2'-*Hydroxy- and* 2'-*Methoxy-flavanones.*

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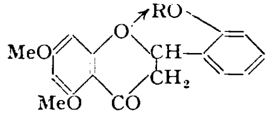
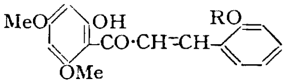
The compounds obtained by Narasimhachari, Rajagopalan, and Seshadri (*Proc. Indian Acad. Sci.*, 1952, **36**, *A*, 231) from the interaction of *o*-hydroxyacetophenones with *o*-hydroxy- and *o*-methoxy-benzaldehydes, and designated as 2'-hydroxyflavanones have been shown to be the respective unchanged parent *o*-hydroxyacetophenones. The preparation of various chalkones and related derivatives is described.

THE isolation from *Citrus limon ponderosa* of a glycoside, citronin, which upon hydrolysis furnished the aglucone, citronetin, has been described by Yamamoto and Oshima (*J. Agric. Chem. Soc., Japan*, 1931, **7**, 312). Degradative evidence, especially the isolation of *o*-methoxycinnamic acid and phloroglucinol rhamnoglucoside from citronin by alkali fission, led them to formulate citronetin as 5 : 7-dihydroxy-2'-methoxyflavanone. This flavanone was synthesised by Shinoda and Sato (*J. Pharm. Soc. Japan*, 1931, **51**, 576) by the Friedel–Crafts condensation of phloroglucinol and *o*-methoxycinnamoyl chloride. However, as the melting point of natural citronetin (204°) was not in good accord with that of 5 : 7-dihydroxy-2'-methoxyflavanone (224°), Narasimhachari, Rajagopalan, and Seshadri (*Proc. Indian Acad. Sci.*, 1952, **36**, *A*, 231) re-investigated the synthesis of this and of 2'-hydroxy- and 2'-methoxy-flavanones.

(I)





(II)

From interaction of salicylaldehyde with 2-hydroxy-4 : 6-dimethoxyacetophenone in the presence of alkali the Indian authors (*loc. cit.*) isolated a product, m. p. 85—86°, which exhibited a blue colour with concentrated nitric acid, a violet ferric reaction in alcohol, a red colour with magnesium and hydrochloric acid, gave a negative boric acid test (Wilson, *J. Amer. Chem. Soc.*, 1939, **61**, 2303), and was only sparingly soluble in aqueous sodium hydroxide. An identical product was obtained from the same two components in the presence of hydrogen chloride (Russell, *J.*, 1934, 218). Furthermore, this compound was also obtained by the alkaline condensation of 2-hydroxy-4 : 6-dimethoxyacetophenone with *o*-methoxybenzaldehyde. This product, m. p. 85—86°, was formulated as 2'-hydroxy-5 : 7-dimethoxyflavanone (I ; R = H). Its analysis was in agreement with the empirical formula $C_{17}H_{16}O_5,1{\cdot}5H_2O$, though it was stated that sublimation under reduced pressure did not change the m. p. or remove the water of crystallisation. If this compound is correctly formulated, its formation from *o*-methoxybenzaldehyde must involve a remarkably easy demethylation of the 2'-methoxy-group in 2'-methoxyflavanones. Seshadri *et al.* (*loc. cit.*) recognised this difficulty but circumvented it by assuming a new type of hydrogen bonding between the ether oxygen atom of the pyrone ring and the 2'-hydroxyl group (as in I; R = H), reminiscent of that existing between the pyrone carbonyl and the 5-hydroxyl group. This " new effect of hydrogen-bond formation " was also invoked to explain the ferric reaction of the compound, the alleged resistance to complete methylation and the inertness to oxidation with iodine and potassium acetate (Narashimhachari, Rajagopalan, and Seshadri, *Proc. Indian Acad. Sci.*, 1953, **37**, *A*, 620) and with hydrogen peroxide (*idem, ibid.*, p. 705).

