Synthesis of New Macrocycles. Part I. Monomeric and Dimeric o-Phthalate Esters

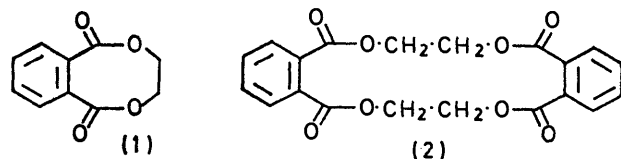By S. E. Drewes * and P. C. Coleman, Department of Chemistry, University of Natal, Pietermaritzburg, South Africa

Condensation of the dipotassium salt of o-phthalic acid with a series of alkyl dibromides of increasing chain length afforded cyclic esters ranging in size from a ten- to a thirty-four-membered ring. Dibromides bearing an uneven number of carbon atoms generally yielded dimeric compounds. while the even numbered dibromides gave mono-meric compounds. The dimeric esters are highly crystalline and appear to exist in fixed conformations.

IN a preliminary communication[1] the synthesis of ten-, eleven-, sixteen-, and eighteen-membered cyclic esters based on o-phthalic acid was described. The present investigation extends this work and has led to the isolation and characterisation of a number of new macrocyclic esters.
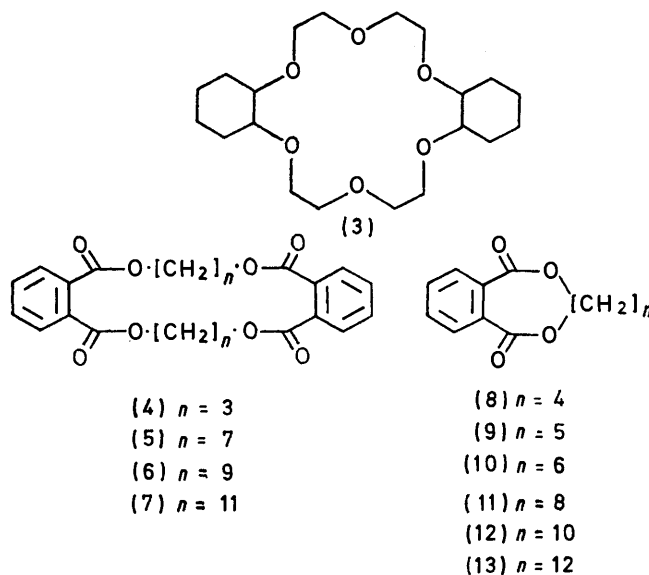
Few syntheses of cyclic esters of o-phthalic acid are known. Spanagel[2] describes the synthesis of cyclic ethylene ester of o-phthalic acid (1) as well as that of the corresponding dimeric ester (2). Yoneda, Yoshida, and

(1)   (2)

Fukui[3] have outlined methods for preparing esters of dicarboxylic acids with dimethylformamide, and we initially used conditions similar to theirs. Ehrhart,[4] using thermolytic depolymerisation,[5] was able to prepare a series of macrocycles from phthalic anhydride and glycols (e.g., pentane-1,5-diol, hexane-1,6-diol). Yields of up to 90% were obtained. The largest ring ester obtained was compound (2), which was the only dimeric compound to be isolated. The yields of compound (2) and the monomeric analogue (1) were less than 5% and Ehrhart suggests that no other dimeric esters were isolated since they are too involatile to distil under the conditions employed (235°). The 'poor' yield of compound (1), an eight-membered ring, is ascribed to

inherent strain in the molecule since the two carbonyl groups are twisted well out of the plane of the benzene ring.

Related compounds are the macrocyclic ethers[6,7] (crown compounds) obtained by Pedersen[8] from the

(3)

(4) n = 3
(5) n = 7
(6) n = 9
(7) n = 11

(8) n = 4
(9) n = 5
(10) n = 6
(11) n = 8
(12) n = 10
(13) n = 12

condensation of catechol and a suitable difunctional reagent. Thus cyclic structures containing up to 60 carbon atoms in the ring were obtained. These macrocyclic ethers form stable complexes with the salts of

[1] L. M. R. Crawford, S. E. Drewes, and D. A. Sutton, Chem. and Ind., 1970, 1351.

