Oxidative Coupling. Part VII.[1] Biogenetic Type Synthesis of Naturally Occurring Xanthones †

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The co-occurrence of isomeric xanthones in certain plant extracts suggests their derivation from a common hydroxylated benzophenone. *In vitro* oxidation of some of these benzophenones produces xanthone mixtures corresponding to oxidative coupling occurring *para* and *ortho* or *para* only to an activating hydroxy-group. The oxidations can also be carried out enzymically.

In our studies towards elucidating the biogenesis of naturally occurring xanthones found in plants, we have concentrated upon the synthesis of xanthones from benzophenones by oxidative coupling reactions carried out under mild, *i.e.*, ' physiological type ', conditions. An earlier publication (Part VI [1]) reported the facile conversion of 2,3′,4-trihydroxybenzophenone into 2,6-dihydroxyxanthone and suggested the role that may be played by oxidative coupling in xanthone biosynthesis. The co-occurrence of 2- and 4-hydroxyxanthone (II and III; R = H) in *Mammea americana* [2] pointed to a cyclisation of 2,3′-dihydroxybenzophenone (I; R = H) by oxidative coupling which occurred either *para* or *ortho* to the 3′-hydroxy-group while the isolation of 1,7- and 1,5-dihydroxyxanthone (II and III; R = OH) from the same source [2] offered a similar derivation from 2,3′,6-trihydroxybenzophenone (I; R = OH). A study of the oxidation of these benzophenones was consequently undertaken.

2,3-Dihydroxybenzophenone (I; R = H) was synthesised and purified with difficulty by direct Friedel–Crafts condensation of 3-methoxybenzoyl chloride with phenol or by Fries rearrangement of phenyl 3-methoxybenzoate, while alternative condensations with anisole followed by selective demethylation [3] did not improve the yield of the 2,3′-isomer over the 3′,4-dihydroxybenzophenone. A more productive synthesis was obtained by condensation of 3-methoxybenzoyl chloride with 2-methoxyphenylcadmium chloride to give 2,3′-dimethoxybenzophenone (23%) followed by demethylation. Oxidation of 2,3′-dihydroxybenzophenone (I; R = H) occurred with several oxidising agents but optimum conversion into xanthone took place with aqueous potassium ferricyanide solution to give a mixture of 2- and 4-hydroxyxanthone (II and III; R = H). The amount of xanthone produced varied with the quantity of oxidant and type of oxidant. Table 1 shows the effect of pH upon the oxidation using potassium ferricyanide solution.

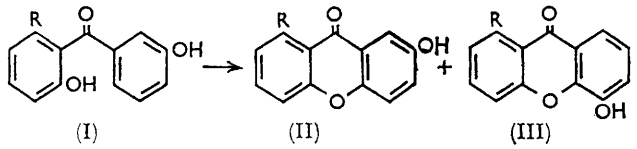
† Preliminary communication, *Chem. Comm.*, 1967, 803.

[1] Part VI, J. R. Lewis and B. H. Warrington, *J. Chem. Soc.*, 1964, 5074.

[2] R. D. Finnegan, J. V. Patel, and P. L. Bachman, *Tetrahedron Letters*, 1966, 6087.

[3] F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Letters*, 1966, 4153.

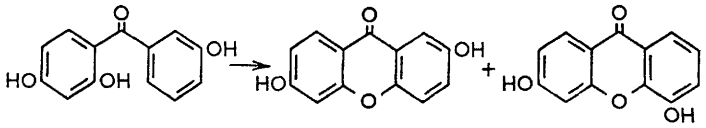
The synthesis of 2,3′,6-trihydroxybenzophenone (I; R = OH) was accomplished by condensation of 3-methoxyphenylcadmium chloride with 2,6-dimethoxybenzoyl chloride followed by demethylation. Oxidation



(I) (II) (III)

of this benzophenone (I; R = OH) could best be achieved using an aqueous acetone solution of potassium permanganate (2 mol.) which produced 1,5-dihydroxyxanthone (III; R = OH) (5%) together with 1,7-dihydroxyxanthone (II; R = OH) (32%). The use of 3 mol. of oxidising agent did not change the yield significantly, benzophenone being recovered in each case. Alkaline potassium ferricyanide gave only trace quantities of the 1,7-dihydroxyxanthone and even after prolonged oxidation most of the benzophenone was recovered unchanged.

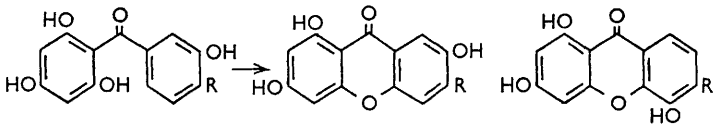
Having established the occurrence of *para* as well as *ortho* oxidative coupling, we re-examined the oxidation of 2,3′,4-trihydroxybenzophenone (IV) since our earlier synthesis of 3,5-dihydroxyxanthone (VI) was suspect.* Complete demethylation of 3-hydroxy-5-methoxyxanthone [1] now afforded 3,5-dihydroxyxanthone (VI), m.p. 315—320°, and paper chromatographic comparisons with the oxidation product of 2,3′,4-trihydroxybenzophenone (IV) showed the presence of both 2,6- and 3,5-dihydroxyxanthones [(V) and (VI) respectively].



(IV) (V) (VI)

Table 2 shows the extent of oxidation using potassium ferricyanide solution under differing pH.