Finally the cyclisation of 2'-hydroxy-2 : 4' : 6'-trimethoxychalkone (II ; R = Me) with boiling acid was reported to furnish (I ; R = H) with the simultaneous demethylation of the 2'-methoxyl group of the resulting flavanone, though the acid-catalysed cyclisations of 2'-hydroxy-2 : 4' : 6'-trimethoxy- (Bargellini and Peratoner, *Gazzetta*, 1919, **49**, 68), 2'-hydroxy-2 : 3' : 4'-trimethoxy- (Cohen and von Kostanecki, *Ber.*, 1904, **37**, 2629), and

2′-hydroxy-2 : 4 : 4′-trimethoxy-chalkone (von Kostanecki, Lampe, and Triulzi, *Ber.*, 1906, **39**, 93) to the respective 2′-methoxyflavanones have previously been reported to be normal.

Such *a priori* unacceptable features prompted us to reinvestigate this problem. We now consider that the compound formulated as 2′-hydroxy-5 : 7-dimethoxyflavanone is actually unchanged 2-hydroxy-4 : 6-dimethoxyacetophenone. In numerous attempts to repeat both the acid- and the alkali-catalysed condensations of this ketone with salicylaldehyde and *o*-methoxybenzaldehyde (by the methods of Seshadri *et al.*, *locc. cit.*) the only solid product isolated by us was the parent ketone identified by analysis, melting point (86°), mixed melting point, and by paper chromatography. Furthermore, 2-hydroxy-4 : 6-dimethoxyacetophenone has the melting point and gives all the colour reactions (with the exception of the magnesium–hydrochloric acid test) ascribed to the flavanone (I; R = H).

In agreement with Bargellini and Peratoner (*loc. cit.*) we have found that the acid-catalysed cyclisation of 2′-hydroxy-2 : 4′ : 6′-trimethoxychalkone (II; R = Me) proceeds normally to produce 5 : 7 : 2′-trimethoxyflavanone (I; R = Me), m. p. 128°, exhibiting all the expected properties and not being demethylated during cyclisation. In addition, the acid-catalysed cyclisation of 2 : 2′-dihydroxy-4′ : 6′-dimethoxychalkone (II; R = H) furnished 2′-hydroxy-5 : 7-dimethoxyflavanone (I; R = H), m. p. 196°, which is instantly soluble in cold dilute alkali, is *devoid* of a ferric reaction, and is rapidly methylated to 5 : 7 : 2′-trimethoxyflavanone (I; R = Me).

The melting point of (I; R = Me) is in close agreement with that recorded by Yamamoto and Oshima (*loc. cit.*) for citronetin dimethyl ether (125°), formulated as 5 : 7 : 2′-trimethoxyflavanone. In consequence, we believe that the structure of citronetin, while still requiring final verification, is in all probability correct.

Repetition of the remaining " 2′-hydroxyflavanone " preparations described by Seshadri *et al.* (*locc. cit.*), has clearly shown that these "2′-hydroxyflavanones" also are the appropriate *o*-hydroxyacetophenones. This conclusion is adequately substantiated by a comparison of the melting points, the colour reactions, the inertness towards oxidation by hydrogen peroxide, and the majority of analyses ascribed to these supposed flavanones and their derivatives, with those of the relevant ketones. Moreover, by standard methods, we have prepared the chalkones isomeric with Seshadri's " flavanones " and find that these styryl ketones are oxidised normally to the corresponding 3-hydroxyflavones and exhibit no abnormal properties.

Although we consider that some hydrogen bonding between the pyrone oxygen and the 2′-hydroxyl group of flavanones is likely (cf. Gallagher, Hughes, O'Donnell, Philbin, and Wheeler, *J.*, 1953, 3770), we conclude that the system does not possess the properties attributed to it by the Indian authors.

[*Note Added in Proof, November* 17*th*, 1954.—Our attention has been directed to a discrepancy in the literature of 2-methoxyflavones. 3-Hydroxy-7 : 2′-dimethoxyflavone, prepared by hydrolysis of the *iso*nitrosoflavanone is described by Kostanecki and Szlagier (*Ber.*, 1904, **37**, 4155) as forming tablets, m. p. 203° (acetate, m. p. 138—139°). Seshadri *et al.* (*Proc. Indian Acad. Sci.*, 1953, **37**, 705) claim to have prepared this compound by oxidation of the chalkone with alkaline hydrogen peroxide, but give m. p. 158—160°. We have now repeated the peroxide oxidation of 2′-hydroxy-2 : 4′-dimethoxychalkone and find, in agreement with Kostanecki and Szlagier (*loc. cit.*), that the flavonol has m. p. 204—205° (acetate, m. p. 138—139°)].

