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THE SYNTHESIS OF SOME SUBSTITUTED MACROCYCLIC ETHER-ESTER COMPOUNDS

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Abstract—A series of macrocyclic ether-esters has been prepared by treating various glycols with adipoyl chloride and various substituted malonyl, succinyl and glutaryl chlorides. The prepared compounds include: 15-ethyl- and 15-phenyl-1,4,7,10,13-pentaoxacyclohexadecane-14,16-dione (**5** and **6**); 15-methyl-, 15-phenyl-, *cis*-cyclohexo-[o]- and benzo-[o]-1,4,7,10,13-pentaoxacycloheptadecane-14,17-dione (**7–10**); *trans,trans*-1,4,7,10,13,18,21,24,27,30-decaoxacyclotetratriacontane-15,32-diene-14,17,31,34-tetraone (**11**); 1,4,7,10,13-pentaoxacyclooctadecane-14,18-dione (**12**); 15,15,16,16,17,17-hexafluoro- and 16-methyl-1,4,7,10,13-pentaoxacyclooctadecane-14,18-dione (**13** and **14**); 1,4,7,10-tetraoxacyclohexadecane-11,16-dione (**15**); and 1,4,7,10,13-pentaoxacyclononadecane-14,19-dione (**16**).

The synthesis and unique cation complexing characteristics of cyclic polyethers were first reported by Pedersen[1] a decade ago. Since that time a large variety and number of macrocyclic compounds have been prepared[2] and their cation complexation properties have been studied extensively.[3–10] It was originally postulated[1] and since confirmed by stability constant measurements[3,4] that a qualitative relationship exists between complex stability and the ratio of cation diameter to ligand cavity diameter. However, it is becoming increasingly evident that complex stability in 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),[11] and one would intuitively predict, on the basis of electrostatics alone, that the stability order $Ba^{2+} > K^+$ would be found for complexes where the ligand cavity would accommodate these cations. Although thermodynamic data are not available for all systems, there have emerged a number of examples where stability orders of $Ba^{2+} \sim K^+$ and $K^+ > Ba^{2+}$ exist.[8] 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 several thia-crown compounds.[12–15] Also, we have reported the synthesis of ether–esters (**1**, **2**),[8,16,17] thioether–esters (**3**),[17] ether–thiolesters,[17] amine–esters,[18] ether–ester–amides (**4**)[18] and ester–amides.[18] A preliminary investigation of the reaction in methanol of Na^+, K^+ and Ba^{2+} with **1** and **2** has been reported.[8] The stability orders $K^+ > Ba^{2+}$ and $K^+ \sim Ba^{2+}$ found[8] for **1** and **2**, respectively, are quite different than that found for 18-crown-6 ($Ba^{2+} > K^+$). The cyclic antibiotic valinomycin also shows selectivity for potassium over barium in methanol. The synthetic compounds **1** and **2** have CO groups available for cation complexation as does valinomycin. The significance of this observation was that it demonstrated the possibility of preparing macrocyclic compounds containing CO oxygen donor atoms which will have cation selective properties closer to those of valinomycin and other naturally occurring cyclic antibiotics. Such synthetic compounds may prove useful as models for the investigation of biological cation transport and selectivity processes.[8]

In this paper we report the synthesis by reaction of appropriate glycols with diacid chlorides[16–18] of ether–ester compounds and several of their substituted derivatives (**5–16**, Fig. 2). The metal complexation properties of these compounds are under investigation and will be reported separately.

The preparation of certain macrocyclic ether–esters has been reported previously. Drewes *et al.*[19–21] have prepared several macrocyclic di- and tetra-esters 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. Their compounds differ from those described here in that they did not contain the repeating ethylene oxide units.

RESULTS AND DISCUSSION

The compounds shown in Fig. 2 were prepared from the appropriate diacid chloride and tetraethylene glycol (except for **15** where triethylene glycol was used). For example, compound **6** was prepared from phenylmalonyl chloride and tetraethylene glycol; compound **14** was prepared from β-methylglutaryl chloride and tetraethylene glycol (Fig. 3). These reactions were carried out in high dilution by adding the starting materials from separate dropping funnels to benzene at 45°. Yields ranged from < 1% to 37%. The compounds which gave the highest yields were generally distilled (18–37%) and were either mono-substituted with small alkyl chains or had no substitution. The compounds giving the lowest yields generally had unsaturated C–C bonds. These were isolated by extraction with hot hexane and then recrystallized, or by column chromatography.