[2] E. W. Spanagel, U.S.P. 2,092,031/1937.

[3] S. Yoneda. Z. Yoshida, and K. Fukui, Kogyo Kagaku Zasshi, 1966, 69, 641 (Chem. Abs., 1967, 66, 10,537).

[4] W. A. Ehrhart, J. Org. Chem., 1968, 33, 2930.

[5] W. H. Carothers and E. W. Spanagel, J. Amer. Chem. Soc.. 1935, 57, 929.

[6] A. Lüttringhaus and K. Ziegler, Annalen, 1937, 528, 155.

[7] K. Ziegler, A. Lüttringhaus, and K. Wohlgemuth, Annalen, 1937. 528, 162.

[8] C. J. Pedersen, J. Amer. Chem. Soc., 1967, 89, 7017.

alkali metals. One of these ethers, dicyclohexyl-18-crown-6-cyclic polyether (3) has been used [9] in mechanistic studies which involved removal of potassium ion through complexation with the crown ether. Present indications are that the phthalate macrocyclic esters complex only weakly or not at all with alkali metal salts.

The eleven compounds (2) and (4)—(13) were prepared by the same procedure, the only variation being an increase in the reaction time with increasing chain length of the dihalide. The yields quoted are thus not necessarily maximum yields (see the Table). A slight molar excess

Compound	Dibromide	Ring size		Reaction time (h)	Yield (%)	M.p. (°C)
(2)	1,2-	16		4	10·1	189
(4)	1,3-	18		8	9·4	193
(5)	1,7-	26	Dimeric	48	6·5	163
(6)	1,9-	30		96	4·2	140—141
(7)	1,11-	34		144	2·7	138—139
(8)	1,4-	10		16	13·2	106
(9)	1,5-	11		24	15·5	101
(10)	1,6-	12	Monomeric	36	7·8	64
(11)	1,8-	14		72	2·6	
(12)	1,10-	16		120	2·8	
(13)	1,12	18		168	3·6	

(10%) of dihalide over phthalic acid salt was used throughout.

N.m.r. and Mass Spectra.—Characterisation of the cyclic esters was mainly by n.m.r. and mass spectrometry. The n.m.r. spectra of the dimeric compounds differed in certain important respects from the monomeric compounds. For all compounds the protons are grouped in three areas at *ca.* τ 2·35 (symmetrical peak of the aromatic protons), 5·60 (sharp triplet or multiplet due to the ' terminal ' methylene protons, *i.e.* the methylene groups adjacent to the carbonyl group), and 7·5—9·0 (broad multiplet or multiplet ending in a sharp peak) (*e.g.*, see Figure and Experimental section).

From the physical and n.m.r. data, several observations can be made: (*a*) Use of an alkyl dibromide bearing an uneven number of carbon atoms invariably leads to the formation of dimeric compounds, *e.g.* (4)—(7). An exception is compound (9) obtained from 1,5-dibromopentane. The even-numbered dibromides yield monomers except in the case of 1,2-dibromoethane. (*b*) In the n.m.r. spectra the triplet due to the terminal methylene protons is always sharp if a dimeric ester is involved. [For compound (2) it is a sharp singlet.] For the monomeric esters this group of signals is much less clearly defined. For all the compounds the signals due to the terminal methylene protons collapsed to a singlet by appropriate irradiation of the upfield (τ 7·5—9·0) methylene protons. It was also clear from the n.m.r. spectra of the three largest monomers [compounds (11)—(13)] that impurities, absent from all other

[9] J. N. Roitman and D. J. Cram, *J. Amer. Chem. Soc.*, 1971, **93**, 2231.

[10] H. Budzikiewicz, C. Djerassi, and D. H. Williams. ' Mass Spectrometry of Organic Compounds,' Holden-Day, San Francisco. 1967, p. 203.

compounds, were present. Contamination was small in compound (11) but was detectable as additional peaks at τ 6·3 and 7·15 in compounds (12) and (13). Redistillation of these particular fractions effected no marked purification. (*c*) The esters are generally crystalline at room temperature but the dimeric compounds have m.p.s well above those of their monomeric counterparts. Isolation of the dimers was a simple procedure whereas the larger monomers required special techniques.

