

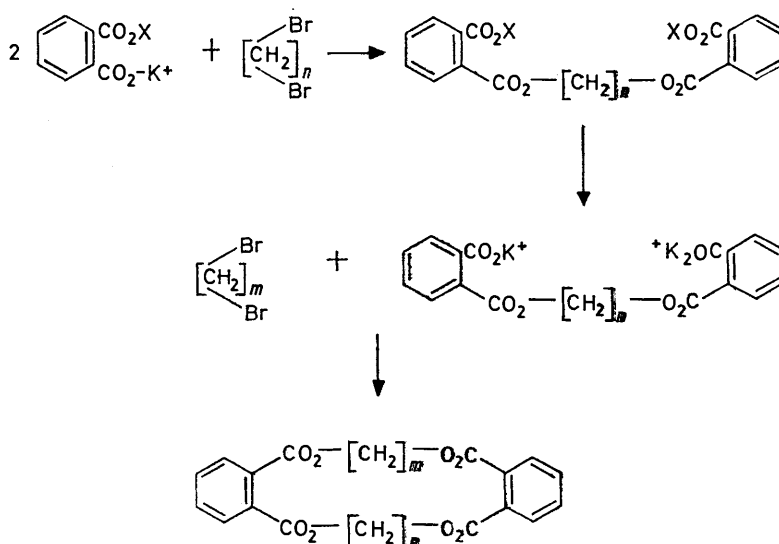
## Synthesis of New Macrocycles. Part IV.<sup>1</sup> Two-step Synthesis of Dimeric Phthalic Acid Esters

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Double esterification of simple alkanediols, such as butane-1,4-diol, by two sequential treatments with 1 mol. equiv. of phthalic anhydride afforded half-esters in which each benzene ring retains a carboxy-group. Ring closure of these diacid intermediates was achieved by reaction with suitable dibromoalkanes. By this technique were obtained 24 new dimeric cyclic esters ranging in ring size from 18 to 36 members.

In an earlier paper<sup>2</sup> a synthesis was outlined for monomeric and dimeric cyclic esters of phthalic acid. Condensation was effected *via* the dihalide-dipotassium dicarboxylate reaction<sup>2</sup> and gave monomeric cyclic esters with dihalides of the type  $X[CH_2]_{2n}X$  and dimers with those of the type  $X[CH_2]_{2m+1}X$ . The ring produced thus always contained an even number of atoms, in keeping with early generalizations of Carothers and Spanagel.<sup>3</sup> Formation of dimers, irrespective of the

carboxy-groups in phthalic acid during reaction of the other group proved unsuccessful (Scheme). Finally, the intermediate (1) was made by the following procedure. Butane-1,4-diol was monoesterified with 1 mol. equiv. of phthalic anhydride (in pyridine) and the product was treated with a further 1 mol. equiv. of the anhydride. The intermediates (1)–(6) were all prepared in this way in almost quantitative yield. These conditions of reaction were based on those used by



SCHEME  $m$  and  $n$  are integers;  $X$  is a blocking group

nature of the dihalide, was achieved in the present investigation by synthesizing a reactive intermediate which could be cyclized to give rings containing even or odd numbers of atoms as desired.

The use of 'partly cyclized' intermediates has proved to be fruitful both for improving yields of cyclic products and for obtaining cyclic products where the direct technique has failed. Thus Boekelheide and his co-workers<sup>4</sup> obtained metacyclophane in 77% yield by the two-step method whereas the direct method employed earlier<sup>5</sup> had given a 12% yield. A similar technique was employed by Pedersen<sup>6</sup> for obtaining the macrocyclic 'crown ethers' based on catechol.

Numerous attempts to block temporarily one of the

<sup>1</sup> Part III, S. E. Drewes and B. G. Riphagen, *J.C.S. Perkin I*, 1974, 1908.

<sup>2</sup> S. E. Drewes and P. C. Coleman, *J.C.S. Perkin I*, 1972, 2148.

<sup>3</sup> W. H. Carothers and E. W. Spanagel, *J. Amer. Chem. Soc.*, 1935, 57, 929.

