

NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

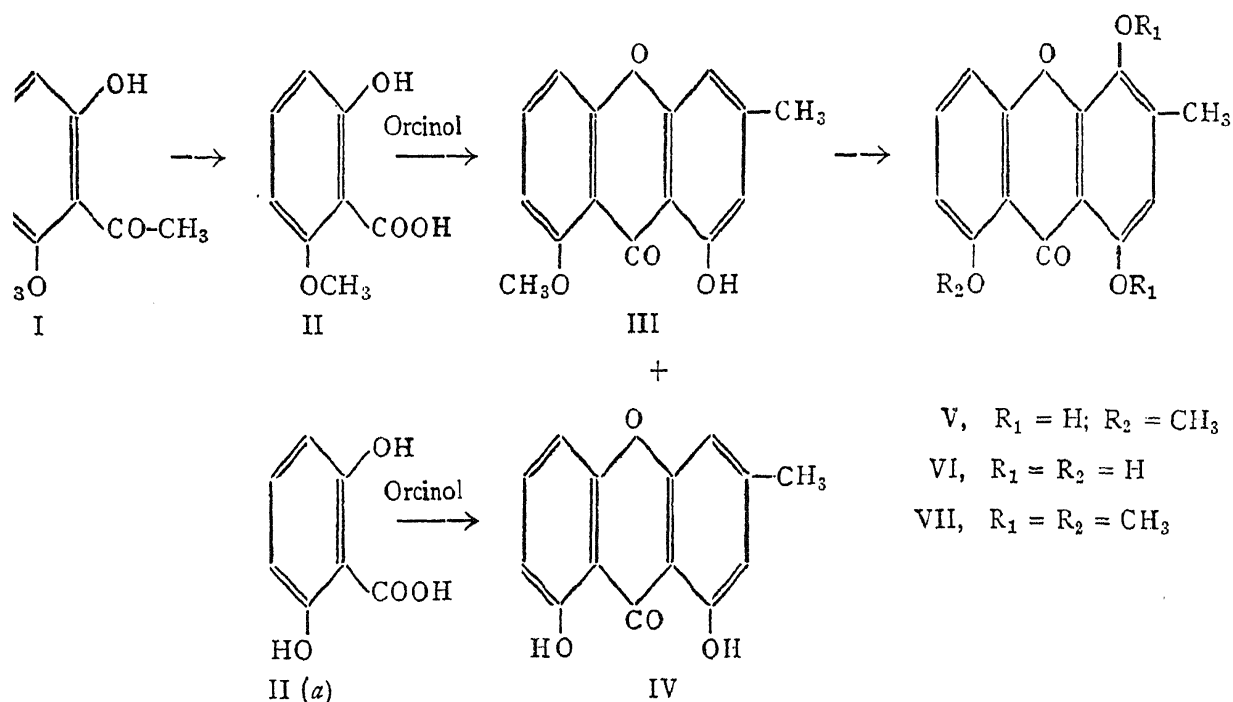
Part L. A Synthesis of Ravenelin

BY V. K. AHLUWALIA AND T. R. SESHADRI, F.A.Sc.

Received May 1, 1956

RAVENELIN¹ is a yellow xanthone occurring in the mycelium of *Helminthosporium ravenelii*, and of *H. turcicum*. These moulds are rather exceptional as compared with the numerous other species of *Helminthosporium* which contain anthraquinone derivatives. The constitution of ravenelin was established by Raistrick *et al.*,¹ and its synthesis carried out by Mull and Nord² utilising Ullmann's method. Since it has a quinol structure, a synthesis involving nuclear oxidation appeared to be more convenient. The feasibility of this procedure was shown by the earlier work of Rao and Seshadri³ who prepared 4-hydroxy euxanthone and that of Pankajamani and Seshadri⁴ who made 1:4-dihydroxy xanthone. The method now finally adopted for the synthesis of ravenelin involves the Nencki reaction and nuclear oxidation with alkaline persulphate. The details are given below:

2-Hydroxy-6-methoxy benzoic acid (II) obtained by the oxidation of the corresponding acetophenone (I) was condensed with orcinol in presence of zinc chloride. The product is found to be a mixture which could be separated by employing their difference in solubility in ethyl alcohol.

