Hydroxylation of Flavanones in the 3-Position.

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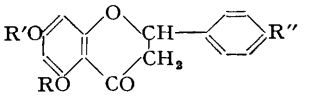
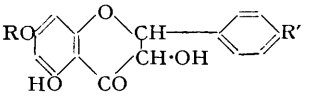
Oxidation of acetoxyflavanones with Fenton's reagent in acid medium yields 3-hydroxy-compounds with simultaneous deacetylation in the 5-position. As by-products arise binuclear compounds by dehydrogenative coupling in the 3-position. The method is of interest in biogenesis.

VARIOUS flavanones are found in Nature along with their 3-hydroxy-derivatives (flavanolones) (Pew, *J. Amer. Chem. Soc.*, 1948, **70**, 3031; Lindstedt, *Acta Chem. Scand.*, 1951, **5**, 121; Mahesh and Seshadri, *J. Sci. Ind. Res., India*, 1954, **13**, *B*, 835). This suggests the existence of a phytochemical hydroxylation process affecting the 3-position of flavanones. Hydroxylation of flavanones at position 3 has been achieved in the laboratory by bromination (Zemplen and Bognar, *Ber.*, 1943, **76**, 452), iodination (Goel, Narasimhachari, and Seshadri, *Proc. Indian Acad. Sci.*, 1954, **39**, *A*, 254), and lead tetra-acetate (Oyamada, *J. Chem. Soc. Japan*, 1943, **64**, 331, 471; Cavill, Dean, McGookin, Marshall, and Robertson, *J.*, 1954, 4573; Kotake, Sakan, and Kubota, *Chem. and Ind.*, 1954, 1562). The use of Fenton's reagent in acid medium has now been examined. This free-radical reaction proceeds satisfactorily and provides good support for the biogenesis of flavanolones because according to Haber and Willstätter (*Ber.*, 1931, **64**, 2844) enzyme oxidation involves free radicals and, further, Fenton's method and enzymic oxidation of a large variety of organic compounds yield similar products (Mackinnon and Waters, *J.*, 1953, 323).

When naringenin triacetate (I; R = R′ = Ac, R″ = OAc) was oxidised by Fenton's reagent in acid medium, a mixture of two compounds was obtained. One of these formed a crystalline lead salt from which it could be recovered. Its ferric chloride colour, composition, and properties suggested that it was 7 : 4′-diacetoxy-3 : 5-dihydroxyflavanone (II; R = Ac, R′ = OAc). That deacetylation had taken place in the 5-position was supported by the observation that naringenin triacetate (I; R = R′ = Ac, R″ = OAc) undergoes partial deacetylation in sulphuric acid, yielding the 7 : 4′-diacetate. The formation of the lead salt depends on the presence of 3- and 5-hydroxyl groups since, among known compounds, naringenin diacetate (I; R = H, R′ = Ac, R″ = OAc) and pinostrobin (I; R = R″ = H, R′ = Me) do not form basic lead salts whereas pinobanksin (II; R =

R′ = H) and its 7-methyl ether (II; R = Me, R′ = H) do. The constitution of the oxidation product as (II; R = Ac, R′ = OAc) is confirmed by its formation also by the oxidation of naringenin diacetate (I; R = H, R′ = Ac, R″ = OAc) under the same conditions. Further, acid hydrolysis yielded 3-hydroxynaringenin (II; R = H, R′ = OH) (Goel, Narasimhachari, and Seshadri, *loc. cit.*). It was dehydrated by acetic anhydride to apigenin triacetate (III).


(I)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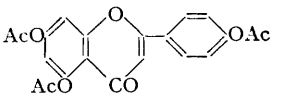
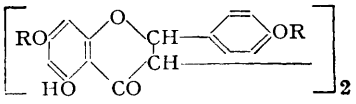

(III)


(IV)

The second product of Fenton oxidation yielded on deacetylation with acid a compound which agreed in composition and molecular weight with the diflavanone formula (IV; R = H). The parent compound should therefore be the partial acetate (IV; R = Ac) and its properties and composition were in agreement with this. Fenton's oxidation of a number of other organic compounds is known to produce such bimolecular products (Merz and Waters, *J.*, 1949, 2427).

Similar oxidation of 5 : 7-diacetoxyflavanone (I; R = R′ = Ac, R″ = H) gave 7-acetoxy-3 : 5-dihydroxyflavanone (II; R = Ac, R′ = H) which was hydrolysed to 3 : 5 : 7-trihydroxyflavanone (II; R = R′ = H).

Earlier, potassium permanganate had been used for the hydroxylation of other compounds in the position α to a carbonyl group : 7 : 2′ : 4′-trimethoxy*iso*flavanone yielded its 3-hydroxy-derivative (Robertson and Whalley, *J.*, 1954, 1440), and 2-benzyl-4 : 6-dimethoxycoumaranone its 2-hydroxy-derivative (Gripenberg, *Acta Chem. Scand.*, 1953, **7**, 1323). This reagent has now been employed for the conversion of 5 : 7-diacetoxyflavanone (I; R = R′ = Ac, R″ = H) into 7-acetoxy-3 : 5-dihydroxyflavanone (II; R = Ac, R′ = H), but it gives rather poor yields compared with Fenton's reagent whose use appears therefore to be of preparative value.

