The Synthesis of Macrocyclic Ether-Esters, Thioether-Esters, And Ether-Thiolesters With The Oxalyl Moiety

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A new series of macrocyclic polyether-diester compounds (**3-12**) have been prepared by treating various oligoethylene glycols or mercaptans with oxalyl chloride. The compounds prepared were: 1,4,7,10,13-pentaoxacyclopentadecane-2,3-dione (**3**), 1,4,7,13-tetraoxa-10-thiacyclopentadecane-2,3-dione (**4**), 1,4,10-trioxa-7,13-dithiacyclopentadecane-2,3-dione (**5**), 1,4,7,10,13,16-hexaoxacyclooctadecane-2,3-dione (**6**), 1,4,7,10,13,16-hexaoxacyclooctadecane-2,3,11,12-tetraone (**7**), 1,4,10,13-tetraoxa-7,16-dithiacyclooctadecane-2,3,11,12-tetraone (**8**), 7,16-dioxa-1,4,10,13-tetrathiacyclooctadecane-2,3,11,12-tetraone (**9**), 1,4,7,10,13,16-hexathiacyclooctadecane-2,3,11,12-tetraone (**10**), 1,4,7,10,13,16,19-heptaoxacycloheneicosane-2,3-dione (**11**), and 1,4,7,10,13,16,19,22-octaoxacyclotetracosane-2,3,14,15-tetraone (**12**).

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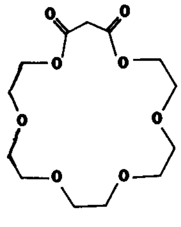
Introduction

The synthesis and complexing properties of macrocyclic polyethers has been studied extensively since first reported by Pederson in 1967 (2). There has been an effort to study these and similar compounds (3-5) because of their ability to complex metal ions (6-13). The synthetic macrocyclic polyethers resemble, in some cases, the structure and complexing properties of naturally occurring antibiotics such as valinomycin and nonactin (6).

In order to systematically study complexation parameters such as cavity size and donor atom type and size, we have attempted to prepare molecules of several series. Previously, we have reported the synthesis of several thiacrown crown compounds (14-17). Also, we have reported the synthesis of ether-esters (11,18-20,22), thioether-esters (19,22), ether-thiolesters (19), amine-esters (20), ether-ester-amides (20), and ester-amides (20).

A preliminary calorimetric investigation of the reaction in methanol of sodium, potassium, and barium ions with compounds **1** and **2** has been reported (11). The stability orders potassium ion > barium ion and potassium ion about equal to barium ion found for **1** and **2**, respectively (11), are quite different than that found for 18-crown-6 (barium ion > potassium ion). The cyclic antibiotic valinomycin like compound **1** shows selectivity for potassium over barium in methanol. It is our hope that we can prepare macrocycles to mimic the selectivities of the naturally occurring cyclic antibiotics and thereby make available models for the investigation of biological cation transportation and selectivity processes.



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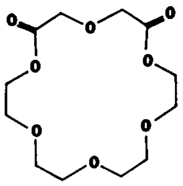

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In this paper we report the synthesis of a new series of macrocyclic polyether-ester, thioether-ester and ether-thiolester compounds with the oxalyl moiety (**3-12**, Chart I). These were made by reacting oxalyl chloride and the appropriate glycol or dimercaptan. The metal complexation properties of compound **6** appear to be similar to those of 18-crown-6. Specific details will be reported at a later date when the complexation studies are complete.

It is significant to note that the incorporation of the oxalyl moiety allows the repeating ethyleneoxide-type structures for these macrocycles. The carbonyl oxygen donor atoms may also contribute to cation selectivity properties and allow these compounds to have properties more closely resembling those of valinomycin and other naturally occurring cyclic antibiotics.

