Synthesis of 7,8,9,10,11,12,20,21,22,23,24,25-Dodecahydrodibenzo[*b*,*m*]-[1,4,12,15]tetraoxacyclodocosin, a Crown Ether

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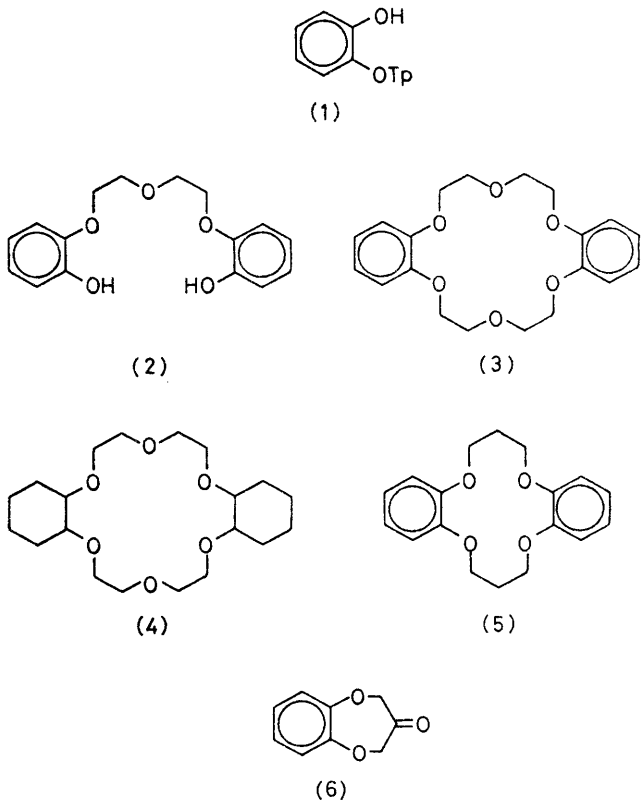
A number of symmetrical diesters and an unsymmetrical type have been synthesised from pyrocatechol. Under conditions in which intramolecular acyloin formation was anticipated the product from one symmetrical compound, ethyl 4-(*o*-ethoxycarbonylpropoxyphenoxy)butyrate, was a cyclic bis-β-keto-ester resulting in reasonable yield from intermolecular Dieckmann cyclisation. Hydrolysis to the 9,22 diketone, and its reduction to 7,8,9,10,11,12,-20,21,22,23,24,25-dodecahydrodibenzo[*b*,*m*][1,4,12,15]tetraoxacyclodocosin ' dibenzo-22-crown-4,' proceeded smoothly. An unsymmetrical intermediate, methyl 4-(*o*-ethoxycarbonylmethoxypropylphenoxy)butyrate, was prepared for similar cyclisation and in preliminary experiments appeared to give acyloin and β-keto-ester products. The method represents a different approach to crown ether systems of certain types.

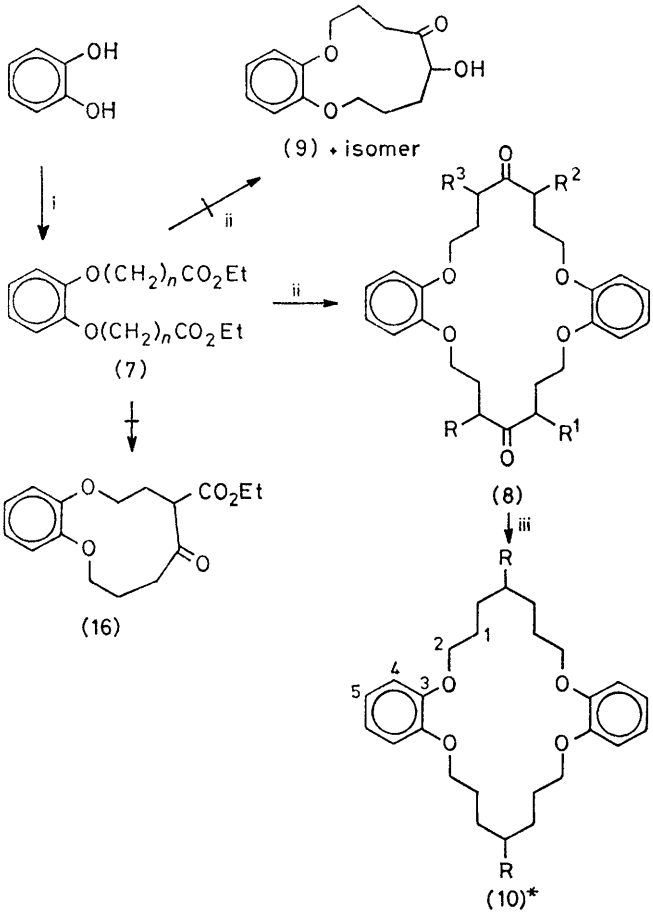
' CROWN ' ethers with unusual complexing properties were discovered [1,2] when some dibenzo-18-crown-6 (3) was formed along with the bis-phenol (2) in the reaction of the monopyranyl ether (1) with 2,2'-dichlorodiethyl ether.† Other types, (4) and (5), were synthesised and



subsequently, nitrogen-containing ' football crowns '.[3] New structures [4,5] and complexing properties have been found.[6]

Few methods other than S_N2 nucleophilic substitutions have been used and there would appear to be scope for other approaches.