The structures of all macrocyclic ether–esters were consistent with those derived from the IR and NMR spectra, elemental analyses, and molecular weight determinations The esters exhibited the expected IR band at 1710–1740 cm^{-1}. The fluorine substituted compound (**13**) gave an IR band at 1780 cm^{-1} as expected.[22] The NMR spectra were particularly instructive. The

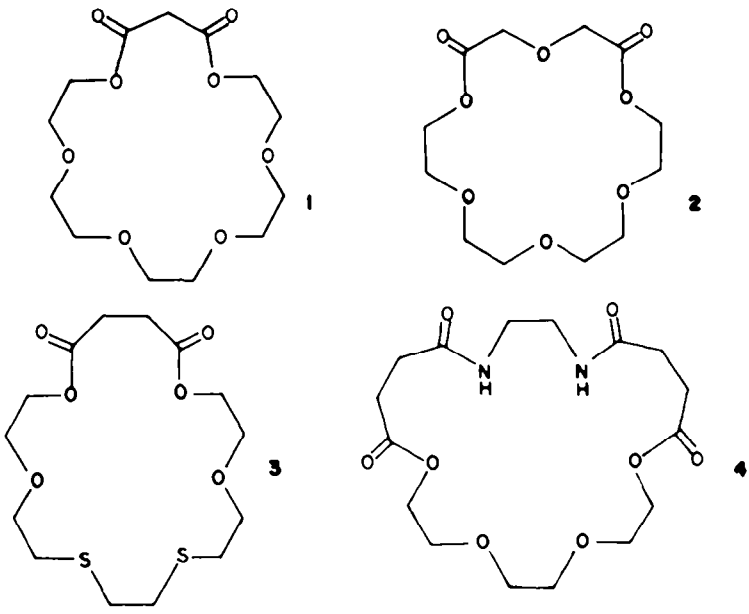

Fig. 1.

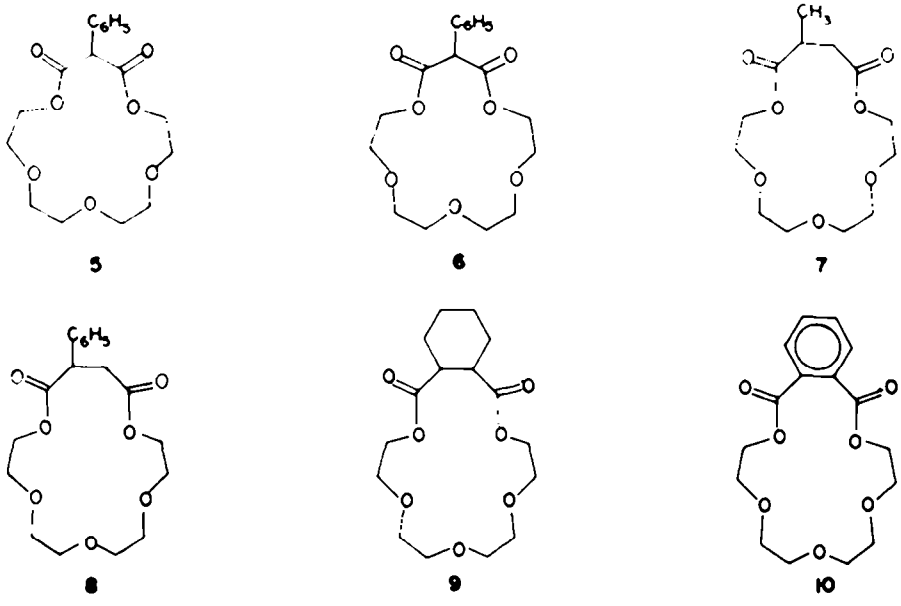

Fig. 2.

ether OCH_2 groups exhibited NMR peaks at δ 3.7 ± 0.1 as expected. The ester $COOCH_2$ groups exhibited NMR peaks at δ 4.3 ± 0.1 similar to the chemical shifts found in the $COOCH_2$ groups of various diethylesters.[17] The C_6H_4 and C_6H_5 groups show NMR peaks at δ 7.33 ± 0.05. The Me groups of the Me and Et substituted compounds gave NMR peaks at δ 1.1 ± 0.1. The vinyl hydrogens of compound **11** exhibited an NMR peak at δ 6.91.