Mass spectrometry was most useful, since the n.m.r. data alone exhibit little difference between a monomer and its corresponding dimer. For example, the integration would be identical and the coupling patterns (apart from the one difference mentioned before) could be very similar.

The mass spectra show a small number of characteristic peaks but for the rest are relatively featureless. All
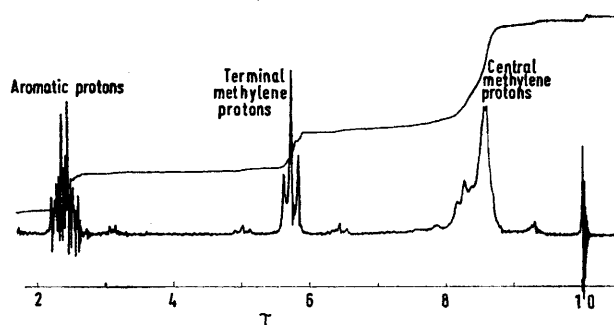
N.m.r. spectrum of compound (5)

compounds show a molecular ion peak, from a 1% relative abundance for compound (2) and 4% for compound (7) to 31·6% for compound (9). Fragment peaks normally associated with phthalates [10] appear in all the spectra: ions at *m/e* 149 (invariably the base peak, protonated anhydride ion), 104, and 76. In all the dimeric compounds, a very diagnostic peak is located at ($M^{+ \bullet}/2 + 1$). This is a prominent peak and varies in intensity between 14 and 100% relative abundance. A possible fragmentation pattern is shown in Scheme 1 for compound (4).

The monomeric esters (8)—(13) do not have the ($M^{+ \bullet}/2 + 1$) peak. The molecular ion peak in the lower members of the series is fairly prominent (up to 32%) but declines in the larger-ring compounds to a value of 1·7% in compound (13). Impurities in compounds (11) and (12) already apparent in the n.m.r. spectra, are probably responsible for the appearance of a prominent peak at *m/e* 161.

I.r. Spectra.—All the esters showed a characteristic carbonyl absorption at 1739—1715 cm^{-1}. Two additional bands (C–O stretching) were located at 1290—1280 and 1135—1129 cm^{-1}.

Ease of Ring Formation.—It is instructive to consider the ease of cyclisation by comparing the present findings with conclusions drawn by Carothers [11] and by Flory.[12]
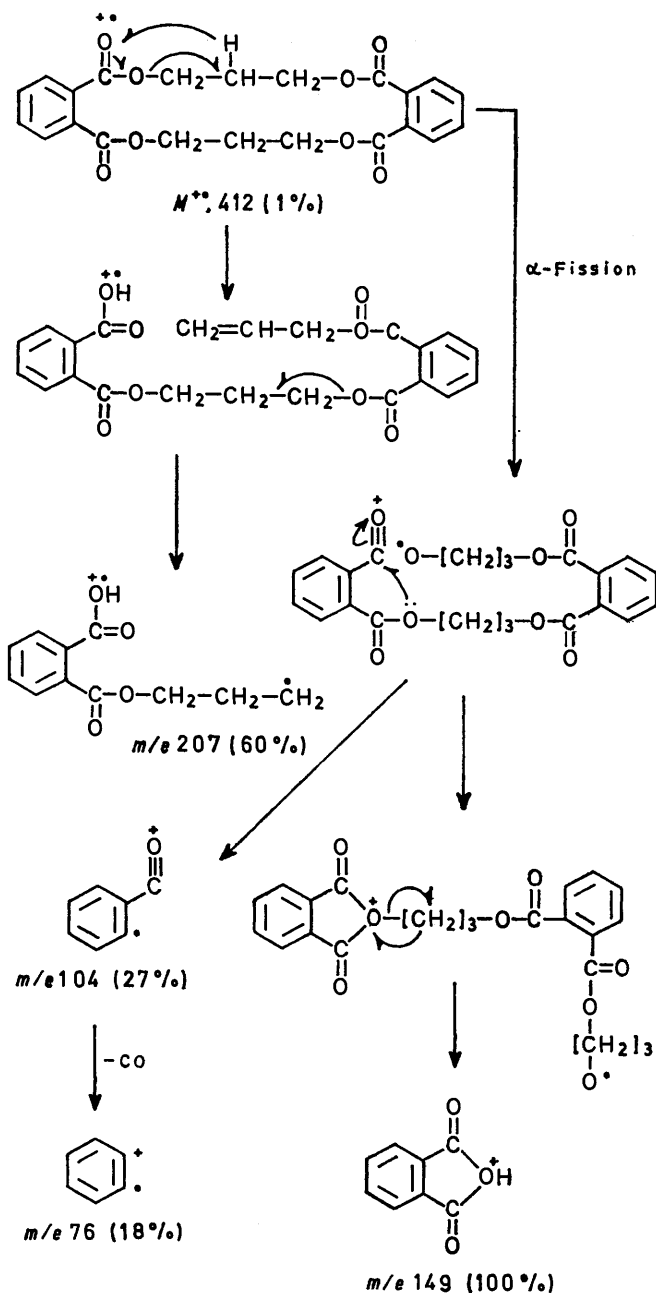
[11] W. H. Carothers, *Chem. Rev.*, 1931, **8**, 353.

