The hydrochloride of compound 14 was dissolved in water, made basic (6 N NaOH), and extracted (CH_2Cl_2). The methylene chloride extracts were washed (water), dried (Na_2SO_4), lightly charcoaled and concentrated in vacuo. The residual oil crystallized on standing, mp 60–63 °C. This material was recrystallized from ether/hexane to give the *meso*-2,3,4,5,5a,11a-hexahydro[1,4]benzodioxino[2,3-*d*]azepine **14**: mp 64–65 °C; NMR δ 6.86 (s, 4), 4.40 (t, 2), 3.40–2.40 (m, 4), 2.40–1.50 (m, 4); IR (Nujol) 3220 (m), 1594 (m), 1492 (s), 1264 (s), 1028 (m), 964 (m), 842 (m), 776 (m), 740 (m) cm^{-1}.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.51; H, 7.47; N, 6.89.

Dextrorotatory *meso*-3-[(2-Oxo-10-bornanyl)sulfonyl]-1,2,4,5,5a,11a-hexahydro[1,4]benzodioxino[2,3-*d*]azepine (15). To a cooled (ice bath) and well-stirred solution of the hexahydrobenzodioxinoazepine **14** (1.6 g, 0.0078 mol) in ethyl acetate (25 mL) was added diisopropylethylamine (1.3 g, 0.01 mol) and *d*-10-camphorsulfonyl chloride (1.96 g, 0.0078 mol). The ice bath was removed and the mixture stirred overnight. Additional ethyl acetate (75 mL) was added to dissolve a precipitate. The solution was washed (2 N HCl, water, saturated $NaHCO_3$, water) and dried (Na_2SO_4), and the ethyl acetate was removed in vacuo. The crystalline residue (3.07 g) was recrystallized from ethanol to give dextrorotatory *meso*-3-[(2-oxo-10-bornanyl)sulfonyl]-1,2,4,5,5a,11a-hexahydro[1,4]benzodioxino[2,3-*d*]azepine (**15**), mp 153.5–155 °C (2.67 g, 0.0064 mol, 64%). Two further recrystallizations from ethanol gave material, mp 154.5–155 °C. There was no change in rotation, $[\alpha]^{25}_D$ +24.92° (*c* 14.645 mg/mL, $CHCl_3$): NMR (Me_2SO) δ 6.86 (s, 4), 4.46 (m, 2), 1.04 (s, 3), 0.82 (s, 3); IR (Nujol) 1740 (s), 1590 (m), 1492 (s), 1323 (s), 1269 (s), 1137 (s), 756 (s), 748 (s) cm^{-1}; CD in CH_3OH (*c* 1 mg/mL)[10] single Cotton effect $[\theta]_{288}$ 3000. [*N,N*-Dimethyl-*d*-camphorsulfonamide CD in CH_3OH (*c* 1 mg/mL) Cotton effect $[\theta]_{288}$ 3200.]

Anal. Calcd for $C_{22}H_{29}NO_5S$: C, 62.98; H, 6.97; N, 3.34. Found: C, 63.28; H, 7.26; N, 3.35.

Conversion of the *d*-Camphorsulfonamide 15 to the Benzodioxinoazepine 14. The *d*-camphorsulfonamide **15** (1.6 g, 0.00382 mol) in benzene (15 mL) was added to Red-al (Aldrich Chemical Co.) (7.7 mL, 0.0267 mol) in benzene (5 mL). The mixture was refluxed for 4.5 h, cooled, and treated with 4 N NaOH (20 mL) for 15 min. The aqueous layer was separated, washed (Et_2O), and discarded. The ether washes and the benzene were in turn washed (2 N NaOH, water), dried (Na_2SO_4), and concentrated in vacuo. The residue (0.98 g, theory 0.78 g) was partially crystalline. It was dissolved in ether and the crystalline material (0.2 g) removed by filtration. The filtrate was concentrated in vacuo. The residue was dissolved in ethyl acetate (10 mL) and treated with dry HCl in ethyl acetate. The crystalline precipitate (0.36 g), mp 233–234 °C, did not give a mixture melting point depression with the previously obtained *meso*-2,3,4,5,5a,11a-hexahydro[1,4]-benzodioxino[2,3-*d*]azepine hydrochloride (**14**). A CD spectrum of the hydrochloride obtained from the above described reduction showed no optical activity in the scanning range (230–400 nm in CH_3OH, *c* 1 mg/mL). A portion of this hydrochloride **14** was converted to the free base **14** as described previously. This free base, mp 59–63 °C, was identical (NMR, IR) with the *meso*-2,3,4,5,5a,11a-hexahydro[1,4]benzodioxino[2,3-*d*]azepine (**14**) previously obtained.