Thaker and Dave<sup>7</sup> for the resolution of optically active diols with phthalic anhydride. It was not possible to prepare compound (1) by direct reaction of 2 mol. equiv. of the anhydride with the diol. Conversion of any of the compounds (1)–(6) into the dipotassium salt, followed by cyclization with a suitable dibromide,<sup>2</sup> then afforded the corresponding cyclic ester (Table). Products containing rings with both odd and even numbers of atoms were obtained, but the yields do not indicate a preference for one or the other. Also, a relatively 'strainless' ester (23) (cyclic dimeric octamethylene ester of phthalic acid) was isolated in almost

<sup>4</sup> W. S. Lindsay, P. Stokes, L. G. Humber, and V. Boekelheide, *J. Amer. Chem. Soc.*, 1961, 83, 943.

<sup>5</sup> W. Baker, J. F. W. McOmie, and J. M. Norman, *J. Chem. Soc.*, 1951, 1114.

<sup>6</sup> C. J. Pedersen, *J. Amer. Chem. Soc.*, 1967, 89, 7017.

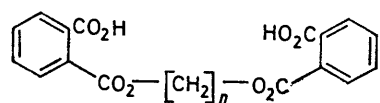
<sup>7</sup> K. A. Thaker and N. S. Dave, *J. Sci. Ind. Res. India*, 1961, 20B, 329.

the same yield (8.4%) as the ester (15) (8.1%), which might be expected to be 'highly-strained' (four methylene groups in one chain and nine in the other). This result probably reflects the fact that these esters are all relatively strainless. The only ester bearing a 'rigid group'<sup>8</sup> in the form of a double bond in one of the chains (31) was obtained in the best yield (31.7%)

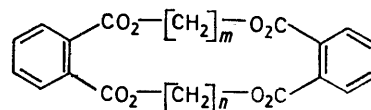
The preferred conformation of the smaller dimeric cyclic esters has been considered,<sup>2</sup> and more recently an X-ray study<sup>9</sup> on the cyclic dimeric ethylene ester of phthalic acid has been completed. N.m.r. data for

absorption. As the symmetry of the molecule is destroyed by uneven length of the methylene chains so the symmetry in the benzene absorption (AABB system) is destroyed and in the extreme case of the non-cyclic diacid intermediates it becomes an ABX system.

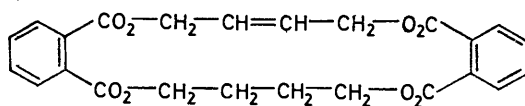
The mass spectra of the cyclic esters followed the previous pattern of fragmentation.<sup>2</sup> Generally the molecular ion peak was small but the ( $M^+ / 2 + 1$ ) peak was prominent in the spectra of the symmetric esters. This latter peak was absent in the spectra



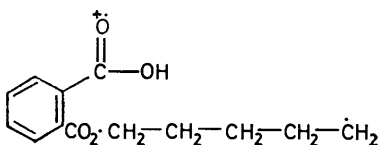
- (1)  $n = 2$       (5)  $n = 8$   
 (2)  $n = 4$       (6)  $n = 10$   
 (3)  $n = 5$       (7)  $n = 12$   
 (4)  $n = 6$



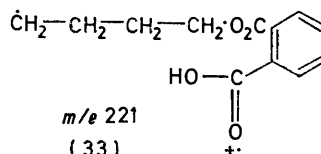
- (8)  $n = 2, m = 6$       (20)  $n = 8, m = 4$   
 (9)  $n = 4, m = 2$       (21)  $n = 8, m = 6$   
 (10)  $n = 4, m = 3$       (22)  $n = 8, m = 7$   
 (11)  $n = m = 4$       (23)  $n = 8, m = 8$   
 (12)  $n = 4, m = 5$       (24)  $n = 8, m = 9$   
 (13)  $n = 4, m = 6$       (25)  $n = 8, m = 12$   
 (14)  $n = 4, m = 7$       (26)  $n = 10, m = 9$   
 (15)  $n = 4, m = 9$       (27)  $n = 10, m = 10$   
 (16)  $n = 5, m = 3$       (28)  $n = 10, m = 11$   
 (17)  $n = 5, m = 5$       (29)  $n = 12, m = 11$   
 (18)  $n = 6, m = 6$       (30)  $n = 12, m = 12$   
 (19)  $n = 6, m = 7$



(31)



$m/e$  235  
(32)



$m/e$  221  
(33)

the present series, showing for example equivalence of the terminal methylene groups in the same half of the chain, suggest a similar, highly symmetrical conformation.

