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CONSTITUENTS OF *MESUA FERREA* L.—I

MESUAXANTHONE A AND MESUAXANTHONE B

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Abstract—Two new yellow pigments, mesuaxanthone A and mesuaxanthone B, and the known euxanthone have been isolated from the heartwood extracts of *Mesua ferrea* L. Evidence is presented to show that mesuaxanthone A is 1,5-dihydroxy-3-methoxy-xanthone and mesuaxanthone B is 1,5,6-trihydroxyxanthone. Mesuaxanthone A has been synthesized.

Mesua ferrea L. (Guttiferae) is a tree indigenous to tropical Asia. From the expressed oil of the seed kernel Bose *et al.* have isolated[1–3] two crystalline antibiotic principles, mesuol and mesuone. As no work has been recorded on the extractives of the heartwood and bark, this paper is concerned with the chemical examination of the heartwood† and a study of the bark will be reported in a separate communication.

Extraction of the heartwood with acetone affords a resinous mixture of pigments from which three yellow crystalline compounds A, B and C have been isolated. Pigment C, has been identified as euxanthone (I) by direct comparison with an authentic specimen.‡ The other two pigments, mesuaxanthone A and B, have not been hitherto reported to occur in Nature. Evidence is presented below to show that mesuaxanthone A is 1,5-dihydroxy-3-methoxyxanthone (II) and mesuaxanthone B is 1,5,6-trihydroxyxanthone (VII).

Mesuaxanthone A (II), m.p. 270–272°, has the empirical formula $C_{14}H_{10}O_5$ and contains one methoxyl group. It gives a brown ferric reaction and forms a diacetate, a dibenzoate and a dimethyl ether (III), revealing the presence of two hydroxyl groups. Demethylation with aluminium chloride results in a trihydroxy compound (V), characterized as its triacetate. The IR spectrum of mesuaxanthone A (strong band at 1650 cm^{-1}) and its UV spectrum, λ_{max} 250, 274 (sh), 310 and 355 $m\mu$ (log ϵ 4·43, 3·80, 4·09 and 3·47) are typical of a polyhydroxyxanthone.[4] Fusion of the dimethyl ether (III) with alkali affords 2,3-dihydroxybenzoic acid and a pale yellow crystalline phenol, m.p. 170°, later shown to be IV, as the major products; phloroglucinol and resorcinol have also been identified in the mother liquors by TLC. These results prove that mesuaxanthone A is a derivative of 1,3,5-trihydroxyxanthone. Mesuaxanthone A dimethyl ether proved to be identical with 1,3,5-trimethoxyxanthone.[5]

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† The plant material for this investigation was collected from the Western Ghats in Travancore.

‡ Kindly provided by Prof. T. R. Seshadri to whom our thanks are due.

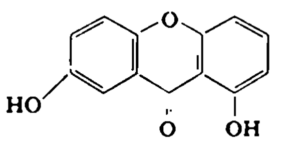
[1] P. Dutt, N. C. Deb and P. K. Bose, *J. Indian Chem. Soc.* **17**, 277 (1940).

[2] D. P. Chakraborty, M. Purkayastha and P. K. Bose, *Proc. Natl. Inst. Sci. India* **25B**, 8 (1959).

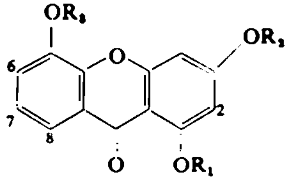
[3] D. P. Chakraborty and P. K. Bose, *Proc. Natl. Inst. Sci. India* **26A**, Supp. I, 1 (1960).

[4] J. C. Roberts, *Chem. Rev.* **61**, 591 (1961).

[5] V. V. Kane, A. B. Kulkarni and R. C. Shah, *J. Sci. Ind. Research, India* **18B**, 28 (1959).



I



II $R_1 = R_3 = H$; $R_2 = Me$
III $R_1 = R_2 = R_3 = Me$
IV $R_1 = H$; $R_2 = R_3 = Me$
V $R_1 = R_2 = R_3 = H$
VI $R_1 = R_2 = H$; $R_3 = Me$

In accordance with most naturally occurring xanthones,[6,*] compound II has an hydroxyl at C-1, supported by the brown ferric reaction and positive Wilson's boric acid test. The second hydroxyl group must be placed at C-5 since mesuaxanthone A is different from the known 1,3-dihydroxy-5-methoxyxanthone[5] (VI). It follows therefore that mesuaxanthone A is 1,5-dihydroxy-3-methoxyxanthone (II). This has been confirmed by synthesis. Condensation of phloroglucinol with 2,3-dihydroxybenzoic acid[8] affords 1,3,5-trihydroxyxanthone (V) identical with the demethylation product of mesuaxanthone A. Selective methylation of the C-3 hydroxyl group[9] yields a product identical with mesuaxanthone A (II).

