Constituents of *Mammea americana* L. Part X.[1] The Isolation of Some Mono- and Di-hydroxyxanthones. Observations on the Synthesis of 1,5-, 3,5-,1,6-, and 1,7-Dihydroxyxanthone †

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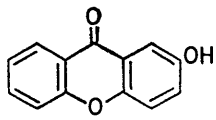
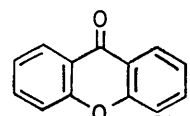
Chromatography of the ethanol extract of mamey seed residues (previously extracted with hexane) provided 2- and 4-hydroxyxanthone along with 1,7-dihydroxyxanthone (euxanthone) and the previously unknown 1,5-dihydroxyxanthone. These substances were identified by comparison with samples prepared independently.

NEARLY all previously published work on the constituents of the seed of *M. americana* (family Guttiferae) has dealt with the de-waxed light petroleum extract known as mamey oil. Some years ago,[2] however, we had occasion to examine more polar extracts of the seed residue remaining after the oil had been removed. These efforts led to the isolation of new natural compounds, one of which was identified as 2-hydroxyxanthone (I).[3] Another compound, m.p. 245—246°, was characterized as a 'C_{12} phenol'[2] on the basis of what are now known to be faulty microanalytical data.

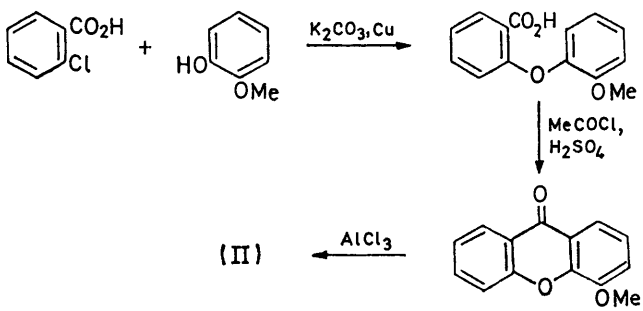


(I)



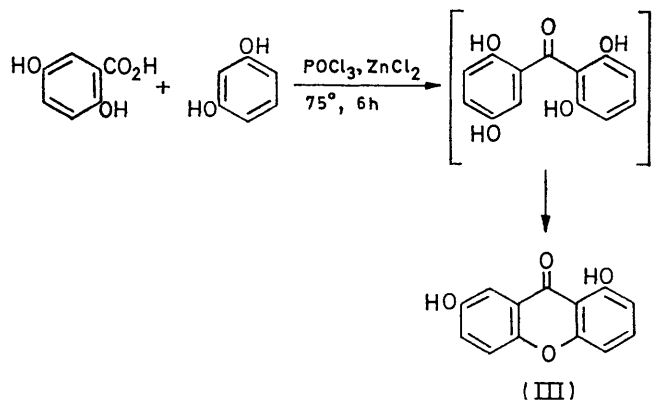
(II)

Re-examination of this substance after its reisolation required its formulation as $C_{13}H_8O_3$ and led to its identification as 4-hydroxyxanthone (II). This assignment was strongly indicated by comparison of spectroscopic properties with those published for all the monohydroxyxanthones,[3-6] and was verified by comparison with a synthetic sample prepared by the Ullmann reaction (Scheme 1).[3,7]



SCHEME 1

Immediately following the elution of compound (II) during the chromatography of the mamey extract, fractions were obtained which yielded bright yellow needles, m.p. 240—241°. Analytical data agreed with the formula $C_{13}H_8O_4$ and spectroscopic data were also in accord with a dihydroxyxanthone structure. A number of dihydroxyxanthones, *e.g.*, 1,4-, 1,6-, 3,4-, and 1,7-, have m.p.s near to that of the plant isolate. The most likely candidate seemed to be the 1,7-isomer, euxanthone (III), since this has been found to occur in other members of the family Guttiferae.[8] This supposition was verified by the preparation of an authentic sample of (III) by two different methods. Although it has been reported[9] that 2,5-dihydroxybenzoic acid does not condense with reactive phenols, we have observed that this condensation with resorcinol can be effected by use of the conditions of Grover, Shah, and Shah,[9] to give



SCHEME 2

euxanthone (III), albeit in low yield (Scheme 2). Although the product of this reaction proved to be identical with the naturally occurring material, it was considered advisable to prepare a sample of (III) by an unambiguous route (Scheme 3); the product in this case was indistinguishable from the other specimens of (III).

In an attempt to devise a shorter preparation of compound (III), the condensation of 2,6-dihydroxybenzoic acid with hydroquinone was studied; however, no euxanthone (III) was formed. Only 1,6-dihydroxy-

† Preliminary communication, R. A. Finnegan, J. K. Patel, and P. L. Bachman, *Tetrahedron Letters*, 1966, 6087.

[1] Part IX, R. A. Finnegan and K. E. Merkel, *J. Pharm. Sci.*, 1972, **61**.

[2] P. L. Bachman, Ph.D. Thesis, Ohio State University, 1965.

[3] R. A. Finnegan and P. L. Bachman, *J. Pharm. Sci.*, 1965, **54**, 633.

[4] R. P. Mull and F. F. Nord, *Arch. Biochem.*, 1944, **4**, 419.

[5] F. Scheinmann, *Tetrahedron*, 1962, **18**, 853.

