

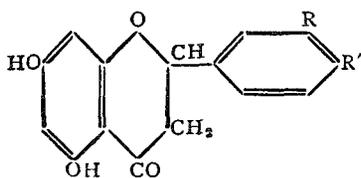
MODIFICATIONS IN THE IODINE OXIDATION OF HYDROXY FLAVANONES AND THEIR METHYL ETHERS

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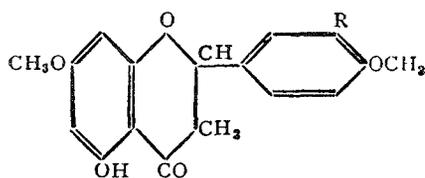
IN a previous publication¹ the action of iodine and silver acetate on flavanones in absolute alcoholic solution was discussed. Naringenin (I *a*) and hesperetin (I *b*) were found to yield the corresponding 3-acetoxy-flavanones while naringenin dimethyl ether (II *a*) and 5:7-dimethoxy-flavanone (III *a*) yielded the corresponding 3-iodo-compounds (IV *a* and III *b*). Considerable difference was recorded regarding the behaviour of these 3-iodo-compounds towards alcoholic potash. The 3-iodo-5-hydroxy-7:4'-dimethoxy flavanone (IV *a*) on treatment with this reagent yielded the corresponding flavone, apigenin-7:4'-dimethyl ether (V *a*) while the 3-iodo-5:7-dimethoxy flavone was reported to yield the corresponding flavonol, galangin-5:7-dimethyl ether (VI *a*). A more detailed study of these reactions has now been made.



I

(*a*) R=H, R'=OH.

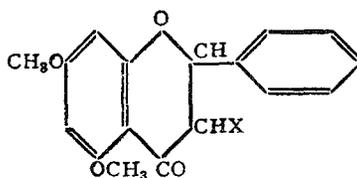
(*b*) R=OH, R'=OCH₃.



II

(*a*) R=H.

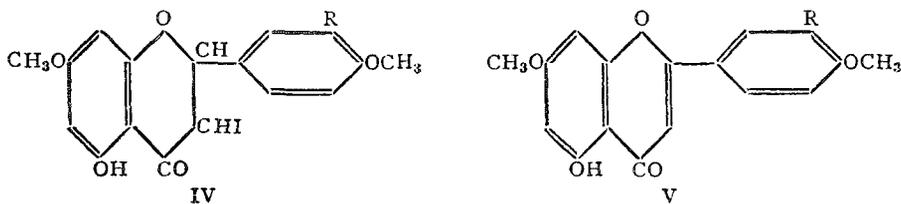
(*b*) R=OCH₃.



III

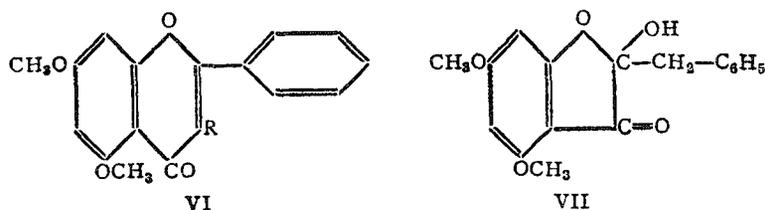
(*a*) X=H.

(*b*) X=I.



In the original procedure of Goel, Narasimhachari and Seshadri,¹ iodine was added to a boiling absolute alcoholic solution of the hydroxy flavanone and silver acetate. The method has not proved to be satisfactory as appreciable quantities of by-products are formed, making the purification of the main product difficult. During the course of the present work it has been found that if iodine is added at room temperature with shaking instead at the temperature of boiling alcohol and the addition is followed by refluxing for two hours, the purification of the product is simpler. Using this modified method naringenin (I *a*), naringenin-7:4'-dimethyl ether (II *a*) and 5:7-dimethoxy-flavanone (III *a*) have given good yields of 3-acetoxy-naringenin, 3-iodo-5-hydroxy-7:4'-dimethoxy flavanone (IV *a*) and 3-iodo-5:7-dimethoxy flavanone (III *b*) respectively. Similarly hesperetin (I *b*) gives a good yield of 3-acetoxy hesperetin and hesperetin 7:3'-dimethyl ether forms the 3-iodo-compound (IV *b*).