We next considered the synthesis of 1,3,7-trihydroxyxanthone (gentisein) (VIII; R = H) since this xanthone occurs in *Gentiana lutea* as its 3-[4] or 7-[5]methyl ether



(VII) (VIII) (IX)

while the isomeric 1,3,5-trihydroxyxanthone (IX; R = H) has been found in *Mesua ferra* as its 3-methyl ether [6] and in *Kielmeyera coriacea* and *K. corymbosa* as its 1,3-dimethyl ether.[7] Both xanthones could arise by oxidative coupling of 2,3′,4,6-tetrahydroxybenzophenone (VII; R = H). We find that oxidation of this benzophenone (VII; R = H) yields only the *para* cyclised product and pH shows an important role in the oxidation. Table 3 summarises the effect of pH upon aqueous potassium ferricyanide oxidations of this benzophenone. Similar results concerning this oxidation were reported, in preliminary form, by Whalley and his collaborators.[8] The failure to isolate 1,3,5-trihydroxyxanthone, corresponding to *ortho*-cyclisation, appears to be due to its rapid decomposition in the oxidising media, since 1,3,7-trihydroxyxanthone can be recovered unchanged after contact with the oxidising solution at all pH except that of 13 and 14 while the 1,3,5-isomer is completely degraded.

TABLE 1

pH	8	9	10	11	12	13	14
2-Hydroxyxanthone	3*	13	27	42	52	53	52
4-Hydroxyxanthone ...	+	+	+	3	7·5	10	8
Benzophenone	+	+	+	+	+	—	—

* Expressed as %, after 1 hour's oxidation.
+ Present after 1 hour; — absent after 1 hour.

TABLE 2

pH	8	9	10	11	12	13	14
2,6-(OH)$_2$ ...	3*	24	50	75	69	82	65
3,5-(OH)$_2$ ...					13		15
Benzophenone	+	+	+	+	+	—	—

* % Yield, after 1 hour's oxidation.

TABLE 3

pH	6	7	8	9	10	11	12	13	14
1,3,7-(OH)$_3$ ...	—	2*	23	51	63	66	61	0	0
1,3,5-(OH)$_3$ ...	—	—	—	—	—	—	—	—	—
Benzophenone	+	+	+	+	—	—	—	—	—

* % Yield, after 1 hour's oxidation.

* We wish to thank Professor R. A. Finnegan for pointing out to us that the structure of our 3,5-dihydroxyxanthone was in fact 3-hydroxy-5-methoxyxanthone.

[4] A. G. Perkin, *J. Chem. Soc.*, 1898, **73**, 666.
[5] L. Canonica and F. Pelizzoni, *Gazzetta*, 1955, **85**, 1007.
[6] T. R. Govindacharic, B. R. Pai, P. S. Subramaniam, U. R. Rae, and N. Muthukumaraswamy, *Tetrahedron*, 1967, **23**, 243.
[7] O. R. Gottlieb, M. T. Magalhaes, M. Cainey, A. A. L. Mesquita, and D. B. Correa, *Tetrahedron*, 1966, **22**, 1777.
[8] (*a*) J. E. Atkinson and J. R. Lewis, *Chem. Comm.*, 1967, 803; (*b*) R. C. Ellis, W. B. Whalley, and K. Ball, *ibid.*, p. 803.
[9] H. D. Locksley, I. Moore, and F. Scheinmann, *Tetrahedron*, 1967, **23**, 2229.

Scheinmann and his collaborators [9] have isolated 1,3,6,7- and 1,3,5,6-tetrahydroxyxanthone (VIII and IX; R = OH) and the benzophenone maclurin (VII; R = OH) from *Symphonia globulifera* and have shown that

maclurin can be converted into 1,3,6,7-tetrahydroxyxanthone (VIII; R = OH) photochemically [10] or in poor yield using alkaline ferricyanide.[11] We have found a pH and time dependence upon ferricyanide oxidation of maclurin, the optimum conditions for oxidation being 2 mol. of ferricyanide under nitrogen for 5 minutes to give a 67% yield of 1,3,6,7-tetrahydroxyxanthone (VIII; R = OH); no 1,3,5,6-tetrahydroxyxanthone (IX; R = OH) could be detected. The failure to isolate any xanthone corresponding to *ortho*-cyclisation is primarily due to its extreme sensitivity to the oxidising conditions employed, it being completely destroyed in potassium ferricyanide solution at pH 14 after 5 minutes contact; the 1,3,6,7-isomer can be recovered under the same conditions.

We consider the mechanism of cyclisation of these benzophenones to involve a one-electron rather than a two-electron transfer process, since any attempt to oxidise a benzophenone with the 3′-hydroxy-group methylated resulted in no cyclisation. Thus 2-hydroxy-3-methoxybenzophenone and 2,4,6-trihydroxy-3-methoxybenzophenone were recovered unchanged after treatment, under a variety of conditions, with potassium ferricyanide, manganese dioxide, or potassium permanganate as oxidising agent. These results are compatible with current ideas regarding phenol oxidation where radical intermediates are primarily involved.[12]

In vivo oxidation of hydroxybenzophenones would most surely take place *via* enzyme participation and the action of oxidase enzymes on phenols has been reported in a number of cases to give the same oxidative cyclisations as has been found for inorganic oxidants.[13] Table 4 shows the extent to which peroxidase and the laccase

TABLE 4

Benzophenone	2,3′-$(OH)_2$	2,3′,4-$(OH)_3$	2,3′,6-$(OH)_3$	2,3′,4,6-$(OH)_4$
Peroxidase ...	*o*/*p*	*o*/*p*	*o*/*p*	—
Laccase	*p*	*o*/*p*	*p*	*p*

Benzophenone	2,3′,4,4′,6-$(OH)_5$	2-OH-3′-OMe	2,4,6-$(OH)_3$-3′-OMe
Peroxidase ...	—	—	—
Laccase	—	—	—

o/*p* both *ortho*- and *para*-cyclised products identified; *p* only *para*-cyclised xanthone; — no xanthones detected.

from *Polystictus versicolor* effect benzophenones. Since hydroxylated but not methoxylated benzophenones are oxidised to xanthones, a parallel type of mechanism involving radical intermediates in these enzyme induced oxidations [14] can be formulated.