[12] P. J. Flory, *Chem. Rev.*, 1946, **39**, 137.

Flory states that if a ring containing five carbon atoms can be formed, this will form exclusively, whereas six- and seven-membered rings are formed in addition to chain compounds, when the structures are suitable.

$M^{+\cdot}$. 412 (1%)

α-Fission

m/e 207 (60%)

m/e 104 (27%)

− CO

m/e 76 (18%)

m/e 149 (100%)

SCHEME 1 Mass fragmentation pattern to show formation of major peaks in dimeric cyclic ester

Larger rings are formed only under special conditions (such as high dilution) which favour intra- over inter-molecular condensation. However, even under these

conditions poor yields of eight- to twelve-membered rings are obtained.

Isolation of the ten—twelve-membered compounds (8)—(10) as major products, contrasts with these conclusions. Incorporation of oxygen into the cyclic system seems to favour cyclisation and Ziegler, Lüttringhaus, and Wohlgemuth [7] have demonstrated that yields of monomeric alkyl ethers of catechol were undepressed for ten- and eleven-membered ring compounds. The isolation of compounds (8)—(10) together with the other cyclic esters indicates that steric factors must operate during the difunctional condensation. Carothers and Spanagel [5] have shown that in the intermediate range, odd-membered rings are more difficult to produce than even-membered ones. They suggest that interferences to ring closure are still operative after cyclisation and since these interferences are greater for the odd numbers, this leads to instability.

The present findings are in agreement with the generalisations of Carothers and Spanagel.[5] Thus, the uneven-numbered dibromides (1,3-, 1,7-, 1,9-, and 1,11-) do not give the odd-membered esters, which would contain 9, 13, 15 and 17 atoms respectively, but instead produce the corresponding even-numbered dimeric compounds as major product. The exception to the rule is compound (9; $n = 5$) which should be dimeric.

It has been re-emphasised [1] that the steric factor which controls the formation of macrocycles must be that of incorporation of a structure leaving at least four carbon atoms lying in one plane with angles of ca. 120°. o-Phthalic acid fit these requirements. Other acceptable compounds are for example, catechol, benzene-1,2-dicarbonitrile, o-phenylenediamine, cyclohex-1-ene-1,2-dicarboxylic acid, and maleic acid. This concept is of course part of the more generalised ' principle of rigid groups ' stated explicitly by Ziegler [13] following the work of Baker et al.[14] An example of recent work employing rigid groups is that of Smolinski and Jamrozik,[15] who condensed 1,2- and 1,8-dihydroxynaphthalenes with the tetrabromohydrin derivative of pentaerythritol.

