675. *Lactones. Part VI.* The Preparation of 5,7-Dihydroxyphthalide, its 5-Methyl Ether, and Related Compounds.*

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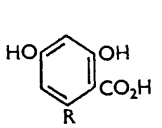
Ethyl dibromo-orsellinate has been converted into 5,7-dihydroxyphthalide by successive photobromination, hydrolysis, and hydrogenolysis; and ethyl everninate has been similarly transformed into 7-hydroxy-5-methoxyphthalide.

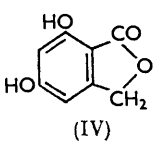
THIS investigation was initiated in order to find a suitable synthesis of 5,7-dihydroxyphthalide (IV) which might be a useful intermediate for synthesis of the acids (I) and (II) [1] elaborated by *Penicillium brevi-compactum*. 5,7-Dihydroxyphthalide could be postulated as a possible intermediate along with orsellinic acid (III) in the biosynthesis of variolaric acid [2] (V), a constituent of the lichen *Lecanora parella* Ach. 7-Hydroxy-5-methoxyphthalide (XIV) was also desired since it might serve as an intermediate for the synthesis of mycophenolic acid [3,4] (VI).



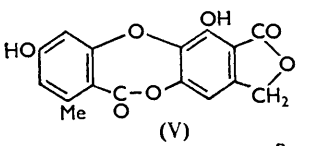
(I) R = CH(OH)·COMe

(II) R = CO·COMe, H_2O

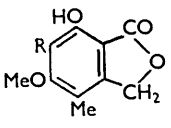
(III) R = Me



(IV)



(V)



(VI)

R = CH_2·CH:CMe·$[CH_2]_2$·CO_2H

5,7-Dihydroxyphthalide has been prepared starting from ethyl dibromo-orsellinate [5] (VII). Photobromination of this ester gave in almost quantitative yield the tribromo-ester (VIII) which on hydrolysis in aqueous dioxan yielded 4,6-dibromo-5,7-dihydroxyphthalide (XI), characterised as its diacetate (XII)—the usual alkaline hydrolysis

* Part V, *J.*, 1957, 1946.

[1] Clutterbuck, Oxford, Raistrick, and Smith, *Biochem. J.*, 1932, **26**, 1441; Oxford and Raistrick, *ibid.*, p. 1902; 1933, **27**, 634, 1473.

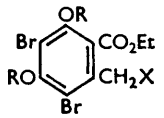
[2] Murphy, Keane, and Nolan, *Sci. Proc. Roy. Dublin Soc.*, 1943, **23**, 71.

[3] Birkinshaw, Raistrick, and Ross, *Biochem. J.*, 1952, **50**, 630.

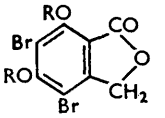
[4] Logan and Newbold, *J.*, 1957, 1946.

[5] Cf. Sonn, *Ber.*, 1928, **61**, 926.

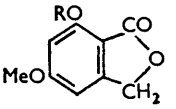
technique [4,6] was not successful. 4,6-Dibromo-5,7-dihydroxyphthalide was not hydrogenolysed to 5,7-dihydroxyphthalide (IV) by the method [4] used to convert 4-bromo-5,7-dimethoxyphthalide (XVIII) into 5,7-dimethoxyphthalide (XV), but use of palladium on calcium carbonate in the presence of alkali [5] was successful.



