

The Synthesis of Novel Macrocyclic Multidentate Compounds from Dioxodioic Acids (1)

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A series of novel macrocyclic multidentate crown compounds have been prepared from a series of dioxodioic acids. The dioxodioic acids were prepared by treating various oligoethylene glycols or amines with maleic, succinic, citraconic, and glutaric anhydrides. The crown compounds were then synthesized from the dioxodioic acid chlorides obtained from the diacids and various oligoethylene glycols or ethylene diamine. The following macrocyclic compounds have been prepared: 1,4,9,12-tetraoxacyclohexadecane-5,8,13,16-tetrone (1); 1,4,7,10,15,18-hexaoxacyclodocosane-11,14,19,22-tetrone (2); 1,4-dioxa-9,12-diazacyclohexadecane-5,8,13,16-tetrone (3); 1,4,7-trioxa-12,15-diazacyclononadecane-8,11,16,19-tetrone (4); 1,4,7,10-tetraoxa-15,18-diazacyclodocosane-11,14,19,22-tetrone (5); 4-benzyl-1,7,12,15-tetraoxa-4-azacyclononadecane-8,11,16,19-tetrone (6); 1,4,7,12,15,18-hexaoxacyclodocosa-9,20-diene-8,11,19,22-tetrone (7); and 9,21-dimethyl-1,4,7,12,15,18-hexaoxacyclodocosa-9,20-diene-8,11,19,22-tetrone (8) (Figure 1).

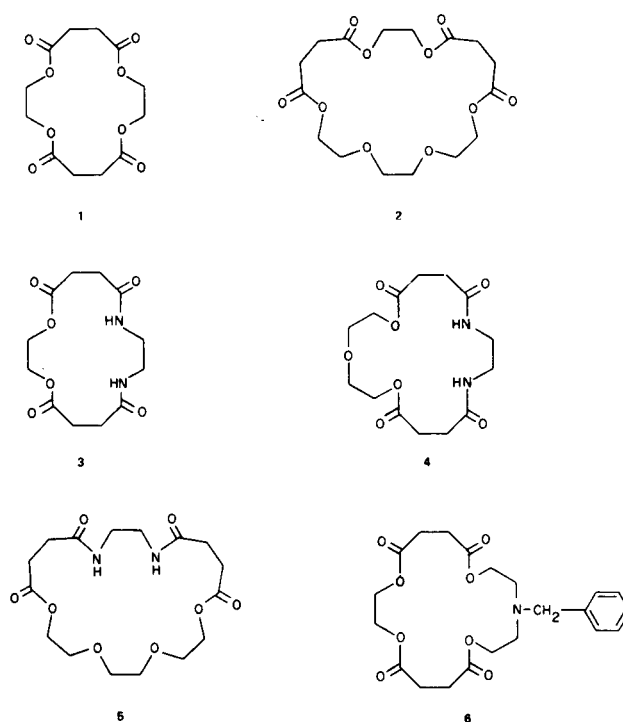
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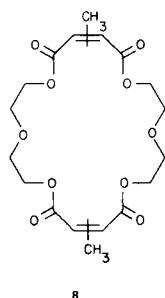
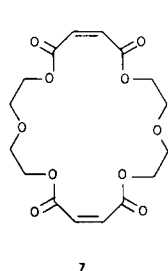
The cation complexing properties of cyclic polyethers have been studied extensively (3-6), and have been found, in certain instances, to resemble those of the cyclic antibiotics valinomycin and nonactin (7). The availability of synthetic cyclic polyethers and related compounds makes possible a systematic study of the factors which determine complex stability and which affect cation selectivity by macrocyclic compounds. One objective of our research program is to prepare and study a series of multidentate compounds which resemble naturally occurring macrocyclic compounds.