During the course of a study of the reaction of the



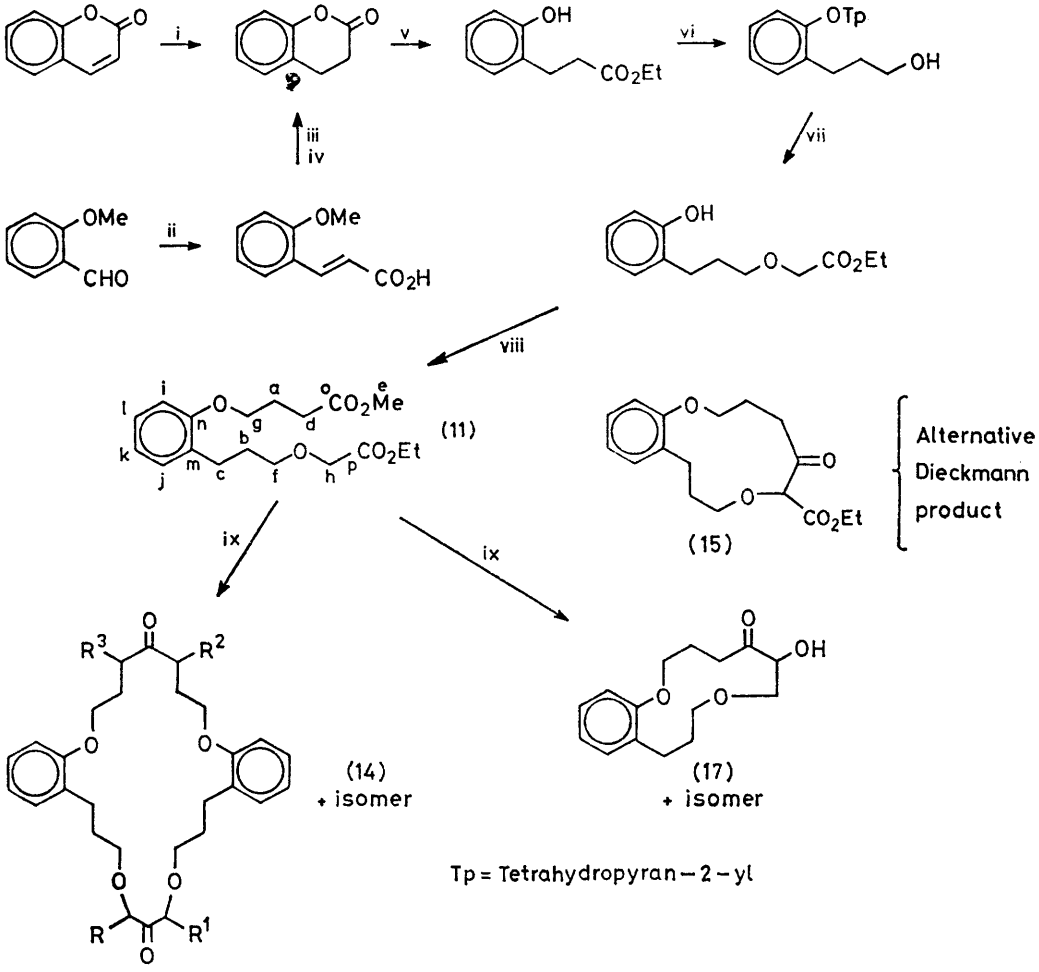
SCHEME 1 *Reactions:* i, K_2CO_3, $Br(CH_2)_3CO_2Et$, Me_2CO; ii, Na–K, PhH; iii, HCl; N_2H_4, KOH, digol

diester (7; $n = 3$) (Scheme 1) with sodium and potassium under high dilution conditions a Dieckmann condensation was found [7] to have occurred to give the

† Formation of compound (3) was attributed to free pyrocatechol resulting from partial tetrahydropyranylation by the method of W. E. Parham *et al.*, (*J. Amer. Chem. Soc.*, 1958, 50, 4187). We have found this an unsatisfactory protective group procedure for phenols.

dimeric β-keto-ester (8; R = R^3 = H, R^1 = R^2 = CO_2Et; R = R^2 = H, R^1 = R^3 = CO_2Et) as a mixture of isomers, rather than the acyloins [such as (9) or its isomer]. Hydrolysis furnished the diketone (8; R = R^1 = R^2 = R^3 = H) which upon reduction gave 7,8,9,10,11,12,20,21,22,23,24,25-dodecahydrodibenzo-[*b*,*m*][1,4,12,15]tetraoxacyclododecosin (10; R = H) (dibenzo-22-crown-4). No indication of the presence of an intramolecularly-formed β-keto-ester (16) was obtained (Scheme 1).

The diester (11) was synthesised by the route shown in Scheme 2 and under similar cyclisation conditions evidence was obtained of β-keto-ester and acyloin (17) formation. Whether the former is a bis-keto-ester (14) or a mono-product such as (15) (Scheme 2) has not been established and this aspect still remains to be investigated.*



SCHEME 2 *Reactions:* i, Ni–Al, OH^-; ii, $CH_2(CO_2H)_2$, Pyr.; iii, Ni–Al, OH^-; iv, Pyr. HCl; v, OEt^-; H^+; vi, $\overline{CH{:}CH(CH_2)_3}$·O, H^+; $LiAlH_4$; vii, NaH, $BrCH_2CO_2^-$; H^+; *p*-TSA, EtOH; viii, oMe, $Br(CH_2)_3CO_2Me$; ix, Na–K, PhH

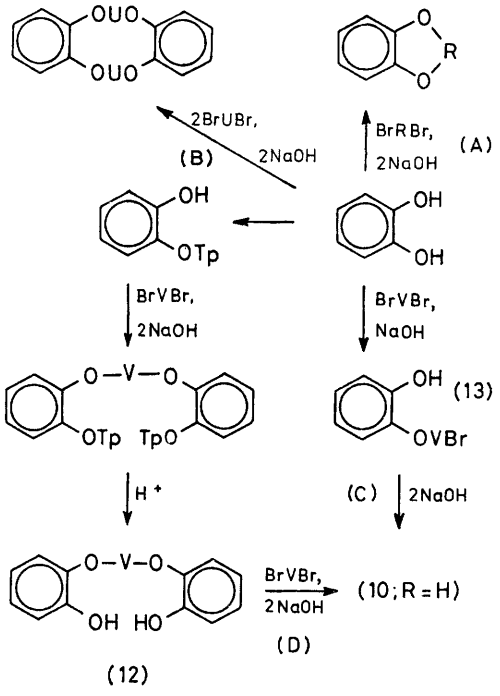
RESULTS AND DISCUSSION

In preliminary experiments with the diester (7) in hot xylene with powdered sodium, ether fission occurred. By the use of a sodium–potassium alloy in benzene, a system which has yielded an acyloin in the thiophen series,[9] the bis β-keto-ester (8), probably as a mixture of constitutional and stereoisomers, was produced with no acyloin. Formed in more than 30% yield, (8) was a gummy mixture with the correct elemental analysis and i.r. absorption due to keto and ester carbonyl groups. Only an intermolecularly produced bis-ketoester appeared to be present and none of the intramolecular mono-product (16). Acidic hydrolysis gave with difficulty by way of the diketomono-ester (*m/e* 540) the diketone (8; R = R^1 = R^2 = R^3 = H) having only keto carbonyl group absorption (i.r.) and the expected ^1H n.m.r. spectrum.

Reduction of the diketone to the diols, probably a

* Acyloin formation from both (7) and (11) had been the original expectation of one of us (J. G.) who commenced this work in the hope of producing steroidal analogues, [*cf.* (9, 17)]; subsequent to his discontinuation of this work in 1965, cyclisation experiments were carried out by J. T. and G. R. B.[7] Synthetic work on the preparation of 3-amino-derivatives of (7) and (11) has also been conducted.[8]

mixture of diastereoisomers (10; R = OH) could only be effected in good yield with lithium aluminium hydride in pyridine solution.[10] By the Huang Minlon procedure under forcing conditions, the diketone afforded the bis-heptamethylene compound (10; R = H). All other reductions (see Experimental section) were ineffective. The substance was identical spectroscopically and chromatographically with the cyclic product of alkylation of [12; V = $(CH_2)_7$] with 1,7-dibromoheptane (Scheme 3, route D).