EXPERIMENTAL

5 : 7 : 2′-*Trimethoxyflavanone* (I; R = Me).—(*a*) A solution of sodium hydroxide (10 g.) in water (10 ml.) and alcohol (20 ml.) containing 2-hydroxy-4 : 6-dimethoxyacetophenone (5 g.) and salicylaldehyde (8 g.) was refluxed for 30 min., in an atmosphere of nitrogen. The crude product, isolated by acidification of the cold solution, was washed with light petroleum (b. p. 60—80°) and purified from alcohol to furnish 2 : 2′-*dihydroxy*-4′ : 6′-*dimethoxychalkone* (6·5 g.) in yellow needles, m. p. 171°, having an intense red ferric reaction in alcohol (Found : C, 67·8; H, 5·1. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%). A solution of this chalkone (4 g.) in alcohol (320 ml.) and 2N-sulphuric acid (80 ml.) was refluxed for 48 hr., and the bulk of the alcohol

was then removed under reduced pressure. After dilution with water (100 ml.) the red, sticky precipitate was separated, and the solution of this in methanol deposited *2′-hydroxy-5 : 7-dimethoxyflavanone* (I; R = H) in almost colourless prisms (0·3 g.), m. p. 196°, instantly soluble in cold 2N-sodium hydroxide and devoid of a ferric reaction in alcohol [Found : C, 67·8; H, 5·3; OMe, 20·6. $C_{15}H_{10}O_3(OMe)_2$ requires C, 68·0; H, 5·4; OMe, 20·7%].

Ether extraction of the aqueous solution furnished more (0·2 g.) of this flavanone which was methylated quantitatively during 30 min. by methyl iodide or methyl sulphate–acetone–potassium carbonate to 5 : 7 : 2′-trimethoxyflavanone, identical with a specimen prepared by route (*b*).

(*b*) A solution of 2′-hydroxy-2 : 4′ : 6′-trimethoxychalkone (1 g.) (prepared from the condensation of 2-hydroxy-4 : 6-dimethoxyacetophenone with *o*-methoxybenzaldehyde or by methylation with methyl sulphate–acetone–potassium carbonate of 2 : 2′-dihydroxy-4′ : 6′-dimethoxychalkone) in 4% aqueous alcoholic sulphuric acid (100 ml.) was refluxed for 24 hr. (*cf.* Seshadri *et al.*, *loc. cit.*). After unchanged chalkone (0·3 g.) had been filtered off from the cooled mixture, the solution was evaporated under reduced pressure to *ca.* 25 ml., and water (100 ml.) added to the residue. Purification of the resultant precipitate from methanol furnished (i) unchanged chalkone (0·1 g.), and (ii) 5 : 7 : 2′-trimethoxyflavanone (0·5 g.) in plates, m. p. 128°, having a negative ferric reaction in alcohol [Found : C, 68·7; H, 6·0; OMe, 29·6. Calc. for $C_{15}H_9O_2(OMe)_3$: C, 68·8; H, 5·8; OMe, 29·6%)]. Bargellini and Peratoner (*loc. cit.*) record m. p. 125°. The mixed m. p. with 2 : 2′ : 4′ : 6′-tetramethoxychalkone (m. p. 125°) was depressed to *ca.* 100°.

3 : 5 : 7 : *2′-Tetrahydroxyflavone* (*Datiscetin*).—When hydrogen peroxide (100-vol.; 7·5 ml.) was added gradually to a solution of 2 : 2′-dihydroxy-4′ : 6′-dimethoxychalkone (0·5 g.) in 30% sodium hydroxide (10 ml.), and the mixture acidified 30 min. later, the precipitated 3 : *2′-dihydroxy-5* : *7-dimethoxyflavone* separated from methanol in cream needles (0·25 g.), m. p. 216—218°, having a green ferric reaction in alcohol [Found: C, 65·1; H, 4·5; OMe, 19·6. $C_{15}H_8O_4(OMe)_2$ requires C, 65·0; H, 4·5; OMe, 19·7%]; the *diacetate* separated from alcohol in needles, m. p. 156° (Found : C, 63·3; H, 4·7. $C_{21}H_{18}O_8$ requires C, 63·3; H, 4·6%).