The yellow phenol obtained in the alkali fusion above analyses for $C_{15}H_{12}O_5$ and contains two methoxyl groups. It gives a brown ferric reaction and its UV spectrum (Fig. 2) is very similar to that of II. This evidence coupled with positive Wilson's boric acid and Gibbs tests suggests it to be IV† and this has been confirmed by a synthesis. Condensation[8] of phloroglucinol monomethyl ether with 2-hydroxy-3-methoxy-benzoic acid gave 1-hydroxy-3,5-dimethoxyxanthone identical with the degradation product above.‡

Mesuaxanthone B (VII), $C_{13}H_8O_5$, m.p. 290°, contains three hydroxyl groups (triacetate, tribenzoate and trimethyl ether) and no methoxyl group. Its IR spectrum exhibits a strong band at 1650 cm^{-1} and the UV spectrum of its triacetate is virtually identical with that of xanthone. The UV spectrum of mesuaxanthone B itself (Fig. 1) has only two intense bands in contrast to that of known naturally occurring xanthones which exhibit three or four intense bands.[4,10] Mesuaxanthone B produces a green colour with ferric chloride and gives a positive Wilson's boric acid test suggesting the presence of a C-1 hydroxyl group. This is supported by the preparation of a yellow dimethyl ether (VIII; positive ferric and Wilson's boric acid tests) with diazomethane, and a colourless trimethyl ether (IX) under more severe conditions. The presence of an o-dihydroxyl grouping in VII is indicated by the characteristic bathochromic shift

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[*] An exception is the recently isolated 2-hydroxyxanthone.[7]

[†] Selective demethylation of the methoxyl group adjacent to the pyrone carbonyl during alkali fusion is not without precedent. See for example, F. Sondheimer and A. Meisels, *Tetrahedron* **9**, 139 (1960).

[‡] Attempts to prepare this compound by methylating II with diazomethane gave unsatisfactory results, the dimethyl ether III being the major product.

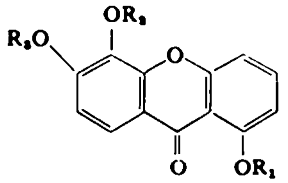
[6] F. M. Dean, *Naturally occurring Oxygen Ring Compounds* p. 266. Butterworths, London (1963).

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

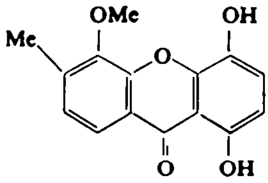
[8] P. K. Grover, G. D. Shah and R. C. Shah, *J. Chem. Soc.* 3982 (1955).

[9] cf. K. R. Markham, *Tetrahedron* **21**, 1449 (1965).

[10] M. L. Wolfrom *et al.*, *J. Org. Chem.* **29**, 689 (1964).



VII $R_1 = R_2 = R_3 = H$
VIII $R_1 = H$; $R_2 = R_3 = Me$
IX $R_1 = R_2 = R_3 = Me$
X $R_1 = H$; $R_2 = R_3 = \rangle CH_2$



XI

of its UV spectrum in the presence of a mixture of boric acid and sodium acetate.[11] This has been confirmed by the preparation of a methylene ether (X). From the yellow colour and positive ferric reaction of this derivative, it is evident that C-1 hydroxyl is not involved in the formation of the methylene ether. Finally, the orientation of the hydroxyl groups in mesuaxanthone B has been established by degradation. Elbs persulphate oxidation of the dimethyl ether (VIII) gives the corresponding quinol XI which on mild oxidation with 3% alkaline hydrogen peroxide[12] furnishes 2-hydroxy-3,4-dimethoxybenzoic acid as the sole product. This evidence proves that the other two hydroxyl groups in VII are at C-5 and C-6. An authentic specimen of 1,5,6-trihydroxy-

