159. *Studies in Mycological Chemistry. Part VI.* A Novel Method for the Degradation of 1-Hydroxyxanthones.*

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A method for degrading 1-hydroxyxanthones, by their conversion into 1,4-dihydroxy-compounds and subsequent mild oxidation to salicylic acids, is described.

The determination of the orientation of the substituent groups in xanthones of plant or animal origin has often proved difficult. In some cases it has not yet been achieved. The great majority, possibly all, of the eighteen known naturally occurring xanthones [1] (seven of which are of fungal or lichen origin) possess in their structures a hydroxyl group in the 1(or 8)-position. At the present time no general and completely acceptable method of degradation of such compounds, as an aid to structural elucidation, appears to have been devised. Fusion of the material with potassium hydroxide has sometimes yielded valuable information but this procedure suffers from at least three disadvantages; first, dealkylation of *O*-alkyl groups occurs; secondly, phenols which are sensitive to oxidation are destroyed; and, thirdly, difficultly resolvable mixtures of phenols, phenolic acids, and hydroxybenzophenones are often produced.[2] We have found [3] that the Haller–Bauer method of degradation [4] is quite widely applicable to fully methylated hydroxyxanthones but the determination of the orientation of the substituents in the products (substituted diphenyl ethers) is generally very difficult.

It is now shown, for certain cases, that if the 1-hydroxyxanthone is hydroxylated in the 4-position (by a modified Elbs persulphate oxidation [5]) then the product is susceptible to *mild* oxidation, yielding the other benzenoid nucleus (A in I), with its attendant groups (if any) intact, in the form of an easily purified and identifiable acid—salicylic or a substituted salicylic acid. By this technique, 1-hydroxyxanthone yielded first 1,4-dihydroxyxanthone (I; R = R′ = H) which was then oxidised with cold, dilute, alkaline hydrogen peroxide to pure salicylic acid in 23% yield. Similarly, 1-hydroxy-7-methoxy-3-methylxanthone gave initially 1,4-dihydroxy-7-methoxy-3-methylxanthone (I; R = OMe, R′ = Me) which, on further oxidation, gave 2-hydroxy-5-methoxybenzoic acid (IV; R = OMe) in 7% yield. Application of this procedure to dihydrosterigmatocystin [1b] did not lead to a salicylic acid but, by spontaneous decarboxylation, to a phloroglucinol derivative. Although this phenol was produced in very poor yield, it proved indispensable in the elucidation of the structure of sterigmatocystin.

Later, a semimicro-technique was devised in which the purification of the intermediate 1,4-dihydroxy-compound was omitted. By this method, which involved other modifications (see Experimental part), 1-hydroxy-7-methoxy-3-methylxanthone was degraded to 2-hydroxy-5-methoxybenzoic acid with an overall yield of 10%. The method appears to be applicable to all 1-hydroxyxanthones which have no other free hydroxyl group and which possess a vacant 4-position. (The absence of a substituent in this position may be conveniently ascertained on a micro-scale by means of the Gibbs test.[6]) The advantage of the method is that, in any case of this kind, the identification of the salicylic acid leads to a definition of the nature and orientation of all the substituents in the xanthone nucleus with the exception of those (if any) in the 2- and the 3-position.

* Part V, *J.*, 1956, 2173.

[1] (*a*) W. Karrer, "Konstitution und Vorkommen der Organischen Pflanzenstoffe," Birkhäuser Verlag, Basel, 1958, pp. 662—667; (*b*) Davies, Kirkaldy, and Roberts, following paper.

[2] Cf. Kulkarni and Merchant, *J. Sci. Ind. Res., India*, 1955, **14**, *B*, 153; *Chem. Abs.*, 1956, **50**, 7012.

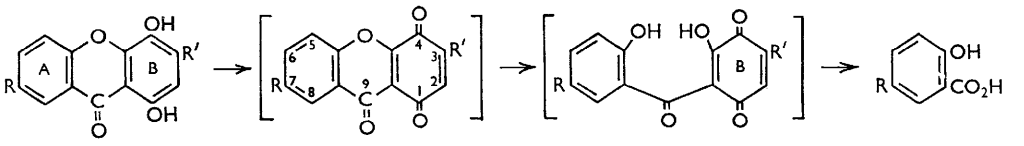
[3] Dobson and Roberts, unpublished work.

[4] *Org. Reactions*, 1957, **9**, 1; cf. Raistrick, Robinson, and White, *Biochem. J.*, 1936, **30**, 1303.

[5] (*a*) Seshadri, *Experientia*, 1955, Suppl., **2**, 258, 14th Internat. Congr. Pure Appl. Chem., Zürich; (*b*) Pankajamani and Seshadri, *J. Sci. Ind. Res., India*, 1954, **13**, *B*, 396; *Chem. Abs.*, 1955, **49**, 11639.

[6] King, King, and Manning, *J.*, 1957, 563.