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Registry No.—**1**, 7664,47-3; **2**, 63588-62-5; **2** hydrobromide, 63588-74-9; **4**, 63588-63-6; **5**, 27350-82-9; **6**, 63588-64-7; **6** HCl, 63588-65-8; **7**, 27354-40-1; **7** HCl, 27507-46-6; **8**, 793-19-1; **9**, 63588-66-9; **10**, 63588-67-0; **11**, 63588-68-1; **12**, 63588-69-2; **13**, 63588-70-5; **14**, 63588-71-6; **14** HCl, 63588-72-7; **15**, 63588-73-8; chlorotrimethylsilane, 75-77-4; methanesulfonyl chloride, 124-63-0; *d*-10-camphorsulfonyl chloride, 21286-54-4.

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(8) We thank Dr. R. Rodebaugh of Central Research, CIBA-GEIGY Corp., Ardsley, N.Y., for these spectra and their interpretation. They were obtained on a Varian CFT-20 instrument.
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Synthesis of a New Series of Macrocyclic Polyether–Diester Ligands[1]

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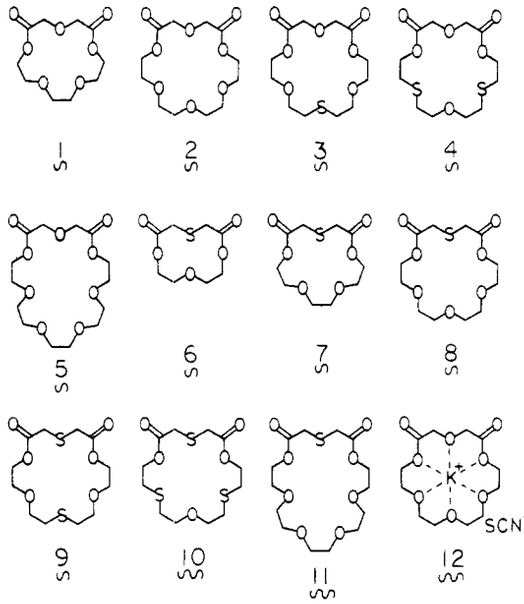
A new series of macrocyclic polyether–diester ligands (**1–11**) have been prepared by treating various oligoethylene glycols and sulfur-containing oligoethylene glycols with diglycolyl and thiodiglycolyl dichlorides. The compounds prepared were: 1,4,7,10,13-pentaoxacyclopentadecane-2,6-dione (**1**), 1,4,7,10,13,16-hexaoxacyclooctadecane-2,6-dione (**2**), 1,4,7,10,16-pentaoxa-13-thiacyclooctadecane-2,6-dione (**3**), 1,4,7,13-tetraoxa-10,16-dithiacyclooctadecane-2,6-dione (**4**), 1,4,7,10,13,16,19-heptaoxacycloheneicosane-2,6-dione (**5**), their 4-thia analogues **7, 8, 9, 10,** and **11**, respectively, and 1,7,10-trioxa-4-thiacyclododecane-2,6-dione (**6**). We have also prepared the potassium thiocyanate complex of **2** (**12**).

The synthesis and unique cation complexing characteristics of a number of cyclic polyethers were first reported by Pedersen[2] a decade ago. Since that time, a large number and variety of macrocyclic compounds have been prepared[3] and their cation complexing properties have been studied extensively.[4–11] It was originally postulated[2] and since confirmed by measurement of stability constants[10] that a qualitative relationship exists between complex stability and the ratio of cation diameter to ligand cavity diameter. It has become increasingly evident, however, that the stability of these complexes depends significantly on other cation and ligand parameters. For example, K^+ and Ba^{2+} have nearly identical ionic radii (1.33 and 1.34 Å, respectively),[12] and on the basis of electrostatics alone, one would predict that the stability order $Ba^{2+} > K^+$ would be found for complexes where the ligand cavity would accommodate these cations. Although

Chart I



thermodynamic data are not available for all systems, a number of examples have emerged where stability orders of $Ba^{2+} \approx K^+$ and $K^+ > Ba^{2+}$ exist.[8,11,13] One of our research objectives is to prepare molecules which will allow us to systematically examine the parameters which affect complex stability and to understand that stability in terms of ΔH and $T\Delta S$ values for complex formation.

We have previously reported the synthesis of numerous thia-crown compounds.[14-17] Recently, we have undertaken the synthesis of macrocyclic ether–esters[8,11,18-21] and their substituted derivatives,[11,20] thioether–esters,[11,19] ether–thiolesters,[19] amine–esters,[21] ether–ester–amides,[21] and ester–amides.[21]