SCHEME 3

Cyclisation of [13; V = $(CH_2)_7$] gave the bis-heptamethylene compound in very low yield (route C) and was less effective than direct interaction by route B.

Routes A, B, and C were used originally [11] with several different dibromo-compounds and are essentially the same type of nucleophilic substitution used later.[12-14,15a] Dibenzo-14-crown-4 (5),[15a,*] was prepared by route B [U = $(CH_2)_3$] in very low yield. Dichloro-compounds [1] and di-4-toluenesulphonates, as in certain recent work,[16] have been employed. High yields of crown compounds were described by Pedersen [1] although this has not generally been found in these reactions. The precursor (2) was prepared [1] ' in good yield ' and thence dibenzo-18-crown-6 in ' 80% yield '. In the present work the yield of the crown-4 compound (10; R = H) was 13% on pyrocatechol, based on the material used. Dieckmann products have not previously been reported by the use of sodium–potassium alloy. The cyclisation of diesters $RO_2C(CH_2)_n CO_2R$ with sodium t-butoxide to yield bis-β-keto-esters has been reported.[17] Dieckmann cyclisation of (7; n = 1) was found [15b] to give only (6).

* The compound was stated to be a new ring system but the authors were evidently unaware of its earlier preparation.[1]

In the present work the intermolecular bis-β-keto-ester, despite the high dilution conditions, presumably arises due to the divergence of the methylene chains in (7) stemming from the orientation at the benzenoid ring. The principle of rigid groups [18,19] gives an analogy. Acyloin formation might well be favoured by performing the reaction in the presence of trimethylsilyl chloride [20] to remove ethoxide ions and protect the product.

Characteristic mass spectra were obtained from the products of the present work. Major peaks resulting from the mixed β-keto-esters, the diketone, and the crown-4 compound were accounted for by α-cleavage with hydrogen transfer and resonance stabilisation. Fragmentation pathways were often validated by metastable peaks (M^*). Comparatively little work has been carried out until recently [21] on the mass spectra of crown compounds.

^{13}C N.m.r. spectra for certain of the intermediates and some crown compounds are summarised in Table 1.

TABLE 1

^{13}C Chemical shifts of macrocyclic ethers and reference compounds

		Carbon atom *				
Compd.	Solvent	1	2	3	4	5
(3)	$CHCl_3$	70.1	69.1	149.1	113.7	121.5
(4)	$CDCl_3$	71.3	68.5	77.9 ‡ 78.8 78.3	25.8	22.2
(5)	$CHCl_3$	29.3	67.5 (t)	150.5 (s)	118.2 (d)	122.0 (d)
(10)	$(CD_3)_2SO$	31.9 †	66.2	157.6	122.5	130.0
18-crown-6	$CHCl_3$	71.1				
(6)	$CHCl_3$	182.0	67.3	132.1	107.6	110.3
(7; n = 3)	$CDCl_3$	24.8	68.5	149.6	114.9	121.6

* Numbering (Scheme 1). † Shifts for other methylene groups not assignable. ‡ These shifts are probably due to stereoisomers in the sample used.

Distinction between the two types of methylene group (C-1, C-2) in (3) and (4) was made on the basis of comparison with 18-crown-6, aralkyl ethers, and aliphatic ethers (*e.g.* di-n-hexyl ether, α-CH_2, 71.0).

The chemical shifts for the aromatic carbons 3, 4, and 5 were assigned by comparison with the standard spectra for 1,2-dimethoxybenzene, ethoxybenzene, methoxybenzene,2-methylphenol, ethylbenzene, and phenoxyethanol and by off-resonance measurements. They are uniformly in the order C-3 > C-5 > C-4 in every case, the ' *meta* ' carbon being much the same as a carbon in benzene itself.[22] The arbitrary assignments described [23] for C-4 and C-5 in (3) are the reverse of the above.

EXPERIMENTAL

Melting points are uncorrected. U.v. absorption spectra were determined for methanol solutions with a Unicam SP 500 spectrometer and i.r. spectra with a Unicam SP 200 instrument. ^1H N.m.r. spectra (with $SiMe_4$ as internal standard) were determined initially (1967) at Queen Elizabeth College by courtesy of the U.L.I.R.S. scheme, later, on a Varian T60 (Brunel University) and by the P.C.M.U. (Harwell). ^{13}C N.m.r. spectra were determined on a CFT 20 Varian instrument at Brunel University (with 0.8 cm probe) with $SiMe_4$ as internal standard through the help of Dr. A. Najam.

Mass spectra were determined (1969) through the courtesy of Mr. F. Bloss (University of Sussex) and through the U.L.I.R.S. G.l.c. was carried out with a Pye Unicam 104 instrument equipped with a flame ionisation detector. Glass columns 5 ft × 3/16 in were used with 3% SE 30 as stationary phase on a support of acid-washed and silanised 80—100 Diatomite C and a nitrogen flow of 45 cm^3/min. The g.l.c. results, determined at a chart speed of 0.5 cm min^{-1} are given as (retention distance, cm) (relative retention, 18-crown-6, =1). T.l.c. was carried out on Kieselgel G (Merck) on analytical plates (0.25 mm layer), 8 × 10 cm; and preparative plates (1 mm layer, 20 × 20 cm. Solvent A was diethyl ether–light petroleum (b.p. 40—60°) (30 : 70, v/v), solvent B, chloroform–formic acid (98%) (99 : 1, v/v), and solvent C, chloroform–ethyl acetate (90 : 10, v/v). Preparative plates were visualised with 0.1% ethanolic Rhodamine 6G and analytical plates with 50% aqueous sulphuric acid followed by charring at 150 °C. Molecular distillations were very kindly undertaken by Mr. P. Ridgway–Watt, Vitamins Ltd., Tadworth, Surrey. Microanalyses were carried out by Drs. Weiler and Strauss and by Rapid Elemental Analyses (Beaconsfield).

Materials:

Methanol and ethanol were dried by the Bjerrum method; pyridine and acetone were dried over KOH and $CaCl_2$ respectively. Dimethyl sulphoxide was heated with calcium hydride and distilled under reduced pressure. Dimethylformamide was distilled and dried over molecular sieve (type 5A). Benzene, toluene, and xylene for the acyloin reactions were refluxed with sodium wire, distilled, and stored with sodium wire present. Sodium hydride was weighed as a 50% dispersion in mineral oil and the latter removed by washing with light petroleum. The surface films on sodium and potassium metals used in the acyloin reaction were cut off under dry xylene. Esters used in the acyloin reaction were dried over anhydrous potassium carbonate. Dihydropyran was refluxed (2 h) with KOH and then distilled through a column packed with short glass tubes.

