh), 1260 (s), 1209 (s), 1140, 1045, 965, 841, 768, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (t, 1 H, SH), 1.83–1.90 (m, 2 H, $SCH_2CH_2CH_2S$), 2.57–2.77 (m, 9 H, SCH_2, and SH).

Preparation of 1,4,8-Trithiacycloundecane (11-ane-S_3)

A 5-L three-necked round-bottom flask, equipped with syringe-drive pump, mechanical stirrer, reflux condenser, heating mantle, and a nitrogen inlet-outlet, was charged with freshly distilled dimethylformamide (DMF, 3 L) and cesium carbonate (26.1 g, 80 mmol). Into one syringe was added a solution of 3-thia-1,6-hexanedithiol (13.4 g, 80 mmol) and sufficient anhydrous DMF to dilute to 50 mL. Into the other syringe was added a solution of 1,3-dichloropropane (9.05 g, 80 mmol) and sufficient anhydrous DMF to dilute to 50 mL. The two solutions were added simultaneously to the rapidly stirred and heated (held at ca 60°C) DMF/Cs_2CO_3 mixture. Upon completion of the addition (22 h), the reaction mixture was stirred for an additional 12 h and was then allowed to cool to room temperature. The reaction mixture was vacuum filtered and the DMF was removed by rotary evaporation to give 21.2 g of a yellow residual solid. The crude material was chromatographed using MPLC on a silica gel column (51 mm diameter × 45 cm length) in 2-g portions, eluting with 20% ethyl acetate in hexane to give 1.132 g (11.1% yield) as a colorless crystalline solid: mp 69–70°C; IR (KBr) 2900, 1440 (s), 1410 (s), 1330–1340, 1290, 1270, 1250, 1240, 1205, 1190, 1140, 1120, 860, 755, 705, 670 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.86–1.92 (m, 4 H, $\mathrm{SCH_2}\mathit{CH}_2\mathrm{CH_2S}$), 2.71–2.80 (m, 4 H, $\mathrm{S}\mathit{CH}_2\mathit{CH}_2\mathrm{S}$), 2.86–3.03 (m, 8 H, $\mathrm{S}\mathit{CH}_2\mathrm{CH_2}\mathit{CH}_2\mathrm{S}$). Anal. Calcd. for $C_8H_{16}S_3$: C, 46.11; H, 7.74; S, 46.15. Found: C, 46.10; H, 7.78; S, 46.08.

Preparation of 1,4,8-Trithiacycloundecan-6-one (Keto-11-ane-S$_3$)

A 5-L three-necked round-bottom flask, equipped with syringe-drive pump, mechanical stirrer, reflux condenser, heating mantle, and a nitrogen inlet-outlet, was charged with freshly distilled dimethylformamide (DMF, 3 L) and cesium carbonate (26.1 g, 80 mmol). Into one syrine was added a solution of 3-thia-1,6-hexanedithiol (13.4 g, 80 mmol) and sufficient anhydrous DMF to dilute to 50 mL. Into the other syringe was added a solution of 1,3-dichloroacetone (10.2 g, 80 mmol) and sufficient anhydrous DMF to dilute to 50 mL. The two solutions were added simultaneously to the rapidly stirred and heated (held at ca 60°C) DMF/Cs_2CO_3 mixture. Upon completion of the addition (22 h), the reaction mixture was stirred for an additional 12 h and was then allowed to cool to room temperature. The reaction mixture was vacuum filtered and the DMF was removed by rotary evaporation to give 24.8 g of a dark brown residual solid. A 4.09-g sample of the crude product was chromatographed using MPLC on a silica gel column (51 mm diameter × 45 cm length), eluting with 20% ethyl acetate in hexane to give 175 mg (6.0% yield) as a colorless crystalline solid: mp 112°C; IR (KBr) 2970, 2875, 1673–1642 (C=O), 1445, 1404, 1398, 1376, 1287, 1270, 1258, 1244, 1210, 1180, 1159, 1055, 924, 911, 882, 850, 736, 699, 617, 548 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.89 (p, 2 H, $\mathrm{SCH_2}\mathit{CH}_2\mathrm{CH_2S}$), 2.72 (t, 2 H, $\mathrm{S}\mathit{CH}_2\mathrm{CH_2CH_2S}$), 2.81 (t, 2 H, $\mathrm{SCH_2CH_2}\mathit{CH}_2\mathrm{S}$), 2.83 (s, 4 H, $\mathrm{S}\mathit{CH}_2\mathit{CH}_2\mathrm{S}$), 3.40 (s, 2 H, $\mathit{CH}_2\mathrm{C(O)CH_2}$), 3.67 (s, 2 H, $\mathrm{CH_2C(O)}\mathit{CH}_2$). Anal. Calcd. for $C_8H_{14}S_3O$: C, 43.21; H, 6.35; S, 43.25. Found: C, 43.19; H, 6.37; S, 43.19.