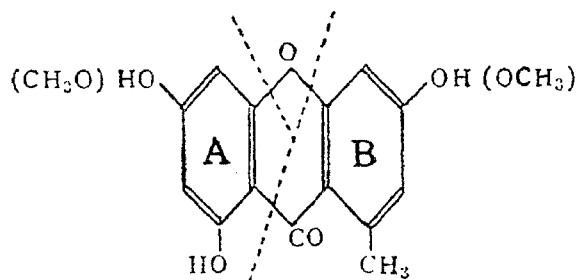


The more soluble fraction was 1-hydroxy-8-methoxy-3-methyl xanthone (III) and the less soluble one consisted of 1:8-dihydroxy-3-methyl xanthone (IV). The latter (IV) can also be readily obtained by the direct condensation of γ -resorcylic acid (II a) with orcinol. In these reactions orcinol is active in the γ -position as the resulting xanthenes give sparingly soluble alkali salts and are insoluble in aqueous sodium carbonate. This γ -reactivity of orcinol was reported earlier by Shah and co-workers⁵ using their modified Nencki reaction. The same xanthenes have been obtained also by the modified Nencki reaction using zinc chloride and phosphorus oxychloride but the yields are comparatively high. The demethylation of the 8-position seems to proceed even more easily in this condensation though it is done at a lower temperature.

Oxidation of 1-hydroxy-8-methoxy-3-methyl xanthone (III) with alkaline persulphate gives the 1:4-dihydroxy compound (V), which when subjected to demethylation with hydriodic acid yields ravenelin (VI) and on methylation gives ravenelin methyl ether (VII).

The observation that ravenelin is soluble in aqueous sodium bicarbonate would appear to be rather extraordinary. The 1:8-dihydroxy xanthone (IV) does not dissolve even in sodium carbonate. Hydroxyl groups in the positions para to the carbonyl, *i.e.*, 3 and 6 positions in xanthenes are usually considered to be acidic, but in the present case a different hydroxyl in the 4-position has enhanced this property so much that the substance becomes soluble in aqueous sodium bicarbonate.

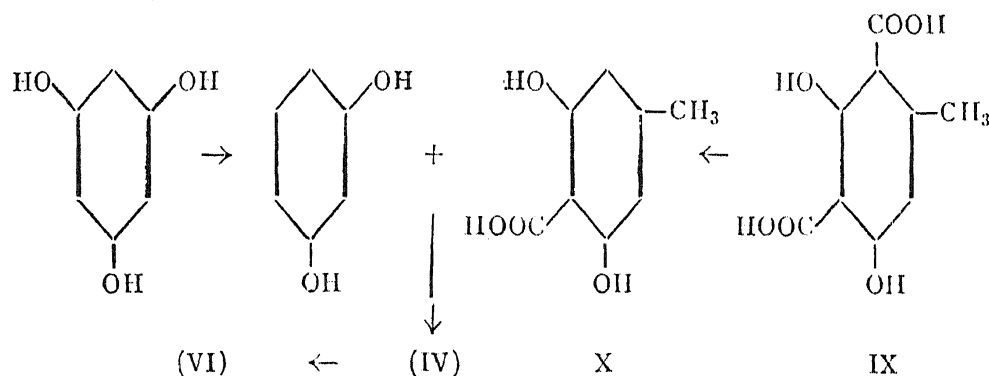
The structure of ravenelin (VI) could be considered to be derived essentially from two parts: (1) orcinol and (2) phloroglucinol linked together by a single carbon atom. The former has undergone oxidation into a hydroxy orcinol unit and the latter reduction into a resorcinol unit.



