Synthesis of New Macrocycles. Part II.[1] Cyclic Esters based on αα′-Dibromo-*o*-xylene

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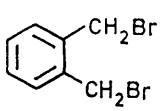
Condensation of αα′-dibromo-*o*-xylene with the homologous series of dicarboxylic acids beginning with oxalic acid and ending with sebacic acid afforded dimeric cyclic esters ranging in ring size from sixteen to thirty-two members. By contrast, the dibromide gave only monomeric cyclic esters in reactions with maleic, citraconic, and *o*-phthalic acids. The influence of the ' rigid group ' on the cyclization reaction is discussed. N.m.r. and mass spectral data for the new esters are presented and suggestions as to the likely conformations of the alicyclic rings, based largely on the n.m.r. evidence, are considered.

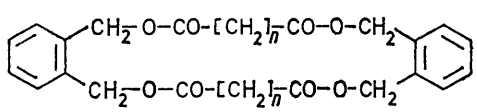
In Part I [1] the condensation of *o*-phthalic acid with alkyl dibromides was described. By utilizing the ' rigid group ' [2] present in *o*-phthalic acid, cyclization was effected for the entire homologous series from 1,2-dibromoethane to 1,12-dibromododecane. For the present investigation the roles of reagents were reversed: αα′-dibromo-*o*-xylene (1), containing the ' rigid group ', was condensed with a series of dicarboxylic acids, starting with the ' rigid ' oxalic acid and proceeding to the completely ' non-rigid ' sebacic acid.

αα′-Dibromo-*o*-xylene (1), apart from having the requisite four carbon atoms coplanar, thus restricting the rotational possibilities during cyclization, also possesses allylic bromine atoms suitable for rapid nucleophilic substitution reactions. For cyclization reactions it has, however, received less attention than its *m*- and *p*-counterparts. 5,6,11,12-Tetrahydrodibenzo[*a*,*e*]cyclooctene and 5,6,11,12,17,18-hexahydrotribenzo[*a*,*e*,*i*]cyclododecene, obtained by Baker and his co-workers [3] *via* a Würtz reaction on (1), represent an early application of its use in cyclizations. More recently Vögtle and Zuber [4] have prepared 5,7,12,14-tetrahydrodibenzo[*c*,*h*]-[1,6]dioxacyclodecin and 5,7,12,14,19,21,26,28-octahydrotetrabenzo[*c*,*h*,*m*,*r*][1,6,11,16]tetraoxacycloeicosin from (1) and αα′-dihydroxy-*o*-xylene. These cyclic ethers were isolated in yields of 15 and 40%, respectively, under carefully controlled conditions involving use of a special high dilution apparatus.

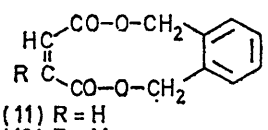
The twelve cyclic esters (2)—(13), previously unreported, were all prepared by the dihalide–dipotassium dicarboxylate reaction [1] in dimethylformamide at ordinary dilutions. All compounds were fully characterized, but (5) and (7) gave unsatisfactory elemental analyses. Yields varied between 0·3 and 35·3% (see Table 1). Most reactions were carried out in boiling solvent, but for the maleic and citraconic acid derivatives lower temperatures were used to avoid isomerization to the corresponding *trans*-acid. Progress of the reaction could be followed by t.l.c. (Kieselgel; chloroform). Invariably completion of reaction coincided with a change in colour of the solution from almost colourless to dark yellow.