EXPERIMENTAL

U.v. spectra were measured in ethanol solution, i.r. spectra as KBr discs or films where appropriate, while the n.m.r. spectra were measured in $CDCl_3$ solution or deuterioacetone where indicated.

2,3′-*Dihydroxybenzophenone* (I, R = H).—(a) 3-*Methoxybenzoyl chloride and phenol.* 3-Methoxybenzoyl chloride (2 g.; prepared from 3-methoxybenzoic acid and phosphorus pentachloride) and phenol (1·5 g.) were dissolved in nitrobenzene (100 ml.), freshly powdered aluminium chloride (4 g.) was added, and the temperature raised to 160° and maintained at this temperature until HCl fumes had ceased to be evolved (45 min.). The reaction mixture was cooled and poured into iced dilute hydrochloric acid solution. Extraction with ether (5 × 100 ml.) followed by washing the ethereal layer with water, drying with anhydrous magnesium sulphate, filtration, and evaporation gave a brown oil (3 g.). Distillation of this oil over the range 140—150°/0·4 mm. gave a yellow viscous oil which showed two components on thin-layer Chromatography (t.l.c.), R_F 0·7 and 0·55 (silica gel; ether). Fractional crystallisation of this oil from benzene gave 3,4′-dihydroxybenzophenone (0·3 g.), m.p. 195—200°,[15] and separation of the mother liquors on t.l.c. (silica gel; ether) followed by elution of the band corresponding to R_F 0·70 gave, after recrystallisation from benzene, 2,3′-dihydroxybenzophenone (I, R = H) (100 mg.) as needles, m.p. 124—126°,[16] $\lambda_{max.}$ 224, 263, and 333 mμ (log ε 4·21, 4·09, and 3·76), $\nu_{max.}$ (CO) 1614, (OH) 3400, 3420 cm.$^{-1}$, (2-OH) τ −1·87, (3′-OH) 1·23, R_F 0·19 (silica gel; chloroform).

(b) 3-*Methoxybenzoyl chloride and anisole.* 3-Methoxybenzoyl chloride (18 g.), anisole (12 g.), and anhydrous aluminium chloride (30 g.) were refluxed in carbon disulphide solution (150 ml.) for 2 hr. After removal of the carbon disulphide by evaporation the residue was hydrolysed with iced dilute hydrochloric acid and extracted with ether (300 ml.). Separation into a neutral (27·9 g.) and phenolic (0·6 g.) fraction was carried out and t.l.c. separation of the phenolic fraction (silica gel; benzene) gave a solid (92 mg.) at R_F 0·8 which crystallised from light petroleum (b.p. 40—60°) to give 2-*hydroxy*-3′-*methoxybenzophenone*, as needles, m.p. 40—42° (Found: C, 73·8; H, 5·5. $C_{14}H_{12}O_3$ requires C, 73·7; H, 5·3%), $\lambda_{max.}$ 225, 263, and 332 mμ (log ε 4·21, 4·06, and 3·68), $\nu_{max.}$ (CO) 1640, (OH) 3400 cm.$^{-1}$, (2-OH) τ −2·01, (3′-OCH_3) 6·14.

A portion of the neutral fraction when completely demethylated showed the presence of 2,3′- and 3,4′-dihydroxybenzophenones; consequently selective demethylation of the 2-methoxy-group was attempted. The neutral fraction (28 g.) in dry methylene chloride (100 ml.) was treated with boron trichloride (25 ml.) for 30 min. at room temperature. Hydrolytic work-up and separation gave a phenolic fraction (9 g.) which crystallised from benzene to give 3-hydroxy-4′-methoxybenzophenone, m.p. 130—133°.[17] The mother-liquor from this crystallisation was separated by preparative t.l.c. (silica gel; benzene) to give 2-hydroxy-3′-methoxybenzophenone at R_F 0·8 (172 mg.) with identical physical properties to that previously reported. 'Selective' demethylation for 5 and 15 min. on the neutral fraction (10 g.) yielded the same benzophenone in 190 and 136 mg. quantities, respectively.

[10] A. Jefferson and F. Scheinmann, *Nature*, 1965, **207**, 1193.
[11] A. Jefferson and F. Scheinmann, *J. Chem. Soc.* (*C*), 1966, 175.
[12] D. H. R. Barton, Pedler Lecture, *Chem. in Britain*, 1967, 330.
[13] A. I. Scott, *Quart. Rev.*, 1965, **19**, 1.
[14] I. Yamazaki, H. S. Mason, and L. Pietle, *J. Biol. Chem.*, 1960, **235**, 2444.
[15] R. Stoemer, *Chem. Ber.*, 1968, **41**, 321.
[16] W. Stadel, *Annalen*, 1894, **283**, 177.
[17] R. Roger and P. Damerseman, *Bull. Soc. chim. France*, 1959, 1682.

(c) *3-Methoxybenzoyl chloride and 2-methoxyphenylcadmium chloride*. 3-Methoxybenzoyl chloride (31 g.; purified by distillation at 80—83°/0·05 mm.) was dissolved in dry benzene (50 ml.) and slowly added to a decanted benzene solution of 2-methoxyphenylcadmium chloride [prepared from 2-bromoanisole (25 ml.) and magnesium turnings (4 g.) in ether (50 ml.) followed by dilution with dry benzene (150 ml.) and 24 hr. contact with powdered anhydrous cadmium chloride (18 g.)] and the mixture stirred for 0·5 hr. followed by 1 hr. reflux. Isolation of a neutral fraction (48 g.) followed by distillation gave *2,3′-dimethoxybenzophenone* (10·6 g.), b.p. 158—160°/0·05 mm. (Found: C, 74·3; H, 5·9. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%), $\lambda_{max.}$ 205sh, 218, 256, and 306 mμ (log ε 4·41, 4·51, 3·98, and 3·62), $\nu_{max.}$ (CO) 1669 cm.$^{-1}$, (2-OCH_3) τ 6·30, (3′-OCH_3) 6·19. Demethylation of the appropriate methoxybenzophenone (92 mg.) occurred by heating under reflux in chlorobenzene (20 ml.) with aluminium chloride (200 mg.) for 1 hr. Isolation of a phenolic fraction (~70 mg.) gave, after crystallisation from benzene, 2,3′-dihydroxybenzophenone (I; R = H), m.p. and mixed m.p. 124—127°.