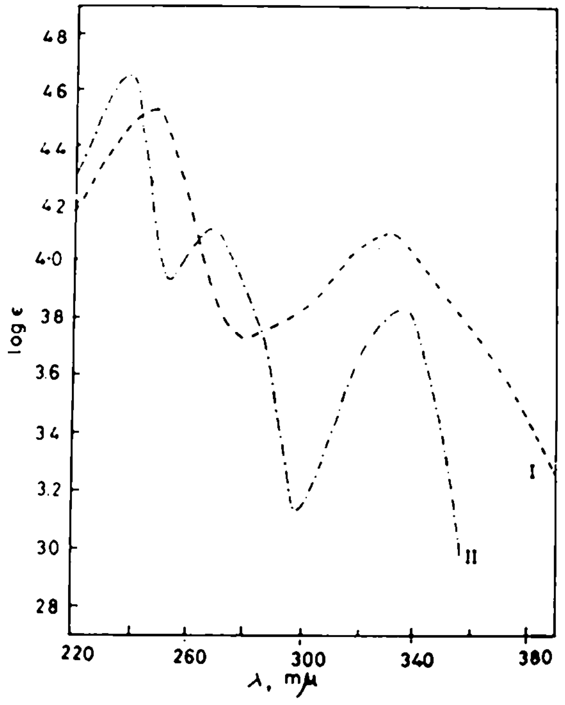


Fig. 1. UV Spectrum of: I. Mesuaxanthone B; II. Mesuaxanthone B triacetate.

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[11] L. Jurd, *Arch. Biochem. Biophys.* 63, 376 (1956).

[12] J. C. Roberts, *J. Chem. Soc.* 785 (1960).

xanthone prepared[13] is be identical with mesuaxanthone B. The compound has not previously been obtained from a natural source.

EXPERIMENTAL[14]

1. *Isolation of the pigments*

The finely ground heartwood (4 kg) of *Mesua ferrea*, previously extracted with pet. ether, was extracted with acetone in the cold. Acetone was distilled off and the resulting dark red resinous residue was dissolved in AcOEt (1 l) and diluted with ether (3 l) slowly, with stirring until pptn was nearly complete. The red amorphous ppt was rejected. The almost clear yellow filtrate was washed thoroughly with water and then extracted successively with ice-cold sat $NaHCO_3$aq (extract A), 2% Na_2CO_3aq (extract B) and 4% NaOHaq (extract C). Evaporation of the organic layer left a negligible residue. The aqueous extracts were acidified with 4N HCl under strong cooling and allowed to stand in the refrigeration overnight. Extract A afforded a dark brown semi-solid which was not investigated. The brownish yellow ppts obtained from extracts B and C were collected, washed thoroughly with ice water and dried.

TLC of the crude pigments revealed that extract B (9 g) consisted largely of *mesuaxanthone* B and extract C (4 g) consisted of nearly equal amounts of *mesuaxanthone* A and euxanthone, contaminated with other impurities. The mixture of mesuaxanthone A and euxanthone was separated by fractional crystallization from alcohol. Mesuaxanthone A separated from the less soluble fraction and from the more soluble part euxanthone was isolated.

Mesuaxanthone B was purified through its sparingly soluble acetate. For this purpose crude air dried mesuaxanthone B (4 g) was heated at 80° with a mixture of pyridine (10 ml) and Ac_2O (10 ml) for 2 hr. After pouring into ice water and leaving in the refrigerator overnight, the ppt was washed with water and dried. Repeated crystallization from AcOEt (Norit) afforded fibrous colourless needles (2·1 g), m.p. 208–210°. For hydrolysis the pure acetate (1 g) was refluxed with alcoholic HCl (10%; 100 ml) for 2 hr and allowed to stand at room temp overnight. The lemon yellow plates of mesuaxanthone B were washed with dil alcohol and dried (0·45 g). Concentration of the mother liquors *in vacuo* afforded more (0·1 g) of the same material.

2. *Euxanthone*

It crystallized from alcohol as bright yellow needles m.p. 238–240°. The *diacetate* separate from benzene as colourless prisms, m.p. 183–184°. The *dimethyl ether* crystallized from alcohol as colourless needles, m.p. 150–152°.