This work reports the synthesis of the following compounds containing multiple ester and amide moieties in addition to ether groups (3-6) (see Figure 1). These compounds include 1,4,9,12-tetraoxacyclohexadecane-5,8,13,16-tetrone (1); 1,4,7,10,15,18-hexaoxacyclodocosane-11,14,19,22-tetrone (2); 1,4-dioxa-9,12-diazacyclohexadecane-5,8,13,16-tetrone (3); 1,4,7-trioxa-12,15-diazacyclononadecane-8,11,16,19-tetrone (4); 1,4,7,10-tetraoxa-15,18-diazacyclodocosane-11,14,19,22-tetrone (5); 4-benzyl-1,7,12,15-tetraoxa-4-azacyclononadecane-8,11,16,19-tetrone (6); 1,4,7,12,15,18-hexaoxacyclodocosa-9,20-diene-8,11,19,22-tetrone (7); and 9,21-dimethyl-1,4,7,12,15,18-hexaoxacyclodocosa-9,20-diene-8,11,19,22-tetrone (8) (Figure 1). Also included is a report of the synthesis of a series of dioxodioic acids

needed for the production of these macrocyclic compounds.

Figure 1





The synthesis of macrocyclic esters has been reported previously. Dewes and coworkers (8-10) have prepared several similar compounds which contain a number of di- and tetra-esters from phthalic and maleic acid systems. They prepared cyclic ester compounds from the reaction of dipotassium salts of phthalic or maleic acid with a series of alkyl and alkynyl dibromides to make 10-34 membered ring compounds. Their compounds, however, did not contain the ethylene oxide moiety. We recently reported the synthesis of crown ether-esters which have one diacid moiety (11,12), but the synthesis of crown ether-esters containing two diacid moieties has not been reported.

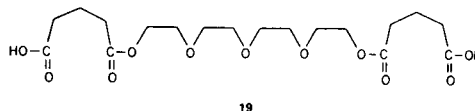
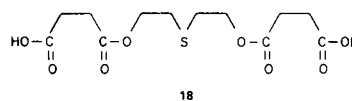
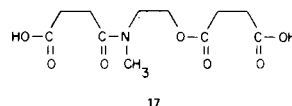
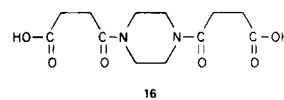
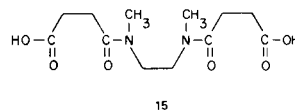
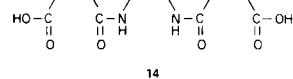
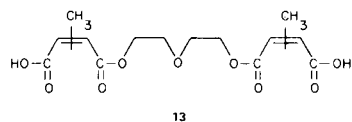
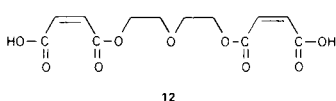
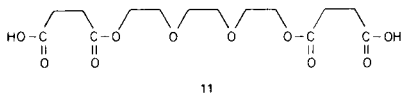
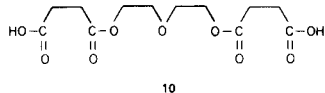
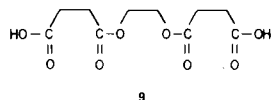
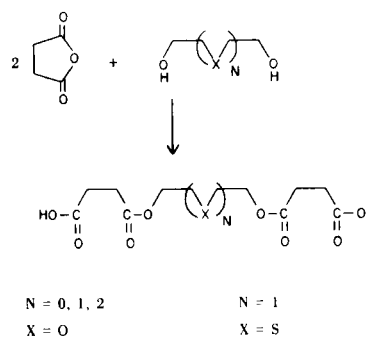


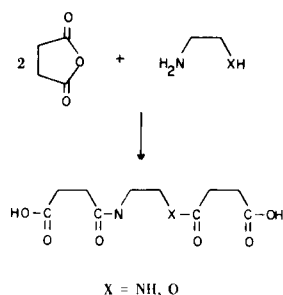
Figure 11



Preparation of Starting Materials

The dioxodioic acids needed for this study were prepared by treating various oligoethylene glycols with succinic, maleic, and citraconic anhydrides. The following compounds have been prepared: ethylene *bis*(hydrogen succinate) (9); oxydiethylene *bis*(hydrogen succinate) (10); ethylenebis(oxyethylene) *bis*(hydrogen succinate) (11); oxydiethylene *bis*(hydrogen maleate) (12); and oxydiethylene *bis*(hydrogen citraconate) (13). Related dioic acids prepared from various diamines and glycols and succinic or glutaric anhydride are also reported in this paper. These include: *N,N'*-ethylenedisuccinamic acid (14); *N,N'*-ethylene-*bis*(*N*-methylsuccinamic acid) (15); γ,γ' -dioxo-1,4-piperazinedibutyric acid (16); 2-(3-carboxy-*N*-methylpropionamido)ethyl hydrogen succinate (17); thiodiethylene *bis*(hydrogen succinate) (18); and oxybis(ethyleneoxyethylene) *bis*(hydrogen glutarate) (19).