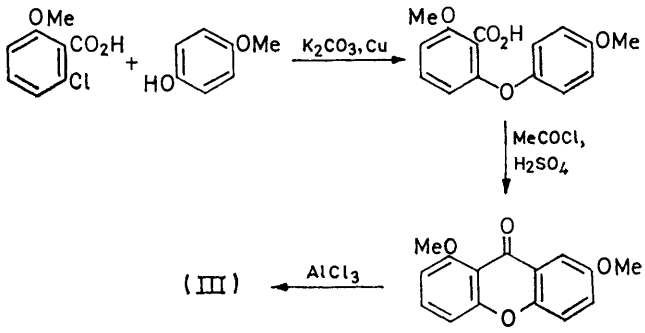
[6] G. E. Bonvicino, H. G. Arlt, jun., K. M. Pearson, and R. A. Hardy, jun., *J. Org. Chem.*, 1961, **26**, 2383.

[7] J. S. H. Davies, F. Lamb, and H. Suschitzky, *J. Chem. Soc.*, 1958, 1790.

[8] For a review see I. Carpenter, H. D. Locksley, and F. Scheinmann, *Phytochemistry*, 1969, **8**, 2013.

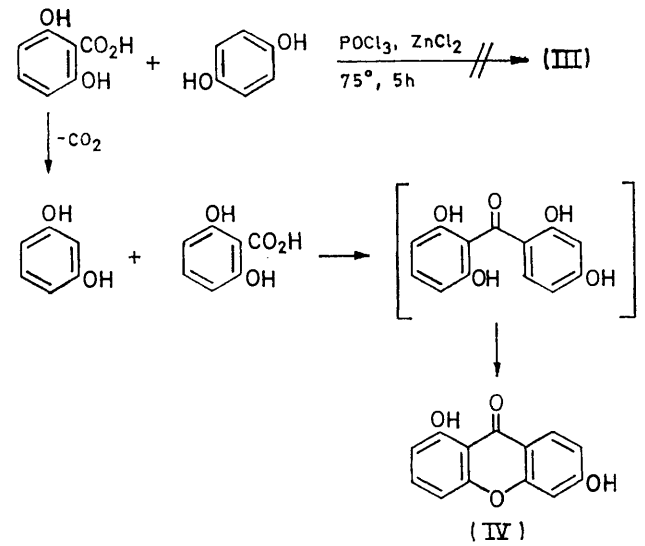
[9] P. K. Grover, G. D. Shah, and R. C. Shah, *J. Chem. Soc.*, 1955, 3982.

xanthone (IV) was isolated, in low yield. This product results from the condensation of the acid with resorcinol, the latter being formed by decarboxylation of the



SCHEME 3

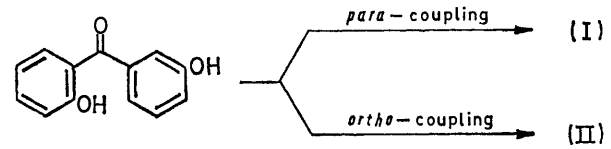
former (Scheme 4).* This observation has also been made independently.[10]



SCHEME 4

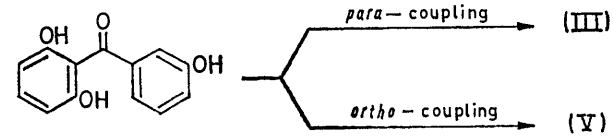
As there was some variation in the reported m.p.s of compound (IV)[4,9–11] and its diacetate,[10,11] the former was prepared by the separate condensation of 2,6-dihydroxybenzoic acid and resorcinol (*cf.* Scheme 4) and was fully characterized as both its diacetate and its dimethyl ether (see Experimental section).

In the chromatography of the mamey seed extract, another crystalline isolate, m.p. 260—261°, was obtained which, in fact, was the first eluted from the column. Analytical and spectroscopic data classified this material as a dihydroxyxanthone isomeric with (III). Both the 1,3-isomer, m.p. 261—262°, and the 1,6-isomer, m.p. 258—259°, were eliminated on the basis of direct comparisons; it therefore appeared that this dihydroxyxanthone had not been previously described.† By this time there had appeared[13] a number of indications supporting the proposal of Lewis[14] that certain naturally occurring xanthones may be generated by an oxidative cyclization of an appropriately hydroxylated benzophenone precursor. Our finding that the 2- and 4-hydroxyxanthones co-occur in *M. americana* lent circumstantial support to that proposal (Scheme 5). Should



SCHEME 5

this process be imagined to account for the presence of euxanthone (III), the requisite benzophenone (Scheme 6)



SCHEME 6

could be expected also to give rise to 1,5-dihydroxyxanthone (V). On this basis we set out to prepare compound (V), at first directly, by the condensation of 2,6-dihydroxybenzoic acid with catechol. This led, however, just as in the condensation with hydroquinone (Scheme 4), to the 1,6-isomer (IV).‡ Accordingly, an unambiguous route (Scheme 7) was used; the product (V), although slightly higher melting (265—266°) than the naturally derived sample (m.p. 260—261°) (mixed m.p. 261—263°) had i.r. and u.v. spectra identical with those of the natural product. Thus, the presence of a second pair of simple xanthones in *M. americana*, biogenetically related as in Scheme 6, is established. Compound (V) has since been discovered in a number of other Guttiferae[8,16–19] and has also been synthesized by an alternative route.[15,17]

In a further attempt to prepare compound (V), the condensation of 2,3-dihydroxybenzoic acid with resorcinol was studied. The desired condensation at the 2-position of resorcinol (*cf.* Scheme 2) did not occur, however. Instead, the tetrahydroxybenzophenone (VI) was

* It is possible that decarboxylation takes place at a later stage.

