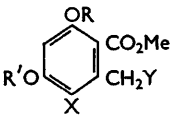
850. *Lactones. Part VII.*[1] *The Synthesis of 5-Hydroxy-7-methoxyphthalide*

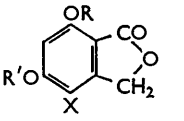
By E. M. Howells and G. T. Newbold

The synthesis of 5-hydroxy-7-methoxyphthalide (X) described here was carried out in 1959, when it was believed that the phenolic phthalide isolated from *Helichrysum arenarium* (Dr. V. Herout, personal communication) had that structure. Subsequently the Czech workers assigned the structure 7-hydroxy-5-methoxyphthalide (XIV) to the natural product,[2] this compound having been previously prepared by Allison and Newbold.[1]

Mild alkaline hydrolysis[3] of methyl 3-methoxy-4-methoxycarbonyl-5-methylphenyl carbonate (I) yielded methyl 4-hydroxy-6-methoxy-2-methylbenzoate [methyl isoeverninate (II)]. Photobromination of compound (II) using 1 mol. of bromine gave methyl 3-bromo-4-hydroxy-6-methoxy-2-methylbenzoate (III). The structure of compound (III) was proved by its ready conversion with diazomethane into the known[4] methyl 3-bromo-4,6-dimethoxy-2-methylbenzoate (IV). The position of substitution of the bromo-group into structure (II) contrasts with the photo-monobromination of ethyl everninate [cf. compound (V)] which gave the side-chain substitution product [cf. compound (VI)] under identical conditions.[1] The difference could be accounted for by the steric effect on the 3-position of the bulky methoxy-group in the 4-position as in compound (V). Methyl



(I) R = Me, R′ = CO·OMe, X = Y = H
(II) R = Me, R′ = X = Y = H
(III) R = Me, R′ = Y = H, X = Br
(IV) R = R′ = Me, X = Br, Y = H
(V) R = H, R′ = Me, X = Y = H
(VI) R = H, R′ = Me, X = H, Y = Br
(VII) R = Me, R′ = H, X = Y = Br



(VIII) R = Me, R′ = H, X = Br
(IX) R = R′ = Me, X = Br
(X) R = Me, R′ = X = H
(XI) R = R′ = Me, X = H
(XII) R = Me, R′ = CO·Me, X = Br
(XIII) R = Me, R′ = CO·Me, X = H
(XIV) R = H, R′ = Me, X = H

isoeverninate with 2 mol. bromine under similar conditions gave methyl 3-bromo-2-bromomethyl-4-hydroxy-6-methoxybenzoate (VII) which, on prolonged reflux in aqueous dioxan, yielded 4-bromo-5-hydroxy-7-methoxyphthalide (VIII). The structure of the compounds (VII) and (VIII) was confirmed by the conversion of compound (VIII) by diazomethane into the known[4] 4-bromo-5,7-dimethoxyphthalide (IX). Attempts to reductively dehalogenate 4-bromo-5-hydroxy-7-methoxyphthalide to 5-hydroxy-7-methoxyphthalide (X) by shaking its ethyl acetate solution with palladium or platinum catalysts in the presence of magnesium oxide in an atmosphere of hydrogen were unsuccessful. This was probably due to the low solubility of compound (VIII), which necessitated the use of a very dilute solution; this was supported by the fact that 4-bromo-5,7-dimethoxyphthalide (IX), normally easily hydrogenolysed to 5,7-dimethoxyphthalide (XI), did not react in similarly dilute ethyl acetate solution. The conversion of 4-bromo-5-hydroxy-7-methoxyphthalide (VIII) into compound (X) can be smoothly effected by acetylation of compound (VIII), forming the 5-acetoxy-compound (XII) which was readily catalytically dehalogenated to 5-acetoxy-7-methoxyphthalide (XIII). This, on alkaline

[1] Part VI. W. R. Allison and G. T. Newbold, *J.*, 1959, 3335.
[2] J. Vrkoč, V. Herout, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1959, **24**, 3938.
[3] E. Fischer and K. Hoesch, *Annalen*, 1912, **391**, 347.
[4] W. R. Logan and G. T. Newbold, *J.*, 1957, 1946.

hydrolysis, afforded 5-hydroxy-7-methoxyphthalide (X), methylation of which with diazomethane gave the known 5,7-dimethoxyphthalide (XI).

