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THE IDENTIFICATION AND CHARACTERIZATION OF *ORTHO*-DIHYDRIC PHENOLS

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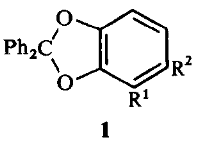
Whilst the benzene-1,2-diol grouping is readily recognized by its chromatographic behaviour on silica impregnated with sodium tetraborate, and the colourations given with iron-III chloride are sometimes diagnostic, a formal proof of this structure requires the preparation of a characteristic derivative. Although dichlorodiphenylmethane reacts readily with benzene-1,2-diol to give the diphenymethylenedioxy (1:1) cyclized product (**1**; $R^1 = R^2 = H$) [1], there have been few examples in natural product chemistry of the use of this reagent for the characterization or identification of *ortho*-dihydric phenols, possibly because the methods employed [2, 3] have been too severe [3] (heating at 170–180°) or unsatisfactory, with the formation of by-products [2, 4]. The structure **2** of the isocoumarin reticulol, since confirmed by synthesis [5], was originally assigned [6] on the basis of a negative reaction with the reagent, a somewhat dangerous assumption since on structure **2** a reaction giving a (1:2) product might have been expected.

As part of a wider investigation of methods for the identification and characterization of *ortho*-dihydric phenols, we have examined the course and scope of this reaction with a number of model compounds, using relatively mild conditions, and have obtained [7] the derivative (**3**, RR = Ph_2C) from fusarentin 6-methyl ether (**3**, R = H).

When equimolar quantities of the reactants were heated at 100°, the desired (1:1) product was obtained in acceptable yield from benzene-1,2-diol in 0.25 hr, from methyl 3,4-dihydroxybenzoate in 1.5 hr, and from methyl 2,3-dihydroxybenzoate in 4 hr. Under milder conditions, more suited to acid-sensitive materials, the product (**1**; $R^1 = R^2 = H$) was obtained after 1 hr heating under reflux in benzene in the presence of potassium carbonate, but methyl 3,4-dihydroxybenzoate required 6 hr, and methyl 2,3-dihydroxybenzoate and fusarentin 6-methyl ether [7] required 18–30 hr heating in toluene. Under these conditions, methyl 2,4-dihydroxybenzoate gave the (1:2) product **4**, but reticulol was recovered unchanged, confirming the earlier observation [6].

The unreliability of the iron-III colour reaction as a diagnostic test is demonstrated by the different results obtained with reticulol and the (±)-3,4-dihydroisocoumarin (**5**), obtained by catalytic hydrogenation of reticulol. Whereas **5** gave the reddish-purple colour characteristic of resorcylic acid derivatives, as has been



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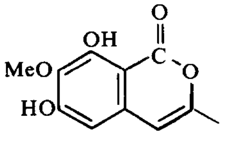

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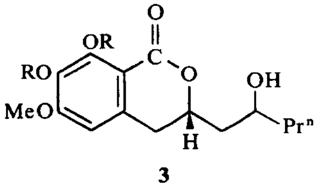

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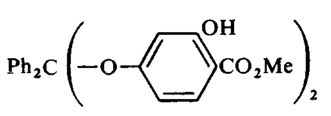

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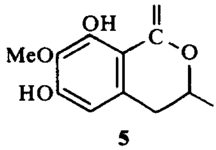

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reported [8] for the naturally-occurring (−)-isomer, reticulol gave the same intense blue-green colour given by the dihydroisocoumarin (**3**, R = H) and methyl 2,3-dihydroxybenzoate. Chromatographic behaviour on borate-impregnated plates, on the other hand, appeared to be a reliable guide to the presence of the benzene-1,2-diol group in these compounds.