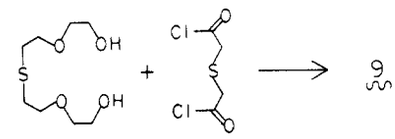
A preliminary calorimetric investigation of the reaction in methanol of Na^+, K^+, Ag^+, and Ba^{2+} with compounds **2** and **8** (Chart I) has been reported.[8,11] The stability order $K^+ \approx Ba^{2+}$ found for **2** is different from that ($Ba^{2+} > K^+$) found for 18-crown-6. Compound **8** shows no heat of reaction with Na^+, K^+, or Ba^{2+} indicating that the log K is small and/or the enthalpy change is near zero. The absence of a heat of reaction may be due to competing steric effects or cavity size considerations much like those described for 1-thia-18-crown-6 or 1,10-dithia-18-crown-6.[15] The synthetic compounds **1–11** have carbonyl groups available for cation complexation as does valinomycin, a cyclic antibiotic which shows selectivity for potassium over barium in methanol. The significance of this observation is that it demonstrates the possibility of preparing macrocyclic compounds containing carbonyl oxygen donor atoms which will have cation selective properties resembling those of the cyclic antibiotics. Such synthetic compounds may prove extremely useful as models for the investigation of biological cation transport and selectivity processes.[8,11]

The preparation of certain macrocyclic esters has been reported previously. Drewes and co-workers[22-24] have prepared several macrocyclic di- and tetraesters from phthalic and maleic acid moieties. They treated the dipotassium salts of phthalic and maleic acids with a series of alkyl and alkynyl dibromides to make 10–34-membered ring compounds. In a recent paper,[25] Drewes and Riphagen reported two compounds derived from 2,2′-dithiodibenzol chloride and tri- and tetraethylene glycol. These compounds are very similar to the compounds reported in this paper in that they are of the ether–ester type.

In this paper we report the synthesis of several polyether–diester compounds by reaction of various oligoethylene glycols and sulfur-containing oligoethylene glycols with diglycolyl and thiodiglycolyl dichlorides (**1–11**, Chart I). We have prepared 1,4,7,10,13-pentaoxacyclopentadecane-2,6-dione (**1**), 1,4,7,10,13,16-hexaoxacyclooctadecane-2,6-dione (**2**), 1,4,7,10,16-pentaoxa-13-thiacyclooctadecane-2,6-dione (**3**), 1,4,7,13-tetraoxa-10,16-dithiacyclooctadecane-2,6-dione (**4**), 1,4,7,10,13,16,19-heptaoxacycloheneicosane-2,6-dione (**5**), 1,7,10-trioxa-4-thiacyclododecane-2,6-dione (**6**), 1,7,10,13-tetraoxa-4-thiacyclopentadecane-2,6-dione (**7**), 1,7,10,13,16-pentaoxa-4-thiacyclooctadecane-2,6-dione (**8**), 1,7,10,16-tetraoxa-4,13-dithiacyclooctadecane-2,6-dione (**9**), 1,7,13-trioxa-4,10,16-trithiacyclooctadecane-2,6-dione (**10**), and 1,7,10,13,16,19-hexaoxa-4-thiacycloheneicosane-2,6-dione (**11**). We have also prepared the potassium thiocyanate complex of **2** (**12**) (see Chart I).

Results and Discussion

The compounds (**1–11**) shown in Chart I were prepared from the appropriate diacid chloride and oligoethylene glycol. Compound **9**, for example, was prepared from thiodiglycolyl dichloride and 1,4,10,13-tetraoxa-7-thiatridecane. The reac-



tions were run under high-dilution techniques by simultaneously dripping each of the reactants into a large volume of benzene that was being stirred rapidly. Yields were generally in the range of 20 to 35% with the notable exception of **6**. A space filling model of compound **6** (yield 4.8%) shows that significant steric and rotational barriers exist in the molecule. A model of the diglycolate analogue shows even greater barriers and all attempts to isolate this analogue were unsuccessful.

The structures proposed for the macrocyclic polyether–diesters are consistent with data derived from IR and NMR spectra, combustion analyses, and molecular-weight determinations. The ester carbonyls all exhibit IR bands at 1715 to 1755 cm^{-1}. Those run as KBr wafers generally show the two carbonyl groups to have different stretching frequencies, while those run neat or as melts show only one wavelength of absorption. For example, compound **2** shows bands at 1715 and 1730 cm^{-1} in the IR spectrum. Preliminary x-ray crystallographic results[26] of compound **2** are consistent with the IR spectral findings, showing that one of the carbonyl groups is approximately 90° out of plane while the other is nearly coplanar with the molecule. The IR spectrum of compound **12**, the potassium thiocyanate complex of **2**, shows only one ester band in the IR spectrum at 1740 cm^{-1}. From this observation we conclude that (i) since the carbonyl stretch has been shifted to a higher resonance frequency, the complex probably does not involve the carbonyl oxygen atoms, and (ii) the molecule is organized in a planar arrangement around the central K^+ ion. All diglycolate esters (**1–5**) exhibit a singlet in the NMR spectrum at δ 4.27 ± 0.05 ($COCH_2O$), while the corresponding singlet for the thiodiglycolate esters (**6–11**) appears at δ 3.44 ± 0.10 ($COCH_2S$). All the macrocyclic diesters (**1–11**) exhibit NMR signals at δ 4.35 ± 0.03 ($COOCH_2$) and δ 3.73 ± 0.04 ($COOCH_2CH_2O$) or δ 2.87 ± 0.02 ($COOCH_2CH_2S$). All ether methylene hydrogen and sulfide methylene hydrogen atoms not classified above exhibit NMR signals at δ 3.67 ± 0.05 and 2.79 ± 0.04, respectively. With the exception of a small downfield shift for all protons, the NMR spectrum of compound **12** is very similar to that of **2**.