Synthetic substituted macrocyclic compounds may prove to be of great value. It is known that in benzene, dicyclohexo-18-crown-6 will dissolve potassium permanganate to form "purple benzene".[23] The permanganate can then be used to perform oxidation reactions in benzene in high yield.[23] A desirable factor in crown preparation is to form crown compounds which offer more hydrocarbon character, like valinomycin, on the outside of the metal-ligand complex. The greater hydrocarbon character allows greater solubility of the complex in the organic solvents. Hence, we present a method and give a few examples of introducing hydrocarbon character into the crown compound.

Compound **10** was isolated as a monohydrate. We have previously observed that the macrocyclic ether–ester and ether–ester–amide compounds were hydroscopic and, indeed, some were isolated as hydrates.[18] Compound **11** is unusual in that it was formed by the reaction of two diacid chlorides and two glycols giving a 34-membered ring. We were unable to isolate any such *bis*-adducts in our other ether–ester forming reactions.[17] Since we were able to form macrocyclic ether–ester compounds of 22-ring members containing the maleic acid moiety,[18] it is possible that the *trans* double bond requires a larger ring. It is also of note that compound **11** is nearly the same size as valinomycin which has 36-ring members. Even though **11** may exist in more than one isomer, no attempt was made to separate the isomers.

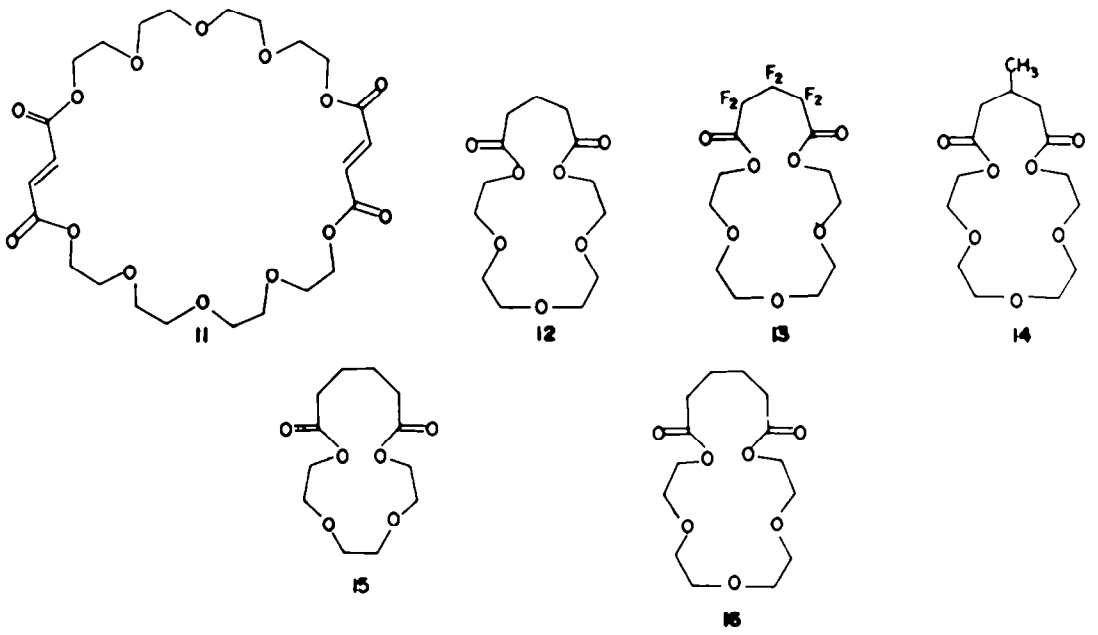

Fig. 2. (*Contd*).

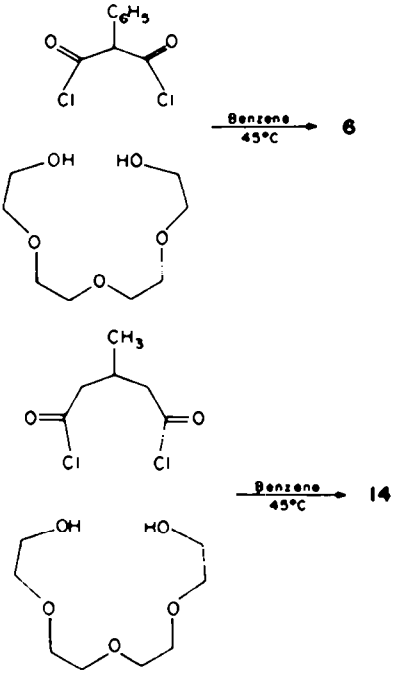

Fig. 3.

