

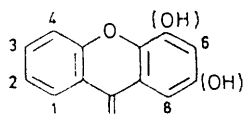
The Chemistry of Fungi. Part LXX.¹ Synthesis of Some Xanthenes

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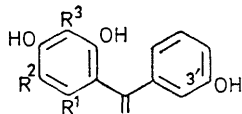
Oxidation with hexacyanoferrate(III) of 2,3',4,6-tetrahydroxybenzophenone (2; R¹ = OH, R² = R³ = H) gave 1,3,7-trihydroxyxanthone (3; R¹ = OH, R² = R³ = H) by a *para*-intramolecular coupling; other 2,3'-hydroxylated benzophenones reacted similarly. The same reagent and 2,4,5'-trihydroxy-2'-methoxy-3-methylbenzophenone (7; R¹ = R² = Me, R³ = H) formed 6-hydroxy-4a-methoxy-5-methylxanthen-2(4aH),9-dione (12) which was aromatised (i) by hydrochloric acid to 4-chloro-2,6-dihydroxy-5-methylxanthone (11) and (ii) by zinc and acetic acid to 2,6-dihydroxy-5-methylxanthone (3; R¹ = R² = H, R³ = Me). Other 2,5'-hydroxylated benzophenones behaved similarly. Whereas hexacyanoferrate(III) produced 1,4,6-trihydroxy-5-methylxanthone (14; R² = H, R¹ = Me) from 2,2',4,5'-tetrahydroxy-3-methylbenzophenone (7; R¹ = R³ = H, R² = Me), the same ketone with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone gave 2-(2,4-dihydroxy-3-methylbenzoyl)-*p*-benzoquinone (8), which rapidly formed 1,4,6-trihydroxy-5-methylxanthone (14; R¹ = Me, R² = H) by an internal Michael addition. Similar results were obtained with cognate benzophenones.

As a result of our interest in complex xanthenes of fungal origin,² we have investigated the oxidative coupling of hydroxylated benzophenones as a general route to xanthenes.³ This process may simulate certain biosynthetic pathways to xanthenes. Similar, but essentially complementary investigations have been reported,⁴ together with appropriate theoretical considerations.

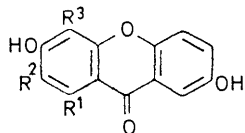
Many naturally occurring xanthenes have oxygen functions at C-5 or C-7, as in formula (1), and may be derived from an appropriate 2,3'-hydroxylated benzophenone by an oxidative, free radical, *ortho*- or *para*-coupling. In this context, oxidation of 2,3',4,6-tetrahydroxybenzophenone (2; R¹ = OH, R² = R³ = H) with potassium hexacyanoferrate(III) solution gave 1,3,7-trihydroxyxanthone (3; R¹ = OH, R² = R³ = H)



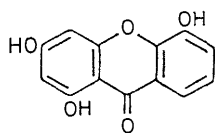
(1)



(2)



(3)



(4)

by *para*-coupling, unaccompanied by any significant quantity of the isomeric 1,3,5-trihydroxyxanthone (4) which would result from the corresponding *ortho*-coupling (*cf.* ref. 4). The orientation of structure (3; R¹ = OH, R² = R³ = H) was defined by the u.v. spectrum which is characteristic of 1,3,7-trihydroxyxanthenes, by the definitive m.p. (170–172°) of the trimethyl ether, which clearly differentiates it from the isomeric 1,3,5-trimethoxyxanthone⁵ (m.p. 219–220°), and by the n.m.r. spectrum. Variants of this system were examined.

Thus, Hoesch condensation of 3-acetoxybenzocyanide

¹ Part LXIX, M. Ahabab, A. D. Borthwick, J. W. Hooper, J. S. Millership, W. B. Whalley, G. Ferguson, and F. C. Marsh, preceding paper.

² E. J. W. Hooper, W. Marlow, W. B. Whalley, A. D. Borthwick, and R. Bowden, *J. Chem. Soc. (C)*, 1971, 3580.

with mono-*O*-methylphloroglucinol gave 3',4,6-trihydroxy-2-methoxybenzophenone (2; R¹ = OMe, R² = R³ = H). The same nitrile with 4-methylresorcinol and 2-methylresorcinol gave 2,3',4-trihydroxy-5-methyl- (2; R¹ = R³ = H, R² = Me) and 2,3',4-trihydroxy-3-methyl- (2; R¹ = R² = H, R³ = Me) benzophenones, respectively. Oxidation of the benzophenone (2; R¹ = OMe, R² = R³ = H) with hexacyanoferrate(III) gave 3,7-dihydroxy-1-methoxyxanthone (3; R¹ = OMe, R² = R³ = H), the orientation of which follows from general considerations and from spectral data. Similarly the benzophenones (2; R¹ = R³ = H, R² = Me) and (2; R¹ = R² = H, R³ = Me) furnished 2,6-dihydroxy-7-methylxanthone (3; R¹ = R³ = H, R² = Me) and 2,6-dihydroxy-5-methylxanthone (3; R¹ = R² = H, R³ = Me), respectively. Collateral evidence for these structures is described later.

Although xanthenes with oxygen at both C-5 and C-7 are of infrequent occurrence in nature, it seemed that a 2,3',5'-trihydroxybenzophenone in which the equivalent 2'- and 6'-positions are each activated by an *ortho*- and a *para*-hydroxy-group would readily couple to give a xanthone of type (6). To test this hypothesis, 2,3',4,5'-tetrahydroxy-5-methylbenzophenone (5) was prepared by the Hoesch condensation of 3,5-diacetoxybenzocyanide with 4-methylresorcinol. However, all attempts, with a variety of conditions and oxidising agents including potassium hexacyanoferrate(III), cerium(IV) sulphate, potassium peroxodisulphate, and potassium permanganate failed. No xanthone was detected and the benzophenone was recovered only partially; maybe the anticipated product (6) was rapidly degraded by the oxidation conditions (*cf.* ref. 4).