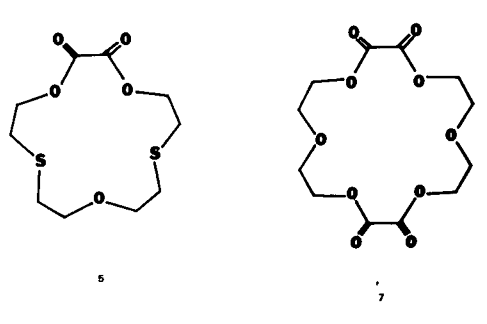

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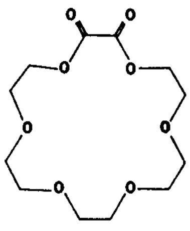
Chart I



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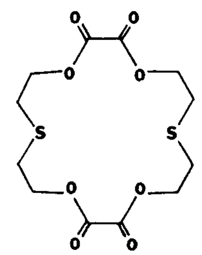

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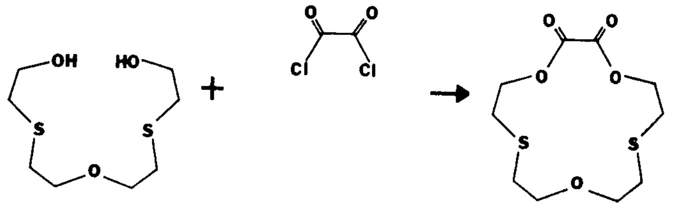

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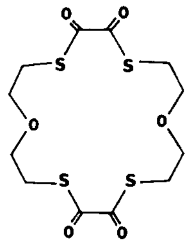

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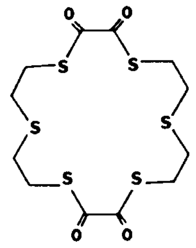

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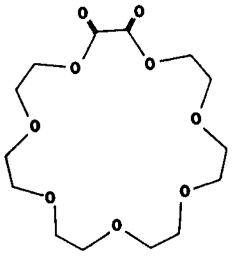

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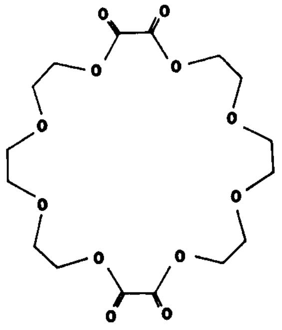

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Results and Discussion

The compounds (**3-12**) shown in Chart I were prepared from the reaction of oxalyl chloride and the appropriate glycol or dimercaptan. For example, compound **5** was prepared from oxalyl chloride and 1,7,13-trioxa-4,10-dithiatridecane. The reactions were run using high dilution techniques. The reactants were slowly added from separate dripping funnels into a large volume of stirring benzene at 40-50°. After the benzene was removed, the crude product was extracted with hot hexane or where the product was a solid, recrystallized. Most of the products were solids which were easily purified. The yields ranged from 2% to greater than 60%.

Compound **3** was purified by the usual hexane extraction and recrystallization to yield 3.7% of a white solid. The entire crude polymeric material was heated to 280° in the presence of magnesium chloride hexahydrate, a depolymerization catalyst (21). An additional 24% yield of compound **3** distilled during this reaction. Carruthers and coworkers used this latter process to prepare a variety of macrocyclic diester compounds (3,21).

Compound **12** was isolated when we attempted to prepare the 12 membered ring from oxalyl chloride and triethylene glycol. We have previously noted the difficulty of isolating 12 ring membered diester compounds (22). A good elemental analysis could not be obtained for compound **12**; however, the other physical properties, including the molecular weight, are consistent with the assigned structure.

The structures proposed for the new macrocyclic compounds are consistent with ir and nmr spectra, molecular weights and elemental analyses. The ir spectra all exhibit ester carbonyl bands at 1740-1780 cm^{-1} or thiolester carbonyl bands at 1660-1680 cm^{-1}. Data from nmr spectra indicate that all ester protons (*i.e.*, $COOCH_2$) appear at 4.49 ± 0.08 δ. Structures which contain the thiolester linkage (**9** and **10**) exhibited nmr signals at 3.34 δ (**10** where the CH_2 is β to sulfur) and 3.69 δ (**9** where the CH_2 is β to oxygen) for the corresponding protons ($COSCH_2$). All ether or thioether linkages exhibit nmr signals at 3.72 ± 0.07 δ (CH_2OCH_2) or 2.87 ± 0.07 δ (CH_2SCH_2).

Table I includes a comparison of compounds **3-12** with similar macrocyclic diester and crown analogues.