EXPERIMENTAL

All IR spectra were obtained on a Hilger and Watts H-1200 Infragraph. A Varian EM-390 spectrophotometer was used to obtain the NMR spectra. The elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. The molecular weights were determined by osmometry using a Hitachi Perkin–Elmer 115 Molecular Weight Apparatus. M.ps are uncorrected.

Starting materials. Some starting diacid chlorides were purchased: perfluoroglutaryl chloride (PCR), *o*-phthaloyl chloride (Aldrich), fumaryl chloride (Aldrich), glutaryl chloride (Aldrich), and adipoyl chloride (MCB). Other diacid chlorides were prepared from the corresponding diacid: ethylmalonic acid (Parish), phenylmalonic acid (Parish), and phenylsuccinic acid (Parish). If the diacid was not readily available, it was prepared from the anhydride using Shriner's method.[24] The anhydrides were purchased: methylsuccinic anhydride (Aldrich), *cis*-1,2-cyclohexanedicarboxylic anhydride (Aldrich) and β-methylglutaric anhydride (Aldrich). The glycols were purchased: triethylene glycol (Baker) and tetraethylene glycol (Aldrich).

General synthesis. The diacid chlorides were prepared by one of two methods. The first method involved the addition of PCl_5 to a mixture of the diacid in cold stirring chloroform. The mixture was slowly warmed to reflux temp. and gently refluxed until gaseous HCl ceased to be evolved. After removal of the chloroform and $POCl_3$, the crude diacid chloride was purified by distillation under reduced pressure. The second method involved the addition of $SOCl_2$ to a mixture of the diacid, pyridine and benzene stirring at room temp. After 3 hr, the benzene was removed by evaporation, and the pyridinium hydrochloride was removed by filtration. In this procedure the diacid chloride was not purified prior to use. The following diacid chlorides were made by the first method: ethylmalonyl chloride, phenylmalonyl chloride and methylsuccinyl chloride. The following diacid chlorides were made by the second method: phenylsuccinyl chloride, *cis*-1,2-cyclohexanedicarboxylic acid dichloride and β-methylglutaryl chloride. All diacid chlorides exhibited a characteristic IR band at 1750–1810 cm^{-1}.

The macrocyclic compounds were prepared by reacting the diacid chloride with the appropriate glycol. The glycol and the diacid chloride each dissolved in 250 ml of benzene were slowly added simultaneously to 800 ml of stirring benzene at 45°. The mixture was stirred at 45–50° for at least 3 days. After the reaction was stopped, benzene was removed under reduced pressure. The crude product was then purified either by distillation, extraction with hot hexane and recrystallization, or by chromatography on alumina using hexane with increasing amounts of chloroform as the eluant. Specific details are given for each compound.

15 - *Ethyl* - 1,4,7,10,13 - *pentaoxacyclohexadecane* - 17,19 - *dione* (5). Ethylmalonyl chloride (10.58 g, 0.063 mole) and tetraethylene glycol (12.24 g, 0.063 mole) were used. A portion of the product was distilled to give a viscous, colorless liquid (2.27 g, 28%), b.p. 146–148°/0.17 mm; IR, 1740 cm^{-1}; NMR, δ 0.97 (t, 3H, CH_3), 1.93 (m, 2H, CH_2CH_3), 3.34 (t, 1H, CH), 3.65 (s, 12H, CH_2OCH_2), 4.30 (m, 4H, $COOCH_2$). (Found: C, 53.66; H, 7.61; mol. wt., 287. Calc. for $C_{13}H_{22}O_7$: C, 53.77; H, 7.65%; mol. wt., 290).

15 - *Phenyl* - 1,4,7,10,13 - *pentaoxacyclohexadecane* - 14,16 - *dione* (6). Phenylmalonyl chloride (27.9 g, 0.129 mole) and tetraethylene glycol (25.0 g, 0.129 mole) were used. A portion of the product was first extracted with hot hexane then recrystallized from hexane to give a white solid (8.28 g, 28%), m.p. 83.5–85°; IR,

1750 cm $^{-1}$; NMR, δ 3.69 (s, 12H, CH_2OCH_2), 4.32 (m, 4H, $COOCH_2$), 4.72 (s, 1H, CH), 7.38 (m, 5H, C_6H_4). (Found: C, 60.12; H, 6.45; mol. wt., 332. Calc. for $C_{17}H_{22}O_7$: C, 60.35; H, 6.55%; mol. wt., 338).

