Studies in the Xanthone Series. Part XII.[1] A General Synthesis of Polyoxygenated Xanthones from Benzophenone Precursors

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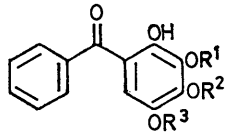
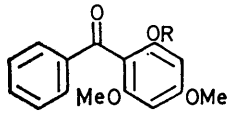
Various 2-mono-, 2,3- and 1,7-di-, 1,3,7-, 1,5,6-, 1,6,7- and 2,3,4-tri-, 1,3,4,7-, 1,3,5,6-, 1,3,6,7-, 1,5,6,7- and 2,3,4,5-tetra-, and 1,3,5,6,7-penta-oxygenated xanthones have been synthesised by preparation of 2-hydroxy-2'-methoxybenzophenones under Friedel–Crafts conditions, and subsequent base catalysed cyclisation to eliminate methanol. Acid or base catalysed selective demethylations of polymethoxyxanthones, and of benzophenones lead to efficient synthesis of natural hydroxymethoxyxanthones, and of hydroxymethoxybenzophenones. Selective methylation procedures are also given.

MANY natural xanthones [2] are not readily accessible by existing methods and an alternative approach was required. Synthetic considerations largely concern orientation control [3] and selective methylation and demethylation. The synthesis of Grover *et al.*[4] from salicyclic acid and phenol derivatives does not always give the required xanthones,[5] and the reaction may be accompanied by unwanted demethylations.[6] The procedure may also lead to benzophenone formation [7] or a multiplicity of products.[8] The alternative now described is an efficient general synthesis, and involves formation [9] of 2-hydroxy-2'-methoxybenzophenones, followed by the quantitative elimination of methanol in the presence of alkali to give xanthones.[10] A similar base catalysed elimination (of water) was noted by Nishikawa and Robinson [11] in 1922, in the synthesis of 1,3-dihydroxyxanthone.

Similar routes [12,13] to highly oxygenated xanthones have been demonstrated recently, but these involve slow acylations [14] of polyhydric phenol derivatives with benzoic acids in trifluoroacetic anhydride. The present report includes syntheses of benzophenones, and mono- to penta-oxygenated xanthones.

Orientation and Demethylation in Benzophenone Synthesis.—The synthesis of benzophenones suitable as precursors for cyclisation to xanthones is conveniently achieved at room temperature by the Friedel–Crafts acylation of methoxybenzene derivatives with the appropriately substituted benzoyl chloride in the presence of aluminium chloride in ether. That preferential *para*-acylation occurs under these conditions is shown by the reaction of benzoyl chloride and veratrole which gives 3,4-dimethoxybenzophenone. In cases where acylation occurs adjacent to a methoxy-group selective demethylation may occur at a site adjacent to the carbonyl group. Thus reaction of benzoyl chloride with 1,2,3,4-tetramethoxybenzene gives the monomethyl ether (1) of scleroin [15] (2) whereas acylation of 1,3,5-trimethoxybenzene gives either hydrocotoin (6) or methylhydrocotoin (7) [16] according to the duration of the reaction. The fact that extended reaction time (30 h) causes *ortho*-monodemethylation has led to convenient syntheses of 2-hydroxy-2'-methoxybenzophenones suitable for cyclisation to xanthones by the elimination of methanol.



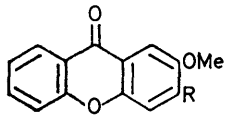


(1) $R^1 = R^2 = R^3 = Me$
(2) $R^1 = R^2 = Me$, $R^3 = H$
(3) $R^1 = R^3 = Me$, $R^2 = H$
(4) $R^1 = H$, $R^2 = R^3 = Me$
(5) As (1) but OMe for OH at C-2
(6) R = H
(7) R = Me

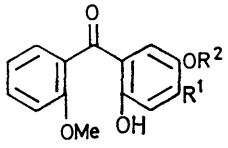
Synthesis of Mono- and Di-oxygenated Xanthones.—2-Mono-,[17] and 2,3-di-oxygenated [18,19] xanthones have previously been prepared from diphenyl ether and phosgene [18] or diphenyl ether and 2-carboxylic acids by an intramolecular acid catalysed acylation.[17,19] The more accessible route to these xanthones now described leads, *inter alia*, to a simple synthesis of 3-hydroxy-2-methoxyxanthone (8) recently isolated from *Ochrocarpos odoratus* (Rafin) Merrill.[20] 2-Methoxybenzoyl chloride and 1,2,4-trimethoxybenzene react in aluminium chloride

[1] Part XI, A. Jefferson, C. I. Stacey, and F. Scheinmann, *J. Chromatography*, 1971, **57**, 547.
[2] I. Carpenter, H. D. Locksley, and F. Scheinmann, *Phytochemistry*, 1969, **8**, 2013, and references therein.
[3] F. M. Dean in ' The Total Synthesis of Natural Products,' ed. J. ApSimon, Wiley, New York, vol. 1, in the press.
[4] P. K. Grover, G. D. Shah, and R. C. Shah, *J. Chem. Soc.*, 1955, 3982.
[5] (*a*) H. D. Locksley, I. Moore, and F. Scheinmann, *J. Chem. Soc.* (*C*), 1966, 430; (*b*) B. Jackson, H. D. Locksley, and F. Scheinmann, *ibid.*, 1967, 785.
[6] E. D. Burling, A. Jefferson, and F. Scheinmann, *Tetrahedron*, 1965, **21**, 2653.
[7] V. V. Kane, A. B. Kulkarni, and R. C. Shah, *J. Sci. Indian Res.*, 1959, **18B**, 28.
[8] B. Jackson, Ph.D. Thesis, University of Salford, 1967.
[9] G. A. Olah, ' Friedel-Crafts and Related Reactions,' Interscience, New York, vol. 3, p. 1.
[10] D. H. R. Barton and A. I. Scott, *J. Chem. Soc.*, 1958, 1767.
[11] H. Nishikawa and R. Robinson, *J. Chem. Soc.*, 1922, **121**, 839.
[12] G. H. Stout and W. J. Balkenhol, *Tetrahedron*, 1969, **25**, 1947.
[13] G. H. Stout, E. N. Christensen, W. J. Balkenhol, and K. L. Stephens, *Tetrahedron*, 1969, **25**, 1961.
[14] D. Taub, C. H. Kuo, H. L. Slates, and N. L. Wendler, *Tetrahedron*, 1963, **19**, 1, and references therein.
[15] M. Gregson, Ph.D. Thesis, University of Sheffield, 1965.
[16] J. Jobst and O. Hesse, *Ber.*, 1877, **10**, 249; *Annalen*, 1879, **199**, 17.
[17] F. Ullmann and M. Zlokasoff, *Ber.*, 1905, **38**, 2111; R. A. Finnegan and P. L. Bachman, *J. Pharm. Sci.*, 1965, **54**, 633.
[18] Y. Asahina and Y. Tanase, *Proc. Imperial Acad.* (*Tokyo*), 1940, **16**, 297.
[19] C. H. Hassall and J. R. Lewis, *J. Chem. Soc.*, 1961, 2312.
[20] H. D. Locksley and I. G. Murray, *Phytochemistry*, 1971, **10**, 3179.

in ether to give first 2-hydroxy-2',4,5-trimethoxybenzophenone (11) by acylation exclusively at the 5-position of 1,2,4-trimethoxybenzene, followed by complete demethylation at the most electron rich *ortho*-ether function of the benzophenone.



(8) R = OH
(9) R = OMe
(10) R = H



(11) R^1 = OMe, R^2 = Me
(12) R^1 = H, R^2 = Me
(13) R^1 = OMe, R^2 = H

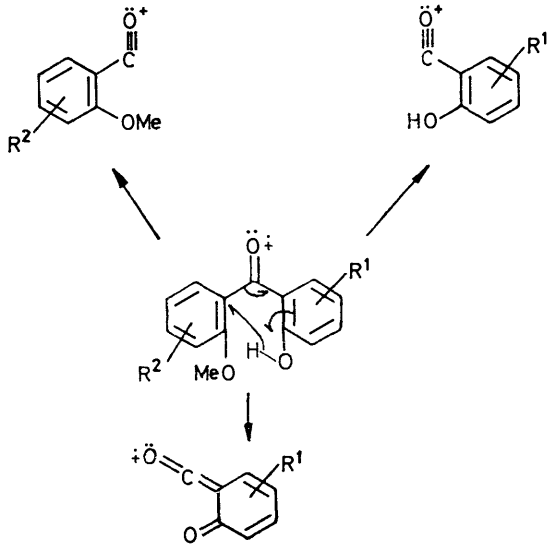
Consecutive cyclisation and selective demethylation to the natural product 3-hydroxy-2-methoxyxanthone (8) was effected with aqueous piperidine, representing a novel use of this reagent. Alternatively, cyclisation alone was effected with a variety of aqueous alkali hydroxides (*e.g.* sodium, potassium, and tetramethylammonium) giving 2,3-dimethoxyxanthone (9) in virtually quantitative yield. A similar synthesis of 1,7-dioxygenated xanthones is available from 1,4-dimethoxybenzene and 2,6-dimethoxybenzoyl chloride.