Compounds were submitted for a combustion analysis only after a satisfactory molecular weight[27] had been determined by osmometry (average error was 2.06% of calculated). This technique was employed to ensure that quoted yields are

Table I. A Comparison of the Physical Properties of the Macrocyclic Polyether–Diesters to their Crown Analogues

Compd	Registry no.	Yield, %	Mp, °C	Bp, °C	Ref
1	63689-58-7	26.4	100.5–101.5	145 (0.2 mm)	
15-Crown-5		14		100–135 (12 mm)	*a*
2	62796-84-3	35.0	78.5–79.5	148 (0.16 mm)	
18-Crown-6		2–93	39.5–40.5		*a*
3	63689-59-8	35.6	113.5–115		
1-Thia(18-crown-6)		36	29.5–30.5	164–170 (0.1 mm)	*b*
4	63689-60-1	19.5	36–36.5		
1.7-Dithia(18-crown-6)		29		174–179 (1 mm)	*b*
5	63689-61-2	25.6		200 (0.2 mm)	
21-Crown-7		18			*a*
6	63689-62-3	4.8	93.5–94.5	155 (1 mm)	
1-Thia(12-crown-4)		14		80–87 (1 mm)	*a*
7	63689-63-4	23.0	85.5–86.5	156 (1 mm)	
1-Thia(15-crown-5)		29		123–124 (0.1 mm)	*a*
8	63689-64-5	20.0	43.5–44.5	181 (0.4 mm)	
1-Thia-(18-crown-6)		36	29.5–30.5	164–170 (0.1 mm)	*b*
9	63689-65-6	11.5	106–107		
1,10-Dithia(18-crown-6)		12	88–89		*a*
10	63689-66-7	31.0			
1,7,13-Trithia(18-crown-6)					*c*
11	63689-67-8	23.1		204 (0.2 mm)	
1-Thia(21-crown-7)					*c*

[a] Reference 3. [b] Reference 15. [c] Has not been reported.

based on monomer formation and to check the purity of samples submitted for analysis.

All compounds (**1–12**) in this series appear to be quite stable. Compounds **1, 2, 5–8,** and **11** were isolated at temperatures of 145–205 °C by vacuum distillation through a short-path distillation apparatus.

Some interesting observations can be made in the comparison of the physical properties and product yields of the macrocyclic polyether–diesters reported here and their crown analogues (see Table I).

A preliminary comparison using calorimetric titration of the cation–ligand interaction in methanol of **2** and 18-crown-6 is available.[8] This comparison is useful in understanding the effect of the ester moieties on the cation complexing properties of macrocyclic ligands. A marked decrease in complex stability as measured by log K is found for the Ba^{2+}, K^+, and Na^+ complexes in going from 18-crown-6 (log K = 7.0, 6.05, and 4.36 kcal/mol, respectively) to **2** (log K = 3.1, 2.79, and 2.5 kcal/mol, respectively). In addition, the relative differences between the log K values for these cations are much smaller in the case of **2.** The decreased stabilities of the cation complexes of **2** are primarily a result of smaller ΔH values,[8] as opposed to the $T\Delta S$ values which favor complexation of **2** relative to 18-crown-6. Compound **8** which shows no heat of reaction with Na^+, K^+, or Ba^{2+} does interact with Ag^+ (log K = 3.05 kcal/mol).

Summary. Through the macrocyclic compounds reported here and by the systematic study of the cation–ligand interaction parameters of these and other compounds,[8,11] we have demonstrated the possibility of modifying the cation-selective properties of several synthetic macrocyclic ligands. These modifications are a significant step in our understanding of the requirements for selective complexation.

Experimental Section

All infrared (IR) spectra were obtained on a Perkin-Elmer Model 457 spectrophotometer. The proton nuclear magnetic resonance (NMR) spectra were obtained on a Varian EM-390 spectrophotometer in deuteriochloroform using tetramethylsilane as an internal standard. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., or by Eisenhower Laboratories, Holly Hill, Fla. The molecular-weight determinations were by osmometry on a Hitachi Perkin-Elmer 115 molecular weight apparatus. Melting points were determined on a Thomas-Hoover capillary-type melting-point apparatus and are uncorrected. Reagent-grade solvents were used without further purification.

Materials. Diglycolyl and thiodiglycolyl dichlorides were prepared from the commercially available acids by the method of Dietrich et al.[28] Diglycolic acid (Aldrich, 100 g, 0.75 mol) was mixed with 700 mL of $CHCl_3$ and cooled in an ice bath. To the cooled mixture, 317 g (1.52 mol) of PCl_5 was added as rapidly as possible. The mixture was allowed to warm to room temperature and was slowly heated to reflux. The reaction mixture was allowed to reflux 36 h. The solvent and most of the $POCl_3$ formed in the reaction were removed under reduced pressure and the remaining oil was distilled. After removal of the residual $POCl_3$ under vacuum, 115 g (90%) of the desired dichloride was obtained, bp 56 °C (0.5 mm).