A number of naturally occurring xanthenes (including the complex xanthenes of the ergoflavin type²) contain oxygen functions at C-1 and C-4. Such a pattern may arise, *inter alia*, from a benzophenone of type (7), by *ortho*-coupling or through the intermediacy of a *para*-quinonoid system of type (8) which undergoes Michael

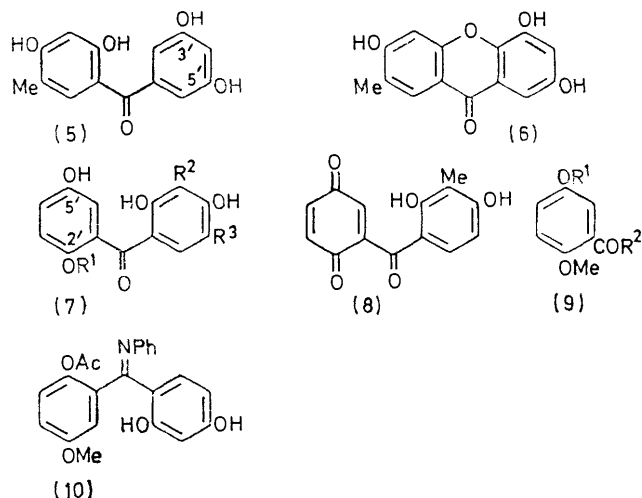
³ Preliminary communication, R. C. Ellis, W. B. Whalley, and K. Ball, *Chem. Comm.*, 1967, 803.

⁴ J. R. Lewis and B. H. Warrington, *J. Chem. Soc.*, 1964, 5074; J. E. Atkinson and J. R. Lewis, *J. Chem. Soc. (C)*, 1969, 281; J. W. A. Findlay, P. Gupta, and J. R. Lewis, *J. Chem. Soc. (C)*, 1969, 2761.

⁵ T. R. Govindachari, B. R. Pai, P. S. Subramaniam, U. R. Rao, and N. Muthukumaraswamy, *Tetrahedron*, 1967, 23, 243.

addition of the hydroxy-group. Since protection of the 2'-hydroxy-group in (7) would inhibit quinone formation, we synthesised a series of 2,5'-dihydroxy-2'-methoxybenzophenones [type (7; R¹ = Me)] by a modified Grover-Shah⁶ process. Thus, 5-hydroxy-2-methoxybenzoic acid was converted successively into the acetate (9; R¹ = Ac, R² = OH), the acid chloride (9; R¹ = Ac, R² = Cl), and thence the anilide (9; R¹ = Ac, R² = NPh). Treatment of this anilide with phosphorus pentachloride formed the chloro-imine which was condensed with the desired phenol to yield the imine of type (10). Hydrolysis of this with acid produced the benzophenone; the overall yield in the sequence was high.

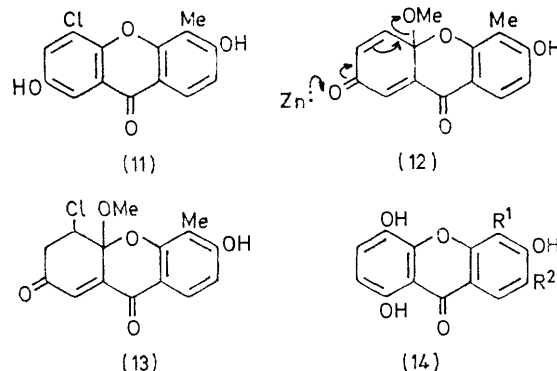
Oxidation with potassium hexacyanoferrate(III) of 2,4,5'-trihydroxy-2'-methoxy-3-methylbenzophenone (7; R¹ = R² = Me, R³ = H) produced by the chloro-imine process, gave a small quantity of 2,6-dihydroxy-5-methylxanthone (3; R¹ = R² = H, R³ = Me). The major product from this oxidation was a substance which we formulate on the basis of chemical and spectroscopic



evidence as 6-hydroxy-4a-methoxy-5-methylxanthone-2(4aH),9-dione (12), formed by coupling *para* to the hydroxy-group [λ_{\max} 228 (log ϵ 4.4), 283 (3.87), 332 (3.68), and 355–395 nm (3.61), τ 7.75 (3 H, s, ArCH₃), 6.63 (3 H, s, OCH₃), 3.45 (1 H, d, *J* 10 Hz), 2.99 (1 H, d, *J* 10 Hz), 2.70 (1 H, s), 2.70 (1 H, d, *J* 8 Hz), and 2.15 (1 H, d, *J* 8 Hz)]. In accord with this view, treatment of (12) with zinc and acetic acid gave (quantitatively), 2,6-dihydroxy-5-methylxanthone, identical with (3; R¹ = R² = H, R³ = Me) derived from oxidative coupling of 2,3',4-trihydroxy-3-methylbenzophenone (2; R¹ = R² = H, R³ = Me). This correlation provides compelling evidence for the structure of this (and cognate) xanthenes. The genesis of (3; R¹ = R² = H, R³ = Me) proceeds from (12) in the presence of zinc as indicated. Aromatisation of (12) also occurred on treatment with hydrochloric acid to yield a substance formulated as 4-chloro-2,6-dihydroxy-5-methylxanthone (11). The spectral data of (11) and those of its dimethyl ether (Experimental section) are compatible

with the derivation of (11) by way of the intermediate (13).