The findings of Pedersen [8] afford information on factors affecting ring closure. Pedersen warns, however, that his yields of compounds do not necessarily represent maximum yields, but it is evident that certain polyether rings are formed more readily than others. The preferred rings are those containing five to six oxygen atoms, each separated from the next by two carbon atoms, for example, compound (14), which was obtained in 80% yield, and also compound (15), obtained in the lowest yield of all the compounds listed (2%). These two compounds are identical except that one contains a rigid group whereas the other does not. By contrast, Yoshino and his co-workers [16] report the synthesis in high yield (20%) of the cyclic amide (16) from condensation of 4,4'-methylenedibenzoyl chloride and 4,4'-methylenedibenzylamine, where there cannot be any assistance from rigid groups.

[13] K. Ziegler in Houben-Weyl ' Methoden der Organischen Chemie,' Verlag Georg Thieme. Stuttgart, 1955, vol. 4/2, p. 729.
[14] W. Baker, J. F. W. McOmie, and W. D. Ollis, J. Chem. Soc., 1951, 200.
[15] S. Smolinski and J. Jamrozik, Tetrahedron, 1971, 27, 4977.
[16] Y. Urushigawa, T. Inazu, and T. Yoshino, Bull. Chem. Soc. Japan, 1971, 44, 2546.

The mechanism of cyclisation in the *o*-phthalate esters is probably closely akin to that advanced by

(14)

(15)

(16)

(17)

(18)
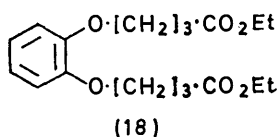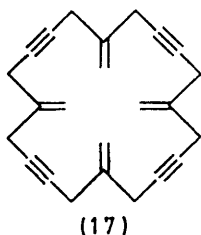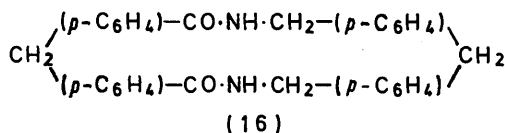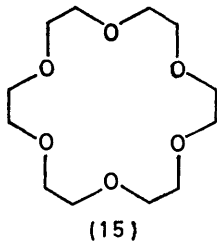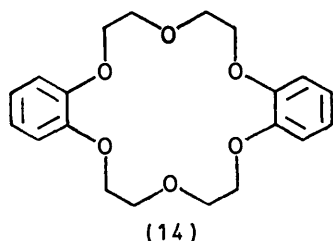
Looker and Sondheimer[17] for the formation of the twenty-membered cyclic tetra-acetylene (17). By analogy, the sixteen-membered dimeric compound (2) could form as shown in Scheme 2. The product (*a*) in
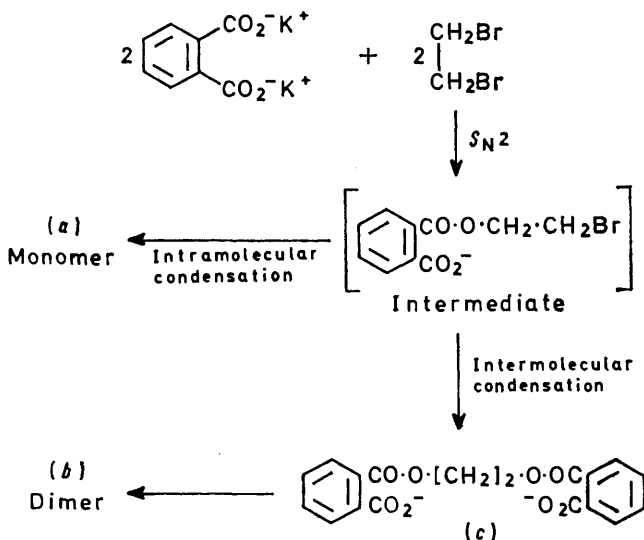

SCHEME 2   Mechanism of the formation of cyclic esters

this Scheme has not been isolated, but Ehrhart[4] was able to obtain it by the thermolytic technique. While (*b*) is the major product (8%), numerous other products, not isolated at present, are formed. This is demonstrated readily by examination of the products by t.l.c.

[17] B. E. Looker and F. Sondheimer, *Tetrahedron*, 1971, **27**, 2567.