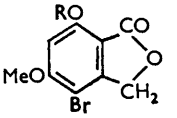
(VII) R = X = H
(VIII) R = H, X = Br
(IX) R = Me, X = Br
(X) R = Me, X = H



(XI) R = H
(XII) R = Ac
(XIII) R = Me



(XIV) R = H
(XV) R = Me

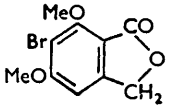


(XVI) R = H
(XVII) R = Ac
(XVIII) R = Me

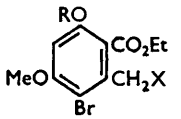
With diazomethane 5,7-dihydroxyphthalide rapidly gave 5,7-dimethoxyphthalide (XV). Ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate (VIII) gave an oil which from its reactions described below must have been the ether (IX); ethyl dibromo-orsellinate (VII) was similarly converted into the ether (X). These methylations contrast with the action of diazomethane on ethyl orsellinate which under these conditions gave ethyl everninate (XXIV), only the 4-hydroxyl group having reacted.[7] Clearly the enhanced acidity of the 6-hydroxy-group in (VII) and (VIII), due to the ring deactivation of the bromine atoms, overcomes the lack of reactivity of the hydroxyl group due to hydrogen-bonding with the ester-carbonyl group.

The crude ethyl 3,5-dibromo-2-bromomethyl-4,6-dimethoxybenzoate (IX), to which reference was made above, was hydrolysed in aqueous dioxan to 4,6-dibromo-5,7-dimethoxyphthalide (XIII); this was also prepared from the phthalide (XI) by means of diazomethane. Replacement of both bromine atoms in the phthalide (XIII) by hydrogen, giving 5,7-dimethoxyphthalide (XV), was effected catalytically in aqueous alkali; on hydrogenolysis with palladium–charcoal in ethyl acetate, the product was 6-bromo-5,7-dimethoxyphthalide (XIX) even after prolonged treatment, and this was fully debrominated by hydrogenolysis in aqueous alkali in the presence of palladium–calcium carbonate.

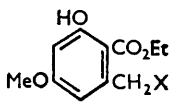
The starting material for the synthesis of 7-hydroxy-5-methoxyphthalide (XIV) was ethyl everninate [7] (XXIV). Photobromination of the ester with 1 mol. of bromine in presence of a little methanol gave mainly ethyl 3-bromo-6-hydroxy-4-methoxy-2-methylbenzoate (XX) [identified as the dimethoxy-ester (XXI) which was also prepared by



(XIX)



(XX) R = X = H
(XXI) R = Me, X = H
(XXII) R = H, X = Br
(XXIII) R = Me, X = Br



(XXIV) X = H
(XXV) X = Br

esterification of the known 4,6-dimethoxy-acid [4]], but in the absence of methanol ethyl 2-bromomethyl-6-hydroxy-4-methoxybenzoate (XXV) was obtained in good yield. This was smoothly hydrolysed to 7-hydroxy-5-methoxyphthalide (XIV) in aqueous dioxan. A small amount of the bromomethyl compound (XXV) was isolated after photobromination in the presence of methanol. Photobromination of ethyl everninate with 2 mol. of bromine gave both nuclear and side-chain bromination: the product, (XXII), on hydrolysis in aqueous sodium carbonate or, better, aqueous dioxan afforded the bromophthalide (XVI).

[6] Eliel, Rivard, and Burgstahler, *J. Org. Chem.*, 1953, **18**, 1679.
[7] Fischer and Hoesch, *Annalen*, 1912, **391**, 347.

The last compound, which was characterised as its acetate (XVII), was readily hydrogenolysed to 7-hydroxy-5-methoxyphthalide (XIV). Ethyl 3-bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate (XXII) was rapidly methylated by diazomethane to give the dimethoxy-ester (XXIII) which on hydrolysis gave the known [4] 4-bromo-5,7-dimethoxyphthalide (XVIII). Both 7-hydroxy-5-methoxyphthalide and its 4-bromo-derivative reacted readily with diazomethane with the respective formation of the diethers (XV) and (XVIII).