Results and Discussions

The formation of compounds **9** and **10** have been reported previously from the glycols and succinic acid; however, no physical constants were given (13). Esterification of glycols with various acids such as terephthalic, fumaric and succinic have also been presented. These products contained one acid group (14). Dioic acids containing amide functions have not been reported although 2,6-piperazine dicarboxylic acids are known (15). Compounds somewhat similar to these have also been reported by other workers (16,17).

The structures proposed for the dioxodioic acid compounds are consistent with those determined from the nmr and ir spectra, elemental analysis of the products or a macrocyclic derivative, and molecular weight determinations. The diacids containing the ester moieties all exhibited an ir band at $1730\text{--}1740\text{ cm}^{-1}$ and a band at $1690\text{--}1720\text{ cm}^{-1}$ indicative of the ester and carboxylic acid carbonyl groups, respectively. Those compounds possessing the amide function (14-17) all contained bands at $1620\text{--}1600$ and $1550\text{--}1500\text{ cm}^{-1}$ indicative of the amide group as well as the ester carbonyl band at $1710\text{--}1740\text{ cm}^{-1}$.

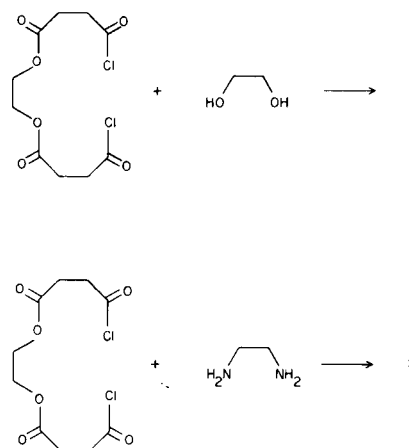
The nmr spectra of the compounds are most revealing. The ethylene hydrogens for the succinic acid portions for all acids derived from succinic anhydride (**9**, **11**, **14**, **15**, **16**, **17**, and **18**) exhibited nmr peaks at $2.68 \pm 0.02\ \delta$ with the exception of compound **10** which exhibited a peak at $2.55\ \delta$. The glutarate propylene hydrogens of compound **19** exhibited a triplet peak at $2.48\ \delta$ and a multiplet at $2.03\ \delta$. The unsaturated compounds **12** and **13** exhibited the usual vinyl hydrogen peaks in the nmr spectra. All ester methylene hydrogens appeared at $4.35 \pm 0.10\ \delta$ while the ether methylene hydrogens appeared at $3.70 \pm 0.10\ \delta$ in the nmr spectra. The hydrogens on the carbon next to sulfur on compound **18** exhibited a peak at $2.86\ \delta$.

The amide diacids (**14-17**) exhibited the expected nmr peaks. For compound **16**, the amide methylene peaks occurred as a triplet at $3.68\ \delta$ with small triplet peaks appearing at $3.40\ \delta$ and $3.88\ \delta$ as well, whose total peak area ($3.40\text{--}3.88\ \delta$) equals eight hydrogens. Spragg, in an nmr study of N,N-disubstituted piperazine derivatives,

found *cis*-, *trans*- isomers with the *trans*- form constituting the major product (**18**). Unusual splitting of the methyl peaks from compounds **15** and **17** were also observed in the nmr at 3.04 and $3.06\ \delta$, respectively. Miron and co-workers also noted such splitting of NMe groups in amide moieties of polymers which they attributed to hindered rotation about the amide bond (19).

Compounds **9-13** can be easily transformed into the corresponding diacid chlorides by the action of thionyl chloride. The acid chlorides were then used to form the macrocyclic compounds. Diacid chlorides for compounds **14-18** cannot be formed by the action of thionyl chloride due to the destruction of the amide function within the diacid (**20**). For example, when compound **14** was treated with thionyl chloride, a cyano bond was observed in an ir of the reaction mixture. Metal complexation studies of these diacids are presently being undertaken and will be reported in a future paper.