2-Hydroxyxanthone (II; R = H).—2-Hydroxyxanthone was prepared as described by Finnegan and Bachman,[18] m.p. 241°, $\lambda_{max.}$ 248, 299, 303sh, and 365 mμ (log ε 4·52, 3·65, 3·62, and 3·86), $\nu_{max.}$ (CO) 1658, (OH) 3320 cm.$^{-1}$, R_F 0·32 (silica gel; chloroform–ethyl acetate, 4 : 1). The methyl ether was obtained by dimethyl sulphate–acetone–K_2CO_3 treatment [18] of the hydroxyxanthone, m.p. 128—129°, $\lambda_{max.}$ 242, 249sh, 297, 302, and 357 mμ (log ε 4·35, 4·38, 3·50, 3·48, and 3·71), $\nu_{max.}$ (CO) 1650 cm.$^{-1}$, R_F 0·08 (silica gel; chloroform).

4-Hydroxyxanthone (III; R = H).—This xanthone was obtained by the method described by Ullmann and Zlokasoff,[19] m.p. 230—233°, $\lambda_{max.}$ 235sh, 251, 280, 291, and 350sh mμ (log ε 4·37, 4·53, 3·75, 3·68, and 3·68), $\nu_{max.}$ (CO) 1640, (OH) 3220 cm.$^{-1}$, R_F 0·32 (silica gel; chloroform).

Oxidation of 2,3′-Dihydroxybenzophenone (I; R = H).—(a) *Potassium ferricyanide*. 2,3-Dihydroxybenzophenone (30 mg.) was dissolved in methanol (1 ml.) and added to B.D.H. buffer solutions (35 ml.) at pH 8—11 or sodium hydroxide solutions (35 ml.) at pH 12—14 containing potassium ferricyanide (140 mg., 2 mol.). The reaction mixture was kept at room temperature for 1 hr., acidified with dilute hydrochloric acid, and extracted with ethyl acetate (3 × 50 ml.). Each ethyl acetate extract was washed with water and the combined extracts dried with anhydrous magnesium sulphate, filtered, and evaporated to dryness. The crude residue was separated by t.l.c. using silica gel and chloroform when bands at R_F 0·08 and 0·32 were isolated and extracted to yield 2- and 4-hydroxyxanthone (II and III; R = H), respectively. Those compounds being identical with the authentic 2- and 4-hydroxyxanthones synthesised independently. A band at R_F 0·09 corresponded to unoxidised benzophenone. Table 1 shows the yields obtained in these oxidations. No improvement was obtained by running the oxidations under nitrogen or with larger quantities of oxidant.

(b) *Potassium permanganate*. The benzophenone (I; R = H) (53 mg.) was dissolved in sodium hydroxide solution (2 ml.; 2M) and a solution of potassium permanganate (2 ml., 2 mol.; 4 × 10^{-2}M) was added dropwise. After 15 min. stirring the colour had discharged and the solution was acidified and worked up in the usual way to give a brown oil (15 mg.). T.l.c. yielded only 2-hydroxyxanthone (1 mg.), identified by R_F and u.v. spectral comparisons.

2,3′,6-Trihydroxybenzophenone (I; R = OH).—2,6-Dimethoxybenzoyl chloride (22 g.; prepared from the acid by treatment with phosphorus pentachloride followed by distillation at 145—155°/0·5 mm.) in dry benzene (50 ml.) was added to 3-methoxyphenylcadmium chloride [prepared from 3-bromoanisole (20 g.) as previously described for 2-bromoanisole]. The reaction was processed as before and worked up to give a neutral fraction which yielded on distillation 2,3′,6-trimethoxybenzophenone (15·6 g.), b.p. 175—185°/0·05 mm. Crystallisation from benzene–light petroleum (b.p. 40—60°) gave a solid, m.p. 121—122° (Found: C, 70·9; H, 6·0. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%), $\lambda_{max.}$ 226, 255, and 312 mμ (log ε 4·22, 3·89, and 3·39), $\nu_{max.}$ (CO) 1670 cm.$^{-1}$, (3′-OCH_3) τ 6·15, (2,6-OCH_3) 6·30. Demethylation, as described prevously, yielded (from 2 g.) a brown viscous oil which by elution with chloroform from an alumina column gave a yellow solid (0·8 g.) crystallising from benzene as *2,3′,6-trihydroxybenzophenone*, m.p. 124—125° (Found: C, 67·8; H, 4·5. $C_{13}H_{10}O_4$ requires C, 57·8; H, 4·4%), $\lambda_{max.}$ 230, 260, 287, and 312 mμ (log ε 4·15, 3·97, 3·80, and 3·67), $\nu_{max.}$ (CO) 1630, (OH), 3315, 3485 cm.$^{-1}$.

1,5- and 1,7-Dihydroxyxanthone.—Both xanthones were kindly supplied by Dr. R. A. Finnegan.[2] 1,5-Dihydroxyxanthone showed R_F 0·3 with silica gel and chloroform while 1,7-dihydroxyxanthone had R_F 0·2. Both xanthones were recovered intact after treatment for 1 hr. with alkaline potassium ferricyanide solution (pH 14).