(Kieselgel; chloroform). There is some evidence that the intermediate (*c*), of low R_F, is present. Brown and Tyman,[18] in synthesising a dimeric product (intermolecular reaction) similar to the *o*-phthalate esters by Dieckmann cyclisation, ascribe the absence of intramolecular product to an unfavourable 'divergent' rather than parallel orientation of the side chains of the starting material, the diester (18).

Conformation of Rings.—Predictions regarding possible conformations of cyclic *o*-phthalate esters with more than four methylene groups in the central ring must be speculative since the large number of methylene groups results in an extremely flexible molecule. At the outset it will be stressed that the presence of *two* rigid end groups (as in the dibenzo-compounds) will impose restrictions on the flexibility of structures. The n.m.r.

TOP   (19)   SIDE

(20)
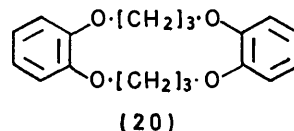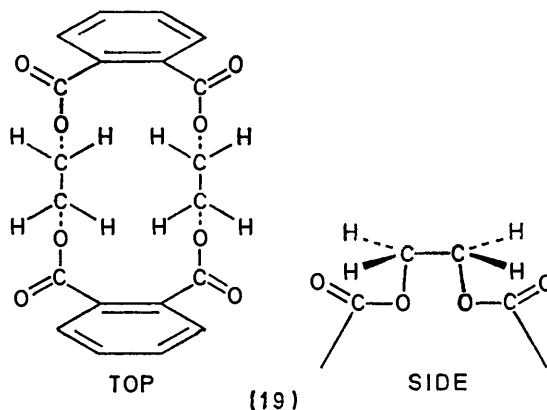
spectrum of compound (2) shows four methylene groups resonating as a sharp singlet at τ 5·35 at 25°. This singlet remains unaltered at $-20°$. The equivalence of the four methylene protons implies an extremely symmetrical molecule in which these eight protons experience the same shielding. Dreiding models indicate that a possible conformation in accord with the above observation is the one shown schematically, (19). In this conformation the two carbonyl groups, the two ester oxygen atoms, and the two methylene carbon atoms composing one half of the macrocyclic ring, all lie in one plane. The corresponding atoms, making up the other half of the ring are similarly in one plane. These two planes are not quite parallel to one another. The rigid portion of the molecule, *i.e.* the benzene rings, are inclined at an angle of *ca.* 65° to one another. The two benzene rings can be regarded as 'conformational anchors' which will 'restrict' the molecule to the

[18] G. R. Brown and J. H. P. Tyman, *Chem. and Ind.*, 1970, 436.

particular conformation. For the larger dimeric compounds, related conformations are probable. In all these compounds the eight 'terminal' methylene protons are again equivalent and appear as a sharp triplet at τ 5·55—5·72 (J 6·0 Hz). A similar triplet is observed for a dimeric sixteen-membered ring (20) derived from catechol.[19]

In the monomeric esters the signal due to the four 'terminal' methylene protons is still centred round τ 5·60 but generally it is a multiplet or a partially-resolved triplet. It is suggested that the monomeric esters are less rigid than their dimeric counterparts and do not reside in any particular conformation.

The 'central' methylene protons for all the cyclic esters lie in the range τ 7·8—8·8. The signal is a multiplet but generally one sharp peak stands out prominently, particularly in the dimeric esters. This observation is again taken to reflect a greater degree of symmetry in the latter compounds.

Choice of Solvent.—The solvent used throughout the investigation was redistilled dimethylformamide. Initially conditions approaching those employed in the high dilution technique were used, but it was subsequently found that these conditions did not improve yields. Other solvents (benzene, xylene, and n-butanol) were used without success.