The novel macrocyclic compounds shown in Figure 1 were prepared by treating the appropriate glycol or ethylene diamine with diacid chlorides prepared from the appropriate dioxodioic acid.



The structures proposed for these compounds are consistent with those determined from the ir and nmr spectra, molecular weight determinations, and elemental analyses. These macrocyclic compounds exhibited ir peaks comparable in some respects to the diacids from which they were derived. The ester moieties all exhibited an ir band at $1720\text{--}1740\text{ cm}^{-1}$ and the amide moieties all exhibited bands at $1660\text{--}1640\text{ cm}^{-1}$ and $1560\text{--}1550\text{ cm}^{-1}$.

The nmr spectra also are comparable to the diacids. The ethylene hydrogens for the succinic acid moieties of compounds (**1-6**) exhibited nmr peaks at $2.65 \pm 0.02\ \delta$. All ester methylene hydrogen appeared at $4.30 \pm 0.10\ \delta$ while the ether methylene hydrogens appeared at $3.50 \pm 0.10\ \delta$. Methylene hydrogens next to nitrogen exhibited nmr peaks at $3.33 \pm 0.10\ \delta$. The vinyl hydrogens of

compounds **7** and **8** exhibited peaks at $6.90 \pm 0.10 \delta$.

Yields for these crown compounds ranged from 1 to 68%. The low yields were a result of the difficulty in purification of the diacid chlorides before reaction with the appropriate glycol. Several of the compounds which were solids exhibited water peaks in ir spectra; however, after vacuum drying, these peaks were greatly reduced or removed entirely. Work is now in progress to determine the complexation properties of these compounds.

EXPERIMENTAL

All ir spectra were obtained on a Hilger and Watts H-1200 Infragraph. The nmr spectra were obtained on a Varian EM-390 spectrometer. The elemental analysis were performed by Galbraith Laboratories, Knoxville, Tennessee. The molecular weight determinations for the diacids were performed either by a base titration or on a Hitachi Perkin-Elmer 115 Molecular Weight Apparatus. Those for the macrocyclic compounds were done on the Hitachi Perkin-Elmer apparatus. Melting points are uncorrected.

Starting Materials.

Most of the starting glycols, amines and anhydrides were used as purchased: ethylene glycol (Mallinckrodt), diethylene glycol (Eastman), triethylene glycol (Baker), 2,2'-(benzylimino) diethanol (Pfaltz and Bauer), ethylenediamine (MCB), piperazine (Aldrich), *sym*-dimethylethylenediamine (Aldrich), 2-(methylamino)-ethanol (Aldrich), thiodiethylene glycol (Fluka), succinic anhydride (Eastman), citraconic anhydride (Aldrich), maleic anhydride (MCB), glutaric anhydride (Aldrich), succinyl chloride (Aldrich).

General Synthesis

The diacids were prepared by slowly adding the glycol or diamine to the anhydride in 500 ml. of benzene at 50° . The resulting mixture was stirred for at least three days. After the reaction was stopped, the upper benzene layer was removed and the lower product layer was purified by recrystallization or by extraction techniques. In the case of most amide compounds, the product solidified in the benzene. After benzene removal, the crude product was recrystallized. Specific details are given for each of the diacid compounds.

The diacid chlorides from compounds **9-13** were prepared by slowly adding 0.4 mole of thionylchloride to the diacid (0.1 mole) in 1 liter of benzene and 2 ml. of pyridine. The resulting mixture was stirred at room temperature for 2 hours. After the reaction was stopped, the mixture was filtered and the benzene was removed under vacuum. The resulting liquid product was not further isolated or characterized but was used directly in the synthesis of the macrocyclic crown compounds.