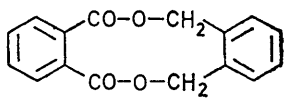
(1)



(2) $n = 0$
(3) $n = 1$
(4) $n = 2$
(5) $n = 3$
(6) $n = 4$
(7) $n = 5$
(8) $n = 6$
(9) $n = 7$
(10) $n = 8$



(11) R = H
(12) R = Me



(13)

From Table 1 the following deductions can be made. (*a*) Highest yields were obtained either when both reactants possessed ' rigid groups ' [compounds (11)—(13)] or where one reactant had a ' rigid group ' and the

[1] S. E. Drewes and P. C. Coleman, *J.C.S. Perkin I*, 1972, 2148.
[2] W. Baker, J. F. W. McOmie, and W. D. Ollis, *J. Chem. Soc.*, 1951, 200.
[3] W. Baker, R. Banks, D. R. Lyon, and F. G. Mann, *J. Chem. Soc.*, 1945, 27.
[4] F. Vögtle and M. Zuber, *Tetrahedron Letters*, 1972, 561.

other was a short chain dicarboxylic acid [compounds (2) and (4)]. The low yield of (3) appears to be anomalous. (*b*) The exclusive formation of dimers from the saturated aliphatic dicarboxylic acids [compounds (2)—(10)] is not explained readily. It is true that cyclic monomers derived from (1) and any of the acids up to pimelic would be classed as medium-sized rings (8—13 atoms), having an eclipsed conformation of the methylene chain which renders their synthesis difficult.[5] However, while this may be valid in part for the glutaric, adipic, and pimelic acid derivatives, it is not the case for the shorter-chain acids. (*c*) Compound (2), derived from oxalic acid, differs from all others in being the only αα′-diketone and by being the product isolated in highest yield. The n.m.r. spectrum suggests that it differs materially in its conformation from the other cyclic dimers. (*d*) The yields of compounds (11)—(13) were very similar and this is not unexpected. The increase in nucleophilicity of the carboxylate anion as a result of the inductive effect of the methyl group was demonstrated readily by the extremely rapid reaction of citraconic acid compared with maleic acid under similar mild conditions (see Table 1).

TABLE 1

Yields and m.p.s of cyclic esters (2)—(13)

Parent acid	Cyclic ester	Ring size	Reaction time (h)	Yield (%)	M.p. (°C)
Oxalic	(2)	16	1·50	35·3	233—5
Malonic	(3)	18	0·75	0·6	215—8
Succinic	(4)	20	1·50	16·0	217
Glutaric	(5)	22	1·00	2·7	173
Adipic	(6)	24	0·75	2·7	144
Pimelic	(7)	26	22·00	0·9	121
Suberic	(8)	28	1·00	7·3	134
Azelaic	(9)	30	1·50	0·3	119
Sebacic	(10)	32	1·00	3·1	135
Maleic	(11)	10	96·00 †	14·2	160
Citraconic	(12)	10	3·00 †	12·6	108
Phthalic	(13)	10	1·75	12·7	148

† Reduced temperature (see Experimental section).

TABLE 2

Chemical shifts (τ) (solvent $CDCl_3$) of protons in cyclic esters (2)—(10)

Ester	Aromatic	Benzylic	Terminal methylene *	Inner methylene
(2)†	2·43(d)	4·53(s)		
(3)	2·65(s)	4·73(s)	6·56(s)	
(4)	2·61(s)	4·80(s)	7·31(s)	
(4)†	2·60(s)	4·77(s)	7·30(s)	
(5)	2·62(s)	4·81(s)	7·60(t)	7·80—8·20
(6)	2·62(s)	4·80(s)	7·65(t)	8·03—8·53
(7)	2·62(s)	4·81(s)	7·67(t)	8·07—8·87
(8)	2·62(s)	4·79(s)	7·68(t)	8·07—8·97
(9)	2·62(s)	4·80(s)	7·67(t)	8·10—8·40
(10)	2·63(s)	4·80(s)	7·68(t)	8·07—8·97

* α to CO. † [$^2H_7$]Dimethylformamide solvent.

Compounds (2)—(13) represent, in each case, the major reaction product. Additional products, obtained in considerably lower yield, have not yet been identified.

N.m.r. and Mass Spectra.—The n.m.r. spectra of (2)—(10) are uncomplicated (Table 2). Without exception the benzylic protons gave sharp singlets, thus implying magnetic equivalence. These signals were further downfield (τ 4·80) than their counterparts in αα′-dibromo-*o*-xylene (τ 5·38). For (2) the signal was even further downfield (τ 4·53), probably owing to the effect of two adjacent carbonyl groups. The monomeric esters (11)—(13) had n.m.r. spectra similar to those of their respective starting materials (Table 3).