The reaction of dipotassium phthalate with alkyl bromide proceeds *via* an S_N2 mechanism (Scheme 3).
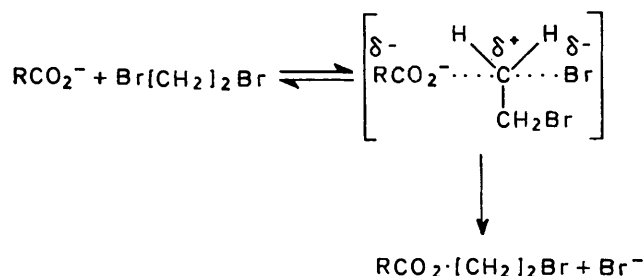
SCHEME 3

In dipolar aprotic solvents such as dimethylformamide this type of bimolecular substitution is much faster, since solvation of the cation is promoted whereas the reactant anion (RCO_2^-) is less solvated (thus unencumbered and highly reactive) than in protic solvents such as water or methanol.[20]

EXPERIMENTAL

N.m.r. spectra were recorded on a Varian T60 instrument and mass spectra were obtained on an A.E.I. MS9 instrument. M.p.s were determined with a Kofler micro-hot-stage apparatus.

The synthesis and isolation was similar for all the cyclic esters, except that the reflux time was increased for the larger esters, and for compounds (11)—(13) distillation under high vacuum (220° at 6 × 10⁻³ mmHg) was necessary for purification.

7,8,17,18-*Tetrahydrodibenzo*[f,n][1,4,9,12]*tetraoxacyclohexadecene*-5,10,15,20-*tetrone, Cyclic Dimeric Ethylene Ester of Phthalic Acid.* (2).—Dipotassium phthalate (10 g,

41 mmol) and 1,2-dibromoethane (8·46 g, 45 mmol) in dimethylformamide (100 ml) were heated under reflux for 4 h. The dimethylformamide was then distilled off under reduced pressure (50°), the residue was poured into cold water (300 ml), and made basic with sodium hydrogen carbonate. Generally a gummy precipitate separated and this was kept at 0° for 12 h. The gum was separated off and then dissolved in hot ethanol. On cooling, crystalline material precipitated out. This was filtered off and washed with ice-cold ethanol to give white needles (800 mg), m.p. 189° (from ethanol) (Found: C, 62·2; H, 4·0. Calc. for $C_{20}H_{16}O_8$: C, 62·5; H, 4·2%), M^+, 384, τ (CDCl₃) 2·38 (8H, m, ArH) and 5·35 (8H, s, 4 × CH₂).

All other esters were prepared and isolated thus, unless described later (see the Table).

8,9,19,20-*Tetrahydro*-7H,18H-*dibenzo*[g,p][1,5,10,14]*tetraoxacyclo-octadecene*-5,11,16,22-*tetrone* (4).—This product was obtained as white *needles* (9·4%), m.p. 193° (from ethanol) (Found: C, 63·9; H, 4·8. $C_{22}H_{20}O_8$ requires C, 64·1; H, 4·9%), M^+, 412, τ (CDCl₃) 2·32 (8H, m, ArH), 5·54 (8H, t, 4 × CH₂), and 7·82 (4H, m, 2 × CH₂).

8,9,10,11,12,13,23,24,25,26,27,28-*Dodecahydro*-7H,22H-*dibenzo*[c,p][1,6,14,19]*tetraoxacyclohexacosene*-5,15,20,30-*tetrone* (5).—This was obtained as white *needles* (6·5%), m.p. 163° (from ethanol) (Found: C, 68·7; H, 7·0. $C_{30}H_{36}O_8$ requires C, 68·7; H, 6·9%), M^+, 524, τ (CDCl₃) 2·35 (8H, m, ArH), 5·70 (8H, t, 4 × CH₂), and 8·57 (20H, m, 10 × CH₂).

8,9,10,11,12,13,14,15,25,26,27,28,29,30,31,32-*Hexadecahydro*-7H,24H-*dibenzo*[c,r][1,6,16,21]*tetraoxacyclotriacontene*-5,17,22,34-*tetrone* (6).—This was obtained as white *needles* (4·2%), m.p. 140—141° (from ethanol) (Found: C, 69·9; H, 7·7. $C_{34}H_{44}O_8$ requires C, 70·3; H, 7·6%), M^+, 580, τ (CDCl₃) 2·35 (8H, m, ArH), 5·70 (8H, t, 4 × CH₂), and 8·63 (28H, m, 14 × CH₂).