EXPERIMENTAL

Mps were taken on a Kofler hot-stage apparatus and are corr. MWs and compositions were obtained from mass spectra recorded with a Varian CH5D (double-focusing) mass spectrometer coupled to a Varian 620L computer. Merck silica gel HF_{254}, and HF_{254} impregnated with 2% sodium tetraborate, were used in TLC and the R_f values quoted are for $CHCl_3$–MeOH (19:1). In PLC Si layers (20 × 20 × 0.075 cm) were developed in this solvent. Petrol had bp 40–60°.

Reactions were carried out with equimolar quantities at the 0.1 mmol level according to the following procedures:

(A) The diol and dichlorodiphenylmethane, in a small tube closed by a drying tube, were heated at 100°. At intervals the mixture was examined by TLC using the diol as standard. The crude product was quickly washed with petrol, dissolved in EtOAc and extracted with cold N NaOH. The recovered neutral fraction was further purified by PLC. Benzene-1,2-diol in 0.25 hr gave the derivative (**1**; $R^1 = R^2 = H$), prisms (MeOH), mp 94° (lit. [1] 93°). (Found: M, 274. Calc. for $C_{19}H_{14}O_2$: M, 274). Methyl 3,4-dihydroxybenzoate, R_f 0.23 (borate R_f 0.00) in 1.5 hr gave the derivative (**1**; $R^1 = H$, $R^2 = CO_2Me$) prisms, mp 100–102°, R_f 0.70, ν_{max} 1710 cm^{-1}. (Found: C, 76.0; H, 5.3%; M, 332. $C_{21}H_{16}O_4$ requires: C, 75.9; H, 4.9%; M, 332). Methyl 2,3-dihydroxybenzoate, R_f 0.55 (borate R_f 0.01) in 4 hr gave the derivative (**1**; $R^1 = CO_2Me$, $R^2 = H$), needles, mp 85–88°, R_f 0.71, ν_{max} 1715 cm^{-1}. (Found: C, 75.9; H, 4.9%; M, 332. $C_{21}H_{16}O_4$ requires: C, 75.9; H, 4.9%; M, 332). Methyl 2,4-dihydroxybenzoate, R_f 0.52 (borate R_f 0.52) yielded no product after 4 hr.

(B) The diol and dichlorodiphenylmethane were heated under reflux in an aromatic hydrocarbon solvent (2–3 ml) in the presence of K_2CO_3. When the reaction was complete (TLC), the solvent was removed *in vacuo* and the residue, in EtOAc, was washed with cold N NaOH, as before, and recovered. The following derivatives were obtained: (**1**; $R^1 = R^2 = H$), C_6H_6, 1 hr: (**1**; $R^1 = H$, $R^2 = CO_2Me$), C_6H_6, 6 hr; (**1**; $R^1 = CO_2Me$, $R^2 = H$), toluene, 18 hr. Methyl 2,4-dihydroxybenzoate after 24 hr in toluene gave the derivative **4**, prisms (MeOH), mp 180–181°, ν_{max} ($CHCl_3$) 3160, 1665, 1615, 1575 cm^{-1}. (Found: C, 69.1; H, 4.5%. $C_{29}H_{24}O_8$ requires: C, 69.6; H, 4.8%). It gave a reddish-brown colour with $FeCl_3$ in aq. EtOH. The parent ion in the MS occurred at *m/e* 333. Reticulol, R_f 0.48 (borate R_f 0.48), was recovered after 24 hr in toluene.

(±) 3,4-*Dihydro*-6,8-*dihydroxy*-7-*methoxy*-3-*methylisocoumarin* (**5**). Reticulol (4 mg) in EtOAc (2 ml) was hydrogenated in the presence of 5% Pd–C (5 mg). The recovered product crystallized from EtOAc–petrol in prisms, mp 120°, ν_{max} (Nujol) 3350, 1650, 1650, 1630, 1590 cm^{-1}, λ_{max} (MeOH) 219, 274, ν 312 nm of the dihydroisocoumarin (**5**), R_f 0.46 (borate R_f 0.46). (Found: M, 224.0685. $C_{11}H_{12}O_5$ requires: M, 224.0685). The (−)-form [8] has mp 148°.

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