TABLE 3

Chemical shifts (τ) (solvent $CDCl_3$) of protons in cyclic esters (11)—(13)

Ester	Aromatic	Benzylic	Methine	Methyl
(11)	2·67(s)	4·77(s)	3·65(s)	
(12)	2·61(s)	4·74(s)	3·90(d)	7·97(d)
(13)	2·11—2·78	4·60(s)		

In the spectrum of (13) the xylene (singlet) and the phthalate signals (multiplet) are readily distinguished.

Mass spectrometry was used to show the presence of monomers or dimers. Earlier evidence [1,6] had shown that cyclic esters are often without a molecular ion peak but instead exhibit an intense [($M^{+\cdot}/2$) + 1] peak. The present series confirmed this finding (see Scheme and Table 4). The monomers (11)—(13) differed from the dimers in having a strong molecular ion peak but no [($M^{+\cdot}/2$) + 1] peak. The characteristic peaks at *m/e* 99, 113, and 149 from (11)—(13), respectively, correspond to the ions (14)—(16), respectively and originate by a common pathway [7] from the ' acid ' half of the molecule.

TABLE 4

Relative abundance (%) of the major peaks (see Scheme) from mass spectral fragmentation of the esters (2)—(10)

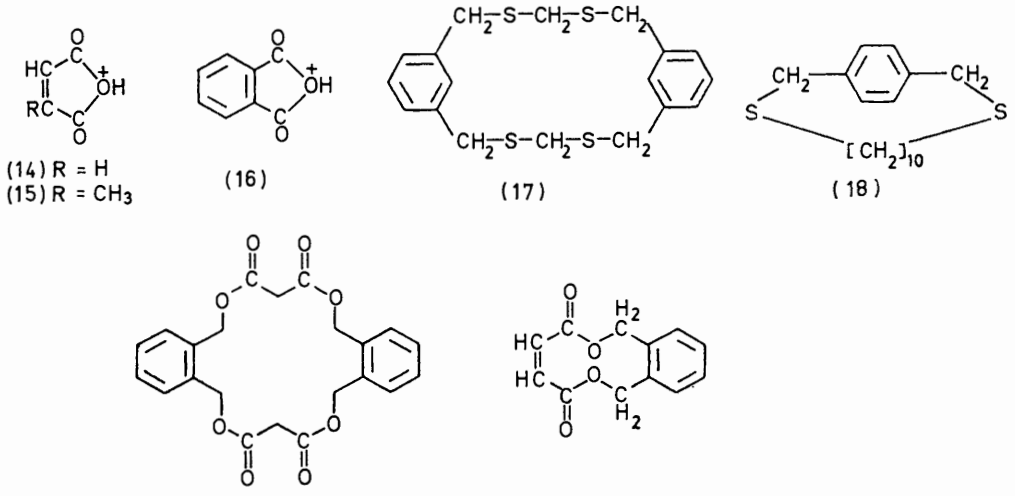
Ester	(*A*) $M^{+\cdot}$	(*B*) $M-$ 119	(*C*) ($M^{+\cdot}/2$) +1	(*D*)	(*E*)	(*F*)	(*G*)	(*H*)	(*I*)
(2)	1·3		7·5	0·5		0·5	38·0	20·0	84·0
(3)	4·0	26·0	38·0	5·1	62·0		27·0	59·0	100·0
(4)		2·0	84·0	24·0	0·8		24·0	8·8	100·0
(5)		1·3	84·0	58·0			21·0	7·0	100·0
(6)		6·4	73·0	29·0			20·0	3·9	55·0
(7)		18·0	100·0	39·0	0·7		8·5	2·7	46·0
(8)		20·0	100·0	81·0	2·1	1·0	12·0	4·0	68·0
(9)		28·0	100·0	84·0	3·2	2·1	14·0	15·0	98·0
(10)		14·0	100·0	77·0	2·3	1·3	8·7	3·9	63·0