EXPERIMENTAL

All infrared (ir) spectra were obtained on a Hilger and Watts H-1200 Infragraph. A Varian EM-390 spectrometer was used to obtain the nuclear magnetic resonance (nmr) spectra. Elemental analyses were preformed by Galbraith Laboratories, Knoxville, Tennessee. The molecular weights were determined by osmometry using a Hitachi Perkin-Elmer 115 Molecular Weight Apparatus. Melting points were determined on a Thomas-Hoover Capillary type melting point apparatus and are uncorrected.

Starting Materials.

Oxalyl chloride was used as purchased from Aldrich. Some of the starting glycols were purchased: diethylene glycol (Aldrich), triethylene glycol (J. T. Baker), tetraethylene glycol (Aldrich), Pen-

Table I

A Comparison of the Physical Properties fo the New Macrocyclic Compounds with Other Macrocyclic Ether-Esters and Crown Analogues

Compound	M.p. (B.p.), °C	% Yields	Reference
3	45-46 (154-166/2mm)	28	
15-crown-5	(100-135/12mm)	14	(a)
2,6-diketo analogue of **3**	100.5-101.5	26.4	(b)
4	88-90	5.7	
1-thia (15-crown-5)	(123-124/0.1)	29	(c)
4-thia-2,6-diketo analogue of **4**	85.5-86.5	23	(b)
5	45-47	7.7	
1,7-dithia (15-crown-5)	(150-151/0.1 mm)	27	(c)
6	84-85	55	
7	162.5-164	4.2	
2,6-diketo analogue of **6**	78.5-79.5	35	(b)
18-crown-6	39.5-40.5	2-93	(d)
8	195-203	14	
4,13-dithia-2,6-diketo analogue of **8**	106-107	11.5	(b)
1,10-dithia (18-crown-6)	88-89	12	(c)
9	208-210	67	
1,4,10,13-tetrathia (18-crown-6)	125-126	4	
10	108-109 dec.	62	
hexathia (18-crown-6)	89-90	1.7-35	(e)
11	----	----	
2,6-diketo analogue of **11**	(200/0.2 mm)	25.6	(b)
21-crown-7		18	(f)
12	68-72	2.5	
24-crown-8		15	(f)

(a) F. L. Cook, T. C. Caruso, M. P. Byrne, C. W. Bowers, D. H. Speck, and C. L. Liotta, *Tetrahedron Letters*, 4029 (1974). (b) Reference (22). (c) Reference (14). (d) Reference (2). (e) L. A. Ochrymowycz, C. P. Mak, and J. D. Michna, *J. Org. Chem.*, 39, 2079 (1974). (f) R. N. Greene, *Tetrahedron Letters*, 1793 (1972).

taethylene glycol (Columbia), 1,7-dioxa-4-thiaheptane (Fluka), 4-oxa-1,7-dithiaheptane (Evans), and 1,4,7-trithioheptane (Aldrich). Hexaethylene glycol (17), 1,4,10,13-tetraoxa-7-thiatridecane (22), and 1,7,13-trioxa-4,10-dithiatridecane (22) were prepared as prepared as previously reported.

General Synthesis.

Oxalyl chloride, dissolved in 250 ml. of benzene, and the appropriate glycol or dimercaptan, dissolved in about 400 ml. of benzene unless otherwise noted, were added dropwise into 800 ml. of stirring benzene at 45°. The mixture was stirred at 45-50° for at least three days. After the reaction was complete, the benzene was removed under reduced pressure. The crude product was then purified by recrystallization or extraction with hot hexane followed by recrystallization. Specific details are given for each compound.

1,4,7,10,13-Pentaoxacyclopentadecane-2,3-dione (**3**).

Oxalyl chloride (19.0 g., 0.15 mole) and tetraethylene glycol (27.2 g., 0.14 mole) were used. The crude reaction mixture was first extracted with hot hexane and then recrystallized from 500 ml. of hexane to yield white crystals (1.4 g., 3.7%), m.p., 45-46.5°; ir (potassium bromide): 1740 cm^{-1}; nmr (deuteriochloroform): δ 3.66 (s. 8 OCH_2OCH_2O), 3,78 (m, 4, $COOCH_2CH_2O$), 4.45 (m, 4,$COOCH_2$).