Demethylation of the foregoing flavone (1 g.) with a mixture of hydriodic acid (*d* 1·7; 2·5 ml.) and acetic acid (25 ml.) on the steam-bath during 1½ hr. furnished 3 : 5 : *2′-trihydroxy-7-methoxyflavone* in prisms (0·27 g.) (from alcohol), m. p. 240°, having a green ferric reaction in alcohol [Found : C, 64·0; H, 3·9; OMe, 10·7. $C_{15}H_9O_5(OMe)$ requires C, 64·0; H, 4·0; OMe, 10·3%].

Demethylation of 3 : 2′-dihydroxy-5 : 7-dimethoxyflavone (0·2 g.) with boiling hydriodic acid (*d* 1·7; 3 ml.)–acetic acid (from 1 ml. of anhydride) during 2 hr. furnished 3 : 5 : 7 : 2′-tetrahydroxyflavone which separated from aqueous acetic acid in pale yellow needles (0·095 g.), m. p. 277—278° undepressed on admixture with authentic datiscetin. The same product was obtained from 3 : 5 : 2′-trihydroxy-7-methoxyflavone or with aluminium chloride in benzene as the demethylating agent.

2 : *2′-Dihydroxy-6′-methoxychalkone.*—The condensation of 2-hydroxy-6-methoxyacetophenone (5 g.) with salicylaldehyde (10 g.) by the method previously described furnished the *chalkone* in orange needles (7 g.), m. p. 141° (from aqueous alcohol), having an intense brown ferric reaction in this solvent [Found : C, 71·4; H, 5·3; OMe, 11·8. $C_{15}H_{11}O_3(OMe)$ requires C, 71·1; H, 5·2; OMe, 11·5%].

Chalkones derived from Paeonol.—A solution of sodium hydroxide (10 g.) in the minimum quantity of water was added to a solution of paeonol (6 g.) and *o*-methoxybenzaldehyde (10 g.) in alcohol (40 ml.). Next day, after the addition of excess of ether, the precipitated sodium salts were collected and dissolved in aqueous acetic acid, and the resultant solid purified from alcohol to furnish 2′-hydroxy-2 : 4′-dimethoxychalkone (9·5 g.) in yellow prisms, m. p. 92° (Kostanecki and Szlagier, *Ber.*. 1904, **37**, 4155, give m. p. 94°), with an intense brown ferric reaction in this solvent (Found : C, 72·1; H, 5·8. Calc. for $C_{17}H_{16}O_4$: C, 71·8; H, 5·7%). Seshadri *et al.* (*Proc. Indian Acad. Sci.*, 1953, **37**, *A*, 707) obtained this compound as a semi-solid.

The condensation of paeonol (2 g.) with salicylaldehyde (4 g.) in the usual manner furnished 2 : *2′-dihydroxy-4′-methoxychalkone* as yellow prisms (from aqueous alcohol) (2·2 g.), m. p. 176—178° (decomp.), having a red-brown ferric reaction in alcohol [Found : C, 71·0; H, 5·2; OMe, 11·9. $C_{15}H_{11}O_3(OMe)$ requires C, 71·1; H, 5·2; OMe, 11·5%].

Methylation of this chalkone, with methyl sulphate–aqueous sodium hydroxide at room temperature, furnished an almost quantitative yield of 2′-hydroxy-2 : 4′-dimethoxychalkone, m. p. 92°, identical with the previously prepared specimen.

The benzylation, during 5 hr., of 2 : 2′-dihydroxy-4′-methoxychalkone with benzyl bromide in boiling acetone containing potassium carbonate furnished *2-benzyloxy-2'-hydroxy-4'-methoxychalkone* (50%), as yellow prisms (from alcohol), m. p. 117° (Found : C, 76·9; H, 5·5. $C_{23}H_{20}O_4$ requires C, 76·7; H, 5·6%), identical with the product (8 g.) obtained by the condensation of paeonol (8 g.) with *o*-benzyloxybenzaldehyde (14 g.) under the usual conditions.

