385. *Studies in Mycological Chemistry. Part IX.* Synthesis of Methyl* 1,3,8-*Trimethoxyxanthone*-4-*carboxylate—a Degradation Product of Sterigmatocystin.*

By John C. Roberts and J. G. Underwood.

Methyl 1,3,8-trimethoxyxanthone-4-carboxylate has been synthesized, in a fourteen-stage process, from resorcinol.

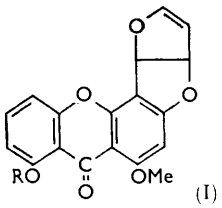
We have previously suggested [1] that sterigmatocystin, a metabolite of *Aspergillus versicolor* (Vuill.) Tiraboschi, has structure (I; R = H). *O*-Methylsterigmatocystin (I; R = Me), on oxidation with a limited amount of potassium permanganate, yielded [1] a hydroxycarboxylic acid which, on complete methylation, gave a compound (A). Evidence

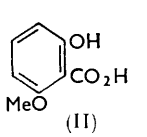
* Part VIII, *J.*, 1962, 40.

[1] Davies, Kirkaldy, and Roberts, *J.*, 1960, 2169.

previously described [1] indicated that this compound was methyl 1,3,8-trimethoxyxanthone-4-carboxylate (V). A synthesis of a compound of this structure is now described.

2,6-Dihydroxyacetophenone was converted, *via* its mono-*O*-methyl derivative, into 2-hydroxy-6-methoxybenzoic acid (II). This acid was caused to react with phloroglucinol, by using a modification of the method of Grover, Shah, and Shah,[2] to give an acceptable yield of 1,3-dihydroxy-8-methoxyxanthone (III; R = R′ = H), which was converted,


(I)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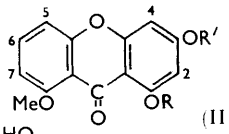
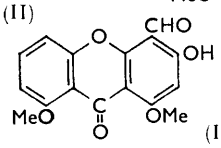
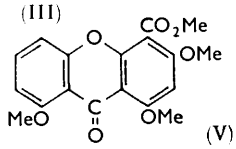

(III)


(IV)


(V)

by the boro-acetate reaction,[3] into 3-acetoxy-1-hydroxy-8-methoxyxanthone (III; R = H, R′ = Ac). Methylation of this substance, under strictly anhydrous conditions, and hydrolysis of the acetoxy-group in the product, led to 3-hydroxy-1,8-dimethoxyxanthone (III; R = Me, R′ = H). When submitted to the Reimer–Tiemann reaction, this substance gave a hydroxy-aldehyde which is formulated as (IV), and not as the isomeric 2-formyl-3-hydroxy-1,8-dimethoxyxanthone, by analogy with the formylation of 3-hydroxyxanthone which has been shown [4] to lead to the 4-formyl derivative since the product was convertible, by a Dakin reaction, into the known 3,4-dihydroxyxanthone.

Oxidation of the hydroxy-aldehyde (IV), with a limited amount of potassium permanganate, and complete methylation of the hydroxy-acid produced, led to the desired xanthone (V) which proved to be identical with the compound (A) mentioned above.

The structure previously allocated to (A) is thus confirmed.

Experimental

M. p.s were determined on the Kofler block. Ultraviolet absorption spectra were determined on ethanolic solutions by means of a Unicam S.P. 700 spectrophotometer. Infrared absorption spectra were taken on compounds in potassium bromide discs, a Unicam S.P. 100 spectrophotometer being used.

2-Hydroxy-6-methoxybenzoic Acid (II).—2,6-Dihydroxyacetophenone was prepared [5] from resorcinol, and converted [6] into its *O*-monomethyl ether, oxidation [7] of which yielded the desired acid, m. p. 134° (lit.,[7] 135°).