† At this time, the 1,5-, 2,5-, and 4,5-dihydroxyxanthones were unknown. The latter two have now been prepared by Merkel.[12]

‡ This result has been observed independently by other workers.[15]

[10] H. D. Locksley, I. Moore, and F. Scheinmann, *J. Chem. Soc.* (*C*), 1966, 430.

[11] C. Graebe, *Annalen*, 1889, **254**, 302.

[12] (*a*) K. E. Merkel, Ph.D. Thesis, State University of New York at Buffalo, 1970; (*b*) R. A. Finnegan and K. E. Merkel, *J. Org. Chem.*, in the press.

[13] J. R. Lewis and B. H. Warrington, *J. Chem. Soc.*, 1964, 5074, and references cited therein.

[14] J. R. Lewis, *Proc. Chem. Soc.*, 1963, 373.

[15] B. Jackson, H. D. Locksley, and F. Scheinmann, *J. Chem. Soc.* (*C*), 1967, 785.

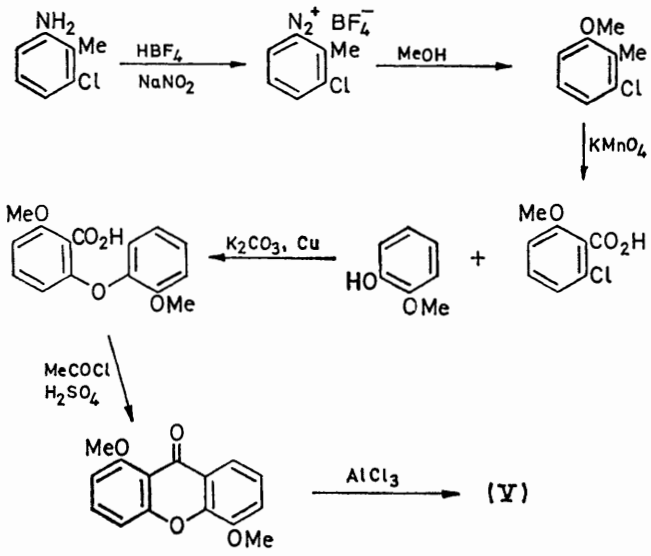
[16] Y. L. Chow and H. H. Quon, *Phytochemistry*, 1968, **7**, 1871.

[17] B. Jackson, H. D. Lcoksley, I. Moore, and F. Scheinmann, *J. Chem. Soc.* (*C*), 1968, 2579.

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

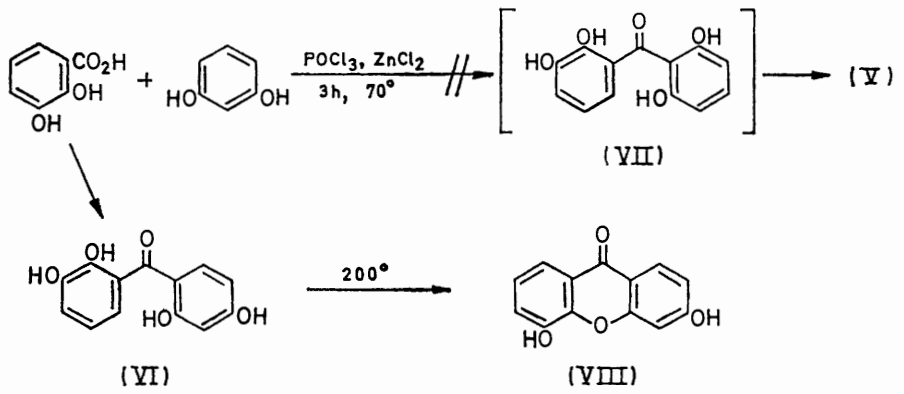
[19] H. D. Locksley and I. G. Murray, *J. Chem. Soc.* (*C*), 1971, 1332.

obtained, in moderate yield (Scheme 8). The fact that a benzophenone was isolated at all mitigated against the