Experimental.—Methyl 4-hydroxy-6-methoxy-2-methylbenzoate (methyl isoeverninate). Methyl 3-methoxy-4-methoxycarbonyl-5-methylphenyl carbonate [3] (1·4 g.) was dissolved in methanol (11·2 c.c.), treated with 1N-aqueous sodium hydroxide (22·4 c.c.) with shaking, and set aside for 2 hr. On acidification and standing, crystalline material separated. Recrystallisation from benzene–light petroleum (b. p. 60—80°) gave *methyl 4-hydroxy-6-methoxy-2-methylbenzoate* (0·9 g., 91%) as plates, m. p. 111—112° (Found: C, 60·9; H, 6·2. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·2%).

The same compound as plates, separating from benzene–light petroleum (b. p. 60—80°), m. p. and mixed m. p. 111—112°, with identical infrared spectrum, was obtained (28% yield) as the alkali-soluble product from methylation of methyl 3-hydroxy-4-methoxycarbonyl-5-methylphenyl carbonate [3] in ether–methanol with diazomethane. The neutral product of the same reaction was methyl 3-methoxy-4-methoxycarbonyl-5-methylphenyl carbonate,[3] m. p. and mixed m. p. 85—86°.

Methyl 3-bromo-4-hydroxy-6-methoxy-2-methylbenzoate. Methyl 4-hydroxy-6-methoxy-2-methylbenzoate (0·177 g.) dissolved in dry carbon tetrachloride (30 c.c.) was maintained under reflux and irradiated by a 150-w tungsten lamp. Bromine (0·144 g., 1 mol.) in dry carbon tetrachloride (0·90 c.c.) was added dropwise over 10 min. Refluxing was continued for 20 min. Removal of the solvent under reduced pressure yielded a residue which on recrystallisation from light petroleum (b. p. 60—80°) gave *methyl 3-bromo-4-hydroxy-6-methoxy-2-methylbenzoate* (0·15 g., 60%) as needles, m. p. 134—135° (Found: C, 43·8; H, 4·3. $C_{10}H_{11}BrO_4$ requires C, 43·7; H, 4·0%).

Methylation of the product with diazomethane and crystallisation from aqueous methanol gave methyl 3-bromo-4,6-dimethoxy-2-methylbenzoate in high yield as needles, m. p. and mixed m. p. 120—121° (lit.,[4] 120—121°), having infrared spectrum in Nujol identical with that of an authentic specimen.

Methyl 3-bromo-2-bromomethyl-4-hydroxy-6-methoxybenzoate. Methyl 4-hydroxy-6-methoxy-2-methylbenzoate (1·3 g.), dissolved in dry carbon tetrachloride (30 c.c.), was maintained under reflux and irradiated by a 150-w tungsten lamp. Bromine (2·12 g., 2 mol.) in dry carbon tetrachloride (13·1 c.c.) was added dropwise over 30 min. and refluxing was continued for a further 1 hr. The solvent was removed under reduced pressure. The residue crystallised from light petroleum (b. p. 60—80°) to give *methyl 3-bromo-2-bromomethyl-4-hydroxy-6-methoxybenzoate* (1·48 g., 62%) as prisms, m. p. 160—161° (Found: C, 34·3; H, 3·1; Br, 44·8. $C_{10}H_{10}Br_2O_4$ requires C, 33·9; H, 2·8; Br, 45·1%).

Any appreciable cutting down of the ratio of carbon tetrachloride to solute affected the yield adversely.