VIII

It has been stated that *H. ravenelii* and *H. turcicum* differ from the majority of *H.* species in producing a xanthone instead of anthraquinone as a metabolic product. However, there is partial resemblance also. As explained in an earlier publication by Aghoramurty and Seshadri,⁶ anthraquinones consist of the combination of two C_8 units; in the xanthone,

ravenelin, there is one C_8 unit. It may further be mentioned that ravenelin is an isomer of lichexanthone which is the only xanthone occurring in lichens. Lichexanthone is also built up of a phloroglucinol and of an orcinol unit; but in it the β -position of the orcinol unit is involved in the condensation. Probably the correct way of analysing the lichexanthone skeleton would be as shown in the formula (VIII), a C_8 -orsellinic acid unit (A) condensing with phloroglucinol (B). From the same standpoint ravenelin could be derived from an orsellinic acid unit and phloroglucinol involving more steps. 3-Carboxy orsellinic acid⁷ (IX) would be the first stage undergoing decarboxylation to *p*-orsellinic acid (X), and condensation with resorcinol followed by nuclear oxidation may be the final stages. This would suggest that the lichen xanthone and mould xanthone have a number of stages common and would support the contention that the fungal part of the lichen is responsible for this synthesis.



EXPERIMENTAL

Condensation of 2-hydroxy-6-methoxy benzoic acid and orcinol: 1-Hydroxy-8-methoxy-3-methyl xanthone (III) and 1:8-Dihydroxy-3-methyl xanthone (IV)

A mixture of 2-hydroxy-6-methoxy benzoic acid (1 g.) and freshly fused zinc chloride (2 g.) was heated to 160° and kept at that temperature for 5 min. to bring it into a uniform melt. Then the temperature was brought down to 140° and maintained for 4 hrs. The product was treated with hot water (50 c.c.), cooled and extracted with ether. The ether solution was washed with dilute sodium carbonate (5%) and left in contact with sodium hydroxide solution (10%, 50 c.c.) with occasional shaking. The precipitated sodium salt was filtered off, suspended in water containing a few drops of concentrated hydrochloric acid and boiled for 10 minutes. The mixture of mono- and di-hydroxy xanthenes separated out as a colourless mass and was crystallised from ethyl alcohol. The more soluble fraction (50 mg.) was 3-methyl-1-hydroxy-8-methoxy xanthone (III). It was finally crystallised from methyl alcohol yielding colourless fibrous hairy needles. It melted

at 140–41° (Found: C, 70.3; H, 4.7; $C_{15}H_{12}O_4$ requires C, 69.8; H, 4.6%). With alcoholic ferric chloride it gave a green colour. The acetate prepared with acetic anhydride and pyridine melted at 155–56°. The less soluble product (50 mg.) was 1:8-dihydroxy-3-methyl xanthone (IV). After two crystallisations from ethyl alcohol it separated as colourless thin rhombic plates and melted at 193–94° (Found: C, 69.7; H, 4.5; $C_{14}H_{10}O_4$ requires C, 69.4; H, 4.2%). It gave a green colour with alcoholic ferric chloride. The acetate prepared by the usual method melted at 196–97°. The same products were obtained by carrying out the condensation at a lower temperature (60–70°) and employing a mixture of zinc chloride and phosphorus oxychloride as condensing agent. The yields of the monohydroxy and dihydroxy compounds were 100 mg. and 400 mg. respectively from 1 g. of the acid.

A sample of 1:8-dihydroxy-3-methyl xanthone (IV) was prepared also by condensing 2:6-dihydroxy benzoic acid (1 g.), orcinol (1 g.) and zinc chloride (3 g.) as given above. It was isolated as the sodium salt and finally crystallised from ethyl alcohol, m.p. 193–94°. Yield 100 mg. Mixed m.p. with the product obtained above was undepressed. The same product (mixed m.p. undepressed) was obtained by carrying out the reaction at a lower temperature (60–70°) in presence of phosphorus oxychloride. Yield 400 mg. from 1 g. of the acid.