15 - *Methyl* - 1,4,7,10,13 - *pentaoxacycloheptadecane* - 14,17 - *dione* (7). Methylsuccinyl chloride (15.15 g, 0.090 mole) and tetraethylene glycol (17.40 g, 0.090 mole) were used. The product (only a portion distilled, 1.81 g, 18%) was a viscous, colorless liquid, b.p. 146–154°/0.10–0.20 mm; IR, 1740 cm $^{-1}$; NMR, δ 1.23 (d, 3H, CH_3), 2.81 (m, 3H, CH_2CH), 3.67 (s, 12H, CH_2OCH_2), 4.23 (m, 4H, $COOCH_2$). (Found: C, 53.61; H, 7.68; mol. wt., 281. Calc. for $C_{13}H_{22}O_7$: C, 53.77; H, 7.65%; mol. wt., 290).

15 - *Phenyl* - 1,4,7,10,13 - *pentaoxacycloheptadecane* - 14,17 - *dione* (8). Phenylsuccinyl chloride (14.90 g, 0.0749 mole) and tetraethylene glycol (14.55 g, 0.0749 mole) were used. The product (0.040 g, 1%) was viscous, colorless liquid isolated by column chromatography; IR, 1740 cm $^{-1}$; NMR, δ 2.98 (m, 3H, CH_2CH), 3.66 (s, 12H, CH_2OCH_2), 4.23 (m, 4H, $COOCH_2$), 7.25 (s, 5H, C_6H_4). (Found: C, 61.41; H, 6.86; mol. wt., 389. Calc. for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86%; mol. wt., 352).

cis - *Cyclohexo* - [*o*] - 1,4,7,10,13 - *pentaoxacycloheptadecane* - 14,17 - *dione* (9). *cis*-1,2-Cyclohexanedicarboxylic acid dichloride (27.0 g, 0.13 mole) and tetraethylene glycol (24.7 g, 0.13 mole) were used. The product (0.018 g, < 1%), a pale yellow liquid, was first extracted with hot hexane then isolated by column chromatography; IR, 1735 cm $^{-1}$; NMR, δ 1.69 (m, 8H), 2.96 (m, 2H, CH), 3.78 (m, 12H, CH_2OCH_2), 4.45 (m, 4H, $COOCH_2$). (Found: C, 58.37; H, 8.12; mol. wt., 337. Calc. for $C_{16}H_{26}O_7$: C, 58.17; H, 7.93%; mol. wt., 330).

Benzo - [*o*] - 1,4,7,10,13 - *pentaoxacycloheptadecane* - 14,17 - *dione* (10). *o*-Phthaloyl chloride (14.33 g, 0.068 mole) and tetraethylene glycol (13.47 g, 0.069 mole) were used. The product (only a portion extracted, 0.26 g, 5%), a monohydrate, was first extracted with hot hexane then recrystallized from hexane to give white crystals, m.p. 70–75°; IR, 1710 cm $^{-1}$; NMR, δ 3.72 (m, 12H, CH_2OCH_2), 4.41 (m, 4H, $COOCH_2$), 7.33 (m, 4H, C_6H_4). (Found: C, 56.27; H, 6.51, mol. wt., 327. Calc. for $C_{16}H_{20}O_7 \cdot H_2O$: C, 56.13; H, 6.48%; mol. wt., 432).

trans,trans - 1,4,7,10,13,18,21,24,27,30 - *Decaoxacyclotetratriacontane* - 15,32 - *diene* - 14,17,31,34 - *tetraone* (11). Fumaryl chloride (15.20 g, 0.10 mole) and tetraethylene glycol (19.36 g, 0.10 mole) were used. The product (0.25 g, 2%), a white solid, was first extracted with hot hexane then recrystallized from EtOH, m.p. 67–71°; IR, 1720 cm $^{-1}$; NMR, δ 3.67 (s, 12H, CH_2OCH_2), 4.40 (t, 4H, $COOCH_2$), 6.91 (s, 2H, vinyl H). (Found: C, 52.34; H, 6.72; mol. wt., 548. Calc. for $C_{24}H_{36}O_{14}$: C, 52.55; H, 6.62%; mol. wt., 548).