The structure of the benzophenone (11) follows from its mass spectral fragmentation. With all benzophenones having a different number of oxygen functions on each ring, rupture either side of the benzophenone carbonyl leads to ions whose masses determine the number of hydroxy- and methoxy-groups on each ring. A further rearrangement occurs in the case of *o*-hydroxybenzophenones in which the phenolic proton is transferred to the adjacent ring (Scheme) as formulated by Ballantine and Pillinger.[21] With 2-hydroxy-2',4,5-trimethoxybenzophenone ketonic fragmentation in mass spectrometry gives ions corresponding to $MeOC_6H_4CO^+$ at *m/e* 135 and $(MeO)_2OHC_6H_2CO^+$ at *m/e* 181 and rearrangement gives the ion at *m/e* 180 corresponding to the keten type fragment (14).

This new synthesis of 2,3-dioxygenated xanthones from the benzophenone intermediate (11) avoids intermediates of low accessibility which are required for the preparation of appropriately substituted diphenyl ethers. Furthermore, the Ullmann reaction generally used for this purpose often requires drastic conditions and gives low yields.[19]

2-Methoxyxanthone [17] isolated from *Kielmayera coriacea* Mart,[22] *K. corymbosa* Mart,[23] and from *Mammea americana* L.[24] also previously synthesised from diphenyl ether intermediates [17] is now more readily prepared from the benzophenone (12). Reaction of 2-methoxybenzoyl chloride with hydroquinone dimethyl ether under the above Friedel–Crafts conditions gave 2-hydroxy-2',5-dimethoxybenzophenone (12) which cyclised readily, in the presence of alkali, to 2-methoxyxanthone (10).

Synthesis of Trioxygenated Xanthones.—The Friedel–Crafts acylation is even more rapid in the synthesis of more highly oxygenated benzophenones. Thus 2,6-dimethoxybenzoylchloride and 1,2,4-trimethoxybenzene react vigorously at room temperature to give 2-hydroxy-2',4,5,6'-tetramethoxybenzophenone (15) again showing complete acylation of the 5-position of 1,2,4-trimethoxybenzene and selective demethylation at the 2-methoxy-group of the benzophenone intermediate (16). The methoxy-group of greatest electron density adjacent to the carbonyl group is also more able to achieve the necessary degree of coplanarity with the carbonyl group required for the demethylation reaction. The structure



(14)
SCHEME

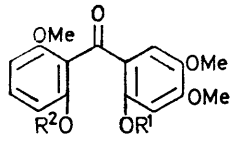
follows at once from mass spectrometry, in which ions corresponding to $(MeO)_2C_6H_3CO^+$ at *m/e* 165, to $(MeO)_2OHC_6H_2CO^+$ at *m/e* 181, and the rearrangement fragment $(MeO)_2OC_6H_2CO^+$ at *m/e* 180 are the major fragments. Furthermore n.m.r. measurements show that there is no heavily shielded methoxy-group [25] required for the alternative structure (17). No self-condensation of the 2,6-dimethoxybenzoic acid portion was observed under these Friedel–Crafts conditions. This contrasts with the alternative conditions of Nencki and Grover in which self-condensation of the resorcylic acid portion predominates.[5]

The benzophenone (15) cyclised quantitatively in the presence of hydroxide ion to 1,6,7-trimethoxyxanthone (18) which has previously only been available from methylation of the metabolite (19) [2] or by prior synthesis of this compound (19) either by chromic acid oxidation

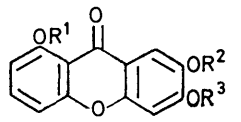
[21] J. A. Ballantine and C. T. Pillinger, *Org. Mass Spectrometry*, 1968, **1**, 425.
[22] O. R. Gottlieb, M. T. Magalhaes, M. Camey, A. A. L. Mesquita, and D. de B. Correa, *Tetrahedron*, 1966, **22**, 1777.
[23] D. de B. Correa, O. R. Gottlieb, and M. T. Magalhaes, *Ann. Acad. Brasil Cienc.*, 1966, **38**, 296.
[24] L. Crombie, D. E. Games, and A. McCormick, *J. Chem. Soc.* (*C*), 1967, 2545, 2553.
[25] H. D. Locksley and I. G. Murray, *J. Chem. Soc.* (*C*), 1970, 392.

of 1,7-dihydroxyxanthone [26,27] or through oxidative coupling of the appropriate tetrahydroxybenzophenone (22).[25]

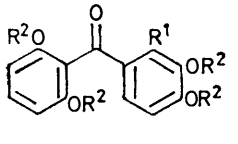
2,6-Dimethoxybenzoyl chloride and 1,2,3-trimethoxybenzene under the same Friedel–Crafts conditions gave 2-hydroxy-2′,3,4,6′-tetramethoxybenzophenone (23) which cyclises in alkali to 1,5,6-trimethoxyxanthone (24).



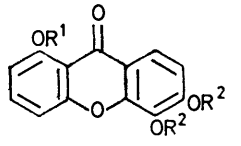
(15) R^1 = H, R^2 = Me
(16) R^1 = R^2 = Me
(17) R^1 = Me, R^2 = H



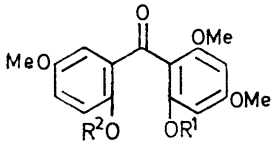
(18) R^1 = R^2 = R^3 = Me
(19) R^1 = R^2 = R^3 = H
(20) R^1 = H, R^2 = R^3 = Me
(21) R^1 = R^2 = H, R^3 = Me



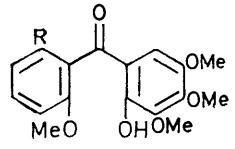
(22) R^1 = R^2 = H
(23) R^1 = OH, R^2 = Me



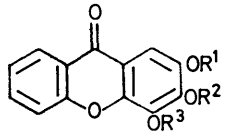
(24) R^1 = R^2 = Me
(25) R^1 = H, R^2 = Me
(26) R^1 = R^2 = H



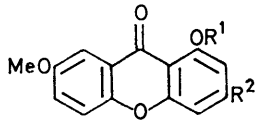
(27) R^1 = Me, R^2 = H
(28) R^1 = H, R^2 = Me
(29) R^1 = R^2 = Me



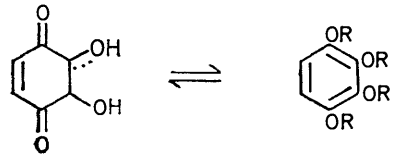
(30) R = H
(31) R = OMe



(32) R^1 = R^2 = R^3 = Me
(33) R^1 = R^3 = Me, R^2 = H
(34) R^1 = Me, R^2 = R^3 = H
(35) R^1 = R^2 = R^3 = H
(36) R^1 = R^2 = Me, R^3 = H
(37) R^1 = R^2 = R^3 = CH_2Ph



(38) R^1 = R^2 = H
(39) R^1 = Me, R^2 = H
(40) R^1 = H, R^2 = OMe
(41) R^1 = Me, R^2 = OMe



(42)

(43) R = H
(44) R = Me

The structure of the benzophenone intermediate (23) again follows from mass spectral and n.m.r. considerations, and confirms the previous suggestions that the most sterically hindered methoxy-group adjacent to the carbonyl group undergoes cleavage.[12] 1,5,6-Trimethoxyxanthone (24) was demethylated with hydrogen bromide in acetic acid to give first 1-hydroxy-5,6-dimethoxyxanthone (25) and then with more prolonged refluxing 1,5,6-trihydroxyxanthone (26), identical with the metabolite isolated from *e.g. Symphonia globulifera* L.[5a]