The ready methylation of all the 7-hydroxyphthalides prepared in this work indicated the expected weakness of the intramolecular hydrogen bond between the carbonyl and the 7-hydroxyl group.[8] The same conclusion was drawn from the infrared spectra of the 7-hydroxyphthalides which showed carbonyl stretching frequencies in the range 1748—1732 cm.$^{-1}$ in chloroform (cf. 7-hydroxyphthalide,[9] 1738 cm.$^{-1}$). While 5,7-dimethoxyphthalide and its 4- and 6-bromo-derivative showed the predicted carbonyl peak at 1764—1761 cm.$^{-1}$ in chloroform (cf. phthalide 1761 cm.$^{-1}$), the 4,6-dibromo-derivative had its peak at 1776 cm.$^{-1}$ in this solvent (1770 cm.$^{-1}$ in Nujol and 1789 cm.$^{-1}$ in carbon tetrachloride); this effect cannot be ascribed to steric factors but may be due to the combined electron-attractive effect of both bromine substituents on their carbonyl group.[10] The effect of structural changes on their ultraviolet spectra in some of the compounds described above has been examined, the maximum (290—335 mμ) nearest the visible region being considered. As a consequence of the weak intramolecular hydrogen bond in the 7-hydroxyphthalides no appreciable shift occurs in this maximum on methylation [8] of the following: 4,6-dibromo-5,7-dihydroxy- Δ(mμ)—2, 5,7-dihydroxy- Δ 0, 4-bromo-7-hydroxy-5-methoxy- Δ—1·5, and 7-hydroxy-5-methoxy-phthalide Δ—1 (data from ref. 4 and this paper). The introduction of a bromo-substituent into the nuclear methyl group in the esters gave a bathochromic shift, thus: (XXI) ⟶ (XXIII) Δ 20, for the corresponding methyl esters [4] Δ 17·5, (VII) ⟶ (VIII) Δ 18, (XXIV) ⟶ (XXV) Δ 11, (XX) ⟶ (XXII) Δ 13. For a 3-bromo-substituent in ethyl everninate [(XXIV) ⟶ (XX)] Δ 8, and for the same change with ethyl 2-bromomethyl-6-hydroxy-4-methoxybenzoate [(XXV) ⟶ (XXII)] Δ 10; hence a nuclear bromine atom gave a smaller bathochromic shift than if it had entered the side chain.

Experimental

Ultraviolet absorption spectra were determined for ethanol solutions. Brominations were in boiling dry carbon tetrachloride in a quartz flask mounted immediately above a 150 w lamp which both heated and irradiated the mixture.

Ethyl 3,5-Dibromo-4,6-dimethoxy-2-methylbenzoate (with J. Highet).—Ethyl dibromo-orsellinate, $\lambda_{max.}$ 224 (ε 28,500), 269 (ε 8500), and 317 mμ (ε 8500) (570 mg.), in methanol (5 c.c.) was treated with excess of ethereal diazomethane. After 2½ hr. evaporation and crystallisation from light petroleum (b. p. 60—80°) gave the *dimethoxy-ester* (610 mg., 98%) as prisms, m. p. 77—78° (Found: C, 38·0; H, 3·8. $C_{12}H_{14}O_4Br_2$ requires C, 37·7; H, 3·7%), $\lambda_{max.}$ 212 (ε 36,000) and 285 mμ (ε 700), $\nu_{max.}$ 1715 (in Nujol), 1727 cm.$^{-1}$ (in chloroform) (ester C=O).

Ethyl 3,5-Dibromo-2-bromomethyl-4,6-dihydroxybenzoate (with J. Highet).—To ethyl 3,5-dibromo-4,6-dihydroxy-2-methylbenzoate [5] (10 g.) in refluxing carbon tetrachloride (150 c.c.) was added during 30 min. bromine (4·52 g., 1 mol.) in carbon tetrachloride (20 c.c.). Refluxing was continued for a further 10 min., then the solvent was removed under reduced pressure. The residue crystallised from light petroleum (b. p. 60—80°) to give *ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate* (11·7 g.) as stout needles, m. p. 122—123° (Found: C, 28·1; H, 2·3. $C_{10}H_9O_4Br_3$ requires C, 27·7; H, 2·1%), $\lambda_{max.}$ 207 (ε 10,700), 234 (ε 15,800), 268 (ε 9000), and 335 mμ (ε 6400), $\nu_{max.}$ 1647 (in Nujol), 1667 cm.$^{-1}$ (in chloroform) (H-bonded ester). The compound in ethanol solution gave a deep purple colour with aqueous ferric chloride.