Dibenzo-18-crown-6 (3) and dicyclohexyl-18-crown-6 (4) (technical) were obtained from Aldrich Chemicals Ltd. Dibenzo-14-crown-4 (5) and the keto-compound (6) were kindly provided by Dr. P. A. Claret (City University).

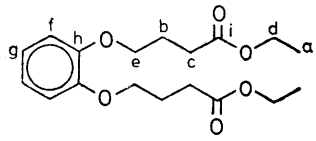
Ethyl 4-bromobutyrate was prepared (79% yield) from γ-butyrolactone and hydrogen bromide, with b.p. 82—84 °C/5 mmHg (lit.,[24] 97—99 °C/25 mmHg), $\nu_{max.}$ 1 740 cm^{-1} (CO). The methyl ester, methyl 4-bromobutyrate, was prepared by the same procedure, as a colourless oil (213 g, 82%), b.p. 60—62 °C/12 mmHg (lit.,[25] 79 °C/20 mmHg), $\nu_{max.}$ 1 740 cm^{-1} (CO).

Ethyl 5-bromovalerate was prepared from cyclopentanone and persulphuric acid followed by hydrogen bromide treatment, b.p. 70—72 °C/1 mmHg (lit.,[26] 80 °C/4 mmHg), $\nu_{max.}$ 1 740 cm^{-1} (CO).

In a similar way methyl 5-bromovalerate was prepared; ^{1}H n.m.r., τ (CCl_4) 6.33 (3 H, s, OCH_3), 6.47—6.70 (2 H, t, CH_2Br), 7.53—7.73 (2 H, t, CH_2CO, and 7.93—8.27 (4 H, m, $2CH_2$). The silver salt of ethyl hydrogen adipate was also used for the preparation of ethyl 5-bromovalerate.

Ethyl 4-(o-*Ethoxycarbonylpropoxyphenoxy*)*butyrate* (7; n = 3).—Several different procedures were examined for the preparation of this compound. Nucleophilic substitutions in the presence of sodium iodide and at elevated temperature gave no advantage over the following method.

Pyrocatechol (27.5 g) in dry acetone (500 cm^3) containing potassium carbonate (140 g) was refluxed (48 h) with ethyl 4-bromobutyrate (96.5 g). The oil obtained by filtration and evaporation of the acetone was dissolved in ether, washed with 5% aqueous sodium hydroxide and then with water, dried, and the residue, upon concentration, distilled to give the *ester* as a colourless oil (51.2 g, 66%), b.p. 202—204 °C/2 mmHg, 167—168 °C/0.05 mmHg, $\nu_{max.}$ 1 740 cm^{-1} (ester OH nil); ^{1}H n.m.r. τ (CCl_4) 3.23 (4 H, m, HAr), 5.77—6.00 (4 H, t, $2CH_2OAr$), 5.97—6.17 (4 H, q, 2-CH_2O), 7.43—7.65 (4 H, t, CH_2CO), 7.77—7.13 (4 H, quin, 2-CH_2), and 8.70—8.94 (6 H, t, $2CH_3$); ^{13}C n.m.r.* δ (p.p.m.;



*(off-resonance in parentheses)

$CDCl_3$) 15.1 (a-c, q), 24.8 (b-c, t), 30.5 (c-c, t), 60.1 (d-c, t), 68.5 (e-c, t), 114.9 (f-c, d), 121.6 (g-c, d), 149.6 (h-c, s), 172.7 (i-c, s) (Found: C, 63.35; H, 7.4. $C_{18}H_{26}O_6$ requires C, 63.90; H, 7.75%); g.l.c. 2.78 (2.46).

In a similar way the corresponding methyl ester was prepared in 56% yield, $\nu_{max.}$ 1 735 cm^{-1} (ester, OH nil); ^{1}H n.m.r. τ ($CDCl_3$), 3.18 (4 H, m, HAr), 5.84—6.07 (4 H, t, $2CH_2$ OAr), 3.35 (6 H, s, $2OCH_3$), 7.45—7.72 (4 H, t, $2CH_2$-CO), and 8.03—8.30 (4 H, quin, $2CH_2$) (Found: C, 61.6; H, 6.85. $C_{16}H_{22}O_6$ requires, C, 61.90; H, 7.15%), g.l.c. 2.59 (2.29).

Diethyl O-*Phenylene Biscarbonate* (7; n = 0).—To pyrocatechol (66.0 g, 0.6 mol) in pyridine (120 cm^3) at 0 °C, ethyl chloroformate (138 cm^3) was added dropwise (1 h). After 1 h on a steam-bath, the mixture was poured into water, extracted with ether and the combined extracts washed with water, dilute sulphuric acid, dilute potassium hydroxide, and water and then dried ($MgSO_4 \cdot H_2O$). Distillation of the recovered product gave a colourless oil (131.0 g, 86%), b.p. 156—158 °C/2 mmHg, $\nu_{max.}$ 1 770 cm^{-1} (CO) (Found: C, 55.95; H, 5.3. $C_{12}H_{14}O_6$ requires C, 56.70; H, 5.50%).

In a similar way to the preparation of the ester (7; n = 3) the ester (7; n = 1) was prepared from pyrocatechol (5.5 g) and ethyl bromoacetate (18.33 g) in acetone (200 cm^3) containing anhydrous potassium carbonate (27.6 g) by refluxing (48 h). The ester (7; n = 4) was prepared from pyrocatechol (0.188 g) and ethyl 5-bromovalerate (0.71 g) by refluxing in acetone (10 cm^3) containing potassium carbonate (1.20 g).

Methyl 4-(o-*Ethoxycarbonylmethoxypropylphenoxy*)*butyrate* (11).—The preparation of the first compound is given in detail since described procedures were erratic.

Dihydrocoumarin. (a) Reduction of coumarin (4.6 g, 0.1 mol) in 3M-sodium hydroxide solution (500 cm^3) at 90 °C on a steam-bath was effected by the cautious addition of Raney nickel (54.0 g; 50% Ni–Al) with stirring and occasional removal of the mixture from the steam-bath. Upon completion of the addition (½ h) and heating (1 h) the mixture was filtered (the pyrophoric Raney nickel was discharged into water immediately after washing). The filtrate and washings were acidified with concentrated hydrochloric acid (400 cm^3) at 80—85 °C. Recovery in the usual way gave an oil (14.0 g, 85%), b.p. 270—272 °C (lit.,[27] b.p. 272 °C)

102—104 °C/1 mmHg, (lit.,[28] 123—125 °C/2 mmHg). The substance could also be prepared by the reverse addition method.[29]

(b) An alternative preparation by the route shown in Scheme 2 was from *o*-methoxybenzaldehyde in the following way.