1,4,7,10,13, - *Pentaoxacyclooctadecane* - 14,18 - *dione* (12). Glutaryl chloride (16.9 g, 0.10 mole) and tetraethylene glycol (19.4 g, 0.10 mole) were used. The product (only a portion distilled, 5.07 g, 31%) was a viscous colorless liquid, b.p. 155–157°/0.65 mm; IR, 1730 cm $^{-1}$; NMR, δ 2.01 (q, 2H, CCH_2C), 2.42 (t, 4H, CH_2CCH_2), 3.65 (s, 12H, CH_2OCH_2), 4.23 (t, 4H, $COOCH_2$). (Found: C, 53.64; H, 7.73; mol. wt., 302. Calc. for $C_{13}H_{22}O_7$: C, 53.78; H, 7.64%; mol. wt., 290).

15,15,16,16,17,17 - *Hexaflouro* - 1,4,7,10,13 - *pentaoxacyclooctadecane* - 14,18 - *dione* (13). Perfluoroglutaryl chloride (24.4 g, 0.089 mole) and tetraethylene glycol (17.27 g, 0.089 mole) were used. The product (only a portion distilled, 3.52 g, 23%) was a viscous, colorless liquid, b.p. 135–143°/0.2–0.3 mm; IR, 1780 cm $^{-1}$; NMR, δ 3.67 (m, 12H, CH_2OCH_2), 4.52 (t, 4H, $COOCH_2$). (Found: C, 38.98; H, 3.97; mol. wt., 398. Calc. for $C_{13}H_{16}F_6O_7$: C, 39.21; H, 4.05%; mol. wt., 398).

16 - *Methyl* - 1,4,7,10,13 - *pentaoxacyclooctadecane* - 14,18 - *dione* (14). β-Methylglutaryl chloride (14.00 g, 0.081) and tetraethylene glycol (16.40 g, 0.084 mole) were used. The product (only a portion distilled, 3.74 g, 37%) was a viscous, colorless liquid, b.p. 130–142°/0.12 mm; IR, 1740 cm $^{-1}$; NMR, δ 1.00 (d, 3H, CH_3), 2.30 (m, 5H, CH_2CHCH_2), 3.57 (s, 12H, CH_2OCH_2), 4.17 (m, 4H, $COOCH_2$). (Found: C, 55.15; H, 7.86; mol. wt., 306 Calc. for $C_{14}H_{24}O_7$: C, 55.25; H, 7.95%; mol. wt., 304).

1,4,7,10 - *Tetraoxacyclohexadecane* - 11,16 - *dione* (15). Adipoyl chloride (40.27 g, 0.22 mole) and triethylene glycol (30.04 g, 0.20 mole) were used. The product (only a portion distilled, 8.06 g, 31%), b.p. 140–143°/0.10–0.13 mm, m.p. 57–58°; IR, 1720 cm $^{-1}$; NMR, δ 1.74 (m, 4H, CCH_2CH_2C), 2.38 (m, 4H, CH_2CCCH_2), 3.63 (s, 8H, CH_2OCH_2), 4.27 (t, 4H, $COOCH_2$). (Found: C, 55.57; H, 7.78; mol. wt., 265. Calc. for $C_{12}H_{20}O_4$: C, 55.37; H, 7.75%; mol. wt., 260).

1,4,7,10,13 - *Pentaoxacyclononadecane* - 14,19 - *dione* (16). Adipoyl chloride (25.05 g, 0.14 mole) and tetraethylene glycol (25.00 g, 0.13 mole) were used. The product (only a portion distilled, 3.04 g, 20%) was a viscous, colorless liquid, b.p. 154–155°/0.06–0.07 mm; IR, 1730 cm $^{-1}$; NMR, δ 1.77 (m, 4H, $CCHCH_2C$), 2.41 (m, 4H, CH_2CCCH_2), 3.68 (s, 12H, CH_2OCH_2), 4.29 (t, 4H, $COOCH_2$). (Found: C, 55.46; H, 8.12; mol. wt., 326. Calc. for $C_{14}H_{24}O_5$: C, 55.25; H, 7.95%; mol. wt., 304).

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