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A series of macrocyclic thioether diester compounds of fourteen-seventeen-membered rings have been prepared from oxalyl, malonyl, substituted malonyl, succinyl, and substituted succinyl, chlorides and various dithiaglycols (compounds **1-12**). A twelve-membered macrocyclic thioether-dithiolester (compound **13**) was also prepared from thiadiglycolyl chloride and 2-mercaptoethyl sulfide.

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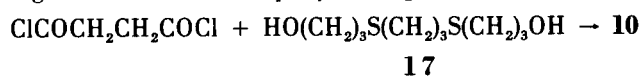
One of our research objectives is to synthesize macrocyclic multidentate compounds which have cation complexing properties similar to those of the naturally occurring macrocyclic antibiotics. We have previously reported the preparation of a variety of synthetic macrocyclic ligands including the thia-crown compounds (**1-3**) and the macrocyclic polyether-diester (4-7). The thia-crown compounds complexed very strongly with silver and mercury (11) ions (**8**) while the macrocyclic polyether-diester were found to complex with the alkali and the alkaline earth cations (**9,10**).

In order to further study the complexing properties of the sulfur containing macrocyclic compounds, we have now prepared a series of fourteen-seventeen-membered ring compounds containing both diester and thioether groups (see Fig. 1). Incorporation of the diester function

allows for a greater ease of preparation of these macrocyclic compounds (**6,7**). The reported compounds are of such a size that they could complex small transition metal cations; however no complexation studies have been done. This paper reports the synthesis of these macrocyclic thioether-diester compounds (see Fig. 1).

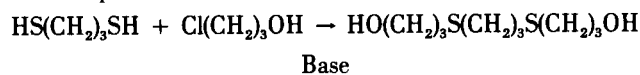
Results and Discussion.

The compounds shown in Fig. 1 were prepared from the appropriate diacid chlorides and dithia glycols. For example, compound **10** was prepared from succinyl chloride and 1,13-dioxo-5,9-dithiatridecane (**17**). These reactions were carried out at high dilution by simultaneously dripping each reactant into rapidly stirring benzene at 50°. The



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starting glycols were each prepared by reacting two equivalents of a chloroalcohol with one equivalent of a dimercaptan in a basic medium.



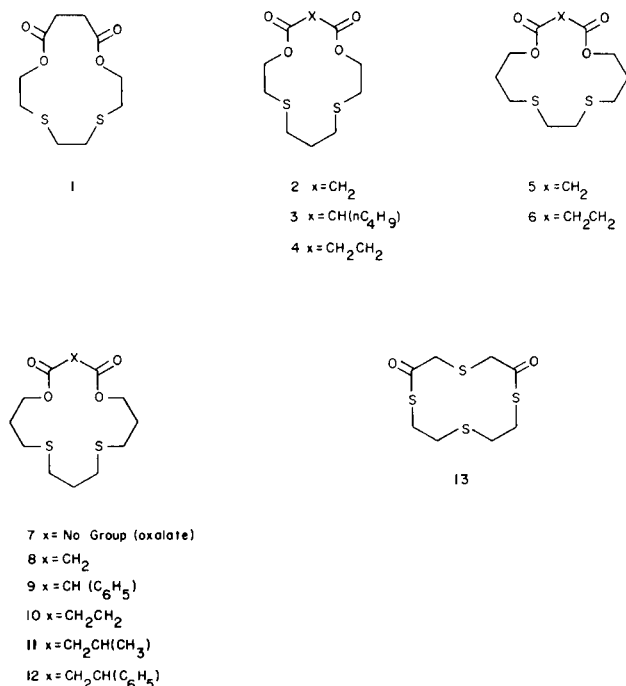
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The glycols all exhibited ir and nmr spectra and molecular weight data which were consistent with their proposed structures. Combustion analyses could not be obtained for glycols **14**, **15** and **17**, however good analyses were obtained on the macrocyclic derivatives that were prepared from each glycol.