Additional product (8.5 g., 24%) was isolated by heating the crude reaction mixture at 280° in the presence of 200 mg. of magnesium chloride hexahydrate (21). The product, which distilled at 154-166°/2 mm, solidified when a crystal of the recrystallized product was introduced.

Anal. Calcd. for $C_{10}H_{16}O_7$: C, 48.38; H, 6.50; mol. wt. 248. Found: C, 48.19; H, 6.63; mol. wt., 247

1,4,7,13-Tetraoxa-10-thiacyclopentadecane-2,3-dione (**4**).

Oxalyl chloride (6.7 g., 0.05 mole) and 1,4,10,13-tetraoxa-7-thiatridecane (10.0 g., 0.048 mole) were used. The crude reaction mixture was first extracted with hot hexane and then recrystallized from hexane to yield white crystals (0.7 g., 5.7%), m.p. 88-90°; ir (potassium bromide): 1740 cm^{-1}; nmr (deuteriochloroform): δ 2.80 (m, 4, OCH_2CH_2S), 3.74 (m, 8, CH_2OCH_2), 4.42 (m, 4, $COOCH_2$).

Anal. Calcd. for $C_{10}H_{16}O_6S$: C, 45.45; H, 6.10; mol. wt., 264. Found: C, 45.32; H, 5.95; mol. wt., 279.

1,4,10-Trioxa-7,13-dithiacyclopentadecane-2,3-dione (**5**).

Oxalyl chloride (7.0 g., 0.06 mole) and 1,7,13-trioxa-4,10-dithiatridecane (11.3 g., 0.05 mole) were used. The crude reaction mixture was first extracted with hot hexane and then recrystallized from hexane and chloroform to yield clear crystals (1.1 g., 7.7%), m.p. 45-57°; ir (potassium bromide): 1740 cm^{-1}; nmr (deuteriochloroform): δ 2.91 (m, 8, SCH_2), 3.70 (t, 4, OCH_2CH_2S), 4.57 (t, 4, $COOCH_2$).

Anal. Calcd. for $C_{10}H_{16}O_5S_2$: C, 42.84; H, 5.75; mol. wt. 280. Found: C, 42.69; H, 5.61; Mol. wt., 296.

1,4,7,10,13,16-Hexaoxacyclooctadecane-2,3-dione (**6**).

Oxalyl chloride (13.8 g., 0.11 mole) and pentaethylene glycol (26.0 g., 0.11 mole) were used. The crude solid was recrystallized several times from chloroform and hexane to yield a white solid (17.7 g., 55%); m.p. 84-85°; ir (potassium bromide): 1760 cm^{-1}; nmr (deuteriochloroform): δ 3.66 (s, 12, OCH_2CH_2O), 3.77 (m, 4,$\mathrm{COOCH_2C}H_2$) 4.51 (m, 4, $\mathrm{COOC}H_2\mathrm{CH_2}$).

Anal. Calcd. for $C_{12}H_{20}O_8$: C, 49.30; H, 6.91; mol. wt., 292. Found: C, 49.21; H, 7.02; mol. wt., 302.

1,4,7,10,13,16-Hexaoxacyclooctadecane-2,3,11,12-tetraone (**7**).

Oxalyl chloride (17.9 g., 0.14 mole) and diethylene glycol (15.0 g., 0.14 g.) were used. The crude reaction mixture was filtered and the solid obtained was recrystallized with chloroform and hexane to yield a white solid (0.95 g., 4.2%), m.p. 162.5-164°; ir (potassium bromide): 1750 cm^{-1}; nmr (deuteriochloroform): δ 3.78 (m, 8, $\mathrm{COOCH_2C}H_2$), 4.48 (m, 9, $\mathrm{COOC}H_2\mathrm{CH_2}$).

Anal. Calcd. for $C_{12}H_{16}O_{10}$: C, 45.00; H, 5.05; mol. wt., 320. Found: C, 44.87; H, 5.10; mol. wt., 327.

1,4,10,13-Tetraoxa-7,16-dithiacyclooctadecane-2,3,11,12-tetraone (**8**).