1,3-Dihydroxy-8-methoxyxanthone (III; R = R′ = H).—A mixture of the foregoing acid (5·5 g.), dry phloroglucinol (5·0 g.), freshly fused zinc chloride (15 g.), and phosphoryl chloride (40 ml.) was heated at 95—100° (bath temp.) for 1½ hr. (The temperature range is critical for this particular reaction.) The cooled mixture was stirred into iced water (500 g.) and was left overnight. The product, collected by filtration, was triturated with aqueous sodium hydrogen carbonate solution, and then with 2N-hydrochloric acid. The residue was washed with water, dried, and extracted (Soxhlet) with acetone. Removal of the acetone and crystallisation of the residue from ethanol gave the *xanthone* (1·2 g., 14%) as yellow needles, m. p. 287°. Sublimation of this material (260°/0·05 mm.) gave a product,* m. p. 289—290° [Found:

* A claim to have synthesized a product (m. p. 277—278°) of this structure has been made [8] but full details are not available.

[2] Grover, Shah, and Shah, *J.*, 1955, 3982.
[3] Dimroth, *Annalen*, 1926, **446**, 97.
[4] Dobson, Ph.D. Thesis, 1960, University of Nottingham.
[5] Russell and Frye, *Org. Synth.*, 1941, **21**, 22.
[6] Baker, *J.*, 1939, 956.
[7] Lund, Robertson, and Whalley, *J.*, 1953, 2439.
[8] Hatsuda, Kuyama, and Terashima, *J. Agric. Chem. Soc. Japan*, 1954, **28**, 998 (*Chem. Abs.*, 1956, **50**, 15,522).

C, 65·0; H, 4·0; OMe, 11·9. $C_{13}H_7O_4(OMe)$ requires C, 65·1; H, 3·9; OMe, 12·0%] which was soluble in 2N-sodium hydroxide and gave a brown ferric reaction in aqueous ethanol.

3-*Acetoxy*-1-*hydroxy*-8-*methoxyxanthone* (III; R = H, R′ = Ac).—To a solution of the preceding xanthone (4·5 g.) in boiling acetic anhydride (25 ml.) was added a solution of boro-acetic anhydride [3] (7 g.) in hot acetic anhydride (15 ml.). The mixture was heated under reflux for 10 min. and was then cooled. The crystalline diacetylborate was collected by filtration and was then boiled with water (150 ml.) for 15 min. The product crystallised from ethanol to give the *xanthone* as yellow needles (4·1 g., 78%), m. p. 188—191°. Sublimation of this substance (175°/0·05 mm.) gave material, m. p. 193° (Found: C, 63·8; H, 4·0. $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0%), which was soluble in boiling 2N-sodium hydroxide and gave a brown ferric reaction in aqueous ethanol.

3-*Acetoxy*-1,8-*dimethoxyxanthone* (III; R = Me, R′ = Ac).—The foregoing xanthone (4·0 g.), methyl iodide (10 ml.), anhydrous potassium carbonate (10 g.), and dry acetone (700 ml.) were heated under reflux for 48 hr., with addition of more methyl iodide (2 × 10 ml.) at suitable intervals. Removal of the solids and evaporation of the filtrate gave material which was crystallised from ethanol, yielding needles (3·6 g., 87%) of the *xanthone*, m. p. 193° raised to 195° by sublimation at 175°/0·05 mm. (Found: C, 64·8; H, 4·4. $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5%). The product gave no ferric reaction and dissolved in boiling aqueous alkali.