The structures for all macrocyclic thioether diester compounds are consistent with those derived from ir and nmr spectra, combustion analyses and molecular weight determinations. The ester carbonyls all exhibited ir bands at 1730-1750 cm^{-1} except for the thiolester (**13**) which exhibited a band at 1690 cm^{-1} . All compounds exhibited nmr peaks at δ 2.6-2.8 (SCH_2) (**1,4**), 4.2-4.4 (COOCH_2) (**4,5**) and 1.92 ± 0.02 ($\text{CH}_2\text{CH}_2\text{CH}_2$). In addition the malonate esters (**2**, **5**, and **8**) exhibited a singlet nmr peak at δ 3.46 ± 0.01 (COCH_2CO) and the succinate esters (**1**, **4**, **6** and **10**) at δ 2.70 ± 0.02 ($\text{COCH}_2\text{CH}_2\text{CO}$). Each of the

FIGURE 1



substituted malonate and succinate esters (**3**, **9**, **11** and **12**) exhibited the expected nmr peaks for the substituents and the adjacent hydrogens.

The nmr spectra for the two phenyl substituted macrocyclic compounds (**9** and **12**) are interesting. In both cases, the nmr peaks attributed to the ester methylene hydrogens split into two sets of multiplets of equal intensity. These peaks show the stereochemical nature of these compounds. One set represents the ester methylene hydrogen on the same face of the macrocyclic compound as the phenyl substituent. The other set can be attributed to the hydrogens on the opposite face.

EXPERIMENTAL

All ir spectra were obtained on a Perkin-Elmer Model 457 spectrophotometer. All nmr spectra were obtained on a Varian EM-390 spectrometer in deuteriochloroform using tetramethylsilane as an internal standard. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee, or MHW Laboratories, Phoenix, Arizona. 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.

Starting Materials.

Most of the starting materials were used as purchased. Thiodiglycolyl chloride (**6**) and the substituted malonyl and succinyl chloride (**5**) were prepared from the corresponding diacids and distilled prior to use. The dithia glycols were prepared as follows:

1,10-Dioxa-4,7-dithiadecane (**14**).

2-Chloroethanol (80.5 g., 1.0 mole) in 250 ml. of ethanol was slowly added to a refluxing mixture of 47.1 g. (0.5 mole) of 1,2-ethanedithiol and 23.1 g. (1.0 mole) of sodium metal in 750 ml. of ethanol. The resulting mixture was refluxed an additional 30 minutes, cooled and filtered. The ethanol was removed under vacuum and the crude yellow product (81 g., 89%) was recrystallized from benzene, m.p. 61-62° (lit., 64°) (**11**); ir: 3400 cm⁻¹; nmr: δ 2.47 (s, 2H, OH), 2.80 (s, 4H, SCH₂CH₂S), 2.80 (t, 4H, SCH₂CH₂O), 3.77 (t, 4H, OCH₂).

Calcd. for C₈H₁₄O₂S₂: mol. wt., 182.3. Found M⁺ 182, mol. wt. 199.

1,11-Dioxa-4,8-dithiaundecane (**15**).

The above procedure using 53.67 g. (0.67 mole) of 2-chloroethanol and 36.0 g. (0.33 mole) of 1,3-propanedithiol was followed. The crude product was distilled to give a yellow viscous oil (46 g., 70%); b.p. 167°/1.5 mm; ir: 3400 cm⁻¹; nmr: δ 1.80 (m, 2H, CH₂CH₂CH₂), 2.50 (s, 2H, OH), 2.75 (overlapping triplets, 8H, SCH₂), 3.80 (t, 4H, OCH₂).

Calcd. for C₇H₁₀O₂S₂: mol. wt., 196.3. Found: mol. wt., 202.

1,12-Dioxa-5,8-dithiadodecane (**16**).

The above procedure using 31.3 g. (0.33 mole) of 3-chloro-1-propanol and 15.5 g. (0.165 mole) of 1,2-ethanedithiol was followed. The crude product (34.4 g., 99%) was recrystallized from benzene; m.p. 51-52° (lit., 53.8°) (**12**); ir: 3400 cm⁻¹; nmr: δ 1.87 (m, 4H, CH₂CH₂CH₂), 2.04 (s, 2H, OH), 2.65 (t, 4H, SCH₂), 2.78 (s, 4H, SCH₂CH₂S), 3.77 (t, 4H, OCH₂).