3. *Mesuaxanthone* A

Recrystallization from alcohol, acetone or AcOEt afforded yellow needles, m.p. 270–272°. (Found: C, 64·86; H, 4·11; OCH_3, 6·03. $C_{14}H_{10}O_5$ requires: C, 65·11; H, 3·88; 1 OMe, 5·82%.) It is sparingly soluble in ether, chf, benzene, AcOEt, acetone and alcohol, and was practically insoluble in dil Na_2CO_3aq.

The *dibenzoate* (pyridine–acid chloride), crystallized from chf, m.p. 268–270°. (Found: C, 72·50; H, 4·20. $C_{28}H_{18}O_7$ requires: C, 72·09; H, 3·86%.) The *diacetate* (pyridine–Ac_2O) crystallized from benzene–pet. ether as colourless plates, m.p. 158–160°. UV: 238, 272, 294, 325–330 (sh) mμ (log ε 4·67, 4·09. 4·22, 3·92). (Found: C, 62·73; H, 4·02. $C_{18}H_{14}O_7$ requires: C, 63·15; H, 4·09%.)

4. *Mesuaxanthone* A *dimethyl ether*

A mixture of mesuaxanthone A (0·6 g), anhydrous K_2CO_3 (4 g) and Me_2SO_4 (2·5 ml) in dry acetone (100 ml) was refluxed for 18 hr. Evaporation of the solvent from the filtered soln followed by addition of water afforded the methyl ether as a colourless solid. Recrystallization from alcohol gave needles (0·48 g), m.p. 219–220°, identical with an authentic specimen of 1,3,5,-trimethoxyxanthone[4] (m.m.p., TLC and IR). UV: 245, 300, 335-340 (sh) mμ (log ε 4·63, 4·23, 3·79). (Found: C, 67·32; H, 5·33; OMe, 15·69. $C_{16}H_{14}O_5$ requires: C, 67·14; H, 4·87; 3 OMe, 15·7%.)

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[13] G. D. Shah and R. C. Shah, *J. Sci. Ind. Res. India* 15B, 630 (1956).

[14] M.ps are uncorrected. The UV spectra 95% EtOH using a Beckmann Model DU Spectrophotometer. Kieselgel G (E. Merck) was used for TLC. Pet. ether refers to b.p. 40–60°.

5. *Demethylation of mesuaxanthone* A

A soln of mesuaxanthone A (0·2 g) in dry benzene (100 ml) was treated with powdered anhyd. $AlCl_3$ (2 g) and the mixture refluxed for 6 hr. The solvent was then distilled, crushed ice and HCl (5 ml) added and the resulting yellow ppt washed and dried. Recrystallization from dil alcohol afforded the demethylated xanthone as yellow microcrystalline ppt (0·12 g), m.p. 298–301°. It gave a deep brown colour with $FeCl_3$.

The *acetate* (pyridine–Ac_2O) crystallized from acetone as colourless needles, m.p. 202–204°, undepressed on admixture with an authentic specimen of 1,3,5-triacetoxyxanthone (*vide infra*). UV: 238, 267, 335 mμ (log ε 4·60, 4·12, 3·83). (Found: C, 61·89; H, 3·72; $C_{19}H_{14}O_8$ requires: C, 61·62; H, 3·8%).

6. *Alkali fusion of mesuaxanthone* A *dimethyl ether*

A mixture of mesuaxanthone A dimethyl ether (0·3 g), powdered NaOH (1·2 g), KOH (1·3 g) and water (0·5 ml) taken in a Ni crucible was placed in a metal bath at 180°. The temp was gradually raised to 260° in the course of 8 min, with stirring, under a stream of N. The melt was held at 260–270° for 4 min and then allowed to cool and then dissolved in ice water (20 ml), acidified with con HCl, and extracted with ether. The ether soln was shaken with $NaHCO_3$aq (2 × 3 ml), the bicarbonate solution acidified with strong cooling and reextracted with ether. After being dried, ether was distilled off and the residue crystallized from benzene–pet. ether giving 2,3-dihydroxybenzoic acid (blue ferric reaction), m.p. 202–204° identical with an authentic specimen.[18]

The ether soln left after extraction with bicarbonate was washed with water, dried and the solvent distilled off. The residue on repeated crystallization from alcohol gave pale yellow needles (60 mg), m.p. 170–171°, identical (m.m.p., IR and TLC) with a synthetic specimen of 1-hydroxy-3,5-dimethoxyxanthone (*vide* below). It gave a brown ferric reaction and positive Wilson's boric acid and Gibbs tests. UV: 245, 310, 335 (sh) 355 mμ (log ε 4·59; 4·24. 3·70, 3·66). (Found: C, 66·57; H, 4·44; OMe, 10·86. $C_{15}H_{12}O_5$ requires: C, 66·18; H, 4·41; 2 OMe, 11·03%.)