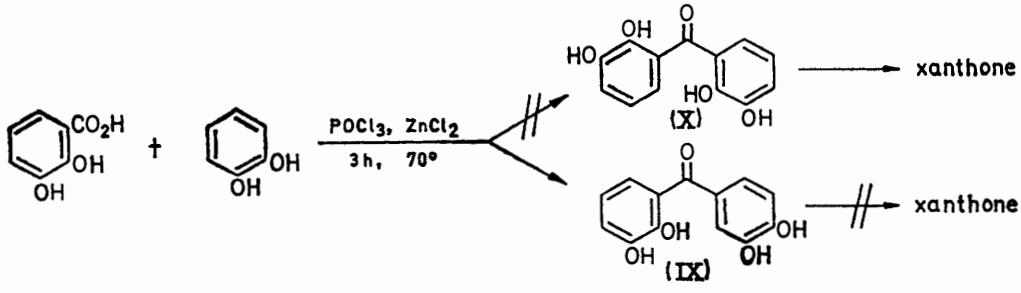


SCHEME 7

alternative structure (VII) since 2,2',6-trihydroxybenzophenones invariably cyclize to xanthones under the conditions of this reaction.[9] That this condensation did not involve decarboxylation and utilization of the resultant catechol was shown by a separate experiment (Scheme 9), which produced a benzophenone (IX) clearly different from (VI), and for which the alternative structure (X) was ruled out since it could not be converted into a xanthone by cyclodehydration.* It was found possible (in any event) to convert the benzophenone (VI) into a xanthone, shown ultimately to be 3,5-dihydroxyxanthone (VIII) (Scheme 8). The identity of (VIII) was not immediately evident since its recorded m.p.[14] was nearly 100° lower than that which we observed. On the other hand, the m.p. of the derived dimethyl ether was in good agreement with that reported.[14,20] Furthermore, this same dimethyl ether was prepared by the procedure (with slight modification [21]) of Noyes and Weldon.[20] Demethylation of this specimen produced compound (VIII), identical with that formed as shown in Scheme 7. The discrepancy was rectified when we discovered that the '3,5-dihydroxyxanthone' of the literature[14]† was in fact 3-hydroxy-5-methoxyxanthone; this has since been verified by Dr. Lewis.[22]



SCHEME 8



SCHEME 9

EXPERIMENTAL

I.r. spectra were measured with a Perkin-Elmer 237 spectrophotometer and u.v. measurements were made with a Perkin-Elmer 202 instrument. ^{1}H N.m.r. spectra were measured with a Varian A60 spectrometer (tetramethylsilane as internal standard) for solutions in [$^2H_6$]dimethyl sulphoxide, [$^2H_6$]acetone, or [^{2}H]chloroform. All solvents used in the isolation work, recrystallizations, *etc.*, were

* Subsequently, compound (X) was prepared by another route and readily dehydrated to produce 4,5-dihydroxyxanthone.[12]

† We thank Dr. Lewis for exchange of samples and information.

[20] D. S. Noyce and J. W. Weldon, *J. Amer. Chem. Soc.*, 1952, **74**, 5144.

[21] J. K. Patel, M.S. Thesis, State University of New York at Buffalo, 1967.

[22] J. E. Atkinson and J. R. Lewis, *J. Chem. Soc.* (*C*), 1969, 281.

either distilled before use or else were of reagent grade. Analyses were performed by the Microanalytical Laboratory, Max-Plank Institut für Kohlenforschung, Mühlheim, Germany, and mass spectral results were obtained from Prof. A. L. Burlingame. Plates for t.l.c. were coated with silica gel G (Merck) and spots were detected by exposure to u.v. light and/or iodine vapour.

Isolation.—Dried and ground seeds (35 kg) of *Mammea americana* L., previously extracted with hexane and benzene,[2] were extracted with ethanol (total 10 l) in a Soxhlet extractor of 5 l capacity mounted on a 12 l pot. Removal of the solvent under reduced pressure afforded a dark viscous oil (300 g). Two portions of this oil (68·8 and 75·6 g) were chromatographed separately over silica gel (1700 g). Elution was carried out with 2-methylpentane, 2-methylpentane–chloroform, chloroform, and chloroform–ethanol; 2 l fractions were collected.

1,5-*Dihydroxyxanthone* (V).—During elution with 3 : 2 (v/v) 2-methylpentane–chloroform, a yellow semisolid was obtained [1·47 g (fractions 26—28) and 1·52 g (fractions 23—25)] from each of the two columns. Recrystallizations from chloroform–2-methylpentane gave 1,5-*dihydroxyxanthone* (V) (0·11 g), m.p. 260—261°; $\nu_{max.}$ (KBr) 3413, 1650sh, 1661sh, 1645, 1277, 1241, 895, 854, 826, 794, 757, 725, and 690 cm^{-1}; $\lambda_{max.}$ (EtOH) 252, 318, and 378 nm (log ε 4·62, 3·92, and 3·73); $\lambda_{max.}$ (EtOH–NaOH) 252, 318, 358, and 416 nm (log ε 4·62, 3·82, 3·93, and 3·86) [Found: C, 68·35; H, 3·65; O, 27·95%; *M* (Rast), 218; *M* (mass spec.) 228. $C_{13}H_8O_4$ requires C, 68·4; H, 3·55; O, 28·05%; *M*, 228].

Although t.l.c. of this material showed only one spot with iodine (R_F 0·14 in chloroform; 0·29 in 2% acetic acid–chloroform), a peak at *m/e* 212 in the mass spectrum suggested some contamination by compound (II). Compound (V) was identical with a synthetic sample of m.p. 265—266° (i.r. and u.v. spectra; mixed m.p. 261—263°).

4-*Hydroxyxanthone* (II).—Continued elution of the columns, with 3 : 2 2-methylpentane–chloroform yielded more yellow semisolid [1·14 g (fractions 29—36) and 0·81 g (26—28)]. Recrystallizations from chloroform–2-methylpentane gave yellow crystals (0·12 g), m.p. 223—225° (sublimes). T.l.c. showed a single spot (R_F 0·09 in chloroform; 0·25 in 2% acetic acid–chloroform); however the mass spectrum showed peaks at *m/e* 228 (dihydroxyxanthone) and 258. The latter peak suggests the presence of a methoxydihydroxyxanthone and a peak in the n.m.r. spectrum at δ 3·7 p.p.m. is consistent with this.