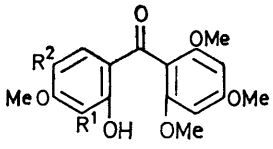
2,5-Dimethoxybenzoyl chloride acylates 1,3,5-trimethoxybenzene to give two isomeric hydroxybenzophenones (27) and (28). The structure of the major product, 2-hydroxy-2′,4′,5,6′-tetramethoxybenzophenone (27) follows from the mass spectrum with fragment ions corresponding to $MeO(OH)C_6H_3CO^+$ at *m/e* 151 and to $MeO(O)C_6H_3CO^+$ at *m/e* 150. The minor product 2-hydroxy-2′,4,5′,6-tetramethoxybenzophenone (28) in contrast has fragment ions corresponding to $(MeO)_2C_6H_3CO^+$ at *m/e* 165, $(MeO)_2OHC_6H_2CO^+$ at *m/e* 181, and $(MeO)_2OC_6H_2CO^+$ at *m/e* 180. Furthermore the n.m.r. spectrum shows a shielded methoxy-group at τ 6·7 consistent with the 6-methoxy-group of the benzophenone (28) in contrast to the isomeric benzophenone (27) where all the methoxy-groups appear below τ 6·5. In addition the aromatic protons of the symmetrical phloroglucinol ring in benzophenone (27) appear as a sharp singlet at τ 3·95 whereas in the isomer where the aromatic protons are no longer equivalent the phloroglucinol protons appear as *meta*-split doublets (J 2 Hz) at τ 4·01 and 4·29. Although the phloroglucinol system has the higher electron density and on this basis selective demethylation should occur in that ring, this is offset by its reduced ability to attain sufficient coplanarity with the carbonyl function. Since the hydroquinone ring can more readily achieve coplanarity with the carbonyl group, demethylation occurs preferentially to give the 2-hydroxy-5-methoxybenzophenone derivative (27) as the observed major product. Both benzophenones (27) and (28) cyclise to 1,3,7-trimethoxyxanthone (41) and give the same monomethyl ether.

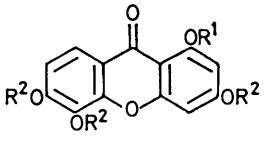
Reaction of 1,2,3,4-tetramethoxybenzene, with 2-methoxybenzoyl chloride gave 2-hydroxy-2′,3,4,5-tetramethoxybenzophenone (30). This cyclised in the presence of dilute alkali to 2,3,4-trimethoxyxanthone (32) and in the presence of aqueous piperidine to the natural product [28] 3-hydroxy-2,4-dimethoxyxanthone (33). Amongst other things the structure follows from pronounced hyper- and batho-chromic shifts in the u.v. spectrum on the addition of sodium acetate which indicate a hydroxy-group *para* to a carbonyl function. In this respect, this xanthone (33) resembled 2-methoxy-3-hydroxyxanthone (8) and 2,4-dihydroxy-3,5-dimethoxybenzophenone (3) which both contain *p*-hydroxycarbonyl functions. Demethylation of 2,3,4-trimethoxyxanthone with either sulphuric acid [22] or, better, hydrobromic acid under controlled conditions, gave the natural product 3,4-dihydroxy-2-methoxyxanthone (34) [23] first isolated by Gottlieb *et al.* from *Kielmeyera corymbosa* (Spr.) Mart. Demethylation under more vigorous conditions with acid gave 2,3,4-trihydroxyxanthone (35) found in *Ochrocarpos odoratus* (Rafin) Merrill.[20] Selective methylation of 3,4-dihydroxy-2-methoxyxanthone (34) in the presence of

[26] M. Nierenstein, *Ber.*, 1913, **46**, 649; A. L. Van Scherpenberg, *Chem. Weekblad*, 1919, **16**, 1146.
[27] F. Ullmann and L. Panchaud, *Annalen*, 1906, **350**, 108.
[28] A. Pimenta, A. A. L. Mesquita, M. Camey, O. R. Gottlieb, and M. T. Magalhaes, *Ann. Acad. Brasil Cienc.*, 1964, **36**, 39.

potassium hydrogen carbonate and one equivalent of dimethyl sulphate in acetone gave 4-hydroxy-2,3-dimethoxyxanthone (36) widely found [22,23,29] in *Kielmeyera* species, but not previously synthesised. These syntheses are facilitated by the ready availability of 1,2,3,4-tetramethyloxybenzene which is now conveniently prepared in the following manner. *cis*-Dihydroxylation of *p*-benzoquinone [30] easily gave the ketone tautomer (42) of 1,2,3,4-tetrahydroxybenzene (43) which methylates with dimethyl sulphate in the presence of potassium carbonate and acetone to give 1,2,3,4-tetramethoxybenzene (44).

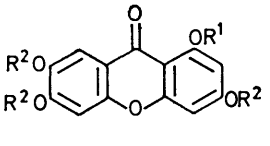
Synthesis of Tetraoxygenated Xanthones.—Both 2,3,4- and 2,4,5-trimethoxybenzoyl chlorides react with

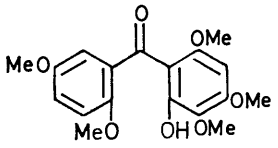




(45) R^1 = OMe, R^2 = H
(46) R^1 = H, R^2 = OMe
(47) OAllyl for OH in (46)
(48) R^1 = CH_2·CH=CH_2, R^2 = OMe

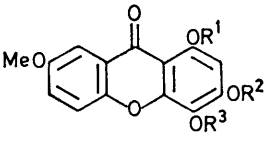
(49) R^1 = R^2 = Me
(50) R^1 = H, R^2 = Me
(51) R^1 = R^2 = H
(52) R^1 = H, R^2 = CH_2Ph
(53) R^1 = Me, R^2 = CH_2Ph
(54) R^1 = Me, R^2 = H

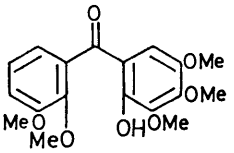




(55) R^1 = R^2 = Me
(56) R^1 = H, R^2 = Me
(57) R^1 = R^2 = H
(57A) As (57) but OMe at C-3 and C-6

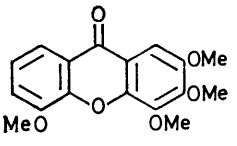
(58)

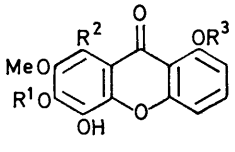




(59) R^1 = R^2 = R^3 = Me
(60) R^1 = H, R^2 = R^3 = Me
(61) R^1 = R^2 = H, R^2 = Me

(62)





(63)

(64) R^1 = Me, R^2 = R^3 = H
(65) R^1 = R^3 = H, R^2 = $CH_2CH{:}CMe_2$

1,3,5-trimethoxybenzene to give the corresponding benzophenones (45) and (46) in which selective *ortho*-demethylation has taken place on the acid-derived ring. The structure of 2-hydroxy-2′,3,4,4′,6′-pentamethoxybenzophenone (45) follows from the fact that the two phloroglucinol protons are equivalent and appear as a singlet at τ 3·94. This is supported by the observation that none of the methoxy-groups are heavily shielded and the structure is in accord with the expectation that the most sterically hindered methoxy-groups adjacent to the carbonyl undergoes demethylation.[31]

The isomeric benzophenone (46) shows similar n.m.r. signals for the phloroglucinol ring and additional structural proof is provided by formation and rearrangement of the allyl ether (47) to give the *C*-allylbenzophenone (48) which shows the disappearance of the C-3 proton while retaining the two phloroglucinol protons as a singlet at τ 3·95.

Both benzophenones (45) and (46) cyclised in the presence of aqueous methanolic sodium hydroxide to give respectively 1,3,5,6- (49) and 1,3,6,7-tetramethoxyxanthone (55). Selective demethylation of both xanthones (49) and (55) with boron trichloride [32] gave the corresponding 1-hydroxyxanthones (50) and (56). Prolonged boiling of the tetramethoxyxanthones (49) and (55) with hydrobromic acid gave the natural tetrahydroxyxanthones (51) and (57) which are widely found, often together, in nature.[2]

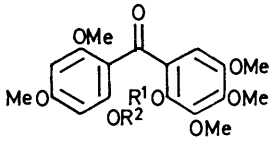
A number of 1,3,4,7-tetraoxygenated xanthones occur in *Frasera* species (family Gentianaceae).[13] These xanthones may be conveniently synthesised from 2-hydroxy-2′,3,4,5′,6-pentamethoxybenzophenone (58) which is obtained from 2,5-dimethoxybenzoyl chloride and 1,2,3,5-tetramethoxybenzene under similar mild Friedel–Crafts conditions. The structure of the benzophenone (58) immediately follows from its mass spectral fragmentation, the observed n.m.r. spectrum which shows one methoxy-group at high field (τ 6·68), and is supported by the structure of the cyclisation product (59). Thus reaction in aqueous alkali gave 1,3,4,7-tetramethoxyxanthone (59). Two further natural products [13] were prepared by successive selective demethylations of 1,3,4,7-tetramethoxyxanthone (59). Reaction with boron trichloride gave 1-hydroxy-3,4,7-trimethoxyxanthone (60) which with refluxing aqueous piperidine gave 1,3-dihydroxy-4,7-dimethoxyxanthone (61).