Anal. Calcd. for C₈H₁₆O₂S₂: C, 45.68; H, 8.62; mol. wt., 210.4. Found: C, 45.66; H, 8.84; mol. wt., 225.

1,13-Dioxa-5,9-dithiatridecane (**17**).

The above procedure using 217.44 g. (2.3 moles) of 3-chloro-1-propanol and 124.46 g. (1.15 mole) of 1,3-propanedithiol was followed. The crude product was distilled to give 180 g. (74%) of a yellow viscous oil, b.p. 178°/0.7 mm; ir: 3400 cm⁻¹; nmr: δ 1.86 (m, 6H, CH₂CH₂CH₂), 2.65 (overlapping triplets, 8H, SCH₂), 3.17 (s, 2H, OH), 3.73 (t, 4H, OCH₂).

Calcd. for C₉H₂₀O₂S₂: mol. wt. 224.4. Found: mol. wt., 229.

General Synthesis.

The macrocyclic compounds were prepared by simultaneously dripping the glycol dissolved in 200 ml. of a 3:1 mixture of benzene and tetrahydrofuran and the diacid chloride dissolved in 200 ml. of benzene into 1000 ml. of rapidly stirring benzene at 50°. The resulting mixture was stirred at 50° for two days. The benzene was then removed under reduced pressure and the crude product extracted with hot hexane (**6**). Specific details are given for each compound.

1,10-Dioxa-4,7-dithiacyclotetradecane-11,14-dione (**1**).

Succinyl chloride (10.32 g., 0.065 mole) and 12.2 g. (0.067 mole) of glycol **14** were used. The product was recrystallized from ethanol to give white prisms, 0.14 g. (0.8%); m.p. 102-103°; ir: 1740 cm⁻¹; nmr: δ 2.68 (s, 4H, SCH₂CH₂S), 2.72 (s, 4H, COCH₂), 2.80 (t, 4H, SCH₂), 4.30 (t, 4H, COOCH₂).

Anal. Calcd. for C₁₀H₁₆O₄S₂: C, 45.43; H, 6.10; mol. wt., 264.4. Found: C, 45.50; H, 6.34; mol. wt., 266.

1,11-Dioxa-4,8-dithiacyclotetradecane-12,14-dione (**2**).

Malonyl chloride (7.06 g., 0.05 mole) and glycol **15** (9.85 g., 0.05 mole) were used. The product (0.3 g., 1.6%) was recrystallized from hexane; m.p. 46-47°; ir: 1740 cm⁻¹; nmr: δ 2.00 (m, 2H, CH₂CH₂CH₂), 2.75 (m, 8H, SCH₂), 3.50 (s, 2H, COCH₂CO), 4.43 (t, 4H, COOCH₂).

Anal. Calcd. for C₁₀H₁₆O₄S₂: C, 45.43; H, 6.10; mol. wt., 264.4. Found: C, 45.49; H, 6.20; mol. wt., 277.

13-*n*-Butyl-1,11-dioxa-4,8-dithiacyclotetradecane-12,14-dione (**3**).

n-Butylmalonyl chloride (8.8 g., 0.044 mole) and 8.67 g. (0.044 mole) of glycol **15** were used. The product was recrystallized from hexane to give white crystals; 0.38 g. (1.5%), m.p. 48-49°; ir: 1740 cm⁻¹; nmr: δ 0.91 (m, 3H, CH₃), 1.40 (m, 4H, CH₂CH₂CH₂), 1.90 (m, 4H, CH₂CH₂CH₂ and CHCH₂), 2.75 (m, 8H, SCH₂), 3.71 (m, 1H, COCH), 4.30 (m, 4H, COOCH₂).

Anal. Calcd. for C₁₄H₂₄O₄S₂: C, 52.52; H, 7.54; mol. wt., 320.5. Found: C, 52.42; H, 7.79; mol. wt., 327.

1,11-Dioxa-4,8-dithiacyclopentadecane-12,15-dione (**4**).