Repeated recrystallizations from acetone–2-methylpentane, followed by three sublimations at 135° and 0·05 mmHg, afforded 4-hydroxyxanthone (II), m.p. 239—242°; $\nu_{max.}$ (KBr) 3322, 1653sh, 1647, 1613, 1605, 905, and 748 cm^{-1}; $\lambda_{max.}$ (EtOH) 235sh, 250, 282, 290, and 353 nm (log ε 4·45, 4·59, 3·80, 3·73, and 3·66); $\lambda_{max.}$ (EtOH–NaOH) 235, 269, 301, 311, and 402 nm (log ε 4·44, 4·51, 3·94, 3·94, and 3·51), identified by i.r. and u.v. spectral comparisons, and mixed m.p. determination (m.p. 239—242°) with a synthetic sample of m.p. 245—246°.

A sample of Bachman's 'C_{12} phenol',[2] m.p. 245—246°, was resubmitted for microanalysis after being dried under high vacuum for 24 h (Found: C, 73·6; H, 3·5. Calc. for $C_{13}H_8O_3$: C, 73·6; H, 3·8%). The i.r. and u.v. spectra of this material were indistinguishable from those of synthetic (II), mixed m.p. 245—246°.

1,7-*Dihydroxyxanthone* (III) (*Euxanthone*).—Immediately following the elution of compound (II), more bright yellow semisolid was obtained from both columns [1·05 g (fractions 37—46) and 0·89 g (fractions 29—40)], from the 3 : 2 2-methylpentane–chloroform eluate. Recrystallizations from chloroform–2-methylpentane gave euxanthone (III) as bright yellow needles (0·11 g), m.p. 240—241°; $\nu_{max.}$ (KBr) 3311, 1639, 1645sh, 1653sh, 1233, 832, 813, 763, 719, and 690 cm^{-1}; $\lambda_{max.}$ (EtOH) 237, 262, 289, 315sh, and 391 nm (log ε 4·53, 4·60, 3·76, 3·38, and 3·90); $\lambda_{max.}$ (EtOH–NaOH) 251, 272sh, 350, and 430 nm (log ε 4·61, 4·53, 3·52, and 3·93) [Found: C, 67·9; H, 3·5; O, 28·35%; *M* (Rast), 197. Calc. for $C_{13}H_8O_4$: C, 68·4; H, 3·55; O, 28·05%; *M*, 228], identical (i.r. and u.v. spectra; mixed m.p. 240—241°) with a synthetic sample of m.p. 240—241°.

2-*Hydroxyxanthone* (I).—During elution with 1 : 1 2-methylpentane–chloroform, yellow semicrystalline material was obtained [0·69 g (fractions 47—55) and 0·84 g (fractions 41—51)] from the two columns. Recrystallization from chloroform–2-methylpentane gave yellow crystals (0·20 g), m.p. 235—238°. Treatment with charcoal in acetone, and recrystallization from acetone–2-methylpentane gave 2-hydroxyxanthone (I), m.p. 242°, identical (i.r., u.v., mixed m.p.) with an authentic sample.[3]

Other Constituents.—The following substances were isolated in amounts too small for characterization beyond the spectral data here recorded: compound A, m.p. 200—205°; $\nu_{max.}$ (KBr) 3472, 1751, 1600, 1440, 1380, 1115, 850, 770, and 703 cm^{-1}; $\lambda_{max.}$ (EtOH) 214, 240sh, 283, and 332 nm; $\lambda_{max.}$ (EtOH–NaOH) 255, 282sh, 302, and 416 nm; compound B, m.p. 215—220°; $\nu_{max.}$ (KBr) 3436br, 1667, 1600, 1500, 1595, 1420, 1310, 1240, 1165, 1100, 1015, 925, 850, 770, and 690 cm^{-1}; $\lambda_{max.}$ (EtOH) 212 and 260 nm; $\lambda_{max.}$ (EtOH–NaOH) 278 nm; compound C, m.p. 280—285°; $\nu_{max.}$ (KBr) 3400—2500vbr, 1700, 1440, 1310, 1190, 1170, 1030, 940, and 800 cm^{-1}; $\lambda_{max.}$ (EtOH) 210 and 270 nm; $\lambda_{max.}$ (EtOH–NaOH) 270 nm; compound D, m.p. 205—207°; $\nu_{max.}$ (KBr) 3300—3500br, 1684, 1600, 1510, 1290, 1120, 1090, 940, 815, and 760 cm^{-1}; $\lambda_{max.}$ (EtOH) 220, 260, and 298 nm; $\lambda_{max.}$ (EtOH–NaOH) 228, 280, and 307 nm.

In addition, Merkel [12a] has isolated, from a polar extract, sucrose and succinic acid (identified by comparison with authentic samples), a long chain fatty acid of m.p. 57—58°, and a yellow solid of m.p. 249—250°; $\nu_{max.}$ (KBr) 3400—3000br, 1639, 1603, 1490, 1473, 1297, 1279, 1252, 1203, 1105, 1085, and 792 cm^{-1}.