3-*Hydroxy*-1,8-*dimethoxyxanthone* (III; R = Me, R′ = H).—The foregoing xanthone (3·5 g.) was warmed (35—40°) with a solution of sodium hydroxide (1·5 g.) in methanol (250 ml.) for 3 hr. Solvent (150 ml.) was removed *in vacuo*, and to the residue were added water (500 ml.) and acetic acid (25 ml.). The gelatinous precipitate was separated by centrifugation, washed with water, and dried. Paper chromatography indicated that this material contained some 1,3,8-trihydroxyxanthone. This crude material was extracted (Soxhlet) with ethanol. Removal of the ethanol gave a white amorphous powder (2·2 g., 73%), m. p. 235—240°, which had no ferric reaction and which was soluble in aqueous alkali. Although this substance appeared to be homogeneous (by paper chromatography, in three different solvent systems), attempts to crystallise it failed. On one occasion a sublimation of the amorphous material yielded the crystalline *xanthone*, m. p. 275—277° (Found: C, 66·3; H, 4·7. $C_{15}H_{12}O_5$ requires C, 66·2; H, 4·4%).

4-*Formyl*-3-*hydroxy*-1,8-*dimethoxyxanthone* (IV).—The foregoing crude xanthone (1·8 g.), 25% aqueous tetraethylammonium hydroxide (30 ml.), water (7 ml.), and chloroform (7 ml.) were heated under reflux, with stirring, for 4 hr. The residual chloroform was removed and the aqueous layer was acidified with 2N-hydrochloric acid. The precipitate was washed with water, dried, and was extracted with cold benzene. Removal of the benzene and crystallisation of the residue from acetone gave the *xanthone* as needles (175 mg., 8·9%), m. p. 248—249°. Sublimation of this substance at 235°/0·05 mm. gave a sample of m. p. 252—253° (Found: C, 64·3; H, 4·2. $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0%), $\lambda_{max.}$ 213, 236, 253, and 336 mμ (log ε 4·27, 4·32, 4·41, and 4·01, respectively). (By recycling the recovered starting material from the Reimer–Tiemann reaction, a further 50 mg. of aldehyde were obtained.) This xanthone-aldehyde was soluble in aqueous alkali, and gave a cherry-red ferric reaction in ethanol, and a red-orange precipitate with Brady's reagent.

Methyl 1,3,8-*Trimethoxyxanthone*-4-*carboxylate* (V).—(i) The hydrated form of this ester [1] was sublimed at 180°/0·05 mm. to give the anhydrous *ester* (substance A—see above) as stout needles, m. p. 203° (Found: C, 62·4, 62·9; H, 4·4, 4·5. $C_{18}H_{16}O_7$ requires C, 62·8; H, 4·7%), $\lambda_{max.}$ 205, 236, and 307 mμ (log ε 4·28, 4·54, and 4·24, respectively).

(ii) A solution of 4-formyl-3-hydroxy-1,8-dimethoxyxanthone (95 mg.) in dry acetone (25 ml.) was heated under reflux, and powdered potassium permanganate (35 mg.) was added in portions during 2 hr. Water (50 ml.) was added, the hot (50°) reaction mixture was filtered, and the residue was washed with hot water. The combined filtrate and washings were adjusted to pH 10 (with 2N-sodium hydroxide), and concentrated *in vacuo* to 50 ml. The solution was acidified and extracted with ether (5 × 10 ml.). The combined ethereal solutions were then extracted with a saturated aqueous solution of sodium hydrogen carbonate (2 × 2 ml.). Acidification of the aqueous extracts gave crude 3-hydroxy-1,8-dimethoxyxanthone-4-carboxylic acid (67 mg., 70%), m. p. 240—245° (decomp.). This acid and diazomethane (*ca.* 5 mol.) were kept in ether at room temperature for 12 hr. Removal of the solvent and excess of the reagent gave a residue which was crystallised from methanol. Fractional sublimation of the product at 180°/0·05 mm. gave the ester (45 mg.) (Found: C, 62·4; H, 4·8%), $\lambda_{max.}$ 206,

236, and 307 mμ (log ε 4·29, 4·56, and 4·25, respectively), m. p. 203° unaltered by admixture with substance A prepared as in method (i). The infrared spectra of the two compounds were virtually identical, both spectra exhibiting strong bands at 1661 (xanthone carbonyl group) and 1733 cm.$^{-1}$ (aryl ester carbonyl group).

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