Salicylaldehyde (146.6 g) methylated with 20% sodium hydroxide and dimethyl sulphate gave *o*-methoxybenzaldehyde (140 g, 86%), b.p. 79—80 °C/0.6 mmHg as long white needles, m.p. 34—36 °C (lit.,[30] 36 °C). The latter (27.2 g, 0.2 mol), malonic acid (22.9g, 0.22 mol), and pyridine (2.4 cm³) were heated on a steam-bath until carbon dioxide evolution ceased. The aqueous phase from the reaction mixture in sodium hydroxide solution was acidified, and the solid crystallised (methanol) to give *o*-methoxycinnamic acid (29.0 g, 85%), m.p. 186—187 °C, (lit.,[31] 186 °C). The latter (17.8 g, 0.1 mol) was reduced in alkaline solution at 90 °C with nickel–aluminium alloy (55 g) and the filtrate from the reaction mixture acidified to give 3-(*o*-methoxyphenyl)-propionic acid which crystallised (light petroleum, 60—80 °C) as white needles (16.8 g, 94%), m.p. 91—92 °C (lit.,[32] 92 °C). The latter (4.0 g) was refluxed (20 min) with pyridinium chloride (33.0 g). The cooled mixture in water was acidified with concentrated hydrochloric acid, extracted with ether and the combined extracts washed with water, concentrated, and the residue distilled to give dihydrocoumarin as a colourless oil (2.0 g, 59%), b.p. 270—272 °C, identical with the product from route (a).

3-(o-*Hydroxyphenyl*)*propionic Acid* (*Melilotic Acid*).—Dihydrocoumarin (3.0 g) was warmed on a steam-bath with 5M-sodium hydroxide (20 cm³) for 15 min and the cooled solution acidified at 0 °C. The solid collected was crystallised from water to give prisms of melilotic acid, m.p. 83—84 °C (lit.,[33] 83 °C).

Ethyl 3-(o-*Hydroxyphenyl*)*propionate*.—Dihydrocoumarin (45.0 g) in dry ethanol (25 cm³) was treated dropwise at 40 °C with sodium ethoxide from sodium (6.9 g) and ethanol (150 cm³). After 1 h the mixture at 0 °C was acidified with concentrated hydrochloric acid and extracted with ether. The combined extracts (100 cm³) were washed with water and 5% sodium hydrogen carbonate and dried ($MgSO_4 \cdot H_2O$); the residue upon evaporation of solvents distilled to give a colourless oil (45.3 g, 76%), b.p. 120—122 °C/1 mmHg which crystallised, m.p. 31—33 °C (lit.,[34] 34 °C), $\nu_{max.}$ 1 750 cm⁻¹ (CO).

Ethyl 3-(o-*Tetrahydropyran*-2-*yloxyphenyl*)*propionate*.—Dihydropyran (32 cm³) was added dropwise (¾ h) to a stirred mixture of ethyl 3-(*o*-hydroxyphenyl)propionate (58.2 g) and concentrated hydrochloric acid (4 drops) at 40 °C. After 2 h the mixture, poured into 2% sodium hydroxide solution (150 cm³) at 0 °C, was extracted with ether; the extract was dried (K_2CO_3) and the residue, upon concentration, distilled to give a colourless oil (62.6 g, 75%), b.p. 149—150 °C/1 mmHg. It gave no colour with ferric chloride; $\nu_{max.}$ 1 750 cm⁻¹ (CO, OH nil).

3-(o-*Tetrahydropyran*-2-*yloxyphenyl*)*propanol*.—Ethyl 3-(*o*-tetrahydropyranyloxyphenyl)propionate (55.5 g) in dry ether (55 cm³) was added to a stirred suspension of lithium aluminium hydride (4.6 g) in dry ether (17.5 cm³) and the mixture refluxed (¾ h). Sodium hydroxide (100 cm³; 0.5%) was added (¼ h) to the cooled mixture at 0 °C and the combined ethereal extracts were dried (K_2CO_3), concentrated, and the residue distilled to give a colourless oil, 3-(*o*-tetrahydropyran-2-yloxyphenyl)propanol, (39.3 g, 83%), b.p. 155—156 °C/1.5 mmHg, $\nu_{max.}$ 3 450 cm⁻¹ (OH); no CO.

Ethyl 3-(o-*Hydroxyphenyl*)*propoxyacetate*.—3-(*o*-Tetrahydropyran-2-yloxyphenyl)propanol (11.82) in dry dimethylformamide (100 cm³) was added to sodium hydride (2.4 g) in dimethylformamide (25 cm³) and the warmed, stirred mixture (1 h) was treated with sodium bromoacetate (12.1 g); it was then heated on a steam-bath (1 h). The residue, obtained by rotary evaporation of the dimethylformamide, in water was acidified with concentrated hydrochloric acid and the combined ethereal extracts were washed with water, dried (K_2CO_3), and evaporated to give a pale yellow oil (12.5 g) which was refluxed in dry ethanol (100 cm³) (24 h) containing toluene-*p*-sulphonic acid (0.2 g). Concentration of the solution, dilution with sodium hydrogen carbonate solution and extraction with ether followed by drying and distillation of the recovered material gave a colourless oil (7.4 g, 65%, b.p., 159—160 °C/1 mmHg, $\nu_{max.}$ 1 720, (CO) and 3 400 cm⁻¹ (OH).

Methyl 4-(o-*Ethoxycarbonylmethoxypropylphenoxy*)*butyrate* (11).—To methanolic sodium methoxide [from sodium (2.3 g) and dry methanol (60 cm³)], ethyl 3-(*o*-hydroxyphenyl)propoxyacetate (24.8 g) in dry methanol (25 cm³) was added and the residual material, after evaporation of the methanol, in dimethylformamide (50 cm³) was treated with methyl 4-bromobutyrate (23.5 g). The mixture was heated at 110 °C (3 h), cooled, diluted with water, and the ethereal extract washed with 5% sodium hydroxide solution, dried and the recovered residue distilled to give a colourless oil b.p. 181—182 °C/0.6 mmHg which crystallised (light petroleum) to give white needles of the ester (11) (19.9 g, 59%), m.p. 32—33 °C (Found: C, 63.35; H, 7.35. $C_{18}H_{26}O_6$ requires C, 63.90; H, 7.75%); g.l.c. 2.60, (2.30), $\nu_{max.}$ 1 740 and 1 775 cm⁻¹ (CO).