2-*Chloro*-6-*methoxytoluene.*—Fluoroboric acid (500 ml) was mixed with water (500 ml) and 2-chloro-6-aminotoluene (150 g) was dissolved in the solution. The amine salt precipitated. While this mixture was stirred and cooled (5—10°), sodium nitrite (75 g) in water (500 ml) was added dropwise. The mixture was then allowed to warm to room temperature. The solid diazonium salt was collected, washed with a little methanol and then with ether, and heated with methanol (1300 ml) on a steam-bath until the evolution of nitrogen ceased. Methanol (*ca.* 1 l) was distilled off under reduced pressure and the residue was poured into cold water (600 ml) and steam distilled. The distillate was extracted with chloroform and the extract was dried ($MgSO_4$). The solvent was removed to give an oily product (85·6 g, 52%), characterized by its i.r. spectrum, and used without further purification. This procedure was more convenient than the one described in the literature.[23]

2-*Chloro*-6-*methoxybenzoic Acid.*—A mixture of 2-chloro-6-methoxytoluene (44·4 g), water (4 l), potassium permanganate (132 g), and 5% sodium hydroxide solution (460 ml)

[23] F. Ullmann and L. Panchaud, *Annalen*, 1906, **350**, 108.

was heated on a steam-bath for 5 h with stirring, then filtered hot. The collected solid was washed with hot water and the combined filtrate and washings were cooled, clarified by ether extraction, and concentrated to 1100 ml. Acidification gave 2-chloro-6-methoxybenzoic acid (21·5 g), m.p. 140—141° (lit.,[24] 141—144).

1,5-*Dimethoxyxanthone*.—Condensation of 2-chloro-6-methoxybenzoic acid (12·2 g) with *o*-methoxyphenol (9·8 g) by use of potassium carbonate (20·4 g) and moist copper [25] in n-butanol (60 ml) was carried out as already described.[3] The crude diphenyl ether (12 g) was cyclized by dissolving it in acetyl chloride (132 ml) and cautiously adding concentrated sulphuric acid (2·4 ml). After the initial reaction subsided, the flask was stoppered and set aside for 10 min. Excess of acetyl chloride (*ca.* 120 ml) was then distilled off and the residue was poured into cold water (800 ml) and extracted with chloroform. The extract was washed thoroughly with saturated sodium hydrogen carbonate solution, 10% potassium hydroxide solution, and water, then dried and evaporated to give a semisolid (1·83 g). Treatment with charcoal and recrystallization from chloroform–2-methylpentane gave colourless shining needles (0·98 g), m.p. 186—188°. One additional recrystallization afforded 1,5-dimethoxyxanthone, m.p. 190°; $\nu_{max.}$ (KBr) 2857, 1667, 1600, 1570, 1493, 1471, 1433, 1351, 1267, 1103, 971, 943, 847, 781, and 724 cm^{-1}; $\lambda_{max.}$ (EtOH) 239sh, 247, 307, and 355 nm (log ε 4·62, 4·67, 3·98, and 3·85) (Found: C, 69·9; H, 4·7; OMe, 24·45. Calc. for $C_{15}H_{12}O_4$: C, 70·3; H, 4·7; 2 × OMe, 24·2%) (lit.,[15] m.p. 194—196°).

1,5-*Dihydroxyxanthone* (V).—A mixture of 1,5-dimethoxyxanthone (500 mg), freshly ground anhydrous aluminum chloride (10 g), and toluene (80 ml) was heated on a steam-bath for 2 h, then cooled. Conc. hydrochloric acid was added dropwise until the reaction subsided. Water (300 ml) was then added and the mixture was extracted with ether several times. The deep red extract was washed with water, then extracted with aqueous 5% sodium hydroxide solution until it was colourless. The deep yellow aqueous alkaline extract was acidified with conc. hydrochloric acid and the resultant precipitate was collected, washed with water, and dried (yield 400 mg, m.p. 261—262°). Treatment with charcoal and two recrystallizations from chloroform–2-methylpentane afforded 1,5-dihydroxyxanthone (V) as bright yellow shining needles, m.p. 265—266° (lit.,[15] 271—273°), identical with the natural product.

4-*Hydroxyxanthone* (II).—This compound, prepared [21] according to Scheme 1, had m.p. 245—246° (lit.,[4] 240—242° [4]), and was identical with the naturally derived material.

1,7-*Dihydroxyxanthone* (III).—This compound, prepared [21] according to Scheme 3, had m.p. 240—241° (lit.,[10] 238—240°; lit.,[26] 236—238°), and was identical with the naturally derived sample.

Condensation of 2,5-*Dihydroxybenzoic Acid with Resorcinol.*—An intimate mixture of 2,5-dihydroxybenzoic acid (10 g), resorcinol (10 g), freshly fused anhydrous zinc chloride (30 g), and phosphoryl chloride (75 ml), was heated at 70—75° in the absence of moisture for 6 h. The mixture was then allowed to cool to room temperature and was poured over crushed ice, in small portions, with stirring. The resulting mixture was then extracted several times with chloroform and the combined extracts were washed with 5% sodium carbonate solution and with water, dried ($MgSO_4$), and evaporated under reduced pressure to give a semisolid, which was recrystallized twice from acetone–2-methylpentane after treatment with charcoal to give shining bright yellow needles of 1,7-dihydroxyxanthone, m.p. and mixed m.p. 240—241°, identical with the foregoing synthetic material (i.r. and u.v. spectra).*