Oxidation of 2,3′,6-Trihydroxybenzophenone (I; R = OH).—(a) *Potassium ferricyanide*. 2,3′,6-Trihydroxybenzophenone (40 mg.) was dissolved in methanol (1 ml.) and added to a solution of potassium ferricyanide (114 mg., 2 mol.) in sodium hydroxide solution (55 ml.; 4%, pH 14). After 1 hr. at room temperature the mixture was acidified and extracted with ethyl acetate to yield, after the usual work-up, a brown oily solid (38 mg.). T.l.c. separation (silica gel; chloroform) gave 1,7-dihydroxyxanthone, R_F 0·2 (~1 mg.) and 2,3′,6-trihydroxybenzophenone, R_F 0·05 (36 mg.). A repeat oxidation for 11 hr. at pH 14 or 1 hr. at pH 12 give a similar result. This 1,7-dihydroxyxanthone was only characterised by its R_F comparison due to the small quantity available. Its u.v. spectrum was basically similar to that of authentic 1,7-dihydroxyxanthone (II; R = OH).

(b) *Potassium permanganate*. The benzophenone (240 mg.) was dissolved in acetone (300 ml.) and a solution of potassium permanganate (330 mg., 2 mol., in water 50 ml.) was added dropwise while stirring during 5 min. After 2 hr. the purple colour had discharged and the mixture was poured into a large excess of water. Subsequent work-up gave a yellow crystalline solid which separated on t.l.c. (silica gel; $CHCl_3$) into 1,7-dihydroxyxanthone (II; R = OH) (77 mg.), R_F 0·2, and 1,5-dihydroxyxanthone (III; R = OH) (12 mg.), R_F 0·2. Both xanthones being identical with the authentic xanthones described previously, benzophenone (I; R = OH) (48 mg.), R_F 0·02, was also recovered. A repeat oxidation using benzophenone (120 mg.), potassium permanganate (248 mg.) in acetone–water (150 ml./25 ml.) gave, after 2 hr. followed by the usual work-up and separation, 1,7-dihydroxyxanthone (36 mg.), 1,5-dihydroxyxanthone (3·6 mg.) together with benzophenone (26 mg.).

(c) *Potassium persulphate*. Potassium persulphate (705 mg., 2 mol.) in sodium hydroxide solution (10 ml.; 4%) at

[18] R. A. Finnegan and P. L. Bachman, *J. Pharm. Sci.*, 1965, **54**, 633.
[19] F. Ullmann and M. Zlokasoff, *Ber.*, 1905, **38**, 2111.

room temperature for 10 min. converted the benzophenone (375 mg.) into 1,7-dihydroxyxanthone (11 mg.) only, benzophenone (30 mg.) also being recovered from the reaction product.

2,3′,4-*Trihydroxybenzophenone* (IV).—This benzophenone was prepared as described previously.[1] Its n.m.r. spectrum showed (2-OH) τ −2·67, (3′-OH) 0·48, (4-OH) 1·23.

3,5-*Dihydroxyxanthone* (VI).—3,5-Dimethoxyxanthone (100 mg.) was refluxed with powdered aluminium chloride (3 g.) in chlorobenzene (30 ml.) for 2 hr. After work-up in the usual way, the product was sublimed at 200—240°/0·22 mm. to give 3,5-*dihydroxyxanthone* (10 mg.), m.p. 315—320° s./d. (Found: C, 68·3; H, 3·4. $C_{13}H_8O_4$ requires C, 68·4; H, 3·5%), $\lambda_{max.}$ 213, 235, 245sh, 270, 307, and 332sh mμ (log ε 4·40, 4·59, 4·51, 4·17, 4·02, and 3·86), $\nu_{max.}$ (CO) 1640, (OH) 3100, 3360 cm.$^{-1}$, R_F 0·74 (Whatman No. 1 paper; 60% acetic acid), R_F 0·08 (paper; n-butanol saturated with ammonia).

2,6-*Dihydroxyxanthone* (V).—This compound was identical with that described [1] with R_F 0·71 (paper; 60% acetic acid) and R_F 0·33 (paper; n-butanol saturated with ammonia).

Oxidation of 2,3′,4-*Trihydroxybenzophenone* (IV).—(a) *Potassium ferricyanide.* 2,3′,4-Trihydroxybenzophenone (40 mg.) was dissolved in methanol (1 ml.) and added to a solution of potassium ferricyanide (172 mg., 3 mol.) in B.D.H. buffer solution (55 ml.; pH 8—11) or sodium hydroxide solution (55 ml.; pH 12—14). The reaction, after being allowed to stand at room temperature for 1 hr., was acidified and extracted with ethyl acetate and worked up to yield a crude reaction product which was sublimed at 200—260°/0·1 mm. to give a xanthone fraction. Table 2 shows the yields of material obtained at varying pH. Each xanthone fraction showed the presence of both 2,6- and 3,5-dihydroxyxanthone and the material obtained from the pH 12 experiment yielded, on t.l.c. separation (Avicel; n-butanol saturated with ammonia), 2,6-dihydroxyxanthone (V) (27·8 mg.), R_F 0·40, and 3,5-dihydroxyxanthone (VI) (4·9 mg.), R_F 0·17, while that obtained at pH 14 yielded (V) (26·4 mg.) and (VI) (5·9 mg.), respectively. Both compounds being identical with the xanthones prepared independently.

(b) *Potassium permanganate.* The benzophenone (IV) (240 mg.) was dissolved in acetone (300 ml.) and a solution of potassium permanganate (330 mg., 2 mol.) in water (50 ml.) was added during 5 min. with stirring. After a further 5½ hr., whence the permanganate colour had disappeared, the mixture was poured into a large volume of water and extracted with ethyl acetate (3 × 100 ml.). After working up the organic layer in the usual way, the phenolic product (51 mg.) was separated, as described previously, into 2,6-dihydroxyxanthone (10 mg.) and 3,5-dihydroxyxanthone (~1 mg.).