Preparation of 1,4,8-Trithiacycloundecan-6-ol (Hydroxy-11-ane-S$_3$)

A 5-L three necked round-bottom flask, equipped with syringe-drive pump, mechanical stirrer, reflux condenser, heating mantle, and a nitrogen inlet-outlet, was charged with freshly distilled dimethylformamide (DMF, 3 L) and cesium carbonate (26.1 g, 80 mmol). Into one syringe was added a solution of 3-thia-1,6-hexanedithiol (13.4 g, 80 mmol) and sufficient anhydrous DMF to dilute to 50 mL. Into the other syringe was added a solution of 1,3-dichloro-2-propanol (10.4 g, 80 mmol) and sufficient anhydrous DMF to dilute to 50 mL. The two solutions were added simultaneously to the rapidly stirred and heated (held at ca 60°C) DMF/Cs_2CO_3 mixture. Upon completion of the addition (22 h), the reaction mixture was stirred for an additional 12 h and was then allowed to cool to room temperature. The reaction mixture was vacuum filtered and the DMF was removed by rotary evaporation to give 18.0 g of a brown residual solid. The crude product was chromatographed using MPLC on a silica gel column (51 mm diameter × 45 cm length) in 2-g portions, eluting with 20% ethyl acetate in hexane to give 1.50 g (10.8% yield) as a colorless crystalline solid: mp 70°C; IR (KBr) 3300–3170 (b, O—H), 2950, 1820 (b), 1435, 1360–1320 (b), 1275, 1250, 1220, 1210, 1130, 1080, 1045, 880, 830, 800, 775, 735, 700, 650–620 (b), 495, 450, 410–390 (b) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.88–2.06 (m, 2 H, $\mathrm{SCH_2}\mathit{CH}_2\mathrm{CH_2S}$), 2.65–3.00 (m, 13 H, SCH$_2$, and OH), 4.18–4.32 (m, 1 H, $\mathit{CH}\mathrm{OH}$). Anal. Calcd. for $C_8H_{16}S_3O$: C, 42.82; H, 7.19; S, 42.86. Found: C, 42.75; H, 7.23; S. 42.78.

Preparation of bis(3-Hydroxypropyl)sulfide [8b]

Thiodi-3,3′-propionic acid (17.8 g, 0.100 mol) in anhydrous THF (300 mL) was slowly added to a suspension of lithium aluminum hydride (11.41 g, 0.30 mol) in anhydrous THF (200 mL) under dry nitrogen atmosphere. After completion of the addition, the reaction was heated to gentle reflux overnight. The reaction mixture was cooled in an ice/water bath and the excess $LiAlH_4$ quenched with a solution of water (25 mL, 1.4 mol) in THF (100 mL). The reaction mixture was allowed to warm to room temperature and was stirred for one hour. $MgSO_4$ (ca. 20 g) was added, and the mixture was stirred for an additional 15 min. The mixture was filtered and then washed with THF (4×). The THF was evaporated from the filtrate under reduced pressure and the yellow viscous residual product was distilled using a Kugelrohr under high vacuum to give 11.0 g (73.2% yield) bis(3-hydroxypropyl)sulfide as a pale yellow liquid.

Preparation of bis(3-Mercaptopropyl)sulfide [8]

A mixture of *bis*(3-hydroxypropyl)sulfide (7.47 g, 49.7 mmol), thiourea (8.68 g, 114 mmol) and concentrated aqueous HCl (33 mL) was refluxed overnight. The reaction mixture was cooled in an ice/water bath and a solution of KOH (19.4 g, 1.2 mol) in H_2O (75 mL) was slowly added. The reaction mixture was heated to reflux and refluxed for 3 h. The reaction mixture was cooled to room temperature and acidified with 10% aqueous HCl. The aqueous solution was extracted with ether (3×), the ether extracts combined, dried ($MgSO_4$), and the ether evaporated to leave a yellow residual liquid that was distilled (Kugelrohr) under high vacuum to give 4.90 g (54.1% yield) bis(3-mercaptopropyl)sulfide as a pale yellow liquid.