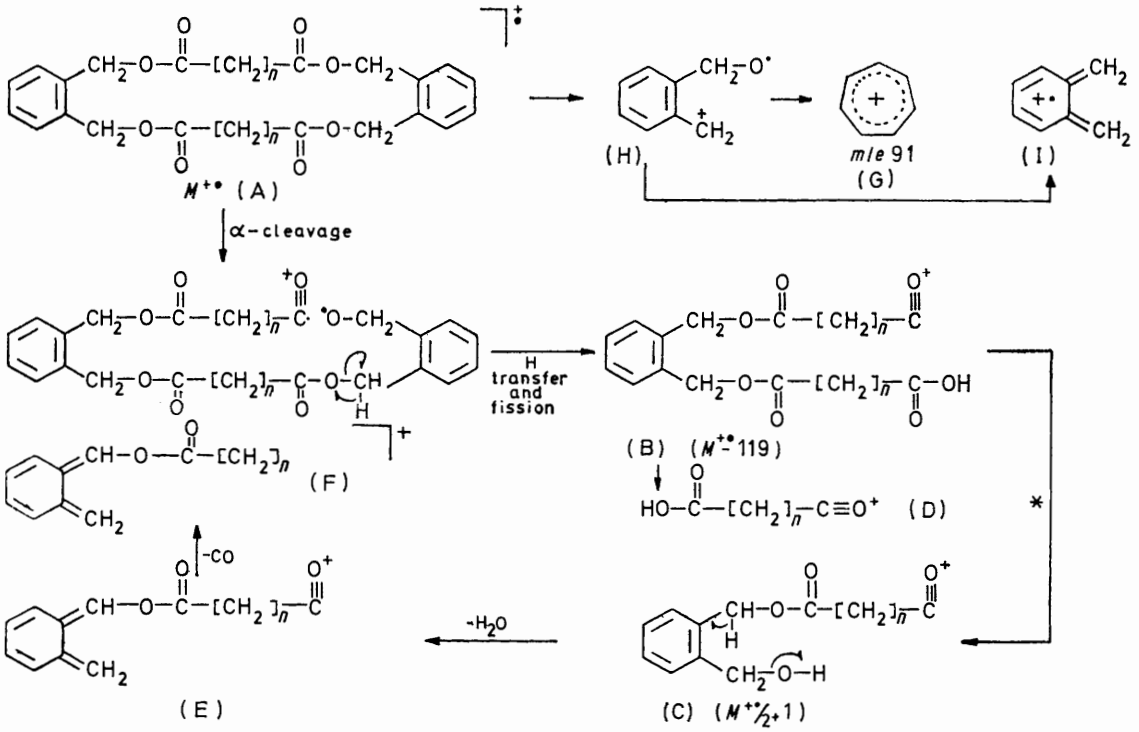
Conformation.—Since the benzylic protons of all the macrocycles investigated resonate as singlets, this suggests either the possibility of a low energy barrier to conformational interchange, or, more likely, the existence of a strongly favoured conformation in which the protons are effectively magnetically equivalent. Related compounds showing similar properties have been discussed [(17),[8] 5,7,12,14-tetrahydrodibenzo[*c,h*][1,6]dioxacyclodecin,[4] and (18) [9]].

For the oxalic ester (2) two ' stepped ' conformations are shown [(19a) and (19b)]. To arrive at these particular

[5] V. Prelog, *J. Chem. Soc.*, 1950, 420.
[6] P. Margaretha, F. P. Schmook, H. Budzikiewicz, and O. E. Polansky, *Monatsh.*, 1968, **99**, 2539.
[7] H. Budzikiewicz, C. Djerassi, and D. H. Williams, ' Mass Spectrometry of Organic Compounds,' Holden-Day, San Francisco, 1967, p. 203.
[8] R. E. Busby and D. Huckle, *J.C.S. Perkin I*, 1972, 1705.
[9] F. Vögtle, *Chem.-Ztg.*, 1970, **94**, 313.