(c) *Potassium persulphate.* Oxidation of the benzophenone (IV) (100 mg.) in sodium hydroxide solution (30 ml.; 4%) with potassium persulphate (235 mg., 2 mol.) with stirring for 0·5 hr. gave, after acidification, work-up, and paper chromatography of the residue, traces of the 2,6-dihydroxyxanthone and the benzophenone (IV).

(d) *Ferric chloride.* The benzophenone (50 mg.) in methanol (1 ml.) was added to an acid solution of ferric chloride (80 mg., 2 mol. in 500 ml. 10% hydrochloric acid). After stirring for 24 hr. the mixture was worked up to yield starting material (15 mg.) only.

(e) *Ammonium ceric sulphate.* This also yielded starting material after 24 hr. reaction in dilute sulphuric acid at room temperature.

(f) *Manganese dioxide.* No oxidation was seen to occur after stirring the benzophenone (52 mg.) in acetone (20 ml.) with freshly prepared manganese dioxide (8 g.) for varying times.

2,3′,4,6-*Tetrahydroxybenzophenone* (VII; R = H).—This benzophenone was best synthesised by Friedel–Crafts condensation, followed by demethylation, rather than by the reported Hoesch reaction.[20] 3-Methoxybenzoyl chloride (8·5 g.) was added to dry phloroglucinol (6·3 g.) in ether, anhydrous aluminium chloride (5·3 g.) added, and the mixture was left at room temperature for 2½ days. After pouring into ice cold dilute acid, work-up yielded a phenolic fraction which on purification by column chromatography (alumina; chloroform) gave 2,4,6-trihydroxy-3′-methoxybenzophenone (1·3 g.) crystallising from benzene, m.p. 168—171° (Found: C, 64·3; H, 4·5. $C_{14}H_{12}O_5$ requires C, 64·5; H, 4·6%), $\lambda_{max.}$ 220, 261, and 306 mμ (log ε 4·36, 3·67, and 4·22), $\nu_{max.}$ (CO) 1638, (OH) 3260 cm.$^{-1}$, (2,6-OH) τ −0·17, (4-OH) 1·04,† (3′-OCH_3) 6·14.

Demethylation of this benzophenone (1 g.) with aluminium chloride in chlorobenzene for 1 hr. gave a solid (0·9 g.) which on repeated crystallisation from benzene–ether (4 : 1) gave 2,3′,4,6-tetrahydroxybenzophenone (VII; R = H) as a yellow solid, m.p. 235—238° decomp.,[20] $\lambda_{max.}$ 220sh, 261, and 306 mμ (log ε 4·33, 3·73, and 4·20), $\nu_{max.}$ (CO) 1638, (OH) 3250 and 3350 cm.$^{-1}$, (2,6-OH) τ −0·45, (3′-OH) 0·73, (4-OH) 1·59,† R_F 0·52 (silica gel; benzene–ethyl acetate–ethanol, 50 : 43 : 7).

1,3,5-*Trihydroxyxanthone* (IX; R = H).—1,3,5-Trihydroxyxanthone was synthesised [6] giving a solid, m.p. 305—306°, $\lambda_{max.}$ 220sh, 247, 313, and 360sh (log ε 4·20, 4·53, 4·21, and 3·62), $\nu_{max.}$ (CO) 1657, (OH) 3330 and 3390 cm.$^{-1}$, R_F 0·58 (silica gel; benzene–ethyl acetate–ethanol, 50 : 43 : 7).

1,3,7-*Trihydroxyxanthone* (VIII; R = H).—This xanthone was prepared by demethylation of 1,3-dihydroxy-7-methoxyxanthone [6] to give m.p. 315—319°,[21] $\lambda_{max.}$ 220sh, 238, 260, 310, and 373 mμ (log ε 4·22, 4·47, 4·55, 4·18, and 3·82), $\nu_{max.}$ (CO) 1655, (OH) 3370 cm.$^{-1}$, R_F 0·70 (silica gel; benzene–ethyl acetate–ethanol, 50 : 43 : 7).

Oxidation of 2,3′,4,6-*Tetrahydroxybenzophenone* (VII; R = H).—(a) *Potassium ferricyanide.* 2,3′,4,6-Tetrahydroxybenzophenone (50 mg.) was dissolved in methanol (1 ml.) and added to a solution of potassium ferricyanide (80 mg., 1·2 mol.) in sodium hydrogen carbonate solution (10 ml.; 10%). The mixture was kept at room temperature for 1 min. when half was removed and worked up; after a further 14 min. the remaining half was processed to yield a phenolic fraction. Similar oxidations were run in sodium hydrogen carbonate or sodium carbonate solutions (pH 11 and 12, respectively) as described in Table 5. Purification of the product of reaction was accomplished by t.l.c. (silica gel; benzene–ethyl acetate–ethanol, 50 : 43 : 7) where the bands at R_F 0·52 and 0·70 corresponded to 1,3,7-trihydroxyxanthone (VIII; R = H) and benzophenone (VII; R = H), respectively. Oxidations were repeated with benzophenone (40 mg.) in different buffer

[20] H. Nishikawa and R. Robinson, *J. Chem. Soc.*, 1922, **121**, 839; see also P. E. Spoerri and A. S. DuBois, *Org. Reactions*, 1949, **5**, 387.