*N.m.r. and Mass Spectra.*—The n.m.r. spectra of the esters and the intermediates are uncomplicated. The aromatic proton signals appear consistently as a multiplet at  $\delta$  7.61 and the 'inner' methylene signals as a multiplet between  $\delta$  2.00 and 1.16. In all the larger rings (upwards of 24 atoms) the terminal methylene signals occur as a single triplet centred at  $\delta$  4.30. By contrast, the terminal methylenes of the smaller rings had different chemical shifts in those cases where considerable differences existed in the lengths of the interconnecting chains. Thus, for the 'unsymmetrical' ring (8) the signals due to the terminal methylenes of the shorter chain appear as a singlet at  $\delta$  4.60 whereas those of the longer chain occur up-field as a triplet at  $\delta$  4.30. A further effect of unequal chain length was to change the symmetry of the benzene

of the non-symmetric compounds. Instead, these esters exhibited two intense ( $M^+ / 2 + 1$ ) peaks, one associated with each half of the molecule. Thus the spectrum of compound (12),  $M^+ 454$ , featured peaks at  $m/e$  235 (19.0%) and 221 (59.5%) due to the ions (32) and (33). The diacid intermediates (1)–(6) showed no molecular ion peaks.

*I.r. and U.v. Spectra.*—The i.r. spectra of the esters were very similar to one another. A gradual increase in the intensity of the  $-\text{CH}_2-$  stretching absorbance at  $2900 \text{ cm}^{-1}$  could be seen, however, as the methylene chain lengthened. In all cases the most prominent peaks were due to the carbonyl absorption at  $1710$ – $1730$  and the C–O stretching vibrations at  $1280$ – $1290$  and  $1125$ – $1135 \text{ cm}^{-1}$ . The u.v. spectra had the characteristic benzene absorption at  $274$  and a slight shoulder at  $282 \text{ nm}$ .

<sup>8</sup> S. E. Drewes and B. G. Riphagen, *J.C.S. Perkin I*, 1974, 323.

<sup>9</sup> M. J. Laing, P. C. Coleman, and S. E. Drewes, *J. S. African Chem. Inst.*, 1974, in the press.

## EXPERIMENTAL

Mass spectra were obtained with a Varian CH7 spectrometer at 70 eV. N.m.r. data for compounds (1)–(31) are available as Supplementary Publication No. SUP 21135 (2 pp.).\*

*Preparation of Tetramethylene Dihydrogen Bisphthalate* (2).—The following method was also employed to prepare all the other diacid intermediates. Phthalic anhydride (30 g, 202 mmol) and butane-1,4-diol (19 g, 210 mmol) in anhydrous pyridine (40 ml) were stirred together for 4 h at 80° under anhydrous conditions. More phthalic anhydride (202 mmol) was then added and the solution was stirred for a further 20 h at 80°. Most of the pyridine was removed *in vacuo* at 50° and benzene (100 ml) was added to the residue. The benzene and residual pyridine were then distilled off under vacuum at 50°. Addition of benzene (100 ml) followed by cooling yielded the crude *product*, which was crystallized first from dilute hydrochloric acid and finally from methanol–water to give white needles (65 g, 83%), m.p. 147° (Found: C, 62.0; H, 4.7. C<sub>20</sub>H<sub>18</sub>O<sub>8</sub> requires C, 62.2; H, 4.7%). Details of the other intermediates are listed in the Table.

7,8,9,10,19,20,21,22-Octahydrodibenzo[c,m][1,6,11,16]tetraoxacycloicosin-5,12,17,24-tetraone (11).—The dipotassium salt of the diacid (2) (10 g, 21 mmol) and 1,4-dibromobutane (5 g, 23 mmol) in dimethylformamide (100 ml) were stirred at 100° for 24 h. The solvent was removed *in vacuo* at 60° and the residue poured into water (300 ml) and made basic with sodium hydrogen carbonate. The mixture was kept at 0° for 48 h, then the gummy precipitate was filtered off and dissolved in hot ethanol. On

\* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1973, Index issue.

cooling white needles were obtained (800 mg, 6.3%), m.p. 140° (from ethanol) (Found: C, 65.3; H, 5.4. C<sub>24</sub>H<sub>24</sub>O<sub>8</sub>