Thiodiglycolyl dichloride was similarly prepared from thiodiglycolic acid (Evans) in an 84% yield, bp 55 °C (0.2 mm).

1,4,10,13-Tetraoxa-7-thiatridecane was prepared by a method similar to that of Brown and Woodward.[29] 2-(2-Chloroethoxy)ethanol (145.8 g, 1.11 mol, 95%, Parish) was dripped into a warm solution of 132.1 g (0.55 mol) of $Na_2S{\cdot}9H_2O$ in 1 L of absolute EtOH. The reaction was allowed to stir at approximately 50 °C until a neutral pH was obtained (5 days). The reaction mixture was acidified and filtered on a glass frit. After the EtOH was removed under reduced pressure, the residual oil was taken up in $CHCl_3$. The resulting solution was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The resulting brown oil was distilled yielding a pale yellow oil (54.2 g, 45.9%), bp 160 °C (0.5 mm) [lit.[29] 180 °C (1.5 mm)].

1,7,13-Trioxa-4,10-dithiatridecane was prepared by a method similar to that of Woodward.[30] To a mixture of 100 g (0.72 mol) of 2-mercaptoethyl ether and 58 g (1.45 mol) of NaOH in benzene was added 118.5 g (1.47 mol) of 2-chloroethanol. The reaction was allowed to reflux for 24 h during which time water was removed via a Dean-Stark trap. The reaction mixture was acidified and filtered to remove the salt. The solvent was removed under reduced pressure and the residual yellow oil was distilled. The product (59.9 g, 36.8%) was a pale yellow oil which solidified upon standing, bp 186 °C (0.6 mm) [lit.[30] 215 °C (2.5 mm)].

General Procedure for Synthesis. The appropriate glycol and diacid chloride, each dissolved in 200 mL of benzene unless otherwise specified, were simultaneously dripped into 1 L of rapidly stirring benzene at 50 °C. The mixture was allowed to stir at 50 °C for at least 2 days during which time HCl gas was evolved. After the reaction was complete, the benzene was removed under reduced pressure. The crude product purified either by vacuum distillation or by continuous

extraction with hot hexane.[31] Specific details are given for each compound.

1,4,7,10,13-Pentaoxacyclopentadecane-2,6-dione (1). Diglycolyl dichloride (16.0 g, 0.094 mol) and triethylene glycol (Baker, 14.1 g, 0.094 mol) were used. After a small forerun, the product (6.17 g, 26.4%) distilled as a colorless oil which crystallized in the receiver: bp 145 °C (0.2 mm); mp 100.5–101.5 °C. The compound exhibited the following spectra: IR (KBr) 1755 cm^{-1}; NMR δ 3.62 (s, 4 H, OCH_2CH_2O), 3.69 (t, 4 H, J = 4.5 Hz, $COOCH_2CH_2O$), 4.27 (s, 4 H, $COCH_2O$), and 4.37 (t, 4 H, J = 4.5 Hz, $COOCH_2$).

Anal. Calcd for $C_{10}H_{16}O_7$: C, 48.38; H, 6.50; mol wt 248.24. Found: C, 48.25; H, 6.48; mol wt 254.

1,4,7,10,13,16-Hexaoxacyclooctadecane-2,6-dione (2). Diglycolyl dichloride (16.0 g, 0.094 mol) and tetraethylene glycol (Aldrich, 18.2 g, 0.094 mol) were used. The product (13.51 g, 49.2%) was distilled, mp 74–76 °C. Redistillation and collection of the fraction at 148 °C (0.16 mm) gave 9.62 g (35.0%) which crystallized in the receiver: mp 78.5–79.5 °C; IR (KBr) 1730, 1715 cm^{-1}; NMR δ 3.63 (s, 8 H, OCH_2CH_2O), 3.71 (m, 4 H, $COOCH_2CH_2O$), 4.28 (s, 4 H, $COCH_2O$), and 4.35 (m, 4 H, $COOCH_2$).

Anal. Calcd for $C_{12}H_{20}O_8$: C, 49.31; H, 6.90; mol wt 292.29. Found: C, 49.27; H, 6.87; mol wt 297.

1,4,7,10,16-Pentaoxa-13-thiacyclooctadecane-2,6-dione (3). Diglycolyl dichloride (13.2 g, 0.077 mol) and 1,4,10,13-tetraoxa-7-thiatridecane (16.24 g, 0.077 mol) were used. The product (9.78 g) was extracted[31] from the crude reaction mixture. Recrystallization of the white solid from $CHCl_3$:ether yielded 8.44 g (35.6%) of small, white crystals, mp 113.5–115 °C. The product exhibited the following spectra: IR (KBr) 1750, 1740 cm^{-1}; NMR δ 2.80 (t, 4 H, J = 6.5 Hz, OCH_2CH_2S), 3.70 (m, 8 H, $COOCH_2CH_2OCH_2$), 4.31 (s, 4 H, $COCH_2O$), and 4.35 (m, 4 H, $COOCH_2$).