4,6-Dibromo-5,7-dihydroxyphthalide.—(*a*) (with J. Highet). A solution of ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate (1·36 g.) in 10% aqueous sodium carbonate

[8] Farmer, Hayes, and Thomson, *J.*, 1956, 3600.
[9] Duncanson, Grove, and Zealley, *J.*, 1953, 1331.
[10] Cf. Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, London, 1958, p. 391.

(136 c.c.) was heated for 1 hr. on the steam-bath, rapidly becoming dark brown. The cooled solution was acidified (Congo-red) with hydrochloric acid (*d* 1·15) and extracted with chloroform (3 × 20 c.c.). The combined chloroform extracts were washed with saturated aqueous sodium hydrogen carbonate (3 × 20 c.c.), and the alkaline washings were acidified (Congo-red) with hydrochloric acid (*d* 1·15). The solution was then extracted with chloroform (6 × 15 c.c.), and these extracts were dried (Na_2SO_4) and evaporated under reduced pressure to a brown solid. Crystallisation from chloroform gave 4,6-*dibromo*-5,7-*dihydroxyphthalide* (100 mg., 10%) as prisms, m. p. 236—238° (decomp.) (Found: C, 29·8; H, 1·4. $C_8H_4O_4Br_2$ requires C, 29·7; H, 1·3%), $\lambda_{max.}$ 224 (ε 38,100) and 304 (ε 9400), inflexion at 212 mμ (ε 14,000), $\nu_{max.}$ 1715 (in Nujol), 1748 cm.$^{-1}$ (in chloroform) (H-bonded phthalide C=O). An ethanolic solution of the compound gave a deep purple colour with aqueous ferric chloride.

(*b*) Ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate (1·0 g.) was refluxed in dioxan (20 c.c.) and water (20 c.c.) for 24 hr. The dioxan was largely evaporated under reduced pressure, the residual aqueous solution allowed to crystallise, and the solid separated and dried. Recrystallisation from chloroform gave 4,6-dibromo-5,7-dihydroxyphthalide (680 mg., 91%) as prisms, m. p. and mixed m. p. 236—238° (decomp.). The identity of the phthalide preparation (*b*) with that of (*a*) was confirmed by comparison of infrared spectra in Nujol mull. Hydrolysis of ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate for 6 hr. with boiling 40% aqueous methanol, aqueous ethanol, absolute methanol, and absolute ethanol gave respectively 24, 55, 20, and 45% yields of the dibromophthalide.

The *diacetate*, prepared by the acetic anhydride–pyridine method, separated from methanol as plates, m. p. 162·5—164·5° (Found: C, 35·6; H, 2·1. $C_{12}H_8O_6Br_2$ requires C, 35·3; H, 2·0%), $\lambda_{max.}$ 217 (ε 41,500) and 296 mμ (ε 2600), $\nu_{max.}$ (in Nujol) 1775 (" phenolic " OAc) and 1751 (phthalide C=O), or (in chloroform) 1779 cm.$^{-1}$.

4,6-*Dibromo*-5,7-*dimethoxyphthalide*.—(*a*) A solution of 4,6-dibromo-5,7-dihydroxyphthalide (1·0 g.) in methanol (40 c.c.) was treated for 1 hr. with an excess of ethereal diazomethane. The solute crystallised from chloroform–methanol to give 4,6-*dibromo*-5,7-*dimethoxyphthalide* (1·02 g.) as needles, m. p. 136·5—138·5° (Found: C, 33·9; H, 2·4. $C_{10}H_8O_4Br_2$ requires C, 34·1; H, 2·3%), $\lambda_{max.}$ 222 (ε 40,200) and 302 mμ (ε 2400).