Another tetramethoxyxanthone that was synthesised is 2,3,4,5-tetramethoxyxanthone (63). Reaction of 2,3-dimethoxybenzoyl chloride with the apionol derivative (44) gave 2-hydroxy-2′,3,3′,4,5-pentamethoxybenzophenone (62). The structure of this benzophenone immediately follows from its mode of mass spectral fragmentation, its n.m.r. spectrum, and from its cyclisation in the presence of alkali to 2,3,4,5-tetramethoxyxanthone (63). The n.m.r. spectrum of the product unambiguously defines its structure with a singlet due to 1-H at τ 2·43 and complex signals due to the aromatic protons 6-H and 7-H, centred at τ 2·69 and 8-H at τ 2·01 (*J* 6·5 and 3·5 Hz). Analogous syntheses of 1,5,6,7-tetraoxygenated xanthones, including

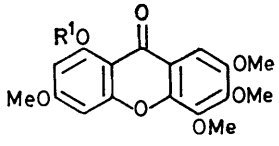
[29] O. R. Gottlieb, A. A. L. Mesquita, E. M. Da Silta, and M. T. de Melo, *Phytochemistry*, 1969, **8**, 665.
[30] E. M. Terry and N. A. Milas, *J. Amer. Chem. Soc.*, 1926, 2647.
[31] A. J. Quillinan and F. Scheinmann, *J. Chem. Soc.* (*C*), 1972, 1382.
[32] F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Letters*, 1966, 4153.

the natural products 1,5-dihydroxy-6,7-dimethoxyxanthone [33] (64) and celebixanthone [2] (65) start from 2,6-dimethoxybenzoyl chloride and 1,2,3,4-tetramethoxybenzene. This work will be discussed in another paper together with the appropriate isoprenylation studies.[34]

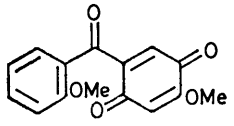
Synthesis of 1,3,5,6,7-*Pentaoxygenated Xanthones.*—The acylation of 1,2,3,4-tetramethoxybenzene with 2,4,6-trimethoxybenzoyl chloride gives 2-hydroxy-2′,3,4,4′,5,6′-hexamethoxybenzophenone (66). The structure of the product (66) follows from its n.m.r. spectrum. Thus the two phloroglucinol protons resonate as a singlet and all the methoxy-groups appear below τ 6·5 indicating the absence of the isomeric benzophenone (67) which should show magnetically different phloroglucinol protons. Cyclisation of the benzophenone (66) with aqueous alkali gave the 1,3,5,6,7-pentamethoxyxanthone (68) which was demethylated with boron trichloride to give 1-hydroxy-3,5,6,7-tetramethoxyxanthone (69). In both cases the n.m.r. spectra show the aromatic protons as a singlet and two *meta*-split doublets to confirm the structures (68) and (69).



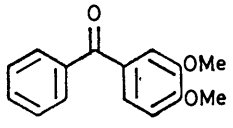
(66) R^1 = H, R^2 = Me
(67) R^1 = Me, R^2 = H



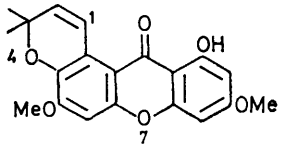
(68) R^1 = Me
(69) R^1 = H



(70)



(71)



(72)

Selective Demethylation. Selective demethylation of methoxybenzophenones and xanthones is possible in either acidic or alkaline media. Different products are obtained depending on the conditions used. Thus boron trichloride at room temperature always selectively demethylates a methoxy-group adjacent to a carbonyl function.[32] Hydrogen bromide in acetic acid also selectively demethylates such a group if the conditions are suitably controlled. A methoxy-group buttressed [6] by two different ether functions demethylates next under acidic conditions followed by methoxy-groups *not para* to a carbonyl function. The final methoxy-group to demethylate is *para* to the carbonyl group. This sequence of demethylation is illustrated in the ether cleavage of 1,6,7-trimethoxyxanthone (18) with hydrogen bromide in acetic acid. 1-Hydroxy-6,7-dimethoxyxanthone is first obtained, then 1,7-dihydroxy-6-methoxyxanthone, and finally 1,6,7-trihydroxyxanthone (19). This sequence is rationalised in terms of chelation for demethylation at the 1-position and then in terms of the relative electronegativity of the ether oxygens at C-6 and C-7. Thus demethylations occur more readily at the 7-methoxy-group on account of its higher electron density. Similarly with 1,3,6,7-tetramethoxyxanthone (55) the rate of demethylation appears to be 1-OMe > 7-OMe > 3- and 6-OMe. 1,7-Dihydroxy-3,6-dimethoxyxanthone was also characterised as the pyrano[3,2-*a*]xanthone (72) which shows highly characteristic chromen doublets (J 10 Hz) at τ 2·12 and 4·30. The very low-field position of the signal at τ 2·12 is due to the proximity of the xanthone carbonyl, and contrasts with more normal values of τ 3·0—3·3.[35] With 1,3,5,6-tetramethoxyxanthone (49) under acidic conditions, the 1-methoxy-group demethylates first followed by demethylation of the 5-methoxy-group.[6] The buttressing effect of two adjacent ether functions may facilitate ether cleavage of the 5-methoxy-group and this effect also occurs in the demethylations of 2,3,4-trimethoxyxanthone (32) to give (34). The methoxy-group that has been buttressed by its neighbours has reduced p–π interaction of the oxygen atom with the benzene ring. As a result the oxygen atom has enhanced electronegativity. An interesting alternative explanation for this type of selective demethylation has been suggested by Dean.[3]

Demethylation of a methoxy-group *para* to a carbonyl function occurs under alkaline conditions. This is not unexpected since the oxygen atom *para* to a carbonyl group is least electronegative. By analogy with demethylations using sodium ethanethiolate [36] it is expected that hydroxide ion attack occurs at the methyl of the methoxy-group. Alkaline demethylation of 2-hydroxy-3,4,5-trimethoxybenzophenone (1) occurs in the presence of aqueous piperidine to give 2,4-dihydroxy-3,5-dimethoxybenzophenone (3). The structure of the product (3) follows from its non-identity with the known isomeric 2,3-dihydroxy-4,5-dimethoxy- [15] and 2,5-dihydroxy-3,4-dimethoxybenzophenones (4) and (2).[15,37] In accordance with the location of a hydroxy-group *para* to the carbonyl the u.v. spectrum of 2,4-dihydroxy-3,5-dimethoxybenzophenone (3) undergoes a marked hyperchromic and bathochromic shift on addition of sodium acetate.

The influence of the *para* carbonyl is also observed in alkaline demethylation studies of 2,3,4-trimethoxyxanthone (32). Refluxing with either aqueous piperidine or tetramethylammonium hydroxide gave 3-hydroxy-2,4-dimethoxyxanthone (33). This product has a u.v. spectrum which undergoes the expected hyperchromic and bathochromic shifts on addition of sodium acetate.

[33] R. A. de Lima and O. R. Gottlieb, *Phytochemistry*, 1972, **11**, 2307.
[34] A. J. Quillinan and F. Scheinmann, forthcoming publication.
[35] H. D. Locksley, A. J. Quillinan, and F. Scheinmann, *J. Chem. Soc.* (*C*), 1971, 3804.
[36] G. I. Feutrill and R. N. Mirrington, *Tetrahedron Letters*, 1970, **16**, 1327; *Austral. J. Chem.*, 1972, **25**, 1719, 1731.
[37] G. Bargellini, *Gazzetta*, 1916, **46**, 1, 249.

2-Hydroxy-2',4,5-trimethoxybenzophenone (11) was converted to 2,5-dihydroxy-2',4-dimethoxybenzophenone (13) in good yield by a novel method, which provides an approach to natural products of this class.[20] The monohydroxybenzophenone (11) on treatment with *DDQ* gave a product which with methanol formed the 2,5-dihydroxybenzophenone (13). The reaction probably proceeds by oxidative demethylation to give the *p*-quinone (70) which can be reduced with methanol[15] to the corresponding hydroquinone (13).