1:4-Dihydroxy-8-methoxy-3-methyl xanthone (V)

A stirred solution of 1-hydroxy-8-methoxy-3-methyl xanthone (1 g.) in pyridine (30 c.c.) and aqueous sodium hydroxide (1.5 g. in 25 c.c. water), at 15–20°, was treated dropwise with potassium persulphate (2 g.) in water (75 c.c.) during 2 hrs. After 24 hrs. at room temperature the deep brown solution was acidified to congo red and the unchanged product filtered off, ether extraction removing the last traces of it. The clear brown aqueous solution was heated in a boiling water-bath with sodium sulphite (4 g.) and concentrated hydrochloric acid (50 c.c.) for 1 hr. It was then cooled and the yellow solid was filtered off and washed with water. The filtrate on ether extraction gave some more of the quinol. It crystallised from ethyl acetate-petroleum ether mixture as orange yellow rectangular plates and melted at 250–52° (decomp.) (Found: C, 66.1; H, 4.3; $C_{15}H_{12}O_5$ requires C, 66.2; H, 4.4%). It gave a brown colour with alcoholic ferric chloride and was sparingly soluble in sodium bicarbonate solution. The diacetate prepared by the acetic anhydride-pyridine method melted at 175–76°.

On methylation with methyl sulphate in acetone and potassium carbonate it gave the methyl ether (1:4:8-trimethoxy-3-methyl xanthone), which

on crystallisation from methyl alcohol melted at 179–80°, agreeing with that recorded for methyl ravenelin.¹

1:4:8-Trihydroxy-3-methyl xanthone (VI) (Ravenelin)

1:4-Dihydroxy-8-methoxy-3-methyl xanthone (0.2 g.) was dissolved in acetic anhydride (5 c.c.) and to the cold solution was added hydriodic acid (5 c.c.). The solution was refluxed for two hours in an oil-bath at 145–50°. It was then poured into ice-cold saturated solution of sodium bisulphite (50 c.c.). The solid product was filtered, dried and crystallised from benzene yielding yellow needles and rectangular rods, m.p. 268–70°. Yield 0.1 g. Mixed m.p. with the natural sample of ravenelin was undepressed. Both the samples had the same absorption spectrum in the visible region with a marked maximum at 400 m μ . The acetate prepared by the acetic anhydride-pyridine method melted at 204–05° agreeing with the earlier record.

We are grateful to Prof. Raistrick, F.R.S., for kindly supplying us with a natural sample of ravenelin.

SUMMARY

2-Hydroxy-6-methoxy benzoic acid condenses with orcinol giving rise to (1) 1-hydroxy-3-methyl-8-methoxy xanthone and (2) 1:8-dihydroxy-3-methyl xanthone. The second is also obtained from γ -resorcylic acid. The first undergoes nuclear oxidation with alkaline persulphate to yield ravenelin-8-methyl ether which is demethylated to ravenelin.

REFERENCES

1. Raistrick, Robinson and White .. *Biochem. Jour.*, 1936, 30, 1314.
2. Mull and Nord .. *Arch. Biochem.*, 1944, 4, 419.
3. Rao and Seshadri .. *Proc. Ind. Acad. Sci.*, 1947, 26 A, 288.
4. Pankajamani and Seshadri .. *Jour. Sci. Ind. Res.*, 1954, 13 B, 396.
5. Grover, Shah and Shah .. *Jour. Chem. Soc.*, 1955, 3982.
6. Aghoramurty and Seshadri.. *Jour. Sci. Ind. Res.*, 1954, 13 A, 114.
7. Seshadri .. *Proc. Ind. Acad. Sci.*, 1944, 20 A, 7.