3 : 7 : *2'-Trihydroxyflavone*.—(*a*) The oxidation, during 30 min., of a solution of 2 : 2'-dihydroxy-4'-methoxychalkone (0·5 g.) in 30% sodium hydroxide (10 ml.) with hydrogen peroxide (100-vol.; 7·5 ml.) furnished 3 : *2'-dihydroxy-7-methoxyflavone* in needles (from alcohol) (0·16 g.), m. p. 176—178°; with an intense green-brown ferric reaction in alcohol [Found : C, 67·8; H, 4·5; OMe, 10·9. $C_{15}H_9O_4(OMe)$ requires C, 67·6; H, 4·3; OMe, 10·9%]. The *diacetate* formed prisms (from alcohol), m. p. 180° (Found : C, 65·0; H, 4·2. $C_{20}H_{16}O_7$ requires C, 65·2; H, 4·4%). Demethylation of the foregoing flavone (1 g.) during 1 hr. in boiling hydriodic acid (*d* 1·7; 10 ml.)–acetic acid (from 5 ml. of anhydride) furnished 3 : 7 : 2'-trihydroxyflavone, m. p. 272—273°, identical with an authentic specimen.

(*b*) The addition, during 20 min., of hydrogen peroxide (100-vol.; 20 ml.) to the well-cooled slurry from aqueous sodium hydroxide (8·5 g.) in the minimum of water and 2-benzyloxy-2'-hydroxy-4'-methoxychalkone (1 g.) in alcohol (50 ml.) furnished *2'-benzyloxy-3-hydroxy-7-methoxyflavone* in prisms (acetic acid) (0·42 g.), m. p. 176°, having an intense dark green ferric reaction in alcohol (Found : C, 74·1; H, 4·8. $C_{23}H_{18}O_5$ requires C, 73·8; H, 4·9%). The *diacetate* formed plates, m. p. 148°, from alcohol (Found : C, 71·7; H, 4·7. $C_{25}H_{20}O_6$ requires C, 72·1; H, 4·8%).

Debenzylation of 2'-benzyloxy-3-hydroxy-7-methoxyflavone (1·5 g.) in acetic acid (25 ml.) containing concentrated hydrochloric acid (18 ml.) on the steam-bath during 1 hr. furnished 3 : 2'-dihydroxy-7-methoxyflavone (0·85 g.) identical with the previously prepared specimen.

3 : *2'-Dihydroxy- and 3-Hydroxy-2'-methoxy-flavone*.—The oxidation with hydrogen peroxide of 2 : 2'-dihydroxychalkone (Geissmann and Clinton, *J. Amer. Chem. Soc.*, 1946, **68**, 698) (0·5 g.) furnished 3 : *2'-dihydroxyflavone* in yellow plates (0·12 g.), m. p. 209°, from alcohol (Found : C, 71·0; H, 4·1. $C_{15}H_{10}O_4$ requires C, 70·9; H, 4·0%); the *diacetate* formed needles, m. p. 124°, from alcohol (Found : C, 67·4; H, 4·4. $C_{19}H_{14}O_6$ requires C, 67·5; H, 4·2%).

Similarly 2'-hydroxy-2-methoxychalkone (Tambor and Guber, *Helv. Chim. Acta*, 1919, **2**, 108) (1 g.) gave *3-hydroxy-2'-methoxyflavone* in pale yellow prisms (0·35 g.), m. p. 215° [Found : C, 71·6; H, 4·5; OMe, 11·3. $C_{15}H_9O_3(OMe)$ requires C, 71·6; H, 4·5; OMe, 11·6%]. The *diacetate* crystallised from alcohol in plates, m. p. 155° (Found : C, 69·9; H, 4·6. $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·6%). Demethylation of this flavone (1 g.) with boiling hydriodic acid (*d* 1·7; 15 ml.) and acetic acid (from 5 ml. of anhydride) during 30 min. gave 3 : 2'-dihydroxyflavone (0·5 g.), identical with the previously prepared specimen.

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