The conversion of 1,3,5,6-tetramethoxyxanthone (49) into the natural[8] 3,5,6-trihydroxy-1-methoxyxanthone (54) followed a method previously described.[31] Tribenzylation of the tetrahydroxyxanthone (51) gave the ether (52) which formed (53) on methylation with dimethyl sulphate. Reductive debenzylation[31] then gave the required metabolite[8] (54).

EXPERIMENTAL

Microanalyses were obtained by Drs. Weiler and Strauss, Oxford, and Mr. J. Jordan, Salford. U.v. spectra were measured in methanol or in chloroform on a Unicam SP 800 recording spectrophotometer, and i.r. spectra as Nujol mulls on a Perkin-Elmer 257 grating spectrophotometer; n.m.r. spectra were measured on Varian A-60 and HA-100 instruments. Analytical and preparative t.l.c. were carried out on silica G (Merck nach Stahl) with thickness of 0·3 and 1·0 mm respectively; column chromatography was on silica gel MFC (Hopkin and Williams). Mass spectra were obtained with A.E.I. MS12 (single focusing) or MS9 (double focusing) instruments operated at 70 eV. Detailed i.r. and analytical data for benzophenones and xanthones are given in Supplementary Publication No. 20684 (6 pp.).*

General Method for Preparation of Benzophenones.—The stated amount of anhydrous rapidly powdered aluminium chloride was added to a sodium-dry ether solution of a benzoyl chloride and a polymethoxybenzene (molar ratio 1 : 1·1). The resulting two-phase, deep red mixture was stirred at room temperature for the appropriate period depending on the degree of demethylation required. The solvent was evaporated off under reduced pressure and the viscous residue was poured into water. The aqueous suspension was acidified with hydrochloric acid and extracted with benzene. Evaporation of the dried ($MgSO_4$) organic layer gave an oil which crystallised from methanol or cyclohexane. Detailed reaction conditions are shown in Table 3.

* For details of Supplementary Publications, see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue 20 (items less than 10 pp. are supplied as full size copies).

TABLE 1

A. U.v. data for benzophenones measured in methanol

Compound	$\lambda_{max.}$/nm ($10^{-3}\varepsilon$)				
(71)	246 (14·2)	282 (10·4)	316 (10·4)		
(30)	246 (8·8)	290 (13·4)			362 (6·2)
(62)	245 (6·7)	273 (13·6)			351 (4·5)
(31)	245 (5·8)	286 (13·6)			360 (5·5)
(5)	253 (15·7)	279 (6·3) †	314 (2·5) †		
(15)	246 (13·0)	283 (14·4)			350 (9·7)
(11)	239 (14·2)	284 (11·6)			351 (8·9)
(13)	243 (13·3)	286 (10·9)			362 (8·1)
(3)	244 (10·4) ‡	303 (11·7)			358 (6·7)

B. U.v. data for xanthones measured in methanol

(8)	230 (31·4)		265 (7·2) ‡		308 (12·1)		348 (9·2)
(9)	242 (43·4)		267 (11·3) †		305 (15·9)		346 (11·9)
(10)	252 (31·6)			292 (4·5) ‡	300 (5·5)		361 (6·3)
(18)	251 (36·6)		267 (12·7) ‡	283 (12·5)	305 (4·6) †	353 (11·9)	358 (12·5)
(20)	251 (35·0)	258 (21·9) ‡	269 (18·6)	288 (12·6)	308 (8·2) ‡		369 (12·1)
(21)	251 (27·1)	260 (15·3) ‡	269 (10·3)	311 (6·3) †	311 (6·3)		360 (9·4)
(24)	238 (48·9)				305 (17·8)		337 (9·8) †
(25)	249 (34·9)		269 (8·3) ‡		311 (14·4)		361 (5·3)
(32)	245 (34·2)			275 (10·4)	302 (11·5)		350 (6·5)
(33)	240 (36·9)			280 (6·8)	313 (13·6)	350 (9·4) ‡	380 (1·6) ‡
(34)	240 (30·1)		258 (28·2)	286 (6·1)			337 (12·8)
(36)	237 (26·0)		256 (33·4)	290 (9·1) ‡	307 (9·9)		354 (5·9)
(40) *	245 (21·3) ‡		262 (42·5)		308 (14·6)		372 (7·5)
(41)	239 (29·5)		255 (40·0)		303 (13·2)		356 (6·6)
(49)	244 (48·2)			287 (12·9)	306 (22·0)		330 (11·1) ‡
(50)	245 (48·2)			282 (10·7)	310 (23·5)		338 (9·33)
(52) *	249 (59·9)		286 (12·0) ‡	319 (30·1)			345 (10·2) ‡
(53) *	249 (58·5)		290 (18·0) ‡	305 (27·6)			325 (14·1) ‡
(54)	244 (47·9)			288 (13·3) ‡	317 (28·5)		342 (10·1)
(55)	247 (30·9) ‡	254 (40·2)	266 (13·3) ‡	300 (16·7)			347 (13·9)
(59)	236 (28·0)	259 (42·7)		300 (10·1) ‡	310 (11·4)		369 (8·7)
(60)	233 (27·6)	264 (36·8)			312 (10·7)		381 (6·8)
(61)	232 (29·6)	268 (32·0)		313 (10·0) ‡	319 (10·4)		388 (6·4)
(63)	247 (27·3)	254 (35·7)	285 (9·5) †	308 (5·2) ‡		353 (6·5) ‡	363 (6·6)
(64) [a]	237 (20·2) ‡	256 (31·7)	275 (11·1) ‡	311 (9·8)			378 (5·6)
(68)	244 (34·4)	253 (43·5)		303 (18·1)		347 (8·6) ‡	351 (8·7)
(69)	240 (22·6)	258 (31·1)	275 (8·7) ‡	312 (15·1)			364 (6·4)

* Measured in chloroform. † Inflection. ‡ Shoulder.

[a] A. J. Quillinan and F. Scheinmann, forthcoming publication.

Cyclisation of 2-Hydroxy-2'-methoxybenzophenones to Xanthones.—Four typical procedures (A)—(D) are given for base catalysed cyclisation of benzophenones to xanthones. All procedures involve refluxing with an aqueous alkali.

(A) *With aqueous metal hydroxide.*—2-Hydroxy-2',3,4,5-tetramethoxybenzophenone (4·5 g) in methanol (30 ml) containing water (20 ml) and sodium hydroxide (6·5 g) was heated under reflux for 5·5 h and the mixture was left overnight. The matted crystalline precipitate was collected, washed, and recrystallised. 2,3,4-Trimethoxyxanthone (3·1 g), m.p. 156—158° (lit.,[22] 153—155°), was obtained as needles from methanol. Similar results were obtained with other metal hydroxides.

(B) *With heterocyclic nitrogen bases.* 2-Hydroxy-2',4,5-trimethoxybenzophenone (2·5 g) in piperidine (30 ml) containing water (25 ml) was heated under reflux for 46 h and the cooled mixture was poured into dilute (4N) hydrochloric acid (150 ml). The mixture was extracted with dichloromethane (2 × 85 ml) and the dried ($MgSO_4$) extract was evaporated to a granular solid. 3-Hydroxy-2-methoxyxanthone (1·8 g), m.p. 241—242° (lit.,[38] 225—

[38] I. G. Murray, Ph.D. Thesis, University of Salford, 1970.