The alcohol mother liquor obtained was examined by TLC on silica gel (benzene:AcOEt:MeOH–20:4:0·5). Three spots were revealed identical respectively with 1-hydroxy-3,5-dimethoxyxanthone, resorcinol and phloroglucinol (in the order of decreasing *Rf*) run as standards alongside.

7. *Synthesis of* 1-*hydroxy*-3,5-*dimethoxyxanthone*

A mixture of 2-hydroxy-3-methoxybenzoic acid (1 g), phloroglucinol monomethyl ether (1·2 g) fused powered $ZnCl_2$ (4 g) and $POCl_3$ (10 ml) was heated at 65–70° for 3 hr. The deep red viscous oily product was cooled and poured onto crushed ice; extracted with ether soln washed with sat $NaHCO_3$aq then with water, dried and the solvent distilled. Repeated crystallization of the residue from alcohol gave pale yellow needles of 1-hydroxy-3,5-dimethoxyxanthone (0·3 g), m.p. 169–170°, identical with the degradation product above. (Found: C, 66·24; H, 4·72. $C_{15}H_{12}O_5$ requires: C. 66·18; H, 4·41%).

8. *Synthesis of mesuaxanthone* A

(i) 1,3,5-*Trihydroxyxanthone*. Anhydrous phloroglucinol (2·4 g), 2,3-dihydroxybenzoic acid (2 g), $ZnCl_2$ (8 g) and $POCl_3$ (20 ml) were stirred at 70° for 2 hr. After being poured into ice water and stirring for 1 hr, the ppt was washed with $NaHCO_3$aq, and water and dried. Sublimation of this crude product at 200–220°/0·1 mm followed by recrystallization of the sublimate from alcohol gave 1,3,5-trihydroxyxanthone as yellow needles (0·5 g), m.p. 300–302° (dec), lit.[8], m.p. 303–304° (dec). The *acetate* prepared in pyridine solution with Ac_2O crystallized from acetone as needles, m.p. 203–204°.

(ii) 1,5-*Dihydroxy*-3-*methoxyxanthone* (*mesuaxanthone* A). A mixture of 1,3,5-trihydroxyxanthone (0·48 g) Me_2SO_4 (0·2 ml) and $NaHCO_3$ (10 g) in dry acetone (200 ml) was refluxed for 10 hr, yielded after recrystallization from acetone 1,5-dihydroxy-3-methoxyxanthone (0·3 g) as yellow needles, m.p. 268–270°, undepressed on admixture with mesuaxanthone A. Their IR spectra were identical. (Found: C, 65·10; H, 3·89. $C_{14}H_{10}O_5$ requires: C, 65·11; H, 3·88%.)

9. *Mesuaxanthone* B

It crystallized from alcohol as lemon-yellow plates, m.p. 288–290° identical (m.m.p., IR and TLC) with an authentic specimen of 1,5,6-trihydroxyxanthone.[10] (Found: C, 63·94; H, 3·10; OMe, Nil. $C_{13}H_8O_5$ requires: C, 63·93; H, 3·28%.)

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[18] F. E. King, J. H. Gilks and M. W. Partridge, *J. Chem. Soc.* **4206** (1955).

The *benzoate* (pyridine–BzCl), crystallized from benzene–pet. ether, m.p. 182°. (Found: C, 73·22; H, 3·75. $C_{34}H_{20}O_8$ requires: C, 73·39; H, 3·60%.) The *triacetate* (pyridine–Ac_2O) crystallized as colourless needles, m.p. 208–210° undepressed on admixture with the acetate prepared from crude mesuaxanthone B (*vide supra*.) (Found: C, 61·60; H, 3·45. $C_{19}H_{14}O_8$ requires: C, 61·62; H, 3·78%.)