Succinyl chloride (10.32 g., 0.067 mole) and 13.13 g. (0.067 mole) of glycol **15** were used. The product was recrystallized from hexane to give white crystals, 0.8 g. (4%); m.p. 55-56°; ir: 1730 cm⁻¹; nmr: δ 1.95 (m, 2H, CH₂CH₂CH₂), 2.70 (overlapping triplets 8H, SCH₂), 2.70 (s, 4H, COCH₂CH₂CO), 4.35 (t, 4H, COOCH₂).

Anal. Calcd. for C₁₁H₁₈O₄S₂: C, 47.46; H, 6.52; mol. wt., 278.4. Found: C, 47.45; H, 6.59; mol. wt., 295.

1,12-Dioxa-5,8-dithiacyclopentadecane-13,15-dione (**5**).

Malonyl chloride (3.38 g., 0.024 mole) and 4.98 g. (0.024 mole) of glycol **16** were used. The product was recrystallized from hexane to give white needles; 0.01 g. (0.1%); m.p. 45°; ir: 1740 cm⁻¹; nmr: δ 2.00 (m, 4H, CH₂CH₂CH₂), 2.70 (m, 8H, SCH₂), 3.46 (s, 2H, COCH₂), 4.30 (t, 4H, COOCH₂).

Anal. Calcd. for C₁₁H₁₈O₄S₂: C, 47.46; H, 6.52; mol. wt., 278.4. Found: C, 47.45; H, 6.77; mol. wt., 277.

1,12-Dioxa-5,8-dithiacyclohexadecane-13,16-dione (**6**).

Succinyl chloride (3.67 g., 0.025 mole) and 5.10 g. (0.025 mole) of glycol **16** were used. The product was recrystallized from hexane to yield fluffy, white crystals; 0.4 g. (5.5%), m.p. 38-38.5°; ir: 1750 cm⁻¹; nmr: δ 1.90 (m, 4H, CH₂CH₂CH₂S), 2.70 (s, 4H, SCH₂CH₂S), 2.70 (t, 4H, SCH₂), 2.80 (s, 4H, COCH₂), 4.28 (t, 4H, COOCH₂).

Anal. Calcd. for C₁₂H₂₀O₄S₂: C, 49.29; H, 6.89; mol. wt., 292.4. Found: C, 49.20; H, 6.87; mol. wt., 290.

1,4-Dioxa-8,12-dithiacyclopentadecane-2,3-dione (**7**).

Oxalyl chloride (6.47 g., 0.05 mole) and 11.20 g. (0.05 mole) of glycol **17** were used. The product was recrystallized from ethanol to yield white crystals, 0.5 g. (3.6%), m.p. 101-102°; ir: 1760 cm⁻¹; nmr: δ 2.05 (m, 6H, CH₂CH₂CH₂), 2.65 (overlapping triplets, 8H, SCH₂), 4.40 (t, 4H, COOCH₂).

Anal. Calcd. for C₁₁H₁₈O₄S₂: C, 47.46; H, 6.52; mol. wt., 278.4.

Found: C, 47.58; H, 6.54; mol. wt., 281.

1,13-Dioxa-5,9-dithiacyclohexadecane-14,16-dione (**8**).

Malonyl chloride (7.06 g., 0.05 mole) and glycol **17** (11.26 g., 0.05 mole) were used. The product (1.1 g., 7.4%) was recrystallized from hexane; m.p. 44-45°; ir: 1740 cm^{-1} ; nmr: δ 1.96 (m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.72 (m, 8H, SCH_2), 3.47 (s, 2H, COCH_2), 4.35 (t, 4H, COOCH_2).

Anal. Calcd. for $\text{C}_{12}\text{H}_{20}\text{O}_4\text{S}_2$: C, 49.29; H, 6.89; mol. wt., 292.4. Found: C, 49.31; H, 7.01; mol. wt., 307.

15-Phenyl-1,13-dioxa-5,9-dithiacyclohexadecane-14,16-dione (**9**).