TABLE 2

A. N.m.r. data for benzophenones [τ values (multiplicity)] in deuteriochloroform

Compound	2-H	3-H	4-H	5-H	6-H	2'-H	3'-H	4'-H	5'-H	6'-H	OH (all s)	Me (all s)
(71)	2·50—2·65 (m)			3·10 (d)	2·50—2·65 (m)	2·18 (q)		2·50—2·65 (m)		2·18 (q)		6·08, 6·08
(7)		4·04 (d)		3·78 (d)				2·30—2·60 (m)			−2·30	6·15, 6·58
(6)		3·77 (s)		3·77 (s)		2·10 (q)		2·38—2·62 (m)		2·10 (q)		6·14, 6·32, 6·32
(1)					3·11 (s)			2·20—2·50 (m)			−2·30	5·95, 6·02, 6·30
(5)					3·22 (s)	2·09 (q)		2·40 (m)		2·09 (q)		6·00, 6·02, 6·14, 6·32
(12)		2·6—3·4 (m)			2·6—3·4 (m)			2·60—3·40 (m)			−1·65	6·33, 6·49
(11)		3·45 (s)			3·19 (s)		2·52 (q)		2·55—3·10 (m)		−2·83	6·06, 6·19, 6·32
(15)		3·45 (s)			3·29 (s)		3·31 (d)	2·58 (q)	3·31 (d)		−2·62	6·08, 6·25, 6·25, 6·38
(30)					3·37 (s)			2·40—3·00 (m)			−2·52	5·93, 6·01, 6·17, 6·36
(31) [a]					3·44 (s)		3·34 (d)	2·59 (q)	3·34 (d)		−2·41	5·95, 6·01, 6·24, 6·24, 6·40
(62)					3·38 (s)				2·80—3·20 (m)		−2·42	6·02, 6·02, 6·06, 6·16, 6·25
(23) *				3·76 (d)	3·06 (d)		3·50 (d)	2·72 (t)	3·50 (d)		−2·28	6·20, 6·22, 6·31, 6·31
(46) *		3·62 (s)			3·41 (s)		3·95 (s)		3·95 (s)		−2·50	6·20, 6·25, 6·39, 6·39, 6·48
(45) *				3·73 (d)	3·02 (d)		3·45 (s)		3·94 (s)		−2·40	6·20, 6·22, 6·24, 6·40, 6·40
(58)				4·22 (s)			3·3 (m)			3·3 (m)	−2·90	6·20, 6·26, 6·36, 6·42, 6·68
(28) *		4·29 (d)		4·01 (d)			3·2—3·4 (m)			3·2—3·4 (m)	−3·29	6·28, 6·34, 6·43, 6·70
(27) *		3·95 (s)		3·95 (s)			2·95—3·35 (m)			2·95—3·35 (m)	−1·70	6·25, 6·39, 6·39, 6·46
(29) *		4·00 (s)		4·00 (s)			3·25 (d)	3·10 (q)		2 82 (m)		6·26, 6·33, 6·43, 6·43, 6·49
(66)					3·52 (s)		3·92 (s)		3·92 (s)		−2·39	6·08, 6·13, 6·16, 6·23, 6·38, 6·44

B. N.m.r. data for xanthones [τ values (multiplicity)] in deuteriochloroform

Compound	1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	OH (all s)	OMe (all s)
(10)	2·40 (d)			2·60—2·90 (m)		2·40 (t)	2·6—2·9 (m)	1·76 (q)		6·20
(9)	2·28 (s)			3·09 (s)		2·20—2·68 (m)		1·51 (q)		5·94, 5·94
(25)		3·16 (d)	2·37 (t)	2·95 (d)			2·95 (d)	1·93 (d)	−2·80	5·95, 5·95
(24)		3·15 (d)	2·35 (t)	2·83 (d)			2·98 (d)	1·90 (d)		6·09, 6·09, 6·11
(20)		3·35 (d)	2·58 (t)	2·25 (d)	3·23 (s)			2·52 (s)	−2·69	6·10, 6·12
(18)		3·20 (d)	2·40 (t)	2·95 (d)	3·14 (s)			2·31 (s)		5·99, 6·03, 6·03
(32)	2·40 (s)					2·2—2·6 (m		1·52 (d)		5·90, 5·90, 6·00
(40)		3·70 (d)		3·60 (d)	2·68 (m)	2·72 (m)		2·40 (m)	−2·90	6·10, 6·15
(41)		3·66 (d)		3·52 (d)	2·68 (m)	2·68 (m)		2·24 (m)		6·00, 6·08, 6·08
(21) *†		3·39 (d)	2·50 (t)	3·16 (d)	3·04 (s)			2·61 (s)	−2·80	6·10
(34) †	2·70 (s)				2·15—2·65 (m)			1·71 (q)		6·02
(33)	2·40 (s)				2·15—2·60 (m)			1·53 (d)	3·48br	5·85, 5·95
(35) †	2·65 (s)				2·2—2·65			1·73 (m)		
(59)		3·58 (s)			2·65 (m)	2·65 (m)		2·28 (m)		6·00, 6·00, 6·08, 6·12
(60) *		3·71 (s)			2·71 (m)	2·71 (m)		2·50 (m)	−2·00	6·13, 6·20, 6·20
(49)		3·78 (d)		3·33 (d)			3·16 (d)	2·08 (d)		6·10, 6·13, 6·13, 6·21
(50)		3·61 (d)		3·43 (d)			2·93 (d)	1·95 (d)	−3·02	5·98, 5·98, 6·09
(55)		3·66 (d)		3·55 (d)	3·21 (s)			2·32 (s)		6·05, 6·05, 6·05, 6·11
(63)	2·43 (s)					2·69 (m)		2·01 (q)		5·81, 5·90, 5·95, 6·00
(68) *		3·76 (d)		3·55 (d)				2·62 (s)		6·08, 6·10, 6·17, 6·19, 6·21
(69) *		3·76 (d)		3·60 (d)				2·70 (s)		6·03, 6·03, 6·13, 6·20
(64) *		3·35 (d)	2·58 (t)	3·10 (d)				2·88 (s)	−2·61	6·08, 6·15
(56)		3·81 (d)		3·81 (d)	3·33 (s)			2·61 (s)	−2·85	6·13, 6·18, 6·25

* Measured at 100 MHz. † Measured in deuterioacetone.

[a] A. J. Quillinan and F. Scheinmann, forthcoming publication.

TABLE 3

Synthesis of benzophenones

Benzophenone [yield (g)]	Benzoyl chloride (g)	Polymethoxybenzene (g)	$AlCl_3$ (g)	in ether (ml)	Duration (h)
(1) (7·7)	(4·3)	1,2,3,4-$(MeO)_4$ (6·0)	12	300	22
(6) (24·5)	(15·2)	1,3,5-$(MeO)_3$ (18)	40	800	8
(7) (19·2)	(15·2)	1,3,5-$(MeO)_3$ (18)	40	800	36
(11) (6·1)	2-MeO (4·8)	1,2,4-$(MeO)_3$ (4·7)	10·5	180	20
(12) (5·0)	2-MeO (5·1)	1,4-$(MeO)_2$ (4·4)	10	300	19
(15) (14·3)	2,6-$(MeO)_2$ (9·2)	1,2,4-$(MeO)_3$ (9·2)	11	350	40
(23) (10·2)	2,6-$(MeO)_2$ (8·3)	1,2,3-$(MeO)_3$ (6·9)	20	300	20
(27) (7·6)					
(28) (3·7)	2,5-$(MeO)_2$ (10·0)	1,3,5-$(MeO)_3$ (9·1)	24	380	28
(30) (43)	2-MeO (24·8)	1,2,3,4-$(MeO)_4$ (26·5)	50	1600	44
(45) (14·2)	2,3,4-$(MeO)_3$ (11·3)	1,3,5-$(MeO)_3$ (8·6)	23	400	15
(46) (26·5)	2,4,6-$(MeO)_3$ (22)	1,3,5-$(MeO)_3$ (16·0)	44	600	21
(58) (14·6)	2,5-$(MeO)_2$ (9·5)	1,2,3,5-$(MeO)_4$ (10·3)	22	200	18
(62) (13·6)	2,3-$(MeO)_2$ (12·5)	1,2,3,4-$(MeO)_4$ (12·5)	30	600	42
(66) (6·9)	2,4,6-$(MeO)_3$ (6·9)	1,2,3,4-$(MeO)_4$ (6·25)	15	300	18
(71) (56)	(40)	1,2-$(MeO)_2$ (40)	80	1500	44

230°), was obtained as needles from methanol, identical with the natural product from *Ochrocarpos odoratus* (Rafin) Merrill. Selective demethylation *para* to the carbonyl (at C-3 or C-6) can be obviated by reducing the reaction time to 8 h. Similar results were obtained by using morpholine as the base.

(C) *With aqueous metal carbonates.* 2-Hydroxy-2′,3,4,6′-tetramethoxybenzophenone (4·1 g) in methanol (20 ml) containing water (45 ml) and potassium carbonate (5 g) was heated under reflux overnight and the cooled mixture was acidified (4N-HCl) and extracted with chloroform (2 × 100 ml). Evaporation of the dried ($MgSO_4$) extract gave an off-white solid. 1,5,6-Trimethoxyxanthone (3·4 g), m.p. 163° (lit.,[39] 150—151°), was obtained as needles from methanol. The synthetic product was identical (n.m.r., u.v., mixed m.p., m.p., and t.l.c.) with the compound obtained by methylating natural 1,5,6-trihydroxyxanthone.

(D) *With tetramethylammonium hydroxide.* 2-Hydroxy-2′,4,5,6′-tetramethoxybenzophenone (3·4 g) in pyridine (40 ml) containing water (30 ml) and tetramethylammonium hydroxide (6 ml; 25% w/v solution in water) was heated under reflux for 15 h and the cooled mixture was acidified (HCl) and extracted with chloroform (2 × 90 ml). Evaporation of the dried ($MgSO_4$) solution gave an almost white solid. 1,6,7-Trimethoxyxanthone (2·8 g), m.p. 202° (lit.,[40] 186—188°), was obtained as needles from methanol. The synthetic product was identical with samples from methylation of the metabolite from *Mammea africana* G. Don.