For the corresponding *dimethyl compound*, the esterification, step vii, was carried out with methanol, ^{13}C n.m.r., δ (p.p.m., $CDCl_3$) 24.8 (a, t), 26.5 (b, t), 29.4 (c, t), 30.4 (d, t), 51.3 (e, e′, q), 66.7 (f, t), 68.2 (g, t), 71.4 (h, t), 111.1 (i, d), 128.6 (j, d), 120.2 (k, d), 130.2 (l, d), 130.2 (m, s), 156.9 (n, s), 171.1 (o, s), 173.6 (p, s); ^1H n.m.r. τ ($CDCl_3$) 2.67—3.30 (4 H, m, HAr), 5.87 (2 H, s, OCH_2CO), 5.86—6.07 (2 H, t, Ar-OCH_2), 6.18, 6.28 (6 H, 2s, OCH_3), 6.29—6.50 (2 H, t, OCH_2, 7.10—7.33 (2 H, t, CH_2Ar), 7.25—7.50 (2 H, t, CH_2CO), and 7.63—8.14 (4 H, 2 quin, 2 CH_2). [See (11), Scheme 2.]

Cyclisation Experiments with Diesters.—To conserve valuable intermediates, model experiments were carried out with diethyl sebacate. The apparatus consisted of a three-necked 500 cm³ flask modified as follows. To one side arm was integrally joined a condenser with an internal coil, and fitted at the upper end with a 100 cm³ Hershberg pressure-equalised funnel. This arrangement permitted high dilution of the diester by means of the refluxing solvent. The drop rate was controlled by raising or lowering a tungsten wire attached to a glass rod which passed out of the top of the funnel through a screw cap gland. A joint at the side of the gland led to an Hg trap, manometer, and vacuum pump connections to allow the entire apparatus to be evacuated and filled with nitrogen. The central neck of the flask had been widened and extended to accommodate a short condenser, and led to a membrane-sealed joint through which the stainless-steel rod of a Vibromix agitator passed into the flask. A perforated metal disc was screwed to the end of the rod. The remaining side neck was replaced by a wide tube sealed to the flask. All ground-glass joints were lightly lubricated and held tight by springs. Compressed air and water used for cooling were precooled by passing through coils immersed in ice–water.

(i) *Ethyl* 4-(o-*Ethoxycarbonylpropoxyphenoxy*)*butyrate*.—The same apparatus was used. Several variations in conditions were tried before the most effective method was found.

(*a*) The diester (8.45 g) was allowed to interact with sodium (2.3 g) in xylene (250 cm³) at 140 °C. The separated xylene solution, washed with aqueous sodium hydrogen carbonate, aqueous sodium hydroxide, and water, was then dried, concentrated, and distilled to give a pale yellow oil, b.p. 155—161 °C/0.05 mmHg.

(*b*) The experiment was identical except that xylene was replaced by toluene. Worked up by the same procedure, the reaction mixture yielded a neutral product which was distilled in a pot still (10^{-3} mmHg) to give five pale-yellow oily fractions.

TABLE 2

Cyclisation experiments with diester (7)

	Solvent	Temp. of reaction (°C)	Metal	Products wt (g) Acidic	Phenolic	Neutral	Comments
(a)	Xylene	140	Na	0.8	3.5	1.1	Complex neutral product.
(b)	Toluene	112	Na	0.8	1.2	2.3	I.r.: $\nu_{max.}$ 1 710, 3 475 cm^{-1} (*cf.* sebacoin) [35]
(c)	Benzene	80	Na–K	0.9	2.0	3.1	I.r.: $\nu_{max.}$ 1 710, 1 735, and 3 400 (small, OH)
(d)	Xylene	Room temp.	Na–K			8.2	I.r.: starting diester.

(*c*) Xylene (100 cm³) was evaporated to half volume in order to dry the apparatus azeotropically; sodium (0.7 g) and potassium (2.7 g) were then added. To the dispersed metals, dry benzene (250 cm³) and the diester (8.45 g) were added as before and the reaction carried out as for diethyl sebacate. The reaction mixture was worked up by successive alkaline extractions as previously.

(*d*) Sodium (0.7 g) and potassium (2.7 g) were dispersed in boiling xylene and the reaction carried out with the diester (8.45 g) at room temperature. The product was a pale yellow oil which proved to be unchanged starting material. The various fractions and conditions for experiments (*a*) to (*d*) are given in Table 2.

(ii) *Methyl* 4-(o-*Ethoxycarbonylmethoxypropylphenoxy*)*butyrate*.—(*a*) The diester (8.45 g) in toluene (250 cm³) was treated with sodium sand (2.3 g) as in the previous experiment. The neutral material obtained after removal of acidic products was molecularly distilled (10^{-3} mmHg) to give four fractions. All showed a single carbonyl absorption at 1 725 cm^{-1} and a weak OH band characteristic of acyloins.

(*b*) An experiment comparable to (*c*) in the preceding series conducted with sodium–potassium resulted in formation of a neutral pale yellow oil (2.8 g) from the diester (4.2 g). The neutral farction was separated into six fractions. By preparative t.l.c. fractions 1, 2, and 4 possessed $\nu_{max.}$ 1 710 and 1 735 cm^{-1} (CO) suggesting the presence of a β-keto-ester. Fractions 3 and 5 possessed ν_{CO} at 1 735 and 1 725 cm^{-1} respectively (suggesting the presence of the starting ester and an acyloin respectively).

Purification of the Neutral Product from Experiment (i) (*c*).—The neutral oil (0.164 g) in chloroform (2 cm³) was purified by t.l.c. in solvent A. Five fractions were obtained with increasing R_F value, (1) 0.022 8 g, (2) 0.022 9 g, (3) 0.097 0 g, (4) 0.006 6 g, and (5) 0.010 5 g. Repurification of the gummy fraction 3 (considerable streaking on the t.l.c. plate was encountered) suggested the presence of a weakly acidic substance or a tautomeric mixture. It gave a positive Ehrlich colour test (orange). Total yield of fractions 2, 3 (0.119 g, 31%); if recovered acidic material is allowed for, the yield is higher [Found: C, 65.8; H, 6.70. $C_{32}H_{40}O_{10}$, the bis-β-keto-ester (8; R = R² = CO_2Et, R¹ = R³ = H), requires C, 65.75; H, 6.90%. The acyloin (9), $C_{14}H_{18}O_4$ requires C, 67.19; H, 7.20); ¹H n.m.r. τ ($CDCl_3$), 3.1 (8 H, s, HAr), 5.65—6.05 [14 H, t, q,] CH_2O and CH($COCH_2$)-CO_2CH_2], 6.83—7.07 (4 H, t, CH_2CO), 7.47—7.96 (8 H, m, CH_2), 8.7—9.02 (6 H, 2t, CH_3); *m/e*, molecular ion, M^+, 584 (2.7%), $C_{32}H_{40}O_{10}$ requires 584; 539 (1.3), 512 (0.4), 429, $C_{24}H_{29}O_7$, (1.45), 293, $C_{16}H_{21}O_{51}$ (2.4), 247 (8.4), 183, $C_{10}H_{15}O_3$, (47), 155, $C_8H_{11}O_3$, (3.4), 137, $C_8H_9O_2$, (3.3), 121, C_8H_9O, (2.0), 110, $C_6H_6O_2$, (4.4), 111, $C_7H_{11}O$, (10.7), 69, C_4H_5O, (12.4). *M**, 131.4, 208.3; ν(film), 3 400 cm^{-1} (OH), 1 710, 1 735 cm^{-1} (CO, ketone, CO, ester).