conformations certain presuppositions have to be made. These are (*a*) that oxalic acid exists in the planar *trans*-conformation;[10-12] (*b*) that the α-diketone system aligns itself preferentially with the two carbonyl groups coplanar and antiparallel (*cf.* Prelog's hypothesis[13] in the atrolactic acid synthesis) during cyclization; and (*c*) that the conformation of oxalic acid in the crystal lattice is the same as that found in solution.[14] An accurate molecular model shows that the sterically demanding *trans*-arrangement is readily accommodated in a dimeric structure, whereas this is not possible in the monomer. The conformation (19b) is preferred over (19a) since the proximity of the carbonyl groups to the benzene rings in the former could explain the observed paramagnetic anisotropic shift (see Table 2).

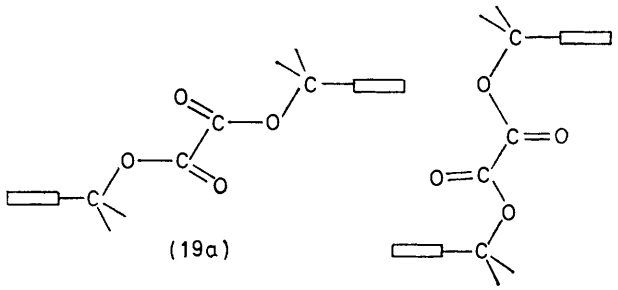




SCHEME Suggested mass spectral fragmentation for esters (2)—(10)

[10] J. M. Robertson and J. Woodward, *J. Chem. Soc.*, 1936, 1817.
[11] E. Y. Cox, M. W. Dougill, and G. A. Jeffrey, *J. Chem. Soc.*, 1952, 4854.
[12] Z. Nahlovska, B. Nahlovsky, and T. G. Strand, *Acta Chem. Scand.*, 1970, **24**, 2617.
[13] V. Prelog, *Helv. Chim. Acta*, 1953, **36**, 308.
[14] J. McKenna, 'Conformational Analysis of Organic Compounds,' Royal Institute of Chemistry, London, 1966, p. 64.

In the dimers (3)—(10) the terminal methylene groups have chemical shift values similar to those for open-chain structures. For example, in the diethyl esters of malonic (τ 6·63), succinic (7·38) and sebacic acid (7·77) these protons resonate at values close to those of their cyclic analogues (τ 6·56, 7·31, and 7·77, respectively). This evidence points to a conformation free of steric strain



(19a) (19b)

and possessing a high degree of symmetry. Such a conformation is shown in (20) for the malonic acid ester. The larger dimeric esters possibly retain the same basic conformation but with more non-eclipsed methylene groups separating the ester carbonyls.

The monomeric esters (11)—(13) probably possess identical conformations. If magnetic equivalence of the benzylic protons is maintained and the double bond remains rigidly *cis* the only likely conformation is the planar one shown in (21) for the maleic acid ester (11). The n.m.r. spectrum of the cyclic ester of citraconic acid (12) shows the methyl signal at τ 7·79, close to the value[15] for the methyl group in dimethyl citraconate (τ 7·98). This is good evidence for the planar, unstrained conformation (21).

Formation of Complexes with Metals.—All attempts to form metal complexes similar to those described[16] for the macrocyclic 'crown' ethers, were unsuccessful. The picrate salt technique[17] was used to test for complex formation.

EXPERIMENTAL

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

The experimental procedure for preparation of the esters followed a fixed pattern. Equimolar proportions of the dipotassium salt of the acid and αα′-dibromo-*o*-xylene in dimethylformamide (50 cm³) were heated under reflux. The dimethylformamide was then removed *in vacuo* at 70° and the residue was poured into cold water and basified ($NaHCO_3$). Continuous extraction (24 h) of the aqueous solution with chloroform, removal of the solvent, and cooling to 0° generally yielded the crystalline product.