Treatment of the dienone (12) with dilute base yielded 2,6-dihydroxy-5-methylxanthone (3; R¹ = R² = H, R³ = Me) in moderate yield, a process which probably



explains the production of this xanthone in low yield from the oxidation of (7; R¹ = R² = Me, R³ = H) with hexacyanoferrate(III). The dienone (12) was produced, but in low yield, by oxidation of the benzophenone (7; R¹ = R² = Me, R³ = H) with chromium(VI) oxide or with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

Analogous products were obtained from the action of potassium hexacyanoferrate(III) upon 2'-methoxy-5-methyl-2,4,5'-trihydroxy- and 2'-methoxy-2,4,5'-trihydroxy-benzophenone.

To complete this investigation we examined the oxidation of several 2,2',5'-trihydroxybenzophenones. Demethylation of 2,4,5'-trihydroxy-3-methyl-2'-methoxybenzophenone (7; R¹ = R² = Me, R³ = H) gave 2,2',4,5'-tetrahydroxy-3-methylbenzophenone (7; R¹ = R² = H, R³ = Me), which furnished, by oxidation with hexacyanoferrate(III), a low yield of 1,4,6-trihydroxy-5-methylxanthone (14; R¹ = Me, R² = H), by *ortho*-coupling, together with traces (t.l.c.) of 2,6-dihydroxy-5-methylxanthone, by *para*-coupling. The structure of (14; R¹ = Me, R² = H) is uniquely defined by the positive reaction with iron(III) and comparison with an authentic sample, synthesised by a standard procedure. Oxidation of the benzophenone (7; R¹ = R³ = H, R² = Me) with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, at 0 °C, gave an unstable compound which we regard as 2-(2,4-dihydroxy-3-methylbenzoyl)-*p*-benzoquinone (8) for the reasons that: (i) this substance melted at 150°, resolidified, and remelted 295–300° (decomp.); the material obtained after resolidification was 1,4,6-trihydroxy-5-methylxanthone; (ii) with iron(III) it gave a red colouration which changed (20 min) to green (characteristic of 1-hydroxyxanthenes); (iii) the i.r. spectrum showed ν_{\max} 3 320, 3 120, 3 045, 1 650, 1 620, and 1 595 cm⁻¹; *cf.* for 1,4,6-trihydroxy-5-methylxanthone, ν_{\max} 3 400, 3 220, 1 650, 1 630, 1 620, and 1 590 cm⁻¹; (iv) the u.v. spectrum showed λ_{\max} 208 (log ϵ 4.30), 220 (4.29), 240infl (4.16), 282infl (3.86), and

⁶ P. K. Grover, G. D. Shah, and R. C. Shah, *J. Chem. Soc.*, 1955, 3982.

340—400 nm (3.69), which had changed after 40 min to λ_{\max} 233 (log ϵ 4.24), 254 (4.16), 283 (4.07), 316 (3.76), and 390 nm (3.67); cf. the similar values, λ_{\max} 231 (log ϵ 4.34), 255 (4.19), 282 (4.18), 317 (3.80), and 385 nm (3.81) for 1,4,6-trihydroxy-5-methylxanthone: (v) the n.m.r. spectrum showed τ [(CD₃)₂SO] 7.88 (3 H), 3.78—3.40 (3 H), 2.83 (1 H), 2.35 (1 H), and -1.03 (1 H); cf. that of 1,4,6-trihydroxy-5-methylxanthone, τ 7.77 (3 H), 3.38 (1 H), 3.02 (1 H), 2.72 (1 H), 2.08 (1 H), and -2.28 (1 H); (vi) a solution in methanol slowly deposited (quantitatively) 1,4,6-trihydroxy-5-methylxanthone. This cumulative evidence is compatible with the formation of (8) as a *p*-quinone which is readily transformed by an intermolecular Michael addition to 1,4,7-trihydroxy-5-methylxanthone, and provides confirmation of our hypothesis that one oxidative route from 2,2',4,5'-tetrahydroxybenzophenones to xanthenes may be by way of the *p*-quinonoid intermediate of type (8).

Oxidation of 2,2',4,5'-tetrahydroxy-3-methylbenzophenone (7; R¹ = R³ = H, R² = Me) or the 5'-methyl ether (7; R³ = H, R¹ = R² = Me) by chromium(VI) oxide produced a low yield of 1,4,6-trihydroxy-5-methylxanthone in each case, a reaction which probably proceeds by way of the quinone (8).

Similar results were obtained with 2,2',4,5'-tetrahydroxy- and 2,2',4,5'-tetrahydroxy-5-methylbenzophenones.

EXPERIMENTAL

The chromic acid-acetone reagent was prepared immediately prior to use by diluting Jones reagent (1 ml) with acetone (7 ml). The 'sodium hydrogen carbonate-acetone' solution used in the oxidations with hexacyanoferrate(III) was prepared by adding water (25 ml) and acetone (25 ml) to saturated aqueous sodium hydrogen carbonate (50 ml). Light petroleum refers to the fraction of b.p. 60—80°.

1,3,7-Trihydroxyxanthone.—2,3',4,6-Tetrahydroxybenzophenone (0.8 g) dissolved in *m*-sodium hydrogen carbonate (40 ml) containing acetone (5 ml) was added with stirring during 1 h to a solution of potassium hexacyanoferrate(III) (5 g) in *m*-hydrogen carbonate (100 ml). After a further 2 h the product was isolated and purified from aqueous methanol to yield 1,3,7-trihydroxyxanthone (0.5 g) in bright yellow needles, m.p. 321—323° (lit.⁷ 318°) (Found: C, 63.7; H, 3.3. Calc. for C₁₃H₈O₆: C, 63.9; H, 3.3%), λ_{\max} 218 (log ϵ 3.99), 268 (4.24), 360 (4.32), 312 (3.93), and 377 nm (3.64). The trimethyl ether formed needles, m.p. 170—172° (lit.⁸ 171—173°) [Found: C, 67.4; H, 5.1; OMe, 32.5. C₁₃H₈O₂(OMe)₃ requires C, 67.1; H, 4.9; OMe, 32.5%]. 1,3,5-Trimethoxyxanthone has m.p. 218—220°, λ_{\max} 209 (log ϵ 4.21), 242 (4.48), 255 (4.60), 303 (4.13), and 359 nm (3.85).