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

solutions (B.D.H.; 70 ml.) containing potassium ferricyanide (160 mg., 3 mol.) for 1 hr. After acidification and work-up the solid fraction was separated on t.l.c. (as above) into 1,3,7-trihydroxyxanthone and starting material. Table 3 indicates the yields obtained. No evidence of the

TABLE 5

Time	1 min.	15 min.	1 hr.
1,3,7-Xanthone pH 11 ...	1 mg.	3 mg.	5 mg.
1,3,7-Xanthone pH 12 ...	1 mg.	—	2 mg.
Time	3 hr.	24 hr.	
1,3,7-Xanthone pH 11 ...	5 mg.	4 mg.	
1,3,7-Xanthone pH 12 ...	2 mg.	1 mg.	

presence of 1,3,5-trihydroxyxanthone was obtained. The oxidation was repeated at pH 11 under a nitrogen atmosphere when the benzophenone produced 1,3,7-xanthone (18·8 mg., 47%) with 2 mol. of ferricyanide and with 3 mol. of ferricyanide for 1 hr., the yield increased to 64% (25·5 mg.). No improvement over this figure could be obtained.

(b) *Potassium permanganate.* The benzophenone (246 mg.) was dissolved in acetone (300 ml.) and a solution of potassium permanganate (316 mg., 2 mol.) in water (50 ml.) was added dropwise while stirring during 5 min. After 0·75 hr. the mixture was worked up, separated by chromatography, to yield 1,3,7-trihydroxyxanthone (6 mg.).

Oxidation of 1,3,7-*Trihydroxyxanthone* (VIII; R = H).—The xanthone (40 mg.) was dissolved in methanol (1 ml.) and added in turn to sodium hydroxide solution (70 ml.) at pH 12, 13, and 14, followed by potassium ferricyanide (160 mg., 3 mol.). After 1 hr. the solutions were acidified and worked up to give the xanthone, which on purification by sublimation gave 28 mg., 16·5 mg., and 16·3 mg. recoveries, respectively.

Oxidation of 1,3,5-*Trihydroxyxanthone* (IX; R = H).—Under similar conditions of oxidation as above, the xanthone (IX; R = H) could be recovered in trace quantities only.

2,3,3′,4,4′,6-*Pentahydroxybenzophenone* (*Maclurin*) (VII; R = OH).—Maclurin obtained commercially contained 1,3,6,7-tetrahydroxyxanthone (VIII; R = H) and was consequently purified by dry column t.l.c.[22] (silica gel; benzene–ethyl acetate–ethanol, 50 : 43 : 7) to give a solid, m.p. 226—230°,[23] $\lambda_{max.}$ 216 and 324 mμ (log ε 4·31 and 4·11), $\nu_{max.}$ (CO) 1640, 1655, (OH) 3360 cm.$^{-1}$, (2,6-OH) τ −0·03, (4-OH) 0·90, (4′-OH) 1·85,† R_F 0·35 (same solvent as above).

1,3,5,6-*Tetrahydroxyxanthone* (IX; R = OH).—This xanthone was obtained from Dr. Scheinmann and showed R_F 0·48 (silica gel; benzene–ethyl acetate–ethanol; 50 : 43 : 7).[11] The tetramethyl ether[24] showed R_F 0·30 (silica gel; benzene–chloroform, 3 : 7).

1,3,6,7-*Tetrahydroxyxanthone* (VIII; R = OH).—Also obtained as above,[11] this xanthone showed R_F 0·48 (silica gel; benzene–ethyl acetate–ethanol, 50 : 43 : 7) while its tetramethyl ether[10] gave R_F 0·2 (silica gel; benzene–chloroform, 3 : 7).

Oxidation of Maclurin (VII; R = OH).—2,3′,4,4′,6-Pentahydroxybenzophenone (VII; R = OH) (500 mg.) was dissolved in various buffer solutions (20 ml.) containing potassium ferricyanide (1·5—12 mol.) and the oxidation allowed to proceed, under nitrogen, for 5 min. to 2 hr. Acidification of the mixture and extraction with ethyl acetate led to a brown solid which yielded, after t.l.c. (silica gel; benzene–ethyl acetate–ethanol, 50 : 43 : 7; in a nitrogen atmosphere) at R_F 0·48, a xanthone which crystallised from ethyl acetate to give 1,3,6,7-tetrahydroxyxanthone (VIII; R = OH), m.p. above 360°, $\lambda_{max.}$ 210, 238, 255, 310, and 362 mμ (log ε 4·25, 4·38, 4·50, 4·19, and 4·09), identical with the authentic sample described previously. Table 6 indicates the extent of the oxidations under various conditions. The xanthone product obtained under * in Table 6 was methylated[11] and the methyl ether so obtained chromatographed (t.l.c., silica gel; benzene–chloroform,

TABLE 6

pH	Time	Mol. of ferricyanide	Yield	Nitrogen atmosphere
9	1 hr.	3	100 mg.	—
12 *	1 hr.	3	160 mg.	—
14	1 hr.	3	215 mg.	—
14	1 hr.	3	275 mg.	+
14	2 hr.	3	145 mg.	—
14	5 min.	12	10 mg.	+
14	5 min.	3	230 mg.	—
14	5 min.	3	270 mg.	+
14 *	5 min.	2	323 mg.	+
14 *	5 min.	1·5	235 mg.	+

3 : 7) to show that only 1,3,6,7-tetramethoxyxanthone, R_F 0·2, was present. At no time was the 1,3,5,6-isomer detected in these oxidations.

Oxidation of 1,3,5,6- *and* 1,3,6,7-*Tetrahydroxyxanthones.*—A mixture (1 : 1) of these two xanthones (100 mg.) was dissolved in sodium hydroxide solution, under nitrogen, (10 ml.; 4%) at pH 14 and potassium ferricyanide solution (10 ml. containing 253 mg., 2 mol.) added. After 5 min., the reaction mixture was acidified and extracted to give in the usual way a brown solid (95 mg.). Methylation gave a neutral fraction (85 mg.) which on t.l.c. (silica gel; benzene–chloroform, 3 : 7) showed that only 1,3,6,7-tetramethoxyxanthone was present, R_F 0·2.