5,10,15,20-*Tetrahydrodibenzo*[f,n][1,4,9,12]*tetraoxacyclohexadecin*-7,8,17,18-*tetraone* (2).—Dipotassium oxalate (2·48 g, 14·8 mmol) and αα′-dibromo-*o*-xylene (3·90 g, 14·8 mmol) in dimethylformamide (50 cm³) gave *white plates* (1·0 g), m.p. 233—235° (from chloroform) (Found: C, 62·0; H, 4·45. $C_{20}H_{16}O_8$ requires C, 62·5; H, 4·2%), $\nu_{max.}$ (KBr) 2910 (C–H str.), 1760 (C=O), 1310, 1290, and 1175 (C–O str.), and 748 cm⁻¹ (4 adjacent aromatic C–H); n.m.r. and mass spectra in Tables 2 and 4.

5,11,16,22-*Tetrahydro*-8H,19H-*dibenzo*[g,p][1,5,10,14]-*tetraoxacyclo-octadecin*-7,9,18,20-*tetraone* (3).—Dipotassium malonate (5·0 g, 27·5 mmol) and (1) (7·25 g, 27·5 mmol) gave *white needles* (30 mg), m.p. 215—218° (from ethyl acetate) (Found: C, 63·75; H, 5·2. $C_{22}H_{20}O_8$ requires C, 64·05; H, 4·9%), $\nu_{max.}$ (KBr) 2900, 1725, 1340, 1160, and 757 cm⁻¹.

5,8,9,12,17,20,21,24-*Octahydrodibenzo*[c,m][1,6,11,16]-*tetraoxacycloeicosin*-7,10,19,22-*tetraone* (4).—*White needles* (90 mg), m.p. 217° (from ethanol) were obtained from dipotassium succinate (5 g, 25·5 mmol) and (1) (6·73 g, 25·5 mmol) (Found: 65·25; H, 5·5. $C_{24}H_{24}O_8$ requires C, 65·45; H, 5·5%), $\nu_{max.}$ (KBr) 2900, 1725, 1280, 1255, 1165, and 758 cm⁻¹.

5,9,10,13,18,22,23,26-*Octahydro*-8H,21H-*dibenzo*[c,n]-[1,6,12,17]*tetraoxacyclodocosin*-7,11,20,24-*tetraone* (5).—Dipotassium glutarate (5·0 g, 23·8 mmol) and (1) (6·29 g, 23·8 mmol) yielded white needles (150 mg), m.p. 173° (from ethyl acetate); no satisfactory C,H analysis, $\nu_{max.}$ (KBr) 2900, 1720, 1210, 1155, and 750 cm⁻¹.

5,8,9,10,11,14,19,22,23,24,25,28-*Dodecahydrodibenzo*[c,o]-[1,6,13,18]*tetraoxacyclotetracosin*-7,12,21,26-*tetraone* (6).—Dipotassium adipate (5·0 g, 22·3 mmol) and (1) (5·89 g, 22·3 mmol) gave *white plates*, (150 mg), m.p. 144° (from ethyl acetate) (Found: C, 67·55; H, 6·6. $C_{28}H_{32}O_8$ requires C, 67·75; H, 6·5%), $\nu_{max.}$ (KBr) 2900, 1720, 1260, 1160, and 757 cm⁻¹.

5,9,10,11,12,15,20,24,25,26,27,30-*Dodecahydro*-8H,23H-*dibenzo*[c,p][1,6,14,19]*tetraoxacyclohexacosin*-7,13,22,28-*tetraone* (7).—Dipotassium pimelate (5·0 g, 21·0 mmol) and (1) (5·5 g, 21·0 mmol) after extended refluxing gave white plates (50 mg), m.p. 121° (from ethyl acetate); insufficient material for satisfactory C,H analysis; $\nu_{max.}$ (KBr), 2910, 1730, 1190, 1165, and 756 cm⁻¹.