Oxalyl chloride (27.9 g., 0.22 mole) and thiodiethylene glycol (24.4 g., 0.20 mole) were used. The crude solid was filtered from the reaction mixture and recrystallized several times from chloroform to yield a white solid (5 g., 14%), m.p. 195-203°; ir, 1760, 1780 cm^{-1}; nmr (δ): 2.93 (m, 8, $\mathrm{C}H_2\mathrm{S}$), 4.43 (m, 8, $\mathrm{COOC}H_2$).

Anal. Calcd. for $C_{12}H_{16}O_8S_2$: C, 40.90; H, 4.58; mol. wt., 352. Found: C, 40.77; H, 4.52; mol. wt., 367.

7,16-Dioxa-1,4,10,13-tetrathiacyclooctadecane-2,3,11,12-tetraone (**9**).

Oxalyl chloride (27.9 g., 0.22 mole) and *bis*-(2-mercapto)ethyl ether (27.6 g., 0.20 mole) were used. The reaction was carried out under nitrogen at 25°. The reaction mixture was filtered to yield a cream colored solid. A portion (1.3 g.) of the solid was recrystallized with chloroform to yield light yellow crystals (.1 g., overall yield calculated to be 67%), m.p. 207.5-210°; ir (potassium bromide): 1660, 1680 cm^{-1}; nmr (deuteriochloroform): δ 3.20 (t, 8, $\mathrm{C}H_2\mathrm{O}$), 3.69 (t, 8, $\mathrm{SC}H_2$).

Anal. Calcd. for $C_{12}H_{16}O_6S_4$: C, 37.49; H, 4.19; mol. wt., 385. Found: C, 37.58; H, 4.17; mol. wt., 404.

1,4,7,10,13,16-Hexathiacyclooctadecane-2,3,11,12-tetraone (**10**).

Oxalyl chloride (27.9 g., 0.22 mole) and *bis*-(2-mercapto)ethyl sulfide (34.0 g., 0.20 mole) were used. The reaction was carried out under nitrogen at 35°. The reaction mixture was filtered to yield a light yellow solid. A portion (5 g.) of the solid was recrystallized in *N,N*-dimethylformamide to yield a white solid (4.2 g., overall yield calculated to be 62%), m.p. 108-109°; ir (potassium bromide): 1670 cm^{-1}; nmr (deuteriochloroform): δ 2.86 (t, 8, $\mathrm{C}H_2\mathrm{SC}H_2$), 3.24 (t, 8, $\mathrm{COSC}H_2$).

Anal. Calcd. for $C_{12}H_{16}O_4S_6$: C, 34.59; H, 3.87. Found: C, 34.68; H, 3.96.

1,4,7,10,13,16,19-Heptaoxacycloheneicosane-2,3-dione (**11**)

Oxalyl chloride (5.4 g., 0.043 mole) hexaethylene glycol (12.07 g., 0.043 mole) were used. The solvent was removed under reduced pressure and most of the residue was placed on an alumina column. Analyses of eluents showed decomposition of the product. The following data was taken from a small (100 mg.) sample of the crude material, ir (neat): 1750, 1770 cm^{-1}; nmr (deuteriochloroform): δ 3.65 (m, 20, $\mathrm{OC}H_2\mathrm{C}H_2\mathrm{O}$), 4.41 (m, 4, $\mathrm{COOC}H_2$).

Anal. Calcd. for $C_{14}H_{24}O_9$: C, 49.99; H, 7.21; mol. wt., 336. Found: C, 49.76; H, 7.12; mol. wt., 338.

1,9,7,10,13,16,19,22-Octaoxacyclotetracosane-2,3,14,15-tetraone (**12**).

Oxalyl chloride (13.9 g., 0.11 mole) and triethylene glycol (15.0 g., 0.10 mole) were used. The crude reaction mixture was first extracted with hot hexane then recrystallized from hexane to yield a white solid (0.5 g., 2.5%), m.p. 68-72°; ir (potassium bromide): 1745, 1755 cm^{-1}; nmr (deuteriochloroform): δ 3.67 (s, 4, $\mathrm{OC}H_2\mathrm{C}H_2\mathrm{O}$), 3.78 (m, 4, $\mathrm{COOCH_2C}H_2$), 4.43 (m, 4, $\mathrm{COOC}H_2$).

Anal. Calcd. for $C_8H_{12}O_6$: mol. wt., 408. Found: mol. wt., 437.

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