The Synthesis of some Substituted Macrocyclic Polyether-Diester Compounds with the Malonyl Moiety

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A series of seven substituted macrocyclic polyether-diester compounds containing the malonyl moiety have been prepared.

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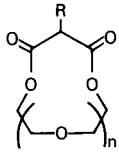
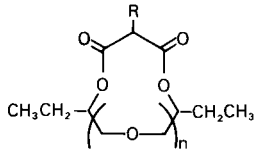
We have previously prepared a variety of macrocyclic polyether-diester compounds (1). The diester compound of nineteen ring members and containing a malonyl moiety (compound **1**) has proved to be interesting in that it exhibited a cation selectivity pattern similar to that for valinomycin, *i.e.*, $K^+ > Ba^{2+}$, as measured by the heat of their reactions in methanol (2,3). Other macrocyclic polyether-diester ligands complex with metal cations in a manner similar to that of 18-crown-6 (3).

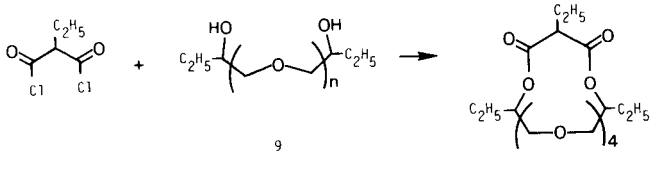
We have now prepared some substituted macrocyclic compounds containing the malonyl moiety. We believe these compounds will also have unusual cation complexation properties. Compounds **2-4** were prepared from pentaethylene glycol and the appropriately substituted malonyl chloride; **5** and **6** from hexaethylene glycol and **7** and **8** from 5,8,11,14-tetraoxaoctadecane-3,16-dione (**9**) (4). For example, compound **7** was prepared from glycol **9** and ethylmalonyl chloride as shown below. The cation complexation properties of these compounds will be reported in a future publication.



1 n=4, R=H
2 n=4, R=C_2H_5
3 n=4, R=C_6H_5
4 n=4, R=n-C_7H_{15}
5 n=5, R=H
6 n=5, R=C_2H_5



7 n=4, R=C_2H_5
8 n=4, R=C_6H_5



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The structures proposed for the macrocyclic compounds are consistent with data derived from their ir and nmr spectra, elemental analyses and molecular weight determinations. The carbonyl bands appeared at 1725-1745 cm^{-1} in the ir spectra. The nmr spectra exhibited peaks attributable to unsubstituted and substituted malonate esters: δ 4.28 ± 0.05 ($COOCH_2$) (compounds **2-6**) (5); 4.92 ± 0.02 (COOC*H*R) (compounds **7** and **8**) (4,6); 3.30 ± 0.05 (COC*H*RCO) (compounds **2**, **4**, **6**, **7**) (7); 4.68 ± 0.04 (CHC_6H_5) (compounds **3** and **8**); and 3.48 ($COCH_2CO$) (compound **5**) (5). Peaks attributable to phenyl hydrogens (**3** and **8**), ethyl (**2**, **6-8**), and *n*-heptyl (**4**) groups as well as to ether hydrogens (3.60-3.75) were also observed in the nmr spectra.

It is interesting to note that the ester methylene hydrogens for compounds **2-4** were split into two sets of peaks of equal intensity. These peaks show the stereochemical nature of these compounds. One set represents the ester methylene hydrogens on the same face of the macrocyclic compound as the substituent and the other set to the hydrogens on the opposite face (8).

EXPERIMENTAL

All ir spectra were obtained on a Beckman Acculab 2 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 MHW Laboratories, Phoenix, Arizona and Galbraith Laboratories, Knoxville, Tennessee. 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.

The starting glycols were prepared as we have previously reported (4,9). The malonic acids were purchased (Aldrich Chemical) except for *n*-heptyl malonic acid which was synthesized (10). The diacid chlorides were prepared from phosphorus pentachloride as reported (7).

General Synthesis.

The macrocyclic compounds were prepared by simultaneously dripping the acid chloride dissolved in 200 ml. of benzene and the glycol in 200 ml. of benzene into 1000 ml. of rapidly stirring benzene at 50°. The resulting mixture was stirred at 50° for at least two days. The benzene

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solvent was then removed under vacuum and the crude product was distilled or recrystallized. Specific details are given for each compound.

18-Ethyl-1,4,7,10,13,16-hexaoxacyclononadecane-17,19-dione (**2**).

Ethylmalonyl chloride (11.9 g., 0.066 mole) and pentaethylene glycol (15.6 g., 0.066 mole) were used. The product was distilled to give 7.74 g. (35%) of a viscious liquid, b.p. 176-182°/0.6 mm; ir: 1730 and 1740 cm^{-1}; nmr: δ 0.98 (t, 3H, CH_3), 1.95 (m, 2H, CH_2), 3.32 (t, $COCHCO$), 3.67 (s, 12H, OCH_2), 3.70 (t, 4H, OCH_2), 4.25 (m, 2H, $COOCH_2$), 4.32 (m, 2H, $COOCH_2$).

Anal. Calcd. for $C_{15}H_{26}O_8$: C, 53.88; H, 7.84; mol. wt., 334.4. Found: C, 53.71; H, 7.93; mol. wt. 339.

18-Phenyl-1,4,7,10,13,16-hexaoxacyclononadecane-17,19-dione (**3**).