Experimental

Hydroxylation of Naringenin Triacetate (I; R = R′ = Ac, R″ = OAc) *to* 7 : 4′-*Diacetoxy*-3 : 5-*dihydroxyflavanone* (II; R = Ac, R′ = OAc).—To a stirred suspension of finely powdered naringenin triacetate (1 g.) in 2N-sulphuric acid (100 c.c.) at 0° hydrogen peroxide (5-vol.; 50 c.c.) and ferrous sulphate solution (2%; 50 c.c.) were run in simultaneously during 45 min. The mixture was then extracted repeatedly with ether, and the extract evaporated, yielding a yellow solid. This was dissolved in alcohol (50 c.c.), and a saturated alcoholic solution of basic lead acetate (150 c.c.) added. A crystalline yellow lead salt separated (600 mg.) which was filtered off (filtrate F) and decomposed with hydrogen sulphide in alcohol. The *product* obtained by evaporating the alcoholic solution crystallised from aqueous alcohol as colourless needles and small rectangular prisms (0·25 g.), m. p. 136—137° (Found : C, 61·0; H, 4·5. $C_{19}H_{16}O_8$ requires C, 61·3; H, 4·3%). It gave a brownish-red colour with ferric chloride and a red colour with magnesium or zinc and hydrochloric acid.

The mother-liquor (F) was heated to the b. p. and hydrogen sulphide passed into it. Lead sulphide was filtered off and the filtrate evaporated to dryness. The residual *di*-(7 : 4′-*diacetoxy*-5-*hydroxyflavanon*-3-*yl*) crystallised from alcohol as colourless flat needles and rectangular plates, m. p. 192—194° (Found : C, 63·9; H, 4·7. $C_{38}H_{30}O_{14}$ requires C, 64·2; H, 4·2%). Yield 250 mg. It gave a brownish-red colour with ferric chloride, a red colour with magnesium and hydrochloric acid, and a pink colour with zinc and hydrochloric acid. This partial acetate (150 mg.) was hydrolysed for 15 min. with boiling alcoholic hydrochloric acid (50 c.c.; 1 : 1). Addition of water (50 c.c.) yielded a sticky solid which crystallised from ethyl acetate–light petroleum as colourless rectangular tablets and prisms, m. p. 210—212° [Found : C, 65·9; H, 4·0%; *M* (cryoscopic), 539. $C_{30}H_{22}O_{10}$ requires C, 66·4; H, 4·0%; *M*, 542]. It gave a reddish-violet colour with ferric chloride, a red colour with magnesium and hydrochloric acid,

and a faint pink colour with zinc and hydrochloric acid. Attempts to dehydrogenate it with selenium dioxide in acetic anhydride led to decomposition.

Hydroxylation of Naringenin Diacetate (I; R = H, R′ = Ac, R″ = OAc) *to* 7 : 4′-*Diacetoxy*-3 : 5-*dihydroxyflavanone* (II; R = Ac, R′ = OAc).—Naringenin diacetate (0·5 g.), prepared by the partial acetylation of naringenin, was subjected to Fenton oxidation and the product worked up as in the above experiment. A pale yellow substance (60 mg.) obtained by the decomposition of the lead salt had m. p. 136—137° alone or mixed with the product obtained by hydroxylation of naringenin triacetate; the mixed m. p. with naringenin diacetate (m. p. 140—141°) was depressed. Naringenin diacetate did not form a basic lead salt. A second product (m. p. 192—194°) which did not give a lead salt was identical with the similar one obtained in the oxidation of naringenin triacetate.

3-*Hydroxynaringenin* (II; R = H, R′ = OH).—The diacetoxyflavanone, m. p. 136—137°, was hydrolysed with alcoholic hydrochloric acid to 3-hydroxynaringenin, flesh-coloured rhombohedral prisms, m. p. 238—240° (decomp.) (from aqueous alcohol), giving a violet colour with ferric chloride and a red colour with magnesium or zinc and hydrochloric acid. A mixed m. p. with Goel, Narasimhachari and Seshadri's sample (*loc. cit.*) was undepressed.

Dehydration of 3-*Hydroxynaringenin to Apigenin Triacetate* (III).—3-Hydroxynaringenin (0·25 g.), refluxed with acetic anhydride (2 c.c.) for 2 hr., afforded apigenin triacetate, rectangular plates (0·1 g.), m. p. 180—181° (from ethyl acetate–light petroleum).

Hydroxylation of 5 : 7-*Diacetoxyflavanone* (I; R = R′ = Ac, R″ = H) *to* 7-*Acetoxy*-3 : 5-*dihydroxyflavanone* (II; R = Ac, R′ = H).—(a) *Fenton's reagent.* 5 : 7-Diacetoxyflavanone (1 g.) was subjected to Fenton oxidation as in the case of naringenin triacetate. The basic lead salt yielded on decomposition a *product* which crystallised from aqueous alcohol as needles, m. p. 90—92° (0·1 g.) (Found: C, 64·5; H, 4·9. $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5%). It gave a brownish-red colour with ferric chloride, a red colour with magnesium and hydrochloric acid, and a pink colour with zinc and hydrochloric acid.

(b) *Neutral permanganate.* 5 : 7-Diacetoxyflavanone (1 g.) was dissolved in acetone (100 c.c.), finely powdered permanganate (5 g.) added, and the mixture stirred for 4 hr. at room temperature. Water (500 c.c.) was then added and the manganese dioxide dissolved by use of sulphur dioxide. The solution was extracted with ether (3 × 200 c.c.), and the ether extract was washed with aqueous sodium hydrogen carbonate and evaporated. The residue was converted by way of the lead salt into the preceding product, needles (35 mg.), m. p. and mixed m. p. 90—92°.

3 : 5 : 7-*Trihydroxyflavanone* (II; R = R′ = H).—7-Acetoxy-3 : 5-dihydroxyflavanone was deacetylated by alcoholic hydrochloric acid to 3 : 5 : 7-trihydroxyflavanone, rectangular prisms (from aqueous alcohol), m. p. and mixed m. p. 172—173° (50 mg.).

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