(*b*) A solution of ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate (700 mg.) in methanol (1 c.c.) and ether (10 c.c.) was treated with an excess of ethereal diazomethane for 4 hr. A sample, on evaporation and dissolution in ethanol, then gave no colour with aqueous ferric chloride. Removal of the solvents gave an oil (725 mg.) [$\nu_{max.}$ (liquid) 1721 cm.$^{-1}$ (ester C=O)]; 350 mg. of this were dissolved in dioxan (20 c.c.), water (10 c.c.) was added, and the solution was refluxed for 24 hr. The dioxan was largely removed under reduced pressure, the aqueous solution cooled, and the separated solid filtered off and dried. Crystallisation from chloroform–methanol gave 4,6-dibromo-5,7-dimethoxyphthalide (244 mg., 85%) as felted needles, m. p. and mixed m. p. 136—138·5°. The infrared spectra of preparations (*a*) and (*b*) in Nujol were identical.

6-*Bromo*-5,7-*dimethoxyphthalide*.—A solution of 4,6-dibromo-5,7-dimethoxyphthalide (200 mg.) in dry ethyl acetate (50 c.c.) was shaken with hydrogen at room temperature and atmospheric pressure in the presence of palladised charcoal (200 mg.; 2·5% of dichloride) and magnesium oxide (400 mg.). When absorption of hydrogen was complete (*ca.* 20 hr.) the mixture was filtered and the insoluble residue extracted with boiling chloroform (100 c.c.). The combined filtrates were evaporated under reduced pressure, and the residue crystallised from chloroform–methanol to give 6-*bromo*-5,7-*dimethoxyphthalide* (70 mg.) as blades, m. p. 207—209° (Found: C, 44·0; H, 3·3. $C_{10}H_9O_4Br$ requires C, 44·0; H, 3·3%); $\lambda_{max.}$ 219 (ε 32,900) and 257 (ε 12,200), inflexion at 287 mμ (ε 1500), $\nu_{max.}$ 1736 (in Nujol), 1764 cm.$^{-1}$ (in chloroform) (phthalide C=O). A mixed m. p. with 4-bromo-5,7-dimethoxyphthalide (lit.,[4] m. p. 246—248°) was 180—200°. The same yield of 6-bromo-5,7-dimethoxyphthalide was obtained when the dibromophthalide was hydrogenated under the same conditions but for 48 hr.

5,7-*Dihydroxyphthalide*.—4,6-Dibromo-5,7-dihydroxyphthalide (500 mg.) was shaken in 2N-aqueous sodium hydroxide (10 c.c.) with hydrogen at room temperature and atmospheric pressure in the presence of palladised calcium carbonate (1·0 g.; 2% of palladium hydroxide [11]). When absorption of hydrogen was complete (*ca.* 30 min.) the mixture was filtered and the filtrate acidified (Congo-red) with hydrochloric acid (*d* 1·15). The solid which slowly separated was filtered off, washed with a little water, and crystallised from aqueous methanol to give

[11] Busch and Stove, *Ber.*, 1916, **49**, 1063.

5,7-dihydroxyphthalide (200 mg., 80%) as blades, m. p. 253—260° (decomp.), darkening at 235°, m. p. 257—260° *in vacuo* (Found: C, 57·7; H, 3·8. $C_8H_6O_4$ requires C, 57·8; H, 3·6%), $\lambda_{max.}$ 216 (ε 35,300), 255 (ε 15,000), and 290 mμ (ε 5000); $\nu_{max.}$ 1724 (in Nujol), 1732 cm.$^{-1}$ (in chloroform) (H-bonded phthalide C=O). A solution of the compound in ethanol gave a reddish-purple colour with aqueous ferric chloride.