Hydrolysis of the Bis-β-keto-ester to the Diketone (8; R = R¹ = R² = R³ = H).—The β-keto-ester (0.685 4 g) in ethanol (10 cm³) with dilute hydrochloric acid (12%; 20 cm³) was refluxed (36 h). The cooled mixture was extracted with chloroform, and the extract washed with aqueous sodium hydroxide. The concentrate obtained by evaporation was purified by t.l.c. (solvent C) and visualised with pyrenesulphonic acid. The recovered product (m.p. 121—125° C), still possessed streaky t.l.c. behaviour; its i.r. spectrum showed strong CO (ketone) and weak CO (ester) absorption. The mass spectrum showed a base peak at *m/e* 512 indicating the diketomonocarboxylate (Found: C, 69.4; H, 7.7. $C_{29}H_{36}O_8$ requires C, 67.96; H, 7.03%). The ¹H n.m.r. spectrum showed a diminished signal for CO_2Et.

The intermediate hydrolysis product (0.059 7 g) in ethanol (2 cm³) was boiled with dilute hydrochloric acid (12%) for 20 h. A solid which had then formed was filtered off, washed with dilute aqueous sodium hydroxide, and water and then dried (0.058 9 g). The i.r. absorption indicated CO, ketone only. Recrystallisation (methanol–chloroform) gave the *diketone* as off-white prisms m.p. 185 °C (Found: C, 70.35; H, 7.35. $C_{26}H_{32}O_6$ requires, C, 70.85; H, 7.27%); *m/e*, molecular ion, M^+, 440 (0.6%), $C_{26}H_{32}O_6$ requires 440; 331, $C_{20}H_{27}O_4$, (0.4), 330, $C_{20}H_{26}O_4$, (0.3), 247 (0.3), 221, $C_{13}H_{17}O_3$, (6.1), 203 (0.3), 183 (0.3), 166 (0.2), 121 (2.5), 111, $C_7H_{11}O$, (40.3), 110, $C_6H_6O_2$, (7.5), 97, C_6H_9O, (4.4), 84 (1.7), 81 (1.6), 69, C_4H_5O, (29.2), 55 (4.4). *M**, 110.3, 55.8, 42.6, 24.4; ¹H n.m.r. τ ($CDCl_3$) 3.14 (8 H, s, HAr), 5.89—6.08 (8 H, t, OCH_2), 7.09—7.33 (8 H, t, CH_2CO), 7.7—8.13 (8 H, q, CH_2); ν(disc) 2 840 and 2 930 (CH_2), 1 695 (CO), 1 590, 1 510 (Ar), 1 260 (C–O–C), 1 120, 1 052, 955, and 745 cm^{-1} (*o*-substitution). The diketone slowly gave a bis-2,4-dinitrophenylhydrazone, m.p. 172—175 °C. With semicarbazide hydrochloride, sodium acetate, and

pyridine, a semicarbazone was slowly formed, m.p. 209—210 °C; no ν_{CO} absorption.

Reduction of the Diketone to the Diol (10; R = OH).—Sodium borohydride in methanol or dimethylformamide gave indeterminate results but pyridine as solvent was an improvement. The diketone (0.116 g) in pyridine (1 cm³) warmed with sodium borohydride (0.065 2 g) and left for 24 h gave the impure diol, m.p. 138—139 °C. Lithium aluminium hydride gave a better result.

The diketone (0.026 1 g) in pyridine (1 cm³) was treated with lithium aluminium hydride (0.120 5 g) and the yellow mixture was left overnight. Addition of ice-cold water and dilute hydrochloric acid, followed by chloroform extraction, evaporation, and crystallisation (ethanol) gave white prisms of the *diol*, m.p. 152—153 °C, probably one of the diastereoisomers (Found: C, 69.4; H, 8.25. $C_{26}H_{36}O_6$ requires C, 69.95; H, 8.11%); ^{1}H n.m.r. τ ($CDCl_3$) 3.1 (8 H, s, HAr), 5.84—6.03 (8 H, t, CH_2O), 6.1—6.3 (2 H, m, C*H*–OH), 7.1 (2 H, s, OH), 7.8—8.3 (16 H, m, CH_2); $\nu_{max.}$(disc) 3 430 cm^{-1} (OH), CO (nil). Catalytic reduction, hydrogenolysis and Clemmensen reduction failed to reduce the diketone.

Wolff-Kishner Reduction of the Diketone.—The diketone (0.015 6 g) and 'digol' (1.5 cm³) containing hydrazine hydrate (0.3 cm³) were heated at 125 °C for 16 h; after addition of potassium hydroxide (0.25 g) the temperature was raised to 180 °C. The mixture was finally heated at 140 °C for 48 h. The cooled solution was diluted with water and the viscous solution extracted with ether and then with chloroform. The two extracts (similar t.l.c.) were combined, washed successively with dilute sulphuric acid, dilute sodium hydroxide, and water, and then dried and evaporated to give, upon addition of ether, a white precipitate which was isolated by filtration. Recrystallisation (methanol–chloroform) gave fibrous needles (0.12 g) of (10; R = H), m.p. 158—159 °C, m.p. undepressed on admixture with the purified product from the reaction of 1,7-di-(*o*-hydroxyphenoxy)heptane with 1,7-dibromoheptane (see below). A further small quantity of the product was separated from the methanolic chloroform filtrate (Found: C, 74.95; H, 8.65. $C_{26}H_{36}O_4$ requires C, 75.65; H, 8.74%); ^{1}H n.m.r. τ ($CDCl_3$), 3.16 (HAr, s), 5.98—6.08 (CH_2O, t), and 8.1—8.47 (CH_2, m,); *m/e* molecular ion, M^+, 412 (13.0%); $C_{26}H_{36}O_4$ requires 412; 315 (0.9), 206, $C_{13}H_{18}O_2$, (2.7), 149 (0.7), 121, C_8H_9O, (4.1), 110, $C_6H_6O_2$ (29.2), 97, C_7H_{13}, (20.3), 53 (29.0); g.l.c. 84.95 (75.2); dibenzo-14-crown-6, 16.0, (14.2); dicyclohexyl-18-crown-6, (technical) 7.0 (6.20), 7.6 (6.72), 7.9 (6.99), 10.9 (9.64); dibenzo-14-crown-4, 5.7 (5.04); 18-crown-6, 1.13 (1.00).