Oxidation of 3′-*Methoxylated Benzophenones.*—(a) 2-*Hydroxy*-3′-*methoxybenzophenone.* This benzophenone (30 mg.) was dissolved in sodium hydroxide solution (35 ml.; 4%) containing potassium ferricyanide (140 mg., 2 mol.) and allowed to react for 1 hr. Work-up gave an oil (30 mg.) which showed a trace of material on t.l.c. at R_F 0·3 (silica gel; benzene) and a major band at R_F 0·8 corresponding to 2-methoxyxanthone and 2-hydroxy-3′-methoxybenzophenone, respectively. The xanthone could not be isolated because of its extremely low yield; the benzophenone was recovered (30 mg.). A repeat oxidation for 2½ days did not improve the yield of xanthone, benzophenone being recovered in high yield. Permanganate oxidation only duplicated the ferricyanide process.

(b) 2,4,6-*Trihydroxy*-3′-*methoxybenzophenone.* This compound (40 mg.) was treated, in buffer solution (70 ml.; pH 6—14), with potassium ferricyanide (160 mg., 3 mol.) for 1 hr. After acidification and work-up the product was shown by t.l.c. to be composed entirely of starting material. When oxidation of the benzophenone (244 mg.) in acetone–potassium permanganate (316 mg., 2 mol.) was undertaken the product obtained in the usual way (219 mg.) was

[22] B. Loev and K. M. Snader, *Chem. and Ind.*, 1965, 15.
[23] R. A. Laidlaw and G. A. Smith, *Chem. and Ind.*, 1959, 1604.
[24] M. L. Wolfrom, F. Komitsky, G. Fraenkel, J. Hooker, E. E. Dickey, P. McWain, A. Thompson, P. M. Mundell, and O. M. Windrath, *J. Org. Chem.*, 1964, **29**, 692.

mainly starting material, no xanthone being observed on t.l.c. examinations.

Enzymic Oxidations.—(a) *Laccase.* A solution of the laccase (500 ml.) from *Polystictus versicolor* [25] was obtained and benzophenone (100 mg.) added in methanol (1 ml.) followed by incubation for 7 days at 25°. Extraction with ethyl acetate and isolation of a phenolic fraction gave, after separation on t.l.c., an impure xanthone fraction (*ca.* 1 mg.). Table 7 shows the compounds present after incubation which were characterised by t.l.c. comparisons.

(b) *Peroxidase.* The benzophenone was dissolved in methanol (1 ml.) and added dropwise to a solution of horse radish peroxidase, hydrogen peroxide (2—3 drops; 30 vol.) was added, and the mixture incubated at room temperature. After work-up in the usual way the products were examined by t.l.c. and the results are summarised in Table 8.

We wish to thank the Science Research Council for the award of a studentship to J. E. A., Drs. Finnegan and Scheinmann for samples, and Dr. Jones (Macauley Institute for Soil Research) for the production of the laccase solution.

[8/1050 *Received, July 24th,* 1968]

[25] G. Benfield, S. M. Bocks, K. Bromley, and B. R. Brown, *Phytochemistry,* 1964, **3**, 79.

TABLE 7

Benzophenone	Wt. (mg.)	Vol. of broth (ml.)	Incubation Time (days)	Temp.	Products isolated
2,3′-Dihydroxy-	50	500	7	R.T.	2-hydroxyxanthone 2,3′-dihydroxybenzophenone
2,3′,4-Trihydroxy-	100	500	2	37°	2,6-dihydroxyxanthone 3,5-dihydroxyxanthone 2,3′,4-trihydroxybenzophenone
2,3′,6-Trihydroxy-	50	500	7	30°	1,7-dihydroxyxanthone 2,3′,6-trihydroxybenzophenone
2,3′,4,6-Tetrahydroxy-	50	300	7	R.T.	1,3,7-trihydroxyxanthone
	100	500	7	R.T.	
	50	300 *	14	R.T.	2,3′,4,6-tetrahydroxybenzophenone
2,3′,4,4′,6-Pentahydroxy- (Maclurin)	50	500	7	R.T.	none
2,4,6-Trihydroxy-3-methoxy-	20	100	2	R.T.	benzophenone recovered
	100	500	7	R.T.	
	50	500	7	R.T.	
	50	300	14	R.T.	

* When this reaction was repeated at pH 6·7 or 9·9, no 1,3,7-trihydroxyxanthone was detected.
R.T. = room temperature (21°).

TABLE 8

Benzophenone	Wt. (mg.)	Wt. of peroxidase (mg.)	Volume of buffer (ml.)	Incubation time (days)	Products isolated
2,3′-Dihydroxy-	15	5	500	5	2-hydroxyxanthone 2,3′-dihydroxybenzophenone
2,3′,4-Trihydroxy-	100	5	500	4	2,6-dihydroxyxanthone
	200	10	1000	5	3,5-dihydroxyxanthone 2,3′,4-trihydroxybenzophenone
2,3′,6-Trihydroxy-	50	5	500	7	1,7-dihydroxyxanthone 1,5-dihydroxyxanthone 2,3′,6-trihydroxybenzophenone
2,3′,4,6-Tetrahydroxy-	50	15	250	3—4	2,3,4,6-tetrahydroxybenzophenone
	100	10	250	3	
	200	10	1000	5	
	50	10	250	11	
2,3,3′,4,4′,6-Pentahydroxy- (Maclurin)	50	5	500	7	none
2,4,6-Trihydroxy-3′-methoxy	50	5	250	2	2,4,6-trihydroxy-3′-methoxybenzophenone
	100	10	250	3	
	30	5	100	5	
	200	10	1000	5	
	50	25	1000	5	
	50	10	250	11	