Ethyl 3-Bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate.—To a refluxing solution of ethyl everninate,[7] $\lambda_{max.}$ 216 (ε 25,000), 263 (ε 15,000), and 301 mμ (ε 6000) (5·0 g.), in carbon tetrachloride (75 c.c.) bromine (7·61 g., 2 mols.) in carbon tetrachloride (20 c.c.) was added dropwise at such a rate that the colour due to the previous addition had virtually disappeared. Approximately 6 hr. were required; the solution was then refluxed for a further 30 min. The solvent was evaporated under reduced pressure, and the residue crystallised from light petroleum (b. p. 60—80°) to give *ethyl 3-bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate* (5·3 g.) as needles, m. p. 103·5—105° (Found: C, 35·8; H, 3·4. $C_{11}H_{12}O_4Br_2$ requires C, 35·9; H, 3·3%), $\lambda_{max.}$ 228 (ε 28,600) and 322 (ε 5800), inflexions 209 (ε 15,200) and 264 mμ (ε 7100), $\nu_{max.}$ 1639 (in Nujol), $\nu_{max.}$ 1661 cm.$^{-1}$ (in chloroform) (H-bonded ester C=O). It gave a reddish-purple colour with ferric chloride (cf. above).

Ethyl 3-Bromo-2-bromomethyl-4,6-dimethoxybenzoate.—A solution of ethyl 3-bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate (1·0 g.) in methanol (20 c.c.) was treated with excess of ethereal diazomethane for 4 hr., whereafter it gave no ferric chloride colour. Evaporation and crystallisation from light petroleum (b. p. 40—60°) gave *ethyl 3-bromo-2-bromomethyl-4,6-dimethoxybenzoate* (880 mg.) as prisms, m. p. 98—100° (Found: C, 37·5; H, 3·8. $C_{12}H_{14}O_4Br_2$ requires C, 37·7; H, 3·7%), $\lambda_{max.}$ 221 (ε 25,400) and 308 mμ (ε 4100), $\nu_{max.}$ 1733 (in Nujol), 1724 cm.$^{-1}$ (in chloroform) (ester C=O). A solution of the ester (500 mg.) in dioxan (20 c.c.) and water (10 c.c.) was refluxed for 24 hr. Concentration of the solution, cooling, separation of the crystals, and recrystallisation from chloroform–methanol gave 4-bromo-5,7-dimethoxyphthalide (89%) as needles, m. p. and mixed m. p. 246—248° (lit.,[4] m. p. 246—248°). The infrared spectra of the two samples in Nujol were identical: $\nu_{max.}$ 1767 (in Nujol), 1763 cm.$^{-1}$ (in chloroform) (phthalide C=O).

4-Bromo-7-hydroxy-5-methoxyphthalide.—(*a*) Water (40 c.c.) was added to a solution of ethyl 3-bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate (1·8 g.) in dioxan (60 c.c.) and the solution refluxed for 24 hr. Concentration under reduced pressure gave a mainly aqueous solution which deposited solid on cooling. Crystallisation of the solid from chloroform gave *4-bromo-7-hydroxy-5-methoxyphthalide* (1·1 g., 88%) as prisms, m. p. 236—238° (decomp.) (Found: C, 41·6; H, 2·85; Br, 30·7. $C_9H_7O_4Br$ requires C, 41·7; H, 2·7; Br, 30·9%), $\lambda_{max.}$ 220 (ε 34,000), 247 (ε 10,100), and 300 mμ (ε 4200), $\nu_{max.}$ 1733 (in Nujol), $\nu_{max.}$ 1742 cm.$^{-1}$ (in chloroform (H-bonded phthalide C=O). It gave a purple colour with ferric chloride (cf. above).

(*b*) Ethyl 3-bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate (500 mg.) was heated in 10% aqueous sodium carbonate (50 c.c.) for 1 hr. on the steam-bath. The solution was cooled, acidified (Congo-red) with hydrochloric acid (*d* 1·15), and extracted continuously with boiling chloroform for 2 hr. The chloroform extract was washed with a little water, dried (Na_2SO_4), and evaporated. Crystallisation of the residue from chloroform gave 4-bromo-7-hydroxy-5-methoxyphthalide (170 mg., 50%) as prisms, m. p. and mixed m. p. 236—238° (decomp.). The infrared spectra of preparations (*a*) and (*b*) in Nujol mull were identical.