Preparation of 1,5,9-Trithiacyclododecan-3-one (Keto-12-ane-S_3)

A 1-L three-necked round-bottom flask, equipped with syringe-drive pump, magnetic stir bar, reflux condenser, heating mantle, and a nitrogen inlet-outlet, was charged with freshly distilled dimethylformamide (DMF, 250 mL) and cesium carbonate (35.4 g, 109 mmol). Into one syringe was added a solution of bis(3-mercaptopropyl)sulfide (19.9 g, 109 mmol) and sufficient anhydrous DMF to dilute to 125 mL. Into the other syringe was added a solution of 1,3-dichloroacetone (13.8 g, 109 mmol) and sufficient anhydrous DMF to dilute to 125 mL. The two solutions were added simultaneously to the rapidly stirred and heated (held at ca 90°C) DMF/Cs_2CO_3 mixture. Upon completion of the addition (6 h), the reaction mixture was stirred for an additional 18 h and was then allowed to cool to room temperature. The reaction mixture was vacuum filtered and the DMF was removed by rotary evaporation to give a dark brown residual solid. The residue was chromatographed in 2-g portions using MPLC on a silica gel column (51 mm diameter × 45 cm length), eluting with 20% ethyl acetate in hexane to give 1.023 g (4.3% yield) keto-12-ane-S_3 as a colorless crystalline solid: mp 104°C; ^{1}H NMR ($CDCl_3$) δ 1.83–1.92 (m, 4 H, $SCH_2CH_2CH_2S$), 2.59–2.78 (m, 8 H, $SCH_2CH_2CH_2S$), 3.52–3.54 (m, 4 H, $SCH_2C{=}O$); IR (KBr) 2951, 2902, 2830, 1694 (s, C=O), 1433, 1416, 1404, 1369, 1346, 1296, 1257, 1240, 1207, 1180, 1155, 1140, 1123, 1071, 1045, 1039, 964, 951, 910, 866, 834, 791, 759, 746, 710, 564 cm^{-1}; Anal. Calcd. for $C_9H_{16}S_3O$: C, 45.72; H, 6.82; S, 40.69. Found: C, 45.67; H, 6.83; S, 40.77.

Preparation of 1,5,9-Trithiacyclododecane-3-ol (Hydroxy-12-ane-S_3)

A solution of bis(3-mercaptopropyl)sulfide (16.81 g, 92.18 mmol) in anhydrous DMF (total volume = 50 mL), and a solution of 1,3-dichloro-2-propanol (11.98 g, 92.18 mmol) in anhydrous DMF (total volume = 50 mL), were added simultaneously via syringe drive pump (at a rate of 5 mL/hour) to a heated (90°C) and stirred slurry of cesium carbonate (30.03 g, 92.18 mmol) in anhydrous DMF (2 L) under dry nitrogen atmosphere. Upon completion of the addition (10 h), the mixture was allowed to cool, the CsCl was filtered off, and the DMF was removed from the filtrate by rotary evaporation to give 29.08 g of a dark brown viscous liquid. The product was purified by chromatography (MPLC, silica gel, 20% EtOAC/hexane; 2.5-g portions, 50 × 5 cm column) to give 4.384 g (19.9% yield) hydroxy-12-ane-S_3 as a colorless crystalline solid: mp 95–97°C; IR (KBr, cm^{-1}) 3513–3220 (s, b, O—H), 2897, 1411, 1307, 1289, 1254, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.84–1.92 (m, 4 H, $SCH_2CH_2CH_2S$), 2.51–3.03 (m, 12 H, $SCH_2CH_2CH_2S$ and SCH_2CHOH), 3.98–4.05 (m, 1 H, CHOH); Anal. Calcd. for $C_9H_{18}S_3$: C, 45.34%; H, 7.61%; S, 40.34%. Found: C, 45.24%; H, 7.62%; S, 40.43%.

X-ray Single Crystal Structure Study of Hydroxy-12-ane-S_3 [13]

Clear colorless crystals of hydroxy-12-ane-S_3 were obtained by vapor diffusion of a solution of the compound in ethyl acetate with pentane. A well formed crystal was mounted in a Rigaku AFC5R diffractometer equipped with scintillation counter and CuKα radiation (λ = 1.54178 Å, Rigaku rotating anode generator run at 50 kV and 100 mA). The θ-2θ technique was used to collect the data ($2\theta \leq 120.0°$) of which those with $I \geq 3\sigma(I)$ were considered observed and were used in the calculations.

The structure was solved by direct methods and refined by full-matrix least-squares techniques. The hydrogen atoms were added to the model in geometrically ideal positions and were not refined. Anisotropic refinement converged at R = 0.038, R_w = 0.053, and GOF = 1.76. The largest peak in the final difference map was 0.63 e^-/A^3.

ACKNOWLEDGMENTS

Acknowledgment is made to the donors of the Petroleum Research Fund administered by the American Chemical Society (PRF #19797-B3), to Research Corporation (Grant Number C-2396), and the National Institutes of Health (NIH Grant R15 GM 40129).

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