## Analytical and physical data for esters

Compd.	Ring size	Yield (%)	M.p. (°C)	Found (%)		Formula	Reqd. (%)	
				C	H		C	H
(1)		80.6	164	60.0	3.6	C <sub>18</sub> H <sub>14</sub> O <sub>8</sub>	60.3	3.95
(2)		86.3	147	62.0	4.7	C <sub>20</sub> H <sub>18</sub> O <sub>8</sub>	62.2	4.7
(3)		83.3	96	62.7	5.1	C <sub>22</sub> H <sub>20</sub> O <sub>8</sub>	63.0	5.05
(4)		85.3	138–140	63.8	5.35	C <sub>22</sub> H <sub>22</sub> O <sub>8</sub>	63.8	5.35
(5)		86.6	128–130	64.9	5.7	C <sub>24</sub> H <sub>20</sub> O <sub>8</sub>	65.1	5.9
(6)		80.0	106–109	66.7	6.3	C <sub>24</sub> H <sub>22</sub> O <sub>8</sub>	66.4	6.45
(7)		78.3	100	67.7	6.9	C <sub>26</sub> H <sub>20</sub> O <sub>8</sub>	67.5	6.85
(8)	20	19.7	147	65.5	5.5	C <sub>26</sub> H <sub>22</sub> O <sub>8</sub>	65.4	5.5
(9)	18	10.1	104	63.9	4.8	C <sub>28</sub> H <sub>20</sub> O <sub>8</sub>	64.1	4.9
(10)	19	12.0	131	64.6	5.15	C <sub>28</sub> H <sub>22</sub> O <sub>8</sub>	64.8	5.2
(11)	20	6.3	140	65.3	5.4	C <sub>30</sub> H <sub>20</sub> O <sub>8</sub>	65.4	5.5
(12)	21	7.1	100	65.9	5.6	C <sub>30</sub> H <sub>22</sub> O <sub>8</sub>	66.1	5.75
(13)	22	13.8	108	66.9	5.9	C <sub>32</sub> H <sub>20</sub> O <sub>8</sub>	66.7	6.0
(14)	23	9.6	115–117	67.6	6.2	C <sub>32</sub> H <sub>22</sub> O <sub>8</sub>	67.2	6.25
(15)	25	8.1	112	68.1	6.7	C <sub>34</sub> H <sub>20</sub> O <sub>8</sub>	68.2	6.7
(16)	20	7.5	165	65.9	5.45	C <sub>34</sub> H <sub>22</sub> O <sub>8</sub>	65.4	5.5
(17)	22	9.1	139	66.9	6.1	C <sub>34</sub> H <sub>24</sub> O <sub>8</sub>	66.7	6.0
(18)	24	8.9	66	67.6	6.6	C <sub>36</sub> H <sub>22</sub> O <sub>8</sub>	67.7	6.5
(19)	25	6.7	60	68.6	6.85	C <sub>36</sub> H <sub>24</sub> O <sub>8</sub>	68.2	6.7
(20)	24	7.3	138	67.2	6.35	C <sub>36</sub> H <sub>26</sub> O <sub>8</sub>	67.7	6.5
(21)	26	7.9	93	68.7	6.85	C <sub>38</sub> H <sub>24</sub> O <sub>8</sub>	68.7	6.9
(22)	27	9.6	89	68.8	7.05	C <sub>38</sub> H <sub>26</sub> O <sub>8</sub>	69.1	7.1
(23)	28	8.4	64–65	69.6	7.35	C <sub>40</sub> H <sub>24</sub> O <sub>8</sub>	69.5	7.3
(24)	29	6.4	75	69.8	7.4	C <sub>40</sub> H <sub>26</sub> O <sub>8</sub>	69.9	7.45
(25)	32	9.4	95	70.9	7.8	C <sub>42</sub> H <sub>24</sub> O <sub>8</sub>	71.0	7.95
(26)	31	3.7	56	70.4	7.85	C <sub>42</sub> H <sub>26</sub> O <sub>8</sub>	70.7	7.8
(27)	32	3.6	78–79	71.0	7.85	C <sub>44</sub> H <sub>24</sub> O <sub>8</sub>	71.0	7.95
(28)	33	3.5	64	71.4	8.25	C <sub>44</sub> H <sub>26</sub> O <sub>8</sub>	71.4	8.1
(29)	35	7.0	75	72.0	8.25	C <sub>46</sub> H <sub>24</sub> O <sub>8</sub>	72.0	8.35
(30)	36	8.6	84	72.0	8.5	C <sub>46</sub> H <sub>26</sub> O <sub>8</sub>	72.3	8.5
(31)	20	31.7	149	66.1	5.05	C <sub>24</sub> H <sub>22</sub> O <sub>8</sub>	65.7	5.05

requires C, 65.4; H, 5.5%). Details of the other cyclic esters, prepared similarly, are given in the Table.

We thank I. Antonowitz for elemental analyses and the South African Council for Scientific and Industrial Research for financial assistance and a Bursary (to P. C. C.).

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