1,6-*Dihydroxyxanthone* (IV), *its Dimethyl Ether, and its Diacetate*.—An intimate mixture of 2,6-dihydroxybenzoic acid (10 g), resorcinol (10 g), freshly fused zinc chloride (70 g), and phosphoryl chloride (130 ml), was heated at 65—70° for 6 h. It was then cooled to room temperature and poured over crushed ice with stirring. The separated orange-coloured solid was collected and washed with saturated sodium hydrogen carbonate solution, then with water, and dried (yield 2·16 g, m.p. 200—203°). Treatment with charcoal and two recrystallizations from aqueous ethanol gave 1,6-dihydroxyxanthone (IV), shining yellow needles (0·53 g), m.p. 258—259° (lit.,[4] 242—243°; lit.,[10] 250—252°; lit.,[9] 246—247°; lit.,[11] 245—246°). Treatment with dimethyl sulphate and potassium carbonate in refluxing acetone afforded 1,6-dimethoxyxanthone, m.p. 178—179° (from chloroform–2-methylpentane); $\nu_{max.}$ (KBr) 2849, 1664, 1623, 1605, 1572, 1479, 1441, 1376, 1340, 1269, 1233, 1163, 1110, 1093, 1026, 952, 848, 800, 775, 719, 685, and 671 cm^{-1}; $\lambda_{max.}$ (EtOH) 233, 246sh, 289, and 345 nm (log ε 4·42, 4·32, 4·04, and 3·88); δ 3·78 and 3·90 p.p.m. (each s, OMe). Acetylation of compound (IV) (acetic anhydride–pyridine) provided 1,6-diacetoxyxanthone, m.p. 154—155° (lit.,[9] 155°; lit.,[11] 124—130°); $\nu_{max.}$ (KBr) 1767, 1664, 1621, 1613, 1471, 1431, 1374, 1333, 1300, 1190, 1145, 1043, 893, 847, 820, 794, 725, and 667 cm^{-1}.

Condensation of 2,3-*Dihydroxybenzoic Acid with Resorcinol.* 2,2′,3,4′-*Tetrahydroxybenzophenone* (VI).—An intimate mixture of 2,3-dihydroxybenzoic acid (10 g), resorcinol (12 g), freshly fused zinc chloride (30 g), and phosphoroyl chloride (70 ml) was heated at 65—70° for 3 h. The mixture was allowed to cool to room temperature and poured in small portions over crushed ice with stirring. The separated orange-coloured solid was collected (yield 7·58 g, m.p. 150—156°). Treatment with charcoal in acetone and recrystallization from aqueous ethanol gave the *benzophenone* (VI) as bright yellow needles (5·06 g), m.p. 155—158°. Recrystallization gave a sample of m.p. 160—161°; $\nu_{max.}$ (KBr) 3311, 1642sh, 1637, 1623, 1603, 1527, 1466, 1361, 1337, 1266, 1124, 862, 840, 760, and 735 cm^{-1}; $\lambda_{max.}$ (EtOH) 220, 290, and 328 nm (log ε 4·29, 4·11, and 4·06); $\lambda_{max.}$ (EtOH–NaOH) 230, 252sh, and 342 nm (log ε 4·21, 4·15, and 4·30) (Found: C, 63·45; H, 4·15. $C_{13}H_{10}O_5$ requires C, 63·4; H, 4·1%).†

2,2′,3,4′-*Tetramethoxybenzophenone*.—A mixture of

* The formation of (III) (*via* acylation of resorcinol at the 2-position) was not expected; however the yield (*ca.* 0·1%) was small and no efforts were made to purify or characterize the remaining material (presumably the benzophenone derived by acylation of resorcinol at the 4-position).

† In accord with Murphy's Law, this condensation reaction is subject to subtle environmental influences. Thus, whereas we performed the reaction with a view to obtaining compound (V) (see Scheme 8) and instead obtained (VI), the reaction was carried out in Dr. Lewis' laboratory with the aim of obtaining (VI), but instead it produced (V).[27] More recently, the reaction has been described as leading to (V) under somewhat different conditions.[15]

[24] F. P. Doyle, J. H. C. Nayler, H. R. J. Waddington, J. C. Hanson, and G. R. Thomas, *J. Chem. Soc.*, 1963, 497.

[25] R. Q. Brewster and T. Geoening, *Org. Synth.*, 1943, Coll. Vol. II, p. 446.

[26] K. S. Pankajamani and T. S. Seshadri, *J. Sci. Ind. Res.* (*India*), 1954, **13***B*, 393.

[27] J. R. Lewis, personal communication, 1966.

2,2′,3,4′-tetrahydroxybenzophenone (VI) (1 g), anhydrous potassium carbonate (20 g), dimethyl sulphate (10 ml), and acetone (200 ml) was refluxed on a steam-bath for 19 h. It was filtered when cool, the acetone was distilled off and the residue was poured into cold water and then extracted with chloroform. The extract was washed with aqueous 5% sodium hydroxide solution and then with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue, an orange oil (0·93 g), was chromatographed on acid-washed alumina (Merck) (30 g). Elution with benzene–2-methylpentane and pure benzene afforded a colourless crystalline solid which on recrystallization from benzene–2-methylpentane gave white *crystals* (0·40 g), m.p. 75—76°; $\nu_{max.}$ (KBr) 2849, 1664, 1605, 1582, 1508, 1481, 1462, 1443, 1427, 1412, 1318, and 1276 cm^{-1}; $\lambda_{max.}$ (EtOH) 221, 277, and 312 nm (log ε 4·34, 4·04, and 3·96) (Found: C, 67·5; H, 5·95; OMe, 40·85. $C_{17}H_{18}O_5$ requires C, 67·55; H, 6·0; 4 × OMe, 41·05%).