Anal. Calcd for $C_{12}H_{20}O_7S$: C, 46.74; H, 6.54; mol wt 308.35. Found: C, 46.56; H, 6.72; mol wt 326.

1,4,7,13-Tetraoxa-10,16-dithiacyclooctadecane-2,6-dione (4). Diglycolyl dichloride (13.68 g, 0.080 mol) and 1,7,13-trioxa-4,10-dithiatridecane (18.11 g, 0.080 mol) were used. The glycol was dissolved in 200 mL of 50/50 THF:benzene. The crude reaction mixture was extracted[31] and the product (5.07 g, 19.5%) was recrystallized from hexane: mp 36–36.5 °C; IR (melt) 1750 cm^{-1}; NMR δ 2.75 (t, 4 H, J = 6.5 Hz, $COOCH_2CH_2SCH_2$), 2.85 (t, 4 H, J = 6.5 Hz, $COOCH_2CH_2S$), 3.64 (t, 4 H, J = 6.5 Hz, SCH_2CH_2O), 4.22 (s, 4 H, $COCH_2O$), and 4.35 (t, 4 H, J = 6.5 Hz, $COOCH_2$).

Anal. Calcd for $C_{12}H_{20}O_6S_2$: C, 44.43; H, 6.21; mol wt 324.42. Found: C, 44.29; H, 6.34; mol wt 336.

1,4,7,10,13,16,19-Heptaoxacycloheneicosane-2,6-dione (5). Diglycolyl dichloride (12.0 g, 0.070 mol) and pentaethylene glycol (Columbia, 16.7 g, 0.070 mol) were used. After a small forerun, the product (6.03 g, 25.6%) distilled as a colorless, viscous oil, bp 200 °C (0.2 mm). The compound exhibited the following spectra: IR (neat) 1750 cm^{-1}; NMR δ 3.67 (d, 12 H, OCH_2CH_2O), 3.73 (m, 4 H, $COOCH_2CH_2O$), 4.30 (s, 4 H, $COCH_2O$), and 4.35 (m, 4 H, $COOCH_2$).

Anal. Calcd for $C_{14}H_{24}O_9$: C, 50.00; H, 7.19; mol wt 336.34. Found: C, 49.81; H, 6.99; mol wt 333.

1,7,10-Trioxa-4-thiacyclododecane-2,6-dione (6). Thiodiglycolyl dichloride (22.45 g, 0.120 mol) and freshly distilled diethylene glycol (Aldrich, 12.73 g, 0.120 mol) were used. The glycol was dissolved in 200 mL of THF to effect solution. Distillation of the crude reaction mixture gave a yellow oil which crystallized in the receiver, bp 155 °C (1.0 mm). The solid was decolorized with Norit and recrystallized from ether to give 1.27 g (4.8%) of small, white crystals, mp 93.5–94.5 °C. The compound exhibited the following spectra: IR (KBr) 1750, 1735 cm^{-1}; NMR δ 3.34 (s, 4 H, $COCH_2S$), 3.74 (m, 4 H, $COOCH_2CH_2O$), and 4.33 (m, 4 H, $COOCH_2$).

Anal. Calcd for $C_8H_{12}O_5S$: C, 43.63; H, 5.49; mol wt 220.25. Found: C, 43.48; H, 5.33; mol wt 225.

1,7,10,13-Tetraoxa-4-thiacyclopentadecane-2,6-dione (7). Thiodiglycolyl dichloride (19.3 g, 0.103 mol) and triethylene glycol (Baker, 15.5 g, 0.103 mol) were used. After a small forerun, the product (6.27 g, 23.0%) distilled as a colorless, viscous oil which crystallized in the receiver: bp 156 °C (0.15 mm); mp 85.5–86.5 °C; IR (KBr) 1740, 1735 cm^{-1}; NMR δ 3.48 (s, 4, H, $COCH_2S$), 3.69 (s, 4 H, OCH_2CH_2O), 3.75 (m, 4 H, $COOCH_2CH_2O$), and 4.35 (m, 4 H, $COOCH_2$).

Anal. Calcd for $C_{10}H_{16}O_6S$: C, 45.45; H, 6.10; S, 12.13; mol wt 264.30. Found: C, 45.84; H, 6.36; S, 12.18; mol wt 265.