3,7-Dihydroxy-1-methoxyxanthone.—Prepared by condensation of *m*-acetoxybenzoyl chloride (3 g) with mono-*O*-methylphloroglucinol (3.5 g) under the conditions of the Hoesch condensation, 3',4,6-trihydroxy-2-methoxybenzophenone (1.6 g) formed pale yellow prisms, m.p. 178° (from aqueous methanol) [Found: C, 64.6; H, 4.8; OMe, 11.8. C₁₃H₈O₄(OMe) requires C, 64.6; H, 4.7; OMe, 11.9%].

A solution of this ketone (0.5 g) in aqueous sodium hydrogen carbonate-acetone (25 ml) was added dropwise to

a stirred solution of potassium hexacyanoferrate(III) (2.5 g) in the same solvent (58 ml) during 0.5 h. Extraction with ethyl acetate 12 h later gave 3,7-dihydroxy-1-methoxyxanthone (0.2 g) in pale yellow needles, m.p. >360° [Found: C, 65.5; H, 4.1; OMe, 12.4. C₁₃H₇O₄(OMe) requires C, 65.1; H, 3.9; OMe, 12.0%]. Unchanged benzophenone (65 mg) was recovered. 3,7-Diacetoxy-1-methoxyxanthone separated from benzene-light petroleum in needles, m.p. 198° (Found: C, 62.9; H, 4.0. C₁₈H₁₄O₇ requires C, 63.2; H, 4.1%).

2,6-Dihydroxy-5-methylxanthone.—Prepared by the Hoesch synthesis from *m*-acetoxybenzoyl chloride (3 g) and 2-methylresorcinol (4.4 g) in ether (75 ml) containing zinc chloride (2 g), 2,3',4-trihydroxy-3-methylbenzophenone separated from aqueous methanol in yellow plates (1.9 g), m.p. 181° (Found: C, 68.6; H, 4.8. C₁₄H₁₂O₄ requires C, 68.8; H, 5.0%).

Oxidation of this ketone as for 3',4,6-trihydroxy-2-methoxybenzophenone gave 2,6-dihydroxy-5-methylxanthone (0.6 g) in micro-prisms, m.p. 330—335° (from ethanol) (Found: C, 69.4; H, 4.3. C₁₄H₁₀O₄ requires C, 69.4; H, 4.2%). The benzophenone (0.3 g) was recovered. 2,6-Diacetoxy-5-methylxanthone separated from benzene-light petroleum in prisms, m.p. 178° (Found: C, 66.3; H, 4.2. C₁₈H₁₄O₆ requires C, 66.3; H, 4.3%). 2,6-Dimethoxy-5-methylxanthone formed needles, m.p. 184° (from benzene-light petroleum) [Found: C, 71.3; H, 5.1; OMe, 21.0. C₁₄H₈O₂(OMe)₂ requires C, 71.1; H, 5.2; OMe, 23.0%].

2,6-Dihydroxy-7-methylxanthone.—Prepared from 4-methylresorcinol (4.4 g) and *m*-acetoxybenzoyl chloride (3 g) by the Hoesch method, 2,3',4-trihydroxy-5-methylbenzophenone (3.2 g) formed yellow needles, m.p. 180° (from aqueous alcohol) (Found: C, 68.6; H, 5.0. C₁₄H₁₂O₄ requires C, 68.8; H, 5.0%).

Oxidation of this ketone (1 g) with ferricyanide gave 2,6-dihydroxy-7-methylxanthone (0.3 g) in needles, m.p. 360° (from ethanol) (Found: C, 69.2; H, 4.4. C₁₄H₁₀O₄ requires C, 69.4; H, 4.2%). 2,6-Diacetoxy-7-methylxanthone formed needles, m.p. 205° (from benzene-light petroleum) (Found: C, 66.4; H, 4.2. C₁₈H₁₄O₆ requires C, 66.3; H, 4.3%). 2,6-Dimethoxy-7-methylxanthone separated from benzene-light petroleum in needles, m.p. 181° [Found: C, 70.7; H, 5.0; OMe, 23.3. C₁₄H₈O₂(OMe)₂ requires C, 71.1; H, 5.2; OMe, 23.0%].

2,3',4,5'-Tetrahydroxy-5-methylbenzophenone.—Prepared from 3,5-diacetoxybenzoyl chloride (2 g) in acetone (30 ml) containing ammonium acetate (8 g) during 2 h with stirring, 3,5-diacetoxybenzamide (1.3 g) formed needles, m.p. 152° (from aqueous methanol) (Found: C, 55.4; H, 4.7; N, 5.9. C₁₁H₁₁NO₆ requires C, 55.7; H, 4.7; N, 5.9%).

A mixture of this amide (1.5 g) and toluene-*p*-sulphonyl chloride (2.3 g) in pyridine (4 ml) was kept at 45 °C during 2 h. On isolation, 3,5-diacetoxybenzoyl chloride separated from aqueous methanol in needles, m.p. 77° (Found: C, 60.2; H, 4.2; N, 6.3. C₁₁H₉NO₄ requires C, 60.3; H, 4.1; N, 6.4%).

Condensation of this nitrile (2 g) with 4-methylresorcinol (5 g) by the Hoesch process gave 2,3',4,5'-tetrahydroxy-5-methylbenzophenone (1.9 g) in prisms, m.p. 263—265° (Found: C, 64.6; H, 4.6. C₁₄H₁₂O₅ requires C, 64.6; H, 4.7%). 2,3',4,5'-Tetramethoxy-5-methylbenzophenone, formed by the dimethyl sulphate-boiling acetone-potassium carbonate process gave needles (quantitatively), m.p. 127°

⁷ J. Shinoda, *J. Chem. Soc.*, 1927, 1983.