The *acetate*, prepared by the acetic anhydride–pyridine method, separated from methanol as plates, m. p. 164—166° (Found: C, 44·2; H, 3·3. $C_{11}H_9O_5Br$ requires C, 43·9; H, 3·0%), $\lambda_{max.}$ 219 (ε 36,700) and 260 mμ (ε 13,900), $\nu_{max.}$ 1779 (" phenolic " acetate C=O) and 1761 (phthalide C=O) (in Nujol) or 1786—1767 cm.$^{-1}$ (broad band) (in chloroform). 4-Bromo-7-hydroxy-5-methoxyphthalide in methanol with an excess of ethereal diazomethane for 1 hr. gave 4-bromo-5,7-dimethoxyphthalide (in good yield), separating from chloroform–methanol as needles, m. p. 246—248° alone or mixed with a specimen prepared by Logan and Newbold.[4] The infrared spectra of the two samples in Nujol were identical.

Ethyl 3-Bromo-6-hydroxy-4-methoxy-2-methylbenzoate.—Ethyl everninate (5·59 g.), which had been dried *in vacuo* at 60°, was dissolved in dry carbon tetrachloride (80 c.c.), and methanol (0·2 c.c.) was added. The refluxing solution was treated with bromine (4·26 g., 1 mol.) in carbon tetrachloride (25 c.c.) dropwise during 30 min. Refluxing was continued for 15 min., the solvent evaporated under reduced pressure, and the resulting yellow gum dissolved in hot light petroleum (b. p. 60—80°). Concentration of the solution and cooling gave crop A, and from similar treatment of the mother-liquor crop B was obtained (see next paragraph). Crop A, on

crystallisation from light petroleum (b. p. 60—80°), gave *ethyl 3-bromo-6-hydroxy-4-methoxy-2-methylbenzoate* (3·2 g.) as needles, m. p. 125—127° (Found: C, 45·7; H, 4·8. $C_{11}H_{13}O_4Br$ requires C, 45·7; H, 4·5%), $\lambda_{max.}$ 218 (ε 28,300), 262 (ε 8900), and 309 mμ (ε 4100), $\nu_{max.}$ 1650 (in Nujol), $\nu_{max.}$ 1655 cm.$^{-1}$ (in chloroform) (H-bonded ester). This gave a deep purple colour with ferric chloride (cf. above).

Ethyl 2-Bromomethyl-6-hydroxy-4-methoxybenzoate.—(*a*) A refluxing solution of dried ethyl everninate (2·0 g.) in carbon tetrachloride (30 c.c.) was treated with bromine (1·53 g., 1 mol.) in carbon tetrachloride (10 c.c.) during 30 min. After 15 minutes' further refluxing the solvent was evaporated under reduced pressure; the residue crystallised from light petroleum (b. p. 60—80°) to give *ethyl 2-bromomethyl-6-hydroxy-4-methoxybenzoate* (1·7 g.), as needles, m. p. 92—93·5° (Found: C, 45·8; H, 4·9. $C_{11}H_{13}O_4Br$ requires C, 45·7; H, 4·5%), $\lambda_{max.}$ 208 (ε 11,200), 224 (ε 17,700), 266 (ε 7100), and 312 mμ (ε 4900), $\nu_{max.}$ 1650 (in Nujol), $\nu_{max.}$ 1661 cm.$^{-1}$ (in chloroform) (H-bonded ester). It gave a pale reddish-brown colour with ferric chloride (cf. above).

(*b*) Crop B from the bromination of ethyl everninate in the presence of methanol recrystallised from light petroleum (b. p. 60—80°), to give ethyl 2-bromomethyl-6-hydroxy-4-methoxybenzoate (0·6 g.) as needles, m. p. and mixed m. p. 92—93°. The preparations had identical infrared spectra in Nujol mull.