10. *Mesuaxanthone* B *trimethyl ether*

Mesuaxanthone B (0·2 g) was refluxed with Me_2SO_4 (1·6 ml) and anhyd K_2CO_3 (2 g) in acetone (75 ml) for 36 hr. Acetone was distilled off from the filtered soln and water added. The ppt was collected, dried and recrystallized from benzene–pet. ether giving colourless needles, m.p. and m.m.p. with a synthetic specimen of 1,5,6-trimethoxyxanthone[18] 150–151°. Their IR spectra were identical. UV: 238, 305, 335–340 (sh) mμ (log ε 4·70, 4·25, 4·00). (Found: C, 67·28; H, 4·68. $C_{16}H_{14}O_5$ requires: C, 67·13; H, 4·89%.)

11. *Mesuaxanthone* B *dimethyl ether*

An ethereal soln of diazomethane (from 10 g of nitrosomethylurea) was added to a cooled soln of mesuaxanthone B (0·5 g) in abs ether (250 ml) and abs MeOH (40 ml). After leaving overnight at room temp, the solvents were evaporated and residue crystallized from alcohol giving the dimethyl ether as pale yellow fibrous needles (0·38 g) m.p. 176°. UV: 242, 265–270 (sh), 310, 335 mμ (log ε 4·55, 3·83, 4·12, 3·82). (Found: C, 66·14; H, 4·69; OMe, 10·43. $C_{15}H_{12}O_5$ requires: C, 66·18; H, 4·41; 2 OMe, 11·03%.)

12. *Methylenation of mesuaxanthone* B

A mixture of mesuaxanthone B (600 mg), anhyd K_2CO_3 (1·5 g) and CH_2I_2 (1·5 ml) in dry acetone (60 ml) was refluxed for 18 hr. After distilling off acetone, water was added and allowed to stand overnight. The pale yellow ppt was washed, dried and recrystallized from benzene–pet. ether, giving the methylenedioxyxanthone as pale yellow needles (0·24 g), m.p. 210–212°. (Found: C, 65·78; H, 3·33. $C_{14}H_8O_5$ requires: C, 65·63; H, 3·12%.)

13. *Persulphate oxidation of mesuaxanthone* B *dimethyl ether*

Potassium hydroxide (0·8 g) in water (10 ml) was added to a soln of mesuaxanthone B dimethyl ether (0·4 g) in pyridine (8 ml). To this well stirred mixture was added during 1 hr a soln of potassium persulphate (1 g) in water (3·4 ml) the temp being maintained at 15–20°. After being stirred at 15–20° for 6 hr, it was left overnight at room temp. Next day the clear brown soln was acidified to Congo-red with conc. HCl and the pptd unreacted material filtered off. The filtrate was extracted with ether twice (100 ml) and the ether extract rejected. The clear brown aqueous soln was heated on the water bath for ½ hr with conc HCl (15 ml) and Na_2SO_3 (1·4 g). The ppt obtained on cooling was washed with water, dried and passed through a column of silica gel in benzene–AcOEt (1:1). Recrystallization from alcohol afforded bright yellow needles of 1,4-*dihydroxy*-5,6-*dimethoxyxanthone* (0·12 g), m.p. 226–228°. UV: 242, 285, 300–305 (sh), 395 mμ (log ε 4·50, 4·19, 4·13, 3·67). (Found: C, 62·38; H, 4·22. $C_{15}H_{12}O_6$ requires: C, 62·50; H, 4·17%.)

14. *Alkaline hydrogen peroxide oxidation of* 1,4-*dihydroxy*-5,6-*dimethoxyxanthone*

A soln of 1,4-dihydroxy-5,6-dimethoxyxanthone (0·1 g) in KOHaq (1%; 15 ml) was treated dropwise with H_2O_2 (3%; 9 ml) at room temp. The initial dark brown colour of the soln gradually became colourless in 2 days. After allowing to stand at room temp for 4 days, the soln was concentrated *in vacuo* (~10 ml) and cooled. Acidification afforded colourless needles. The product was isolated by extraction with AcOEt, shaking with sat $NaHCO_3$aq (2 × 4 ml), acidification with HCl and reextraction with AcOEt. After washing with water the extract was dried and AcOEt removed. Crystallization of the residue from AcOEt–pet. ether afforded needles, m.p. 169–171° undepressed on admixture with authentic 2-hydroxy-3,4-dimethoxybenzoic acid.[19] Their IR spectra were identical.

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[19] L. Ramachandra Rao and C. V. Reddy Sastry, *Tetrahedron* **19**, 1371 (1963).