⁸ M. Bergmann and P. Dangschat, *Ber.*, 1919, 52, 371.

(from benzene-light petroleum) (Found: C, 68.2; H, 6.3; OMe, 38.2. $C_{18}H_{20}O_5$ requires C, 68.3; H, 6.4; OMe, 39.2%).

5-Acetoxy-2-methoxybenzotrile.—Interaction of methyl 2,5-dihydroxybenzoate (26 g) in boiling acetone (350 ml) containing potassium carbonate (100 g) with benzyl bromide (20 ml) during 3 h gave *methyl 5-benzyloxy-2-hydroxybenzoate* (30 g) in plates, m.p. 113° (from acetone-light petroleum) (Found: C, 69.9; H, 5.4. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.5%). Methylation of this ester (30 g) with dimethyl sulphate (30 ml) in boiling acetone (400 ml) containing potassium carbonate (121 g) was completed in 6 h to yield *methyl 5-benzyloxy-2-methoxybenzoate* (31 g), which separated from light petroleum-acetone in plates, m.p. 48–50° [Found: C, 70.6; H, 5.9; OMe, 21.8. $C_{15}H_{13}O_3(OMe)$ requires C, 70.6; H, 5.9; OMe, 22.8%].

Hydrochloric acid (10N; 120 ml) was added to a solution of the preceding ester (31 g) in acetic acid (175 ml) and the mixture was warmed (70 °C) during 3 h. After dilution with water (200 ml) and extraction with ethyl acetate, 5-hydroxy-2-methoxybenzoic acid (15.2 g) was obtained as needles, m.p. 156° (from water) (for material prepared by an alternative process, lit.,⁸ m.p. 156°). *5-Acetoxy-2-methoxybenzoic acid* formed needles, m.p. 129° (from aqueous methanol) [Found: C, 57.1; H, 4.7; OMe, 14.6. $C_9H_7O_4(OMe)$ requires C, 57.1; H, 4.8; OMe, 14.8%].

Prepared by the thionyl chloride method, 5-acetoxy-2-methoxybenzoyl chloride (6.9 g) in acetone (50 ml) was stirred for 1.5 h with ammonium acetate (27 g) to yield *5-acetoxy-2-methoxybenzamide* (3.2 g), which formed plates, m.p. 136° (from water) (Found: C, 57.6; H, 5.1; N, 6.9. $C_{10}H_{11}NO_4$ requires C, 57.4; H, 5.3; N, 6.7%).

Dehydration of this amide (3 g) with toluene-*p*-sulphonyl chloride (3.6 g) in pyridine (6 ml) at 45 °C during 2 h gave *5-acetoxy-2-methoxybenzotrile*, which formed needles (2 g), m.p. 87° (from aqueous methanol) [Found: C, 63.2; H, 4.8; N, 7.5; OMe, 16.5. $C_9H_6NO_2(OMe)$ requires C, 62.8; H, 4.8; N, 7.3; OMe, 16.2%].

2,4,5'-Trihydroxy-2'-methoxybenzophenone.—Prepared from 5-acetoxy-2-methoxybenzoyl chloride (1.2 g) and aniline (1.9 g) in benzene (10 ml) during 2 h, *5-acetoxy-2-methoxybenzanilide* (1.2 g) formed prisms, m.p. 128° (from aqueous methanol) (Found: C, 66.9; H, 5.2; N, 4.9. $C_{16}H_{15}NO_4$ requires C, 67.4; H, 5.3; N, 4.9%). A mixture of this anilide (3 g), phosphorus pentachloride (3 g), and toluene (30 ml) was refluxed during 12 h. Removal of solvent under reduced pressure left *N*-[(5-acetoxy-2-methoxyphenyl)chloromethylene]aniline (3 g) as a yellow oil which was used without further purification.

A solution of this derivative (3 g) in methylene chloride (5 ml) was added to a stirred solution of resorcinol (2.4 g) in ether (30 ml), followed by aluminium trichloride (2.2 g) dissolved in ether (20 ml). Next day, the solvents were removed *in vacuo* and hydrochloric acid (2N; 50 ml) was added cautiously to the residue. After isolation with ethyl acetate *N*-[5-acetoxy- α -(2,4-dihydroxyphenyl)-2-methoxybenzylidene]aniline (3.4 g) formed bright yellow prisms, m.p. 218° (from methanol) [Found: C, 69.8; H, 5.1; N, 3.8; OMe, 9.0. $C_{21}H_{16}NO_4(OMe)$ requires C, 70.0; H, 5.1; N, 3.7; OMe, 8.2%].

A solution of this aniline (3 g) in sulphuric acid (20%; 300 ml) was refluxed in nitrogen during 5 h. On cooling, *2,4,5'-trihydroxy-2'-methoxybenzophenone* separated and was purified from aqueous methanol to yield pale yellow needles

(1.9 g), m.p. 194° [Found: C, 64.6; H, 4.8; OMe, 11.9. $C_{13}H_9O_4(OMe)$ requires C, 64.6; H, 4.7; OMe, 11.9%].

Demethylation of this benzophenone (0.2 g) in a boiling mixture of acetic acid (3 ml) and constant b.p. hydrobromic acid (1.5 ml) during 2 h gave *2,2',4,5'-tetrahydroxybenzophenone* (0.15 g) in yellow needles, m.p. 237°, giving an intense green colouration with iron(III) in alcohol (Found: C, 63.5; H, 4.1. $C_{13}H_{10}O_5$ requires C, 63.4; H, 4.1%).