Phenylmalonyl chloride (8.1 g., 0.037 mole) and 8.3 g. (0.037 mole) of glycol **17** were used. The product (4.6 g., 34%) was recrystallized from hexane, m.p. 79.5-80°; ir: 1740 cm^{-1} ; nmr: δ 1.95 (m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.68 (t, 8H, SCH_2), 4.15 (m, 2H, COOCH_2), 4.45 (m, 2H, COOCH_2), 4.65 (s, 1H, COCH), 7.35 (s, 5H, aromatic H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{24}\text{O}_4\text{S}_2$: C, 58.67; H, 6.46; mol. wt., 368.5. Found: C, 58.83; H, 6.74; mol. wt., 369.

1,13-Dioxa-5,9-dithiacycloheptadecane-14,17-dione (**10**).

Succinyl chloride (10.32 g., 0.067 mole) and 15.01 g. (0.067 mole) of glycol **17** were used. The product was recrystallized from hexane to give white needles, 1.5 g. (8.8%), m.p. 40-41°; ir: 1730 cm^{-1} ; nmr: δ 1.90 (m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.60 (m, 8H, SCH_2), 2.65 (s, 4H, COCH_2), 4.25 (t, 4H, COOCH_2).

Anal. Calcd. for $\text{C}_{13}\text{H}_{22}\text{O}_4\text{S}_2$: C, 50.95; H, 7.24; mol. wt., 306.5. Found: C, 50.81; H, 7.23; mol. wt., 314.

15-Methyl-1,13-dioxa-5,9-dithiacycloheptadecane-14,17-dione (**11**).

Methylsuccinyl chloride (8.45 g., 0.05 mole) and 11.2 g. (0.05 mole) of glycol **17** were used. The product was recrystallized from ethanol and then hexane to yield white crystals, 0.15 g. (0.9%), m.p. 31-31.5°; ir: 1740 cm^{-1} ; nmr: δ 1.22 (d, 3H, CH_3), 1.92 (m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.65 (m, 8H, SCH_2), 2.66 (d, 2H, COCH_2), 2.83 (m, 1H, COCH), 4.25 (m, 4H, COOCH_2).

Anal. Calcd. for $\text{C}_{14}\text{H}_{24}\text{O}_4\text{S}_2$: C, 52.47; H, 7.55; mol. wt., 320.5. Found: C, 52.46; H, 7.51; mol. wt., 328.

15-Phenyl-1,13-dioxa-5,9-dithiacycloheptadecane-14,17-dione (**12**).

Phenylsuccinyl chloride (9.4 g., 0.04 mole) and 8.96 g. (0.04 mole) of glycol **17** were used. The product was recrystallized from hexane to yield white crystals, 0.8 g. (5.2%), m.p. 76-77°; ir: 1730 cm^{-1} ; nmr: δ 1.90 (m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.60 (m, 8H, SCH_2), 2.65 (d, 2H, COCH_2), 3.20 (t, 1H, COCH), 4.05 (m, 2H, COOCH_2), 4.42 (m, 2H, COOCH_2), 7.30 (s, 5H, aromatic H).

Anal. Calcd. for $\text{C}_{19}\text{H}_{26}\text{O}_4\text{S}_2$: C, 59.66; H, 6.85; mol. wt., 382.6. Found: C, 59.51; H, 6.91; mol. wt., 372.

1,4,7,10-Tetrathiacyclododecane-2,6-dione (**13**).

Thiodiglycolyl chloride (18.6 g., 0.1 mole) and 15.4 g. (0.1 mole) of

2-mercaptoethyl sulfide were used. The product was recrystallized from ethanol to yield fine, white needles, 0.3 g. (1.1%), m.p. 134-139°; ir: 1680 cm^{-1} ; nmr: δ 2.95 (m, 4H, SCH_2), 3.23 (m, 4H, COSCH_2), 3.58 (s, 4H, COCH_2S).

Anal. Calcd. for $\text{C}_8\text{H}_{12}\text{O}_2\text{S}_4$: C, 35.80; H, 4.51; mol. wt., 268.4. Found: C, 36.00; H, 4.35; mol. wt., 323; M^+ , 268.

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