All macrocyclic crown compounds except compound **1** were prepared by treating the diacid chlorides from compounds **9-13** with the appropriate glycol or ethylenediamine. The glycol and diacid chloride each dissolved in 200 ml. of benzene or THF were slowly added simultaneously to 600 ml. of stirred benzene at 50° . Excess ethylene diamine was added where appropriate to complex the hydrochloric acid generated during the reaction to avoid complexation in the amide containing crown compounds. The resulting mixture was stirred at $50-60^\circ$ for at least two days. After the reaction was stopped, benzene was removed under vacuum. The crude product was then purified by recrystallization or by

alumina chromatography using hexane with increasing amounts of chloroform as the eluant. Specific details are given for each crown compound.

Diacids.

Ethylene *bis*(Hydrogensuccinate) (**9**).

Ethylene glycol (31 g., 0.50 mole) and succinic anhydride (100 g., 1.00 mole) were used. The product (127.71 g., 97.5%) was recrystallized from an ethylacetate-hexane mixture, m.p. dec. $> 80^\circ$; ir: 1740, 1705, 1170 cm^{-1} ; nmr: (δ) 2.68 (s, 8H, $\text{OCCH}_2\text{CH}_2\text{COOH}$), 4.34 (s, 4H, COOCH_2), 9.93 (s, 2H, COOH). Molecular weight: Calcd: 262.2. Found: 262.7. A satisfactory elemental analysis was obtained via its derivatives, compounds **1**, **3** and **6**.

Oxydiethylene *bis*(Hydrogensuccinate) (**10**).

Diethylene glycol (53 g., 0.50 mole) and succinic anhydride (100 g., 1.00 mole) were used. The product (127 g., 84%) was recrystallized from an ethylacetate-hexane mixture; m.p. $70-72^\circ$; ir: 1720, 1680, 1180 cm^{-1} ; nmr (deuterium oxide): (δ) 2.66 (s, 8H, $\text{OCCH}_2\text{CH}_2\text{COOH}$), 3.64 (t, 4H, OCH_2), 4.18 (t, 4H, OOCCH_2). Molecular weight: Calcd: 306.3. Found: 276. A satisfactory elemental analysis was obtained via its derivative, compound **4**.

Ethylenebis(oxyethylene) *bis*(Hydrogensuccinate) (**11**).

Triethylene glycol (75.1 g., 0.50 mole) and succinic anhydride (100 g., 1.00 mole) were used. The product crystallized after one week at 5° (166.6 g., 95%). It was purified by recrystallization from an ethyl acetate-hexane mixture, m.p. $60-62^\circ$; ir: 1725, 1690, 1185 cm^{-1} ; nmr: (δ) 2.68 (s, 8H, $\text{OCCH}_2\text{CH}_2\text{COOH}$), 3.67 (s and t, 8H, CH_2OCH_2), 4.30 (t, 4H, COOCH_2), 10.57 (s, 2H, COOH). Molecular weight: Calcd: 350.4. Found: 365. A satisfactory elemental analysis was obtained via its derivatives, compounds **2** and **5**.

Oxydiethylene *bis*(Hydrogenmaleate) (**12**).

Diethylene glycol (106 g., 1.00 mole) and maleic anhydride (196 g., 2.00 mole) were used. The product (300 g., 99%) was dissolved in 500 ml. of an aqueous sodium bicarbonate solution and extracted with 500 ml. of chloroform. The aqueous solution was then acidified with dilute hydrochloric acid and extracted with chloroform. The purified product was a viscous liquid; ir: 1725, 1645, 1200 cm^{-1} ; nmr: (δ) 3.85 (t, 4H, CH_2OCH_2), 4.45 (t, 4H, COOCH_2), 6.45 (s, 4H, vinyl hydrogens), 10.75 (s, 2H, COOH). Molecular weight: Calcd: 302.3. Found: 325. A satisfactory elemental analysis was obtained via its derivative, compound **7**.

Oxydiethylene *bis*(Hydrogencitraconate) (**13**).

Diethylene glycol (84.0 g., 0.37 mole) and citraconic anhydride (40.0 g., 0.75 mole) were used. The product (62.0 g., 51%) was purified as reported above for compound **4** to give a viscous liquid; ir: 1725, 1650, 1200 cm^{-1} ; nmr: (δ) 2.10 (s, 6H, CH_3), 3.70 (t, 4H, CH_2OCH_2), 4.35 (t, 4H, COOCH_2), 5.95 (s, 2H, vinyl hydrogen), 9.30 (s, 2H, COOH), also small peaks at 2.25 and 6.85 δ . Molecular weight: Calcd: 330.0. Found: 346. A satisfactory elemental analysis was obtained via its derivative, compound **8**.