Oxidation of 2,4,5'-Trihydroxy-2'-methoxybenzophenone.—*Method A*. A solution of this benzophenone (1 g) in aqueous sodium carbonate (1M; 50 ml) was added dropwise to a stirred solution of potassium hexacyanoferrate(III) (2.4 g) in water (50 ml) during 0.5 h. After a further 0.5 h the solution was acidified with 5N-hydrochloric acid and the products were extracted with ethyl acetate. Purification of this extract from methanol gave *6-hydroxy-4a-methoxyxanthen-2(4aH),9-dione* (0.4 g) in orange needles, m.p. >360° [Found: C, 65.0; H, 4.1; OMe, 11.7. $C_{13}H_7O_4(OMe)$ requires C, 65.1; H, 3.9; OMe, 12.0%]. Preparative t.l.c. of the mother liquors on silica gave *2,6-dihydroxyxanthone* (21 mg), m.p. >360° (lit.,⁹ >360°), characterised as the *2,6-dimethyl ether*, which separated from methanol in needles, m.p. 166° [Found: C, 69.8; H, 4.9; OMe, 23.5. Calc. for $C_{13}H_6O_2(OMe)_2$: C, 70.3; H, 4.7; OMe, 24.2%] (lit.,⁹ m.p. 166–167°).

Method B. Oxidation of *2,4,5'*-trihydroxy-2'-methoxybenzophenone (0.13 g) dissolved in acetone (5 ml) by addition during 1 min of a solution (1.1 ml) of chromic acid-acetone reagent, followed by immediate dilution with water (30 ml) and extraction with ethyl acetate, gave a mixture which was separated by t.l.c. on silica to yield (*a*) *6-hydroxy-4a-methoxyxanthen-2(4aH),9-dione* (3 mg), identical (R_F , i.r., and u.v.) with that prepared by Method A; (*b*) unchanged benzophenone (48 mg), identical with an authentic specimen; and (*c*) *1,4,6-trihydroxyxanthone* (12 mg), m.p. 302–305°, identical (i.r. and u.v.) with an authentic specimen.

Method C. A solution of *2,3-dichloro-5,6-dicyanoquinone* (DDQ) (80 mg) and *2,4,5'*-trihydroxy-2'-methoxybenzophenone (130 mg) in methanol (1 ml) was maintained at 0 °C during 48 h. After isolation, the product was separated by t.l.c. on silica to yield *6-hydroxy-4a-methoxyxanthen-2(4aH),9-dione* (10 mg), identified by m.p., mixed m.p., R_F , i.r., and u.v., together with unchanged benzophenone (30 mg) (m.p., mixed m.p., and i.r. spectrum).

A solution of the xanthendione (0.1 g) in acetic acid (10 ml) containing hydrochloric acid (10N; 0.5 ml) gave *4-chloro-2,6-dihydroxyxanthone* (95 mg) in pale yellow needles, m.p. 299–302° (decomp.) (from methanol) (Found: C, 56.0; H, 3.2; Cl, 13.0. $C_{13}H_7ClO_4H_2O$ requires C, 55.6; H, 3.2; Cl, 12.6%). *4-Chloro-2,6-dimethoxyxanthone*, prepared quantitatively with dimethyl sulphate-acetone-potassium carbonate, formed needles, m.p. 185° (from methanol) [Found: C, 61.9; H, 3.9; Cl, 12.1; OMe, 21.8. $C_{13}H_5ClO_2(OMe)_2$ requires C, 62.0; H, 3.8; Cl, 12.2; OMe, 21.4%].

A solution of the xanthendione (100 mg) in *m*-sodium hydroxide (5 ml) during 10 min gave *2,6-dihydroxyxanthone* (40 mg), identical with the previously prepared specimen.

2,4,5'-Trihydroxy-2'-methoxy-5-methylbenzophenone.—Prepared from *N*-[(5-acetoxy-2-methoxyphenyl)chloromethylene]aniline (3 g) and 4-methylresorcinol (2.7 g),

⁹ O. P. Mittal and T. R. Seshadri, *J. Sci. Ind. Res., India*, 1955, **14B**, 76.

N-[5-acetoxy- α -(2,4-dihydroxyphenyl)-2-methoxy-5-methylbenzylidene]aniline formed yellow needles (3.2 g), m.p. 221—222° (from methanol) [Found: C, 70.7; H, 5.5; N, 3.4; OMe, 7.6. $C_{22}H_{18}NO_4(OMe)$ requires C, 70.6; H, 5.4; N, 3.6; OMe, 7.9%]. Hydrolysis of this aniline (3 g) as previously described gave 2,4,5'-trihydroxy-2'-methoxy-5-methylbenzophenone (1.9 g), in pale yellow needles, m.p. 199° (from aqueous methanol) [Found: C, 65.2; H, 5.2; OMe, 10.5. $C_{14}H_{11}O_4(OMe)$ requires C, 65.7; H, 5.2; OMe, 11.3%]. Prepared quantitatively with dimethyl sulphate-acetone-potassium carbonate, 2,2',4,5'-tetramethoxy-5-methylbenzophenone separated from acetone-light petroleum in needles, m.p. 130° [Found: C, 68.3; H, 6.2; OMe, 38.1. $C_{14}H_8O(OMe)_4$ requires C, 68.3; H, 6.4; OMe, 39.2%].

Demethylation of 2,4,5'-trihydroxy-2'-methoxy-5-methylbenzophenone (1.5 g) in refluxing acetic acid (21 ml) containing constant-boiling hydrobromic acid (10.5 ml) during 2 h gave 2,2',4,5'-tetrahydroxy-5-methylbenzophenone (1.1 g) in yellow needles, m.p. 244° (from aqueous methanol) (Found: C, 64.4; H, 4.6. $C_{14}H_{12}O_5$ requires C, 64.6; H, 4.7%).