The degradation may involve compounds (II) and (III) as intermediates. *p*-Benzoquinonyl ethers such as (II) (which are vinylogous esters) are known to undergo alkaline hydrolysis easily to yield hydroxyquinones, *e.g.*, (III). Compound (III) (as a β-diketone) would be susceptible to alkaline hydrolysis and (as a hydroxyquinone) to oxidation to the final product (IV) with concomitant destruction of nucleus B. It is probably significant that the reaction mixture possesses initially a dark-red colour (characteristic of hydroxyquinones in alkaline solution) which subsequently fades to a very pale yellow.



(I) (II) (III) (IV)

We hope to apply this method of degradation to some naturally occurring xanthones of incompletely defined structures.

Experimental

Degradation of 1,4-*Dihydroxyxanthone*.—The dark red solution of this substance [5b] (50 mg.) in 1% aqueous sodium hydroxide (18 ml.) was treated with 3% hydrogen peroxide solution (10 ml.). The colour faded to yellow in 2 hr. The solution was kept at room temperature for 18 days, then filtered and acidified to pH 1 with 2N-hydrochloric acid. The product was isolated by a method similar to that described below (but on approximately twice the scale) for the isolation of 2-hydroxy-5-methoxybenzoic acid (semimicro-procedure), and recrystallised from the minimum volume of boiling water as needles (7 mg.), m. p. 158—159°. It gave a purple ferric reaction in water and did not depress the m. p. of salicylic acid. No other acid could be detected by paper chromatography [7] in the mother-liquor of the recrystallised product.

1,4-*Dihydroxy*-7-*methoxy*-3-*methylxanthone*.—Potassium hydroxide (1·44 g.) in water (20 ml.) was added to a solution of 1-hydroxy-7-methoxy-3-methylxanthone [8] (0·8 g.) in pyridine (16 ml.). To the stirred mixture was added, during 1½ hr., a solution of potassium persulphate (1·6 g.) in water (60 ml.). After having been kept at room temperature for 22 hr., the solution was acidified to Congo Red with concentrated hydrochloric acid, and the precipitate was removed. The filtrate was extracted with ether (2 × 120 ml.) and the extract was discarded. To the aqueous solution were added sodium sulphite (2·0 g.) and concentrated hydrochloric acid (25 ml.). The solution was heated at 100° for ½ hr., then cooled, and the precipitate was collected, washed, dried (0·37 g.), recrystallised from 2-ethoxyethanol, and washed with ethanol. The resulting *xanthone* (0·20 g., 24%) formed golden-brown, rectangular plates, decomp. >236° [Found (on a sample dried *in vacuo* at 100°): C, 66·0; H, 4·6. $C_{15}H_{12}O_5$ requires C, 66·2; H, 4·4%]. This substance gave a negative Gibbs test and a brown-green ferric reaction in ethanol, and dissolved in 2N-sodium hydroxide giving an intense reddish-brown colour.

Degradation of 1,4-*Dihydroxy*-7-*methoxy*-3-*methylxanthone*.—To a solution of the xanthone (50 mg.) in aqueous 1% sodium hydroxide (15 ml.) was added 3% hydrogen peroxide (9 ml.). The mixture was kept for 4 days at room temperature, and the product isolated as described above. Evaporation of the dried ether extracts yielded 2-hydroxy-5-methoxybenzoic acid (4·3 mg.), needles (from water) (2·2 mg.), identified by m. p. and mixed m. p. (145°) and blue ferric reaction in water.

Semimicro-procedure.—1-Hydroxy-7-methoxy-3-methylxanthone (40 mg.) was oxidised by persulphate as described above but on a smaller scale. The crude 1,4-dihydroxy-7-methoxy-3-methylxanthone was filtered off and washed with water. A 1% solution of sodium hydroxide (6 ml.) was poured over the filter, and to the dark-red solution of the xanthone thus obtained was added, in 4 hr., 1·7% hydrogen peroxide solution (4 ml.). The mixture was kept at room temperature for 48 hr. and was then filtered from a little brown amorphous material. The pale-yellow filtrate, after the addition of 2N-hydrochloric acid (1 ml.) to reduce the pH to *ca.* 1, was extracted with ether (2 × 10 ml.). The combined ethereal solutions, after having been washed with water (2 ml.), were extracted with a 5% solution of sodium hydrogen carbonate (5 ml.)

[7] Bate-Smith and Westall, *Biochim. Biophys. Acta*, 1950, **4**, 427.
[8] Grover, Shah, and Shah, *J.*, 1955, 3982.

and then with water (3 ml.). The combined aqueous extracts were acidified with 2N-hydrochloric acid and extracted with ether (2 × 10 ml.). The combined ethereal solutions were washed with water (2 ml.), dried (Na_2SO_4), and evaporated to give a semicrystalline solid (5·5 mg.). This recrystallised from 0·5 ml. of boiling water to give colourless needles (2·6 mg.), m. p. 144—145°, which were identified (see above) as 2-hydroxy-5-methoxybenzoic acid.

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