1,7,10,13,16-Pentaoxa-4-thiacyclooctadecane-2,6-dione (8). Thiodiglycolyl dichloride (19.0 g, 0.102 mol) and tetraethylene glycol (Aldrich 19.8 g, 0.102 mol) were used. After a small forerun, the product (6.29 g, 20.0%) distilled as a colorless, viscous oil which solidified upon standing: bp 181 °C (0.4 mm); mp 41–43 °C. Recrystallization of this material from $CHCl_3$: hexane gave long, white needles; mp 43.5–44.5 °C. The compound exhibited the following spectra: IR (melt) 1740 cm^{-1}; NMR δ 3.54 (s, 4 H, $COCH_2S$), 3.71 (s, 8 H, OCH_2CH_2O), 3.77 (m, 4 H, $COOCH_2CH_2O$), and 4.35 (m, 4 H, $COOCH_2$).

Anal. Calcd for $C_{12}H_{20}O_7S$: C, 46.74; H, 6.54; S, 10.40; mol wt 308.36. Found: C, 46.95; H, 6.62; S, 10.48; mol wt 306.

1,7,10,16-Tetraoxa-4,13-dithiacyclooctadecane-2,6-dione (9). Thiodiglycolyl dichloride (14.6 g, 0.078 mol) and 1,4,10,13-tetraoxa-7-thiatridecane (16.4 g, 0.078 mol) were used. The crude reaction mixture was extracted[31] to give 3.71 g of crude product, mp 98–102 °C. The product (2.91 g, 11.5%) was obtained by recrystallization from $CHCl_3$: ether as white platelets: mp 106–107 °C; IR (KBr) 1740, 1730 cm^{-1}; NMR δ 2.83 (t, 4 H, J = 6.5 Hz, OCH_2CH_2S), 3.50 (s, 4 H, $COCH_2S$), 3.71 (m, 8 H, $COOCH_2CH_2OCH_2$), and 4.32 (m, 4 H, $COOCH_2$).

Anal. Calcd for $C_{12}H_{20}O_6S_2$: C, 44.43; H, 6.21; mol wt 324.42. Found: C, 44.51; H, 6.26; mol wt 335.

1,7,13-Trioxa-4,10,16-trithiacyclooctadecane-2,6-dione (10). Thiodiglycolyl dichloride (14.96 g, 0.080 mol) and 1,7,13-trioxa-4,10-dithiatridecane (18.11 g, 0.080 mol) were used. The product was extracted[31] from the crude reaction mixture and decolorized with Norit. The viscous oil was taken up in $CHCl_3$ and ether was added until the solution went cloudy. After the solution had been cooled at −25 °C for 12 h, the top layer was discarded and the bottom layer was dried under vacuum. The product (8.44 g, 31%), a viscous oil, exhibited the following spectra: IR (neat) 1740 cm^{-1}; NMR δ 2.78 (t, 4 H, J = 6.3 Hz, SCH_2CH_2O), 2.88 (t, 4 H, J = 7.2 Hz, $COOCH_2CH_2S$), 3.43 (s, 4 H, $COCH_2S$), 3.68 (t, 4 H, J = 6.3 Hz, SCH_2CH_2O), and 4.32 (t, 4 H, J = 7.2 Hz, $COOCH_2$).

Anal. Calcd for $C_{12}H_{20}O_5S_3$: C, 42.33; H, 5.92; mol wt 340.48. Found: C, 42.58; H, 6.03; mol wt 343.

1,7,10,13,16,19-Hexaoxa-4-thiacycloheneicosane-2,6-dione (11). Thiodiglycolyl dichloride (16.84 g, 0.090 mol) and pentaethylene glycol (Columbia, 21.45 g, 0.090 mol) were used. The product was extracted[31] from the crude reaction mixture. The yellow, viscous oil was distilled to give a colorless, viscous oil (7.31 g, 23.1%), bp 204 °C (0.2 mm). The compound exhibited the following spectra: IR (neat) 1735 cm^{-1}; NMR δ 3.47 (s, 4 H, $COCH_2S$), 3.68 (s, 12 H, OCH_2CH_2O), 3.74 (m, 4 H, $COOCH_2CH_2O$), and 4.33 (m, 4 H, $COOCH_2$).

Anal. Calcd for $C_{14}H_{24}O_8S$: C, 47.72; H, 6.86; mol wt 352.41. Found: C, 47.61; H, 6.79; mol wt 358.

1,4,7,10,13,16-Hexaoxacyclooctadecane-2,6-dione–Potassium Thiocyanate Complex (12). Potassium thiocyanate (0.3966 g, 4.081 × 10^{-3} mol) and **2** (1.1928 g, 4.081 × 10^{-3} mol) were dissolved in 20 mL of anhydrous MeOH. The solvent was allowed to evaporate to approximately 5 mL and the flask was cooled to −25 °C. After precipitation was complete, the crystalline product was filtered on a glass frit. The complex, recrystallized from MeOH:$CHCl_3$, gave small, clear prisms: mp 169–169.5 °C; IR (KBr) 2060, 1740 cm^{-1}; NMR δ 3.72 (s, 8 H, OCH_2CH_2O), 3.79 (m, 4 H, $COOCH_2CH_2O$), 4.34 (s, 4 H, $COCH_2O$), and 4.48 (m, 4 H, $COOCH_2$).