Oxidation of 2,4,5'-trihydroxy-2'-methoxy-5-methylbenzophenone (1 g), by Method A, gave (i) 6-hydroxy-4a-methoxy-7-methylxanthen-2(4aH),9-dione (0.5 g) in orange needles, m.p. 201° (from methanol) [Found: C, 66.6; H, 4.7; OMe, 10.5. $C_{14}H_9O_4(OMe)$ requires C, 66.2; H, 4.4; OMe, 11.4%], and (ii) 2,6-dihydroxy-7-methylxanthone (55 mg), identical (m.p., mixed m.p., i.r., and u.v.) with an authentic sample.

Addition of zinc dust (1 g) to a solution of this xanthone (50 mg) in methanol (9 ml) containing acetic acid (1 ml), followed by boiling for 0.5 min, gave 2,6-dihydroxy-7-methylxanthone (37 mg), identical (m.p., mixed m.p., i.r., and u.v.) with the previously prepared specimen.

Hydrochloric acid (10*N*; 0.5 ml) was added to a solution of this dihydroxyxanthone (60 mg) in acetic acid (3 ml). After 10 min water (10 ml) was added; purification of the precipitate from methanol gave 4-chloro-2,6-dihydroxy-7-methylxanthone (55 mg) in pale yellow needles, m.p. 304—307° (Found: C, 60.5; H, 3.2; Cl, 13.0; OMe, 0. $C_{14}H_9ClO_4$ requires C, 60.8; H, 3.3; Cl, 12.8; OMe, 0%). Prepared quantitatively with dimethyl sulphate-acetone-potassium carbonate, 4-chloro-2,6-dimethoxy-7-methylxanthone formed prisms, m.p. 271° (from light petroleum-chloroform) [Found: C, 62.6; H, 4.5; Cl, 11.6; OMe, 19.3. $C_{14}H_7ClO_2(OMe)_2$ requires C, 63.1; H, 4.3; Cl, 11.6; OMe, 20.4%]. The dihydroxyxanthone (20 mg) was dissolved in sodium hydroxide solution (*N*; 5 ml). After 10 min the solution was carefully acidified with cold *N*-hydrochloric acid, to yield 2,6-dihydroxy-7-methylxanthone (10 mg).

Oxidation of 2,4,5'-trihydroxy-2'-methoxy-5-methylbenzophenone (0.14 g), by Method B, gave (i) 1,4,6-trihydroxy-7-methylxanthone (10 mg) in yellow needles, m.p. 309—313° (decomp.) (from methanol) (Found: C, 65.0; H, 4.2. $C_{14}H_{10}O_5$ requires C, 65.1; H, 3.9%), further characterised as the 1,4,6-trimethyl ether, which formed needles, m.p. 185° (from acetone-light petroleum) [Found: C, 67.6; H, 5.2; OMe, 32.1. $C_{14}H_7O_5(OMe)_3$ requires C, 68.0; H, 5.4; OMe, 31.0%], (ii) 6-hydroxy-4a-methoxy-7-methylxanthen-2(4aH),9-dione (2.5 mg), and (iii) unchanged benzophenone (50 mg).

Oxidation of 2,4,5'-trihydroxy-2'-methoxy-5-methylbenzophenone (0.1 g), by Method C, gave the xanthendione (2.7 mg) together with the parent benzophenone (50 mg).

2,4,5'-Trihydroxy-2'-methoxy-3-methylbenzophenone.—

Prepared from *N*-[(5-acetoxy-2-methoxyphenyl)chloromethylene]aniline (3 g) and 2-methylresorcinol (2.7 g), *N*-[5-acetoxy- α -(2,4-dihydroxyphenyl)-2-methoxy-3-methylbenzylidene]aniline formed bright yellow prisms (3 g), m.p. 187—189° (from methanol) [Found: C, 70.4; H, 5.4; N, 3.3; OMe, 8.0. $C_{22}H_{18}NO_4(OMe)$ requires C, 70.6; H, 5.4; N, 3.6; OMe, 7.9%].

Hydrolysis of this aniline (3 g) gave 2,4,5'-trihydroxy-2'-methoxy-3-methylbenzophenone in pale yellow needles (1.9 g), m.p. 210° [Found: C, 65.7; H, 5.1; OMe, 11.5. $C_{14}H_{11}O_4(OMe)$ requires C, 65.7; H, 5.2; OMe, 11.3%].

Demethylation of this benzophenone (0.2 g) with boiling acetic acid (3 ml) and hydrobromic acid (1.5 ml) during 2 h gave 2,2',4,5'-tetrahydroxy-3-methylbenzophenone (0.15 g) in pale yellow needles, m.p. 238—240° (from aqueous methanol) (Found: C, 64.4; H, 4.9. $C_{14}H_{12}O_5$ requires C, 64.6; H, 4.7%).

Oxidation of 2,4,5'-trihydroxy-2'-methoxy-3-methylbenzophenone (1 g), by Method A, gave 6-hydroxy-4a-methoxy-5-methylxanthen-2(4aH),9-dione (0.20 g) in yellow prisms, m.p. >360° (from methanol) [Found: C, 66.2; H, 4.6; OMe, 10.4. $C_{14}H_9O_4(OMe)$ requires C, 66.2; H, 4.4; OMe, 11.4%], together with 2,6-dihydroxy-5-methylxanthone (30 mg) identical with the previously prepared specimen. Reaction of this dihydroxyxanthone (100 mg) dissolved in acetic acid (10 ml) containing 10*N*-hydrochloric acid (0.5 ml) during 10 min gave 4-chloro-2,6-dihydroxy-5-methylxanthone (80 mg), which formed pale orange prisms, m.p. 334—337° (decomp.) (from ethanol) (Found: C, 61.1; H, 3.4; Cl, 12.7. $C_{15}H_9ClO_4$ requires C, 60.8; H, 3.3; Cl, 12.8%). 4-Chloro-2,6-dimethoxy-5-methylxanthone, prepared in the normal manner, formed needles, m.p. 278° (from methanol) [Found: C, 62.8; H, 4.2; Cl, 12.4; OMe, 20.5. $C_{14}H_7ClO_2(OMe)_2$ requires C, 63.1; H, 4.3; Cl, 11.6; OMe, 20.4%].