Phenylmalonyl chloride (15.3 g., 0.07 mole) and 16.7 g. (0.07 mole) of pentaethylene glycol were reacted. The crude reaction mixture was extracted with hot hexane for 24 hours. The solid hexane extract was recrystallized from hexane to yield 11.3 g. (42%) of a fine white powder, m.p. 67-70°; ir: 1730 and 1750 cm^{-1}; nmr: δ 3.68 (s, 12H, OCH_2), 3.71 (t, 4H, OCH_2), 4.23 (m, 2H, $COOCH_2$), 4.33 (m, 2H, $COOCH_2$), 4.72 (s, 1H, $COCHCO$), 7.40 (m, 5H).

Anal. Calcd. for $C_{19}H_{26}O_8$: C, 59.82; H, 6.61; mol. wt., 382.4. Found: C, 59.68; H, 6.75; mol. wt., 383.

18-*n*-Heptyl-1,4,7,10,13,16-hexaoxacyclononadecane-17,19-dione (**4**).

n-Heptylmalonyl chloride (15 g., 0.062 mole) and 15 g. (0.062 mole) of pentaethylene glycol were used. Part of the crude reaction product was distilled to give 5.4 g. (35%) of product, b.p., 198-203°/1.3 mm; ir: 1730 and 1740 cm^{-1}; nmr: δ 0.90 (t, 3H, CH_3), 1.30 (s, 10H, CH_2), 1.85 (m, 2H, CH_2), 3.38 (t, 1H, $COCHCO$), 3.66 (s, 12H, OCH_2), 3.72 (t, 4H, OCH_2), 4.22 (m, 2H, $COOCH_2$), 4.30 (m, 2H, $COOCH_2$).

Anal. Calcd. for $C_{20}H_{36}O_8$: C, 59.39; H, 8.97; mol. wt., 404.5. Found: C, 59.30; H, 8.95; mol. wt., 403.

1,4,7,10,13,16,19-Heptaoxacyclodocosane-20,22-dione (**5**).

Malonyl chloride (7.1 g., 0.05 mole) and 14.1 g. (0.05 mole) of hexaethylene glycol were used. The crude product was distilled to give 10 g. (57%) of a pale yellow liquid; b.p., 196-198/0.8 mm; ir: 1720 and 1735 cm^{-1}; nmr: δ 3.48 (s, 2H, $COCH_2CO$), 3.68 (s, 16H, OCH_2), 3.70 (m, 4H, OCH_2), 4.32 (m, 4H, $COOCH_2$).

Anal. Calcd. for $C_{15}H_{26}O_9$: C, 51.42; H, 7.48; mol. wt., 350.4. Found: C, 51.30; H, 7.61; mol. wt., 321.

21-Ethyl-1,4,7,10,13,16,19-heptaoxacyclodocosane-20,22-dione (**6**).

Ethylmalonyl chloride (8.45 g., 0.05 mole) and 14.12 g. (0.05 mole) of hexaethylene glycol were reacted. The crude product was distilled to give 5.0 g. (26%) of a viscous yellow oil, b.p., 169-163°/1 mm; ir: 1725 and 1735 cm^{-1}; nmr: δ 0.97 (t, 3H, CH_3), 1.93 (m, 2H, CH_2), 3.36 (t, 1H, $COCHCO$), 3.65 (s, 16H, OCH_2), 3.72 (t, 4H, OCH_2), 4.29 (m, 4H, $COOCH_2$).

Anal. Calcd. for $C_{17}H_{30}O_9 \cdot \frac{1}{2}H_2O$: C, 52.74; H, 8.14; mol. wt., 387.4. Found: C, 52.74; H, 7.94; mol. wt., 345.

2,15,18-Triethyl-1,4,7,10,13,16-hexaoxacyclononadecane-17,19-dione (**7**).

Ethylmalonyl chloride (6.03 g., 0.036 mole) and 10.5 g. (0.036 mole) of 5,8,11,14-tetraoxatetradecane-3,16-diol were used. The crude product was distilled to give 5.35 g. (39%) of a pale yellow liquid; b.p., 175-180°/1 mm; ir: 1725 and 1735 cm^{-1}; nmr: δ 0.92 (m, 9, CH_3), 1.65 (m, 4H, CH_2), 1.92 (m, 2H, CH_2), 3.25 (m, 1, $COCHCO$), 3.56 (m, 4H, OCH_2), 3.64 (two singlets, 12H, OCH_2), 4.90 (m, 2H, $COOCH$).

Anal. Calcd. for $C_{19}H_{34}O_8$: C, 58.44; H, 8.78; mol. wt., 390.5. Found: C, 58.60; H, 8.89; mol. wt., 364.

2,15-Diethyl-18-phenyl-1,4,7,10,13,16-hexaoxacyclononadecane-17,19-dione (**8**).

Phenylmalonyl chloride (10 g., 0.046 mole) and 13.5 g. (0.046 mole) of 5,8,11,14-tetraoxaoctadecane-3,16-diol were used. The crude product was distilled to give 17.7 g. (88%) of a viscous, yellow liquid, b.p., 198-203°/1.5 mm; ir: 1730 cm^{-1}; nmr: δ 0.90 (m, 6H, CH_3), 1.62 (m, 4H, CH_2), 3.52 (m, 4H, OCH_2), 3.62 (s, 4H, OCH_2), 3.68 (s, 8H, OCH_2), 4.66 (s, 1, $COCHCO$), 4.95 (m, 2H, $COOCH$), 7.30 (m, 5H).

Anal. Calcd. for $C_{23}H_{34}O_8$: C, 63.00; H, 7.82; mol. wt., 438.5. Found: C, 63.16; H, 7.88; mol. wt., 415.

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