Anal. Calcd for $(C_{12}H_{20}O_8)$ KSCN: C, 40.09; H, 5.18. Found: C, 40.09; H, 5.18.

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Registry No.—**12**, 63703-88-8; 2-(2-chloroethoxy)ethanol, 628-89-7; 2-mercaptoethyl ether, 2150-02-9; 2-chloroethanol, 107-07-3; diglycolyl dichloride, 21062-20-4; triethylene glycol, 112-27-6; tetraethylene glycol, 112-60-7; 1,4,10,13-tetraoxa-7-thiatridecane, 64036-00-6; 1,7,13-trioxa-4,10-dithiatridecane, 7426-02-0; pentaethylene glycol, 4792-15-8; thiodiglycolyl dichloride, 7646-91-5; diethylene glycol, 111-46-6.

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Carbon-13 Nuclear Magnetic Resonance Spectra of Thiols and Thiolacetates: Lipoic Acid and Derivatives

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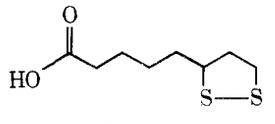
The ^{13}C NMR spectra of lipoic acid [5-(1,2-dithiolan-3-yl)pentanoic acid], lipoamide [5-(1,2-dithiolan-3-yl)pentanamide], dihydrolipoamide (6,8-dithioloctanamide), 6-*S*-acetyl-6,8-dithioloctanamide, 8-*S*-acetyl-6,8-dithioloctanamide, and methyl 6,8-*S*-diacetyl-6,8-dithioloctanoate are reported. Substituent effect parameters for primary and secondary –SH and –*S*-acetyl groups and primary $-CO_2H$, $-CONH_2$, –COCl, and $-CO_2Me$ groups have also been determined.

In connection with studies on the biochemistry of lipoic acid,[4,5] a complete analysis of the chemical shifts of lipoic acid and derivatives was needed. In this paper, we report the ^{13}C resonance assignments for lipoic acid (**1**), lipoamide (**2**), dihydrolipoamide (**3**), 6-*S*-acetyl-6,8-dithioloctanamide (**4**),



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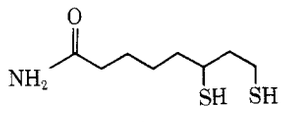

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8-*S*-acetyl-6,8-dithioloctanamide (**5**), and methyl 6,8-*S*-diacetyl-6,8-dithioloctanoate (**6**).

The ^1H-coupled ^{13}C spectra permitted unequivocal assignment of the 6 and 8 carbons of **1–6**. The remaining resonance assignments were made on the basis of T_1 measurements and were further verified by comparison with calculated chemical-shift values. To determine the calculated values, we measured the ^{13}C spectra of octanoic acid, octanamide, octanoyl chloride, methyl octanoate, 1-butanethiol, *S*-acetyl-1-butanethiol, 2-butanethiol, *S*-acetyl-2-butanethiol, propane-1,3-dithiol, and 1,3-*S*-diacetylpropane-1,3-dithiol and made chemical shift assignments. The α, β, γ, and δ substituent effects for primary and secondary –SH and –*S*-acetyl groups were determined, and were used in conjunction with the chemical shifts of the appropriate octanoic acid derivative to calculate expected chemical shifts for several lipoic acid derivatives.

Experimental Section

Lipoic acid and lipoamide were purchased from Sigma. Dihydrolipoamide was prepared by reducing lipoamide with $NaBH_4$.[6] 8-*S*-Acetyl-6,8-dithioloctanamide and 6-*S*-acetyl-6,8-dithioloctanamide were prepared by the enzymatic acetylation of dihydrolipoamide. This was accomplished by coupling the reverse of the physiological reaction catalyzed by the dihydrolipoyl transacetylase component of the pyruvate dehydrogenase complex to the phosphotransacetylase reaction.[6-8] Unreacted dihydrolipoamide [the enzyme reaction uses only the (–) isomer of dihydrolipoamide] was removed from the benzene extract by forming the dithioacetyl derivative of 2-pyridinecarboxaldehyde and then extracting with aqueous acid.

Methyl 6,8-*S*-diacetyl-6,8-dithioloctanoate was prepared from lipoic acid in several steps. First, we treated lipoic acid with methanol and concentrated H_2SO_4 to yield methyl lipoate, which we reduced with $NaBH_4$ to yield methyl 6,8-dithioloctanoate. Then acetylating with acetic anhydride and pyridine yielded methyl 6,8-diacetyl-6,8-dithioloctanoate in a fraction that distilled at 150 °C (0.2 mm).[6]

All other compounds were of either commercial origin or were prepared by standard procedures. The thiolacetates were generally prepared from the thiol and acetyl chloride.

Carbon-13 NMR spectra were obtained with a Varian XL-100-15 spectrometer operating at a frequency of 25.2 MHz and equipped with Nicolet TT-100 Data System with quadrature phase detection and 20K of memory, allowing 16K data points, 8K points in the frequency domain. All spectra of commercially available materials were mea-