N,N'-Ethylenedisuccinimide Acid (**14**).

Ethylenediamine (30 g., 0.50 mole) and succinic anhydride (100 g., 1.00 mole) were used. The product (125.1 g., 96%) was recrystallized from 95% ethanol which contained about 2% of *N*

hydrochloric acid; m.p. 159-161°; ir: 3300, 1690, 1640, 1550 cm^{-1} ; nmr (deuterium oxide): (δ) 2.68 (2t, 8H, $\text{OCCH}_2\text{CH}_2\text{COOH}$), 3.36 (s, 4H, CONHCH_2).

Anal. Calcd. for $\text{C}_{10}\text{H}_{16}\text{O}_6\text{N}_2$: C, 46.15; H, 6.20; N, 10.76. MW, 260.2. Found: C, 46.06; H, 6.25; N, 10.68; MW, 270.

N,N'-Ethylene bis(*N*-Methylsuccinamic Acid) (15).

sym-Dimethylenediamine (5 g., 0.057 mole) and succinic anhydride (11.35 g., 0.114 mole) were used. The product (17 g., 99%) was recrystallized from 95% ethanol which contained about 2% of 6 *N* hydrochloric acid, m.p. 130-132°; ir: 1740, 1620, 1510 cm^{-1} ; nmr (deuterium oxide): (δ) 2.68 (s, 8H, $\text{OCCH}_2\text{CH}_2\text{COOH}$), 3.04 (m, 6H, NCH_3), 3.64 (t, 4H, CONCH_2).

Anal. Calcd. for $\text{C}_{12}\text{H}_{20}\text{O}_6\text{N}_2$: C, 49.99; H, 6.99; N, 9.72; MW, 288.3. Found: C, 49.91; H, 7.04; N, 9.87; MN, 288.

γ,γ' -Dioxo-1,4-piperazinedibutyric Acid (16).

Piperazine (21.5 g., 0.25 mole) and succinic anhydride (50 g., 0.50 mole) were used. The product (54.5 g., 76%) was recrystallized from hot ethanol, m.p. 156.6-158.5°; ir: 3000, 1720, 1600, 1490 cm^{-1} ; nmr (deuterium oxide): (δ) 2.69 (2t, 8H, $\text{OCCH}_2\text{CH}_2\text{COOH}$), 3.68 (t, 8H, CONCH_2).

Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{O}_6\text{N}_2$: C, 50.35; H, 6.34; N, 9.78; MW, 286.5. Found: C, 50.14; H, 6.41; N, 9.93; MW, 280.

2-(3-Carboxy-*N*-methylpropioamido)ethyl Hydrogensuccinate (17).

2-(Methylamino)ethanol (18.76 g., 0.25 mole) and succinic anhydride (50 g., 0.50 mole) were used. The product (68.3 g., 99%) was a viscous liquid; ir: 1740, 1620, 1510 cm^{-1} ; nmr: (δ) 2.69 (2t, 8H, $\text{OCCH}_2\text{CH}_2\text{COOH}$), 3.05 (2d, 3H, NCH_3), 3.68 (t, 2H, CONCH_2), 4.28 (t, 2H, COOCH_2), 9.90 (s, 1H, COOH), 10.57 (s, 1H, COOH).

Anal. Calcd. for $\text{C}_{11}\text{H}_{17}\text{O}_7\text{N}$: C, 48.00; H, 6.23; N, 5.09; MW, 277.3. Found: C, 47.85; H, 6.36; N, 5.21; MW, 275.

Thiodiethylene bis(Hydrogen succinate) (18).

Thiodiethylene glycol (30.55 g., 0.25 mole) and succinic anhydride (50 g., 0.50 mole) were used. The product (30.7 g., 38%) was recrystallized from ethanol, m.p. dec. > 120°; ir: 1720, 1160 cm^{-1} ; nmr: (δ) 2.70 (s, 8H, $\text{OCCH}_2\text{CH}_2\text{COOH}$), 2.86 (t, 4H, CH_2SCH_2), 4.30 (t, 4H, COOCH_2), 7.85 (s, 2H, COOH). Molecular weight: Calcd: 322.3. Found: 326.