4-Bromo-5-hydroxy-7-methoxyphthalide. Methyl 3-bromo-2-bromomethyl-4-hydroxy-6-methoxybenzoate (0·95 g.) was dissolved in dioxan (30 c.c.) and water (20 c.c.) and heated under reflux for 44 hr. The solvent was removed under reduced pressure. White material separated and was recrystallised from chloroform–acetone to give *4-bromo-5-hydroxy-7-methoxyphthalide* (0·63 g., 89%) as an amorphous solid, m. p. 290° (decomp.) (Found: C, 42·0; H, 3·0; Br, 30·7. $C_9H_7BrO_4$ requires C, 41·7; H, 2·7; Br, 30·8%). The material was sparingly soluble in chloroform.

Methylation of the phthalide with diazomethane followed by crystallisation from light petroleum (b. p. 60—80°) gave 4-bromo-5,7-dimethoxyphthalide in good yield as needles, m. p. and mixed m. p. 246—248° (lit.,[4] 246—248°), having infrared spectrum in Nujol identical with an authentic spectrum.

5-Acetoxy-4-bromo-7-methoxyphthalide. 4-Bromo-5-hydroxy-7-methoxyphthalide (0·14 g.) was dissolved in acetic anhydride (5 c.c.) containing concentrated sulphuric acid (1 drop). The solution was heated on a steam-bath for 2½ hr., poured into cold water, and set aside for 30 min. The precipitated solid was collected and recrystallised from benzene–light petroleum (b. p. 60—80°) to give 5-acetoxy-4-bromo-7-methoxyphthalide (0·12 g., 74%) as plates, m. p. 142—143° (Found: C, 43·7; H, 3·4. $C_{11}H_9BrO_5$ requires C, 43·9; H, 3·1%).

5-Acetoxy-7-methoxyphthalide. 5-Acetoxy-4-bromo-7-methoxyphthalide (0·45 g.,) was dissolved in dry ethyl acetate (35 c.c.) and shaken with hydrogen for 40 hr. at room temperature and atmospheric pressure in the presence of pre-reduced Adams catalyst (0·45 g.) and magnesium

oxide (0·8 g.). Filtration and extraction of the residual solid with chloroform (3 × 50 c.c.) yielded, on evaporation of the combined liquids, a white amorphous solid which was recrystallised from benzene–light petroleum (b. p. 60—80°) to give *5-acetoxy-7-methoxyphthalide* (0·27 g., 81%) as stout needles, m. p. 161—162° (Found: C, 59·3; H, 4·9. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%).

5-Hydroxy-7-methoxyphthalide. 5-Acetoxy-7-methoxyphthalide (0·28 g.) was dissolved in 1N-potassium hydroxide (9 c.c.) and heated on a steam-bath for 1½ hr. The solution was cooled and acidified (Congo Red), and the material which separated on further cooling was collected and recrystallised from methanol to give 5-hydroxy-7-methoxyphthalide (0·19 g., 82%) as prisms, m. p. 280—283° (decomp., in a sealed tube) (Found: C, 60·1; H, 4·8. $C_9H_8O_4$ requires C, 60·0; H, 4·5%).

Methylation of the phthalide with diazomethane followed by crystallisation from chloroform–light petroleum (b. p. 60—80°) afforded 5,7-dimethoxyphthalide in good yield as needles, m. p. and mixed m. p. 151—153° (lit.,[4] 151—153°), having infrared spectrum in Nujol identical with that of an authentic specimen.

We thank Professor P. L. Pauson for his interest and the D.S.I.R. for an Award (to E. M. H.).

THE UNIVERSITY OF STRATHCLYDE, GLASGOW C.1.

[Present addresses: (E. M. H.) THE JOHN DALTON COLLEGE OF TECHNOLOGY, MANCHESTER 1. (G. T. N.) CHESTERFORD PARK RESEARCH STATION, FISONS PEST CONTROL, LTD., NR. SAFFRON WALDEN, ESSEX. [*Received, January 6th,* 1965.]