General Procedures for Selective Demethylation.—(a) *With boron trichloride.* The *o*-methylarylcarbonyl compound (1 g) in dichloromethane (50 ml) was stirred with boron trichloride (1 g) in dichloromethane (20 ml) for 0·3 h and the complex was poured into water (1 l) and stirred until the deep red or orange complex decomposed to a pale yellow solution. The mixture was extracted with dichloromethane (2 × 60 ml) and the solvent evaporated from the combined dried ($MgSO_4$) extracts. The resulting *o*-hydroxycarbonyl compound (*ca.* 0·9 g) was crystallised from a suitable solvent (usually methanol).

(b) *With piperidine.* The *p*-methoxyarylcarbonyl compound (1·5 g) in piperidine (30 ml) and water (30 ml) was refluxed for 45—65 h and the cooled mixture was poured into 4N-hydrochloric acid. The resulting suspension was extracted with dichloromethane or chloroform (3 × 100 ml), the organic layer was washed with 2N-hydrochloric acid (200 ml) and water (200 ml), and dried ($MgSO_4$). Evaporation of the solvent gave a precipitate (1·2 g) which was recrystallised. The following demethylations serve as examples. (i) 2-Hydroxy-3,4,5-trimethoxybenzophenone (I) gave 2,4-*dihydroxy*-3,5-*dimethoxybenzophenone* (3), m.p. 182—184° (from methanol), $\lambda_{max.}$ ($10^{-3}\varepsilon$) in the presence of sodium acetate 220 (37·3), 247 (12·3), 272sh (5·0), and 372 (22·2) nm [Found: C, 65·6; H, 5·2%; *M* (mass spectrum), 274. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·15%; *M*, 274]. (ii) 2,3-Dimethoxyxanthone (9) gave 3-hydroxy-2-methoxyxanthone (8) as needles, m.p. 241—242° (from methanol), identical with an authentic sample, prepared as described previously. (iii) 2,3,4-Trimethoxyxanthone (32) gave 3-hydroxy-2,4-dimethoxyxanthone (33), m.p. 201—202° (lit.,[23] 224—226°), as needles from methanol, identical with a natural sample kindly supplied by Professor O. R. Gottlieb, $\lambda_{max.}$ ($10^{-3}\varepsilon$) in the presence of acetate 232 (42·5), 272 (11·2), 350sh (13·0), and 380 (22·8) nm. (iv) 1-Hydroxy-3,4,7-trimethoxyxanthone (60) gave 1,3-dihydroxy-4,7-dimethoxyxanthone (61) as a brilliant yellow powder, m.p. 283—285° (decomp.) (from methanol), $\lambda_{max.}$ ($10^{-3}\varepsilon$) in the presence of acetate 212 (44·4), 230sh (32·8), 275 (25·2), 325sh (10·4), 347 (9·2), and 407 (7·2) nm.

(c) *With* DDQ–*methanol.* 2-Hydroxy-2,4,5-trimethoxybenzophenone (300 mg) in benzene (30 ml) containing DDQ (275 mg) was refluxed for 1·5 h, the filtrate was evaporated to dryness, and the resulting brown oil was boiled with methanol. The residue on evaporation was chromatographed on silica gel, eluting with benzene–ethyl acetate (4 : 1). The main band (yellow, black under u.v. light; R_F *ca.* 0·5) was removed, stripped with chloroform (100 ml), and the resulting solid, after evaporation, crystallised from ethyl acetate–petroleum (b.p. 100—120°) as a brilliant yellow powder (0·165 g), m.p. 195—196°. 2,5-*Dihydroxy*-2,4-*dimethoxybenzophenone* had $\lambda_{max.}$ ($10^{-3}\varepsilon$) in the presence of acetate 218 (17·3), 243 (13·3), 286 (10·9), and 362 (8·1) nm, $\lambda_{max.}$ ($10^{-3}\varepsilon$) in the presence of hydroxide ion 215 (21·7), 261 (15·7), 290sh (9·3), and 416 (4·8) nm [Found: C, 65·5; H, 5·2%; *M* (mass spectrum), 274. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·15%; *M*, 274].

The dihydroxybenzophenone re-formed 2-hydroxy-2′,4,5-trimethoxybenzophenone, m.p. 104—105°, identical with an authentic sample, on treatment with ethereal methanolic diazomethane for 4·5 h.

(d) *With hydrogen bromide in glacial acetic acid.* The appropriate polymethoxyxanthone (*ca.* 3 g) was refluxed with hydrogen bromide in glacial acetic acid (40 ml; 45% w/v) for the specified period, according to the products desired.

Where refluxing for >1 h was required, further hydrogen bromide in glacial acetic acid (10 ml) was added after each hour. The partially-evaporated solution was then decomposed with water (500 ml) and the crystalline product (*ca.* 2·5 g) withdrawn. The following dimethylations serve as examples. (i) 1,5,6-Trimethoxyxanthone. Reaction under the above conditions for 14 min gave 1-hydroxy-5,6-dimethoxyxanthone, m.p. 186—187°, identical with samples prepared above. Extended reaction for 8 h gave 1,5,6-trihydroxyxanthone, m.p. 300° (decomp.), identical with the natural product from *Ochrocarpos odoratus* (Rafin) Merrill.[38] (ii) 1,6,7-Trimethoxyxanthone. Reaction under the above conditions for 15 min gave 1-hydroxy-6,7-dimethoxyxanthone, m.p. 203°, as yellow needles from methanol, identical with an authentic sample. Reaction for 3·5 h gave 1,7-*dihydroxy*-6-*methoxyxanthone*, m.p. 269—270°, as a bright yellow crystalline solid from methanol, $\lambda_{max.}$ ($10^{-3}\varepsilon$) in the presence of acetate 218 (21·5), 250 (24·9), 267sh (12·8), 290 (9·3), and 370 (10·1) nm, $\lambda_{max.}$ ($10^{-3}\varepsilon$) in the presence of hydroxide 218 (32·4), 259 (26·5), 290sh (10·3), and 390 (8·5) nm [Found: C, 65·0; H, 4·1%; *M* (mass spectrum), 258. $C_{14}H_{10}O_5$ requires C, 65·1; H, 3·9%; *M*, 258]. Reaction for 18 h gave 1,6,7-trihydroxyxanthone as yellow needles from methanol, m.p. 283—287° (decomp.), identical with an authentic sample of the natural product from *Mammea africana* L.[41] (iii) 1,3,5,6-Tetramethoxyxanthone gave 1-hydroxy-3,5,6-trimethoxyxanthone after 15 min under the above conditions. The product, as yellow needles from methanol, m.p. 187°, was identical with an authentic sample. Further reaction for 15 h gave 1,3,5,6-tetra-

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

[40] B. Jackson, H. D. Locksley, and F. Scheinmann, *J. Chem. Soc.* (*C*), 1969, 2201.

[41] I. Carpenter, H. D. Locksley, and F. Scheinmann. *J. Chem. Soc.* (*C*), 1969, 2421.