Oxybis(ethyleneoxyethylene) bis(Hydrogen glutarate) (19).

Tetraethylene glycol (194 g., 1.00 mole) and glutaric anhydride (228.2 g., 2.00 mole) were used. The product (400 g., 95%) was a viscous liquid; ir: 1740, 1150 cm^{-1} ; nmr: (δ) 2.03 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.48 (t, 8H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 3.66 (s and t, 12H, CH_2OCH_2), 4.28 (t, 4H, COOCH_2), 10.32 (s, 2H, COOH).

Anal. Calcd. for $\text{C}_{18}\text{H}_{30}\text{O}_{11}$: C, 51.18; H, 7.16; MW, 422.4. Found: C, 50.98; H, 7.12; MW, 448.

Macrocyclic Compounds.

1,4,9,12-Tetraoxacyclohexadecane-5,8,13,16-tetrone (1).

Succinyl chloride (15.0 g., 0.097 mole) and ethylene glycol (6.0 g., 0.097 mole) were used. The viscous product (19.0 g., 68%), was purified by alumina chromatography and partially crystallized upon standing; ir: 1740 cm^{-1} ; nmr: (δ) 2.70 (s, 8H, $\text{COCH}_2\text{CH}_2\text{CO}$), 4.34 (s, 8H, COOCH_2).

Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{O}_8$: C, 50.00; H, 5.60; MW, 288.3. Found: C, 49.82; H, 5.62; MW, 286.

1,4,7,10,15,18-Hexaoxacyclodocosane-11,14,19,22-tetrone (2).

Ethylenebis(oxyethylene bis(hydrogensuccinate) dichloride

from 11 (15.48 g., 0.04 mole) and ethylene glycol (2.73 g., 0.04 mole) were used. The viscous product (0.20 g., 0.5%) was purified by alumina chromatography; ir: 1740 cm^{-1} ; nmr: (δ) 2.67 (s, 8H, $\text{COCH}_2\text{CH}_2\text{CO}$), 3.67 (s, 4H, CH_2OCH_2), 3.73 (t, 4H, $\text{COOCH}_2\text{CH}_2\text{O}$), 4.26 (t, 4H, COOCH_2), 4.33 (s, 4H, $\text{COOCH}_2\text{CH}_2\text{OOC}$).

Anal. Calcd. for $\text{C}_{16}\text{H}_{24}\text{O}_{10}$: C, 51.05; H, 6.44; MW, 376.4. Found: C, 50.72; H, 6.60; MW, 352.

1,4-Dioxo-9,12-diazacyclohexadecane-5,8,13,16-tetrone (3).

Ethylene bis(hydrogensuccinate) dichloride from 9 (13.69 g., 0.05 mole) and excess ethylene diamine (6.0 g., 0.1 mole) were used. The product (6.0 g., 46%) was extracted and recrystallized from chloroform, m.p. 190-192°; ir: 3300, 3120, 1725, 1640, 1560 cm^{-1} ; nmr (deuterium oxide): (δ) 2.64 (m, 8H, $\text{COCH}_2\text{CH}_2\text{CO}$), 3.38 (s, 4H, $\text{NHCH}_2\text{CH}_2\text{NH}$), 4.39 (s, 4H, $\text{COOCH}_2\text{CH}_2\text{OOC}$).

Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_6$: C, 50.38; H, 6.30; N, 9.78; MW, 286.3. Found: C, 50.10; H, 6.19; N, 9.65; MW, 280.

1,4,7-Trioxa-12,15-diazacyclononadecane-8,11,16,19-tetrone (4).

Oxydiethylene bis(hydrogensuccinate) dichloride from 10 (34.3 g., 0.1 mole) and excess ethylene diamine (12.6 g., 0.21 mole) were used. The product (2.69 g., 8%) was extracted and recrystallized from chloroform, m.p. 167-168°; ir: 3300, 3100, 1740, 1660 and 1555 cm^{-1} ; nmr (deuterium oxide): (δ) 2.63 (m, 8H, $\text{COOCH}_2\text{CH}_2\text{CONH}$), 3.35 (s, 4H, $\text{NHCH}_2\text{CH}_2\text{NH}$), 3.80 (t, 4H, CH_2OCH_2), 4.28 (t, 4H, COOCH_2).

Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_7 \cdot 3\text{H}_2\text{O}$: N, 7.29; MW, 384. Found: N, 7.23; MW, 350.

1,4,7,10-Tetraoxa-15,18-diazacyclodocosane-11,14,19,22-tetrone (5).

Ethylenebis(oxyethylene) bis(hydrogensuccinate) dichloride from 11 (38.2 g., 0.10 mole) and excess ethylenediamine (12.6 g., 0.21 mole) were used. The product (3.74 g., 10%) was extracted and recrystallized from chloroform, m.p. 159-161°; ir: 3300, 3100, 1725, 1640, 1550 cm^{-1} ; nmr: (δ) 2.63 (m, 8H, $\text{COCH}_2\text{CH}_2\text{CO}$), 3.44 (m, 4H, $\text{NHCH}_2\text{CH}_2\text{NH}$), 3.70 (t, 8H, CH_2OCH_2), 4.30 (t, 4H, COOCH_2), 6.62 (s, 2H, NH).

Anal. Calcd. for $\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}_8$: C, 51.33; H, 7.00; N, 7.48; MW, 374.4. Found: C, 51.08; H, 7.16; N, 7.28; MW, 399.

4-Benzyl-1,7,12,15-tetraoxa-4-azacyclononadecane-8,11,16,19-tetrone (6).

Ethylene bis(hydrogensuccinate) dichloride from 9 (29.9 g., 0.1 mole) and 2,2'-(benzylimino)diethanol (14.1 g., 0.07 mole) were used. The product (1.5 g., 5%) was purified by alumina chromatography; ir: 1740 cm^{-1} ; nmr: (δ) 2.63 (d, 8H, $\text{COCH}_2\text{CH}_2\text{CO}$), 2.78 (t, 4H, $\text{NCH}_2\text{CH}_2\text{O}$), 3.68 (s, 2H, PhCH_2N), 4.13 (t, 4H, $\text{NCH}_2\text{CH}_2\text{O}$), 4.30 (d, 4H, $\text{COOCH}_2\text{CH}_2\text{COO}$), 7.26 (s, 5H, aromatic).

Anal. Calcd. for $\text{C}_{21}\text{H}_{27}\text{NO}_8 \cdot 2\text{H}_2\text{O}$: N, 3.06; MW, 457. Found: N, 3.20; MW, 454.

1,4,7,12,15,18-Hexaoxacyclodocosane-9,20-diene-8,11,19,22-tetrone (7).

Oxydiethylene bis(hydrogenmaleate) dichloride from 12 (7.5 g., 0.02 mole) and diethylene glycol (2.34 g., 0.02 mole) were used. The product (1.32 g., 16%) was recrystallized from 100% ethanol, m.p. 127.5-128°; ir: 1720 cm^{-1} ; nmr: (δ) 3.76 (t, 8H, CH_2OCH_2), 4.45 (t, 8H, COOCH_2), 6.95 (s, 4H, vinyl H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{20}\text{O}_{10}$: C, 51.64; H, 5.37; MW, 372. Found: C, 51.45; H, 5.50; MW, 389.

9,21-Dimethyl-1,4,7,12,15,18-hexaoxacyclodocosa-9,20-diene-8,11,19,22-tetrone (8).

Oxydiethylene bis(hydrogencitraconate) dichloride from **13** (21 g., 0.06 mole) and diethylene glycol (5.0 g., 0.05 mole) were used. The product (0.11 g., 1%) was purified by alumina chromatography; ir: 1720 cm^{-1} ; nmr: (δ) 2.05 (s, 6H, CH_3), 3.70 (m, 8H, CH_2OCH_2), 4.32 (m, 8H, COOCH_2), 5.90 (s, 2H, vinyl H), also small peaks at 2.27 and 6.83 δ .

Anal. Calcd. for $\text{C}_{18}\text{H}_{24}\text{O}_{10}$: C, 53.99; H, 6.04; MW, 400. Found: C, 53.80; H, 6.06; MW, 388.

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