5,8,9,10,11,12,13,16,21,24,25,26,27,28,29,32-*Hexadecahydrodibenzo*[c,q][1,6,15,20]*tetraoxacyclo-octacosin*-7,14,23,-30-*tetraone* (8).—From dipotassium suberate (5·0 g, 19·8 mmol) and (1) (5·24 g, 19·8 mmol), *white needles* were obtained (400 mg), m.p. 134° (from ethyl acetate) (Found: C, 69·4; H, 7·25. $C_{32}H_{40}O_8$ requires C, 69·55; H, 7·3%), $\nu_{max.}$ (KBr), 2900, 1730, 1220, 1160, and 756 cm⁻¹.

5,9,10,11,12,13,14,17,22,26,27,28,29,30,31,34-*Hexadecahydro*-8H,25H-*dibenzo*[c,r][1,6,16,21]*tetraoxacyclotriacontin*-7,15,24,32-*tetraone* (9).—Dipotassium azelate (5·0 g, 18·8 mmol) and (1) (4·96 g, 18·8 mmol) gave white needles (15 mg), m.p. 119° (from ethyl acetate) (Found: C, 70·3; H, 7·75. $C_{34}H_{44}O_8$ requires C, 70·3; H, 7·65%), $\nu_{max.}$ (KBr), 2900, 1725, 1230, 1175, and 754 cm⁻¹.

5,8,9,10,11,12,13,14,15,18,23,26,27,28,29,30,31.32,33,36-*eicosahydrodibenzo*[c,s][1,6,17,22]*tetraoxacyclodotriacontin*-7,16,25,34-*tetraone* (10).—Dipotassium sebacate (6·0 g, 21·4 mmol) and (1) (5·66 g, 21·4 mmol) gave *white needles* (200 mg), m.p. 135° (from ethyl acetate) (Found: C, 71·1; H, 8·25. $C_{36}H_{48}O_8$ requires C, 71·0; H, 7·95%), $\nu_{max.}$ (KBr), 2900, 1730, 1220, 1205, 1160, and 757 cm⁻¹.

1,8-*Dihydro*-2,7-*benzodioxacyclodecin*-3,6-*dione* (11).—Dipotassium maleate (5·0 g, 25·8 mmol) and (1) (6·80 g, 25·8 mmol) in dimethylformamide at 60—70° for 96 h gave *white needles* (800 mg), m.p. 160° (from ethanol) (Found: C,

[15] P. J. Collin and S. Sternhell, *Austral. J. Chem.*, 1966, **19**, 317.
[16] C. J. Pedersen, *J. Amer. Chem. Soc.*, 1967, **89**, 7017.
[17] C. J. Pedersen, *Fed. Proc.*, 1968, **27**, 1305.

66·25; H, 4·55. $C_{12}H_{10}O_4$ requires C, 66·05; H, 4·6%), $\nu_{max.}$ (KBr), 2930, 1710, 1275, and 1150 cm^{-1}.

1,8-*Dihydro*-4-*methyl*-2,7-*benzodioxacyclodecin*-3,6-*dione* (12).—Dipotassium citraconate (5·0 g, 24·0 mmol) and (1) (6·35 g, 24·0 mmol) in dimethylformamide (50 cm^3), after stirring for 16 h at 20° and then 3 h at 50—60°, gave *white plates* (700 mg), m.p. 108° (from ethanol) (Found: C, 67·05; H, 5·1. $C_{13}H_{12}O_4$ requires C, 67·25; H, 5·2%), $\nu_{max.}$ (KBr), 2910, 1720, 1255, and 1125 cm^{-1}.

7,12-*Dihydrodibenzo*[c,h][1,6]*dioxacyclodecin*-5,14-*dione* (13).—Dipotassium phthalate (5·0 g, 20·5 mmol) and (1) (5·41 g, 20·5 mmol) gave *white plates* (700 mg), m.p. 149° (from ethanol) (Found: C, 71·35; H, 4·5. $C_{16}H_{12}O_4$ requires C, 71·65; H, 4·5%), $\nu_{max.}$ (KBr), 1730, 1280, 1140, and 750 cm^{-1}.

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