Reaction of o-(*Tetrahydropyran-2-yloxy*)*phenol with* 1,7-*Dibromoheptane: Preparation of* 7-(o-*Hydroxyphenoxy*)-1-*bromoheptane and* 1,7-*Di*(o-*hydroxyphenoxy*)*heptane.*—1,7-Dibromoheptane (b.p. 84—88 °C/1 mmHg) was obtained by interaction of heptane-1,7-diol with hydrobromic acid (48%) and concentrated sulphuric acid, followed by washing with concentrated sulphuric acid, and aqueous sodium carbonate. *o*-Tetrahydropyran-2-yloxyphenol (b.p. 95—100 °C/1 mmHg) was obtained from pyrocatechol and dihydropyran with the addition of a drop of concentrated hydrochloric acid, followed by alkaline washing.

To sodium hydride (0.450 8 g; 50% dispersion) in dimethylformamide (6 cm³), *o*-tetrahydropyran-2-yloxyphenol (1.656 3 g) was added. After hydrogen evolution was complete 1,7-dibromoheptane (2.095 7 g) in dimethylformamide (1.5 cm³) was added (6 h) to the stirred mixture which was then left (16 h). Dilution with ether, removal of sodium bromide (0.845 2 g) by filtration, and alkaline washing of the filtrate (recovered 'pyranyloxycatechol', 0.220 5 g) followed by water washing and drying gave the product (2.836 0 g). T.l.c. (analytical) in solvent A indicated two spots, corresponding to mono- and di-substituted products. Preparative t.l.c. of the crude product (0.46 g) gave two bands which, worked up, yielded (upper band) 7-(*o*-hydroxyphenoxy)-1-bromoheptane as an oil (0.133 6 g), and a solid (0.570 g) (the lower band), m.p. 81—82 °C, [recrystallised from light petroleum (b.p. 60—80 °C)] to give the disubstituted product, 1,7-*di*(o-*hydroxyphenoxy*)*heptane* [Found (for the oil): C, 57.8; H, 7.1; *M*, 288. $C_{13}H_{19}BrO_2$ requires, C, 54.36; H, 6.62%; *M*, 288; correct analytical figures could not be obtained due to the presence of an impurity, probably the cyclised product, $C_{13}H_{28}O_2$ (C, 72.22; H, 12.9%), particularly in alkaline washing]. For the solid (Found: C, 71.5; H, 7.65. $C_{19}H_{24}O_4$ requires C, 72.13; H, 7.59%); *m/e*, molecular ion, M^+, 316 (6.1%), $C_{19}H_{24}O_4$ requires 316; 206 (0.9), 149 (0.2), 123 (1.1), 110 (26.1), 97 (9.4), 95 (4.1), 81 (3.9), 77 (2.2), 69 (3.9), 65 (2.9), 55 (30.1), 41 (8.9).

Preparative t.l.c. of the reaction product before removal of the protective group gave a different proportion of mono- to di-substitution products than after removal of the group, suggesting that prolonged toluene-*p*-sulphonic acid treatment was destroying some of the mono-product. The nature of the decomposition was not found, although it was thought to be cyclisation.

1,7-*Di*-(o-*hydroxyphenoxy*)*heptane.*—(*a*) To sodium hydride (0.225 3 g; 50% dispersion) was added *o*-(2-tetrahydropyranyloxy)phenol (0.845 8 g) in dimethylformamide (1 cm³) followed by 1,7-dibromoheptane (0.501 4 g) in one portion. After being warmed and stirred (16 h), the mixture was worked up as before to give, after alkali washing, water washing and drying, an oil (0.941 8 g). Analytical t.l.c. indicated substantially one spot corresponding to the low band, the disubstitution product in the preceding preparation. Repurification gave the pure product, m.p. undepressed on admixture.

Although removal of the protective group was effected by refluxing the crude product in methanol with toluene-*p*-sulphonic acid (16 h), this step was found to be superfluous since in preparative t.l.c., recovery had been first carried out and partial removal of the protective group was found to occur during the dilute sulphuric acid washing (to remove the visualising agent, Rhodamine 6G).

(*b*) *Reaction of pyrocatechol with* 1,7-*dibromoheptane.* Pyrocatechol (0.60 g) and 1,7-dibromoheptane (2.80 g) in ethanol (1.8 cm³) containing M-ethanolic potassium hydroxide (1.8 cm³) was refluxed (1 h). The ethereally extracted mixture was washed with water to remove pyrocatechol and the residue, upon evaporation, extracted with light petroleum. The recovered product showed four bands (analytical t.l.c.) and the second and fourth from the base line agreed in R_F value with 1,7-di-(*o*-hydroxyphenoxy)-heptane and 7-bromo-1-(*o*-hydroxyphenoxy)heptane respectively. In a further experiment with 1,7-dibromoheptane (3.7 g) and pyrocatechol (0.8 g) in ethanol (2.4 cm³) containing M-ethanolic potassium hydroxide (2.4 cm³), a prolonged reaction time gave an excess of the disubstituted product.

Reaction of 1,7-*Di*-(o-*hydroxyphenoxy*)*heptane with* 1,7-*Dibromoheptane.*— 1,7-Di-(*o*-hydroxyphenoxy)heptane (0.088 9 g) in n-butanol (1.0 cm³) was treated with sodium hydroxide (0.026 g) in water (0.065 cm³) and to the hot solu-

tion 1,7-dibromoheptane (0.129 g) in n-butanol (0.1 cm^3) was added from a 50 μl syringe. The mixture was refluxed for 20 h at 130 °C, diluted with water, and the n-butanol steam-distilled off. The residual material was extracted with chloroform which was then washed with sodium hydroxide solution. The recovered material showed four components (analytical t.l.c.) and 0.137 6 g was preparatively purified (solvent B) to give (i) a top band (0.002 g), (ii) a second band (0.077 5 g), (iii) a third band (0.020 0 g), and (iv) a base-line band. The material recovered from band (ii) in the usual way was treated in ethereal solution with light petroleum and a solid (0.006 g) collected by filtration. The viscous oil from the filtrate (0.064 2 g) yielded more solid. The first solid recrystallised (ether–light petroleum) as white prisms of (10; R = H), m.p. 158—159 °C showing no depression of m.p. with the product of the Dieckmann reaction, hydrolysis, and reduction.

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