Reduction of the xanthendione (40 mg) with zinc dust (0.8 g) in acetic acid-methanol gave 2,6-dihydroxy-5-methylxanthone (33 mg), identical with an authentic specimen.

Oxidation of 2,4,5'-trihydroxy-2'-methoxy-3-methylbenzophenone (0.14 g), by Method B, gave unchanged benzophenone (43 mg) and 1,4,6-trihydroxy-5-methylxanthone (10 mg) in yellow needles, m.p. 315° (decomp.) (from methanol) (Found: C, 65.3; H, 4.1. $C_{14}H_{10}O_5$ requires C, 65.1; H, 3.9%), as the only characterisable product; use of Method C gave unchanged ketone (45 mg) and 6-hydroxy-4a-methoxy-5-methylxanthen-2(4aH),9-dione (<5 mg). The trimethyl ether was identical with an authentic specimen (q.v.).

1,4,6-Trihydroxy-5-methylxanthone.—A mixture of 2,6-dihydroxybenzoic acid (2 g) and 2-methylresorcinol (2 g) was heated at 70 °C for 2 h in a mixture of phosphoryl chloride (5 ml) and zinc chloride (2 g). Purification of the product from methanol gave 1,6-dihydroxy-5-methylxanthone (0.5 g) in yellow prisms, m.p. 259° (Found: C, 69.6; H, 4.3. $C_{14}H_{10}O_4$ requires C, 69.4; H, 4.2%). The dimethyl ether separated from acetone-light petroleum (b.p. 60—80°) in prisms, m.p. 194° [Found: C, 71.1; H, 5.2; OMe, 23.0. $C_{14}H_8O_2(OMe)_2$ requires C, 71.1; H, 5.2; OMe, 23.0%].

1-Hydroxy-6-methoxy-5-methylxanthone formed yellow needles, m.p. 196° [from benzene-light petroleum (b.p. 60—80°)] [Found: C, 70.0; H, 4.9; OMe, 12.0. $C_{14}H_9O_3(OMe)$ requires C, 70.3; H, 4.7; OMe, 12.1%]. Oxidation of this monomethyl ether by the Elbs-peroxodisulphate method gave 1,4-dihydroxy-6-methoxy-5-methylxanthone in

pale yellow needles, m.p. 238° (from methanol) [Found: C, 65.9; H, 4.5; OMe, 11.6. $C_{14}H_9O_4(OMe)$ requires C, 66.2; H, 4.4; OMe, 11.4%]. 1,4,6-Trimethoxy-5-methylxanthone formed prisms, m.p. 198° [from light petroleum (b.p. 60–80°)] [Found: C, 67.7; H, 5.5; OMe, 28.4. $C_{14}H_7O_2(OMe)_2$ requires C, 68.0; H, 5.4; OMe, 31.0%].

Oxidation of 2,2',4,5'-Tetrahydrobenzophenone.—Oxidation of this benzophenone (490 mg), by Method A, gave 1,4,6-trihydroxyxanthone (80 mg) and unchanged ketone (60 mg); Method B with the benzophenone (130 mg) gave 1,4,6-trihydroxyxanthone (36 mg), together with unchanged benzophenone (20 mg) (identical with authentic specimens). 2,3-Dichloro-5,6-dicyanoquinone (DDQ) (220 mg) was added to a solution of 2,2',4,5'-tetrahydrobenzophenone (240 mg) in ethanol (2 ml) at 0 °C (Method C). The mixture was kept overnight at 0 °C; 2-(2,4-dihydroxybenzoyl)-*p*-benzoquinone separated as orange needles (170 mg), m.p. 155–158° with solidification and remelting at 292–298°, giving a red colouration with iron(III) in alcohol, which became green during *ca.* 5 min.

When a solution of this quinone (50 mg) in methanol (10 mg) was refluxed during 10 min, 1,4,6-trihydroxyxanthone (45 mg) separated on cooling, identical (m.p., mixed m.p., i.r., and u.v.) with an authentic sample.

Oxidation of 2,2',4,5'-Tetrahydroxy-5-methylbenzophenone.

—By Method A, the benzophenone (520 mg) furnished 1,4,6-trihydroxy-7-methylxanthone (100 mg), together with unchanged ketone (100 mg); by Method B the ketone (130 mg) gave 1,4,6-trihydroxy-7-methylxanthone (47 mg). By Method C, the benzophenone (100 mg) gave 2-(2,4-dihydroxy-5-methylbenzoyl)-*p*-benzoquinone (30 mg) in deep orange prisms, m.p. 150° followed by resolidification and remelting at 295–300° (decomp.). The initial intense red-brown colouration with iron(III) in alcohol rapidly became green.

Oxidation of 2,2',4,5'-Trihydroxy-3-methylbenzophenone.—Oxidation by Method A of this ketone (350 mg) gave 1,4,6-trihydroxy-5-methylxanthone (32 mg) and unchanged benzophenone (130 mg); by Method B, the benzophenone (130 mg) gave 1,4,6-trihydroxy-5-methylxanthone (30 mg) together with parent benzophenone (8 mg). By Method C, this benzophenone (130 mg) gave 2-(2,4-dihydroxy-3-methylbenzoyl)-*p*-benzoquinone in deep yellow prisms (52 mg), m.p. *ca.* 200° with subsequent resolidification and remelting at 315° (decomp.). The initial intense red-brown colour with iron(III) soon became green.

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