3,5-*Dihydroxyxanthone* (VIII).—2,2′,3,4′-Tetrahydroxybenzophenone (VI) (3 g) was heated with water (120 ml) in a stainless steel bomb in an oil-bath maintained at 200° for 48 h. The mixture was cooled and filtered and the solid, after drying (yield 2·42 g), had m.p. 300° (sublimes). Treatment with charcoal and recrystallization from aqueous ethanol provided shining light yellow needles (VIII), m.p. 312—313° (lit.,[13] 217—220°; lit.,[22] 315—320°).

3,5-*Dimethoxyxanthone by Methylation of the Xanthone* (VIII).—A mixture of 3,5-dihydroxyxanthone (VIII) (1 g), anhydrous potassium carbonate (15 g), dimethyl sulphate (8 ml), and anhydrous acetone (200 ml) was refluxed on a steam-bath for 22 h, allowed to cool, and filtered. The filtrate was evaporated nearly to dryness and dilute aqueous alkali was added to the residue. The resultant precipitate was washed with N-potassium hydroxide solution and then repeatedly with water and dried, to give 3,5-dimethoxyxanthone (1·15 g), m.p. 170—172°. Recrystallization from chloroform–2-methylpentane afforded colourless shining needles, m.p. 175—176° (lit.,[13] 170—172°; lit.,[20] 173·5—174·5°); τ 3·74 and 3·83 p.p.m. (each s, OMe).

3,5-*Diacetoxyxanthone*.—3,5-Dihydroxyxanthone (VIII) (0·57 g) was dissolved in pyridine (5 ml) and acetic anhydride (5 ml) was added to the stirred solution. After 24 h at room temperature the mixture was poured into water (100 ml) and the precipitate was collected, washed with water, and dried. The product was treated with charcoal and recrystallized from chloroform–2-methylpentane to yield the *diacetate* (0·59 g) as colourless shining needles, m.p. 151—152°; $\nu_{max.}$ (KBr) 1773, 1667, 1613, 1603, 1490, 1443, 1370, 1205, 1143, 1099, 1012, 980, 909, 893, 870, 840, 800, 752, 735, 695, and 662 cm^{-1}; τ 2·18 and 2·28 p.p.m. (2 × Me) (Found: C, 65·25; H, 3·75; Ac, 26·4. $C_{17}H_{12}O_6$ requires C, 65·4; H, 3·85; 2 × Ac, 27·6%).

3,5-*Dimethoxyxanthone by the Method of Noyce and Weldon*.[20]—With only slight modification (*i.e.* use of the diazonium fluoroborate in the first stage),[21] the method of Noyce and Weldon yielded 3,5-dimethoxyxanthone, m.p. 174—175° (lit.,[13] 170—172°; lit.,[20] 173·5—174·5°), indistinguishable from the sample prepared by methylation of (VIII).

3,5-*Dihydroxyxanthone* (VIII) *by Demethylation*.—A mixture of 3,5-dimethoxyxanthone prepared by the method of Noyce and Weldon (0·50 g), freshly ground anhydrous aluminum chloride (10 g), and toluene (80 ml) was heated on a steam-bath for 2 h, then allowed to cool to room temperature. Conc. hydrochloric acid was added dropwise until the reaction subsided. Water (300 ml) was added and the mixture was extracted with ether several times. The deep red ethereal solution was washed with water and extracted with aqueous 5% sodium hydroxide until colourless. The deep yellow alkaline phase was then acidified with conc. hydrochloric acid and the precipitate was collected and air-dried to give the dihydroxyxanthone (VIII) (0·35 g), m.p. 313—314° (lit.,[22] 315—320°), indistinguishable from the sample prepared by the cyclodehydration reaction.

Condensation of 2,3-*Dihydroxybenzoic Acid with Catechol*. 2,3,3′,4′-*Tetrahydroxybenzophenone* (IX).—An intimate mixture of 2,3-dihydroxybenzoic acid (10 g), catechol (12 g), freshly fused zinc chloride (30 g), and phosphoryl chloride (70 ml) was heated at 65—70° for 3 h, allowed to cool to room temperature, and cautiously poured over crushed ice with stirring. The resultant orange-coloured precipitate was collected, washed with water, and air-dried to give the crude product (8 g), m.p. 130—136°. Treatment with charcoal and recrystallization from boiling water afforded colourless shining *crystals* (5·19 g), m.p. 141—142°; $\nu_{max.}$ (KBr) 3425, 3356, 3247, 1669, 1613, 1603, 1499, 1471, 1346, 1299, 1250, 1235, 1195, 1122, 1072, 952, 869, 840, 817, 763, 746, and 714 cm^{-1}; $\lambda_{max.}$ (EtOH) 228, 254, 278sh, and 330 nm (log ε 4·00, 4·11, 3·72, and 3·59); $\lambda_{max.}$ (EtOH–NaOH) 244 and 291 nm (log ε 4·27 and 4·10) (Found: C, 62·7; H, 4·1; O, 33·15. $C_{13}H_{10}O_5$ requires C, 63·4; H, 4·1; O, 32·5. $C_{13}H_{10}O_5$,0·25H_2O requires C, 62·25; H, 4·2; O, 33·55%).

Heating this product (0·8 g) in water (60 ml) in a stainless steel bomb for 48 h at 200° gave no reaction.

The isomer (X), 2,2′,3,3′-tetrahydroxybenzophenone, has m.p. 121—122° and is readily dehydrated to give 4,5-dihydroxyxanthone, m.p. 350° (decomp.).[12a]

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