8,9,10,11,12,13,14,15,16,17,27,28,29,30,31,32,33,34,35,36-*Eicosahydro*-7H,26H-*dibenzo*[c,t][1,6,18,23]*tetraoxacyclotetratriacontene*-5,19,24,38-*tetrone* (7).—This was obtained as white *needles* (2·7%), m.p. 138—139° (from ethanol) (Found: C, 71·3; H, 8·3. $C_{38}H_{52}O_8$ requires C, 71·7; H, 8·2%), M^+, 636, τ (CHCl₃) 2·35 (8H, m, ArH), 5·72 (8H, t, 4 × CH₂), and 8·70 (36H, m, 18 × CH₂).

3,4,5,6-*Tetrahydro*-2,7-*benzodioxacyclodecene*-1,8-*dione* (8).—The *compound* was obtained as white needles in high yield (13·2%), m.p. 106° (from ethanol) (Found: C, 65·2; H, 5·5. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%), M^+, 220, τ (CDCl₃) 2·35 (4H, m, ArH), 5·63 (4H, m, 2 × CH₂), and 8·07 (4H, m, 2 × CH₂).

4,5,6,7-*Tetrahydro*-3H-2,8-*benzodioxacycloundecene*-1,9-*dione* (9).—Of all the cyclic esters this one was obtained in highest yield (15·5%), as needles, m.p. 101° (lit.,[4] 100·8—102·3°) (from ethanol) (Found: C, 66·5; H, 6·1. Calc. for $C_{13}H_{14}O_4$: C, 66·6; H, 6·0%), M^+, 234, τ (CDCl₃) 2·37 (4H, m, ArH), 5·68 (4H, m, 2 × CH₂), and 8·24 (6H, m, 3 × CH₂).

3,4,5,6,7,8-*Hexahydro*-2,9-*benzodioxacyclododecene*-1,10-*dione* (10).—This was obtained as white needles (7·8%), m.p. 64° (lit.,[4] 63·7—64·5°) (from ethanol) (Found: C, 67·7; H, 6·5. Calc. for $C_{14}H_{16}O_4$: C, 67·7; H, 6·5%), M^+, 248, τ (CDCl₃) 2·42 (4H, m, ArH), 5·62 (4H, t, 2 × CH₂), and 8·29 (8H, m, 4 × CH₂).

Cyclic Octamethylene, Decamethylene, and Dodecamethylene Esters of Phthalic Acid, (11)—(13).—These three esters were obtained in low yield (2·6, 2·7, and 3·6%, respectively), were non-crystalline, and generally difficult to isolate. Pre-

[19] A. W. Archer and P. A. Claret, *Chem. and Ind.*, 1969. 171.
[20] A. J. Parker, *Chem. Rev.*, 1969, **69**, 1.

cipitation from water yielded a gum in each case and this was still contaminated with the dibromide. Purification was achieved by distillation under high vacuum (200—220° at 6.3×10^{-3} mmHg) but C and H analyses were unsatisfactory: 3,4,5,6,7,8,9,10-*octahydro*-2,11-*benzodioxacyclotetradecene*-1,12-*dione* (11), M^+, 276, τ (CDCl$_3$) 2·38 (4H, m, ArH), 5·60 (4H, m, $2 \times$ CH$_2$), and 8·57 (12H, m, $6 \times$ CH$_2$); 3,4,5,6,7,8,9,10,11,12-*decahydro*-2,13-*benzodioxacyclohexadecene*-1,14-*dione* (12), M^+, 304, τ (CDCl$_3$) 2·45 (4H, m, ArH), 5·80 (4H, m, $2 \times$ CH$_2$), and 8·80 (16H, m, $8 \times$ CH$_2$);

3,4,5,6,7,8,9,10,11,12,13,14-*dodecahydro*-2,15-*benzodioxacyclo-octadecene*-1,16-*dione* (13), M^+, 332, τ (CDCl$_3$) 2·38 (4H, m, ArH), 5·75 (4H, m, $2 \times$ CH$_2$), and 8·77 (20H, m, $10 \times$ CH$_2$).