Ethyl 3-Bromo-4,6-dimethoxy-2-methylbenzoate.—(*a*) Ethyl 3-bromo-6-hydroxy-4-methoxy-2-methylbenzoate (250 mg.) in methanol (10 c.c.) with an excess of ethereal diazomethane (2 hr.) gave *ethyl 3-bromo-4,6-dimethoxy-2-methylbenzoate* (190 mg.), prisms [from light petroleum (b. p. 40—60°)], m. p. 83—84·5° (Found: C, 47·3; H, 4·85. $C_{12}H_{15}O_4Br$ requires C, 47·5; H, 5·0%), $\lambda_{max.}$ 207 (ε 35,400) and 288 mμ (ε 3300), $\nu_{max.}$ 1715 (in Nujol), $\nu_{max.}$ 1721 cm.$^{-1}$ (in chloroform) (ester C=O).

(*b*) 3-Bromo-4,6-dimethoxy-2-methylbenzoic acid [4] similarly gave prisms, m. p. 80—82° not depressed on admixture with preparation (*a*), which had the same infrared spectrum in Nujol mull.

7-Hydroxy-5-methoxyphthalide —(*a*) 4-Bromo-7-hydroxy-5-methoxyphthalide (1·5 g.) was dissolved in warm 2N-aqueous sodium hydroxide (40 c.c.), and the cooled solution was shaken at room temperature and atmospheric pressure in the presence of palladised calcium carbonate (2·5 g.; 2% of palladium hydroxide). Absorption of hydrogen was complete after *ca.* 1½ hr.; then the mixture was filtered, the filtrate acidified (Congo-red) with hydrochloric acid (*d* 1·15), and the precipitate separated, washed with water, and dried. Crystallisation from acetone–light petroleum (b. p. 60—80°) gave *7-hydroxy-5-methoxyphthalide* (830 mg., 77%) as prisms, m. p. 186—188° (Found: C, 60·1; H, 4·7. $C_9H_8O_4$ requires C, 60·0; H, 4·5%), $\lambda_{max.}$ 217 (ε 37,800), 255 (ε 15,600), and 291 mμ (ε 4300); $\nu_{max.}$ 1733 (in Nujol), 1748 cm.$^{-1}$ (in chloroform) (H-bonded phthalide C=O). This gave a purple colour with ferric chloride (cf. above).

(*b*) A solution of ethyl 2-bromomethyl-6-hydroxy-4-methoxybenzoate (400 mg.) in dioxan (8 c.c.) was treated with water (2 c.c.), and the solution refluxed for 24 hr., concentrated under reduced pressure, allowed to cool, and filtered. Recrystallisation of the product from acetone–light petroleum (b. p. 60—80°) gave 7-hydroxy-5-methoxyphthalide (250 mg., 90%) as prisms, m. p. and mixed m. p. 185—187°, identical in infrared spectrum with preparation (*a*) in Nujol mull.

5,7-Dimethoxyphthalide.—5,7-Dihydroxyphthalide in methanol (10 c.c.) with ethereal diazomethane (*ca.* 1 hr.) gave 5,7-dimethoxyphthalide as needles (from chloroform–methanol), m. p. and mixed m. p. 151—153° (lit.,[4] m. p. 151—153°). The specimens had identical infrared spectra in Nujol [$\nu_{max.}$ 1748 (in Nujol), 1761 cm.$^{-1}$ (in chloroform) (phthalide C=O)].

5,7-Dimethoxyphthalide was also prepared by the action of diazomethane on 7-hydroxy-5-methoxyphthalide in 80% yield, and by hydrogenolysis (palladium–calcium carbonate) of 4,6-dibromo-5,7-dimethoxyphthalide in 75% yield or of 6-bromo-5,7-dimethoxyphthalide in 70% yield.

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