hydroxyxanthone, m.p. 300° (decomp.), identical with an authentic sample. (iv) 1,3,6,7-Tetramethoxyxanthone gave 1-hydroxy-3,6,7-trimethoxyxanthone, m.p. 232—234° (from methanol), identical with an authentic sample after 30 min demethylation. After 3 h 1,7-dihydroxy-3,6-dimethoxyxanthone, m.p. 235—237°, was isolated, and formed yellow needles from methanol [Found: C, 62·4; H, 4·15%; *M* (mass spectrum), 288. Calc. for $C_{15}H_{12}O_6$: C, 62·5; H, 4·2; *M*, 288]. The pyrano-derivative (72), formed by treating the above dihydroxyxanthone with excess of 3-bromo-3-methylbut-1-yne and potassium carbonate in boiling acetone for 180 h, formed lustrous needles from ethanol. 11-*Hydroxy*-5,9-*dimethoxy*-3,3-*dimethylpyrano*[3,2-a]*xanthen*-12-*one* had m.p. 243° and R_F 0·85 in benzene–ethyl acetate (17 : 3), $\lambda_{max.}$ ($10^{-3}\varepsilon$) 210 (25·4), 243 (36·9), 264 (29·3), 321 (27·5), and 378 (7·7) nm, τ ($CDCl_3$) −3·18 (1H, s, OH), 2·12 and 4·30 (1H, both d, *J* 10 Hz, chromen CH=), 3·39 (1H, s, 6-H), 3·83 (2H, s, 8- and 10-H), 6·16 and 6·26 (both 3H, s, MeO), and 8·75 (6H, s, 2Me) [Found: C, 67·95; H, 5·0%; *M* (mass spectrum), 354. $C_{20}H_{18}O_6$ requires C, 67·8; H, 5·1%; *M*, 354]. After 18 h, 1,3,6,7-tetramethoxyxanthone demethylated to 1,3,6,7-tetrahydroxyxanthone, m.p. 270° (decomp.), identical with an authentic sample of the natural product. (v) 2,3,4-Trimethoxyxanthone gave 3,4-dihydroxy-2-methoxyxanthone as needles from methanol, m.p. 257—259° (lit.,[22] 243—245°), after 18 min demethylation. The compound was identical with an authentic sample of the natural product. After 5 h 2,3,4-trihydroxyxanthone was obtained as a solid which crystallised from methanol as needles, m.p. 275—278° (lit.,[22] over 300°) (decomp.) [Found: C, 63·75; H, 3·4%; *M* (mass spectrum), 244. Calc. for $C_{13}H_8O_5$: C, 63·9; H, 3·3%; *M*, 244]. The *tribenzyl ether*, prepared by treating the trihydroxyxanthone with an excess of benzyl chloride in the presence of potassium carbonate in boiling acetone for 8 h, crystallised from ethanol as needles, m.p. 153—154°, τ ($CDCl_3$) 1·53 (1H, m), 2·20—2·70 (19H, m), and 4·70—4·75 (6H, m, $3CH_2$), $\nu_{max.}$ 1658, 1619, 1610, 1599, 1150, 1097, 735, and 695 cm^{-1} (Found: C, 79·2; H, 5·1. $C_{34}H_{26}O_5$ requires C, 79·4; H, 5·1%).

Preparation of C- *and* O-*Allylbenzophenones.*—2-*Allyloxy*-2′,4,4′,5,6′-*pentamethoxybenzophenone.* 2-Hydroxy-2′,4,4′,5,6′-pentamethoxybenzophenone (0·95 g) in acetone (70 ml) containing potassium carbonate (2·4 g) and allyl bromide (2·1 g; excess) was refluxed overnight. Evaporation of the filtered solution gave an oil which formed needles from light petroleum (b.p. 80—100°). 2-*Allyloxy*-2′,4,4′,5,6′-*pentamethoxybenzophenone* (0·81 g) was obtained, m.p. 140—142°, $\nu_{max.}$ 1645, 1610, 1530, 1281, 1140, 1209, and 810 cm^{-1}, τ ($CDCl_3$; 100 MHz) 2·65 (1H, s, 6-H), 3·69 (1H, s, 3-H), 4·02 (2H, s, 3′- and 5′-H), 6·22, 6·28, 6·44, 6·44 (all 3H, s, MeO), 4·3—4·65 (1H, m, CH=), 5·00 (2H, m, $=CH_2$), and 5·85 (2H, d, *J* 7 Hz, OCH_2) (Found: C, 65·15; H, 6·1. $C_{21}H_{24}O_7$ requires C, 64·95; H, 6·25%).

3-*Allyl*-2-*hydroxy*-2′,4,4′,5,6′-*pentamethoxybenzophenone.* 2-Allyloxy-2′,4,4′,5,6′-pentamethoxybenzophenone (0·500 g) in *NN*-dimethylaniline (10 ml) was refluxed for 4 h and the cooled mixture was poured into 2N-hydrochloric acid. The resulting suspension was extracted with chloroform (75 ml) and the washed (HCl, then water) and dried ($MgSO_4$) organic layer was evaporated to an oil which did not crystallise. Chromatography on silica gel, eluting with benzene–ethyl acetate gave pure 3-*allyl*-2-*hydroxy*-2′,4,4′,5,6′-*pentamethoxybenzophenone* (0·31 g) as a pale yellow oil, τ ($CDCl_3$; 100 MHz) −2·40 (1H, s, OH), 3·45 (1H, s, 6-H), 3·98 (2H, s, 3′- and 5′-H), 6·25, 6·28, 6·41, 6·41, 6·50 (all 3H, s, MeO), 4·1—4·3 (1H, v, 1H, CH=), 5·00 (2H, m, $=CH_2$), and 6·61 (d, *J* 7 Hz, CH_2) (Found: C, 64·65; H, 5·95. $C_{21}H_{24}O_7$ requires C, 64·95; H, 6·25%).

Procedures Involving Selective Methylation.—(a) 3,5,6-*Trihydroxy*-1-*methoxyxanthone.* 1,3,5,6-Tetrahydroxyxanthone (3·6 g) in acetone (190 ml) containing anhydrous potassium carbonate (7·5 g) and benzyl chloride (7·0 g; excess) was refluxed until reaction was complete (t.l.c.; 3·5 h). Evaporation of the filtrate gave a solid, the chloroform-soluble fraction of which crystallised from ethanol as needles (2·9 g). 3,5,6-*Trisbenzyloxy*-1-*hydroxyxanthone* had m.p. 160—161°, $\nu_{max.}$ 1665, 1610, 1165, 805, 743, and 695 cm^{-1}, τ ($CDCl_3$) −3·02 (1H, s, OH), 2·02 and 2·97 (both 1H, d, *J* 9 Hz, 8- and 7-H), 2·40—2·65 (15H, m, Ph), 3·48 and 3·58 (both 1H, d, *J* 2·5 Hz, 4- and 2-H), and 4·75, 4·81, and 4·89 (all 2H, s, CH_2) (Found: C, 77·2; H, 5·05. $C_{34}H_{26}O_6$ requires C, 77·0; H, 4·95%). Methylation with excess of dimethyl sulphate–potassium carbonate in acetone gave 3,5,6-*trisbenzyloxy*-1-*methoxyxanthone* as needles from ethanol, m.p. 182—183°, $\nu_{max.}$ 1667, 1610, 1130, 815, and 730 cm^{-1}, τ ($CDCl_3$) 1·92, 2·97 (both 1H, d, *J* 9 Hz, 8- and 7-H), 2·35—2·65 (15H, m, 3Ph), 3·42 and 3·52 (both 1H, d, *J* 2·5 Hz, 4- and 2-H), 4·75, 4·78, and 4·83 (all 2H, s, CH_2), and 6·03 (3H, s, MeO) (Found: C, 77·25; H, 5·35. $C_{35}H_{28}O_6$ requires C, 77·2; H, 5·2%).

This compound (0·5 g) in ethanol (100 ml) containing platinum oxide (95 mg) was shaken under hydrogen overnight and the filtrate was evaporated. The residue crystallised from methanol to give 3,5,6-*trihydroxy*-1-*methoxyxanthone* (0·18 g) as a microcrystalline solid, m.p. >300° (decomp.) [lit.,[8] 294° (decomp.)] (Found: C, 61·45; H, 3·65. Calc. for $C_{14}H_{10}O_6$: C, 61·3; H, 3·7%). Methylation of the above compound with excess of dimethyl sulphate gave 1,3,5,6-tetramethoxyxanthone, m.p. 145°, identical with an authentic sample.

(b) 4-*Hydroxy*-2,3-*dimethoxyxanthone.* 3,4-Dihydroxy-2-methoxyxanthone (0·75 g) in acetone (50 ml) containing potassium hydrogen carbonate (1·0 g) and dimethyl sulphate (0·38 g) (1·1 mole ratio) was heated under reflux overnight. The chloroform-soluble fraction of the evaporated filtrate crystallised from ethanol to give 4-*hydroxy*-2,3-*dimethoxyxanthone* (0·75 g) as needles, m.p. 224—226° (lit.,[23] 218—219°), $\lambda_{max.}$ ($10^{-3}\varepsilon$) in the presence of acetate 210 (29·1), 236 (24·3), 255 (24·3), 275 (13·6), 305 (9·1), and 350sh (6·4) nm, $\lambda_{max.}$ ($10^{-3}\varepsilon$) in the presence of hydroxide 213 (48·6), 235sh (24·3), 275 (23·1), 298 (10·0), 335 (7·6), and 396 (3·95) nm [Found: C, 66·0; H, 4·6; *M* (mass spectrum), 272. $C_{15}H_{12}O_5$ requires C, 66·2; H, 4·45%; *M*, 272]. The synthetic compound was identical with a sample of the natural product kindly supplied by Professor O. R. Gottlieb.

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