Treatment with pyridine or with alcoholic potash of 3-iodo-naringenin-7:4'-dimethyl ether (IV *a*) and of 3-iodo-hesperetin-dimethyl ether (IV *b*) yielded apigenin-7:4'-dimethyl ether (V *a*) and luteolin-7:3':4'-trimethyl ether (V *b*) respectively. 3-Iodo-5:7-dimethoxy-flavanone (III *b*) behaved somewhat differently; when treated with pyridine it yielded chrysin dimethyl ether (VI *b*), whereas on treatment with alcoholic potash it gave a mixture of chrysin dimethyl ether (VI *b*), 3-hydroxy-5:7-dimethoxy flavone (VI *a*) and 2-hydroxy-2-benzyl-4:6-dimethoxy coumaranone (VII). The separation of this mixture has been effected by using the difference in the solubilities of the components in aqueous alkali of different concentrations.



A probable explanation of the above difference in behaviour of the iodo-flavanones with alkali, may be found in the relative stability of the flavanone structures concerned. In the case of 3-iodo-5:7-dimethoxy flavanone (III *b*) only a portion seems to react in the original flavanone form and undergo loss of hydrogen iodide to yield the corresponding flavone (VI *b*). But the greater portion seems to undergo other changes as the result of substitution of iodine by hydroxyl and ring opening. The major product is found to be 2-hydroxy-2-benzyl-4:6-dimethoxy-coumaranone (VII) arising from ring closure in a different way. A small yield of the corresponding flavonol, galangin-5:7-dimethyl ether (VI *a*), is also formed as the result of dehydrogenation of the 3-hydroxy flavanone of the appropriate configuration² (equatorial hydroxyl). On the other hand in the case of the dimethyl ethers of naringenin and hesperetin (II *a* and II *b*), on account of the presence of a free hydroxyl group in the 5-position, the flavanone structure has greater stability; when treated with alcoholic potash the oxide ring does not open out so readily and only removal of hydrogen iodide takes place producing apigenin-7:4'-dimethyl ether (V *a*) and luteolin-7:3':4'-trimethyl ether (V *b*).

A modification in the iodine oxidation of hydroxy flavanones to flavones using fused potassium acetate in glacial acetic acid and iodine has been recently reported.³ By this modified method naringenin (I *a*) and hesperetin (I *b*) have been reported to undergo smooth conversion (60-70%) to yield the corresponding flavones, apigenin and diosmetin respectively. Since there is a special difference between the hydroxy flavanones and their partial methyl ethers in the action of iodine and silver acetate in absolute alcohol, a typical example, hesperetin dimethyl ether, has also been examined by this method.³ The flavone, luteolin-7:3':4'-trimethyl ether (V *b*), is obtained in less yield and it is accompanied by the corresponding 3-iodo-flavanone (IV *b*). The separation of this mixture is best effected by fractional precipitation from ethyl acetate solution using light petroleum. The iodo-flavanone could however be converted into flavone by the action of pyridine. It was identical with the sample obtained by the action of iodine and silver acetate. It would now appear that though it is the exclusive product when silver acetate is employed, it happens to be produced as a minor product even when potassium acetate is used.

EXPERIMENTAL

3-Acetoxy-naringenin

The modified procedure now employed is as follows: To a mixture of naringenin (1 g.) and silver acetate (2 g.) in absolute alcohol

(60 c.c.) was added iodine in the same solvent (0.85 g. in 40 c.c.) gradually during one hour with constant shaking at room temperature (20° C.). The iodine was decolourised within a few minutes of addition. The mixture was then either refluxed for 2 hours or allowed to stand at room temperature for 24 hours, the silver salt filtered off and the alcohol evaporated to dryness when a pale yellow coloured solid separated. It was first crystallised from ethyl acetate and light petroleum mixture and later from ethanol when it separated as tiny prisms (0.65 g.), m.p. 228–30° (decomp.).¹

3-Hydroxy naringenin

The hydrolysis by means of acid has been carried out as follows; the earlier method using alkali¹ was not fully satisfactory.

The above compound (0.3 g.) was refluxed with alcoholic hydrochloric acid (1 : 1, 20 c.c.) for half an hour. The alcohol was removed under reduced pressure and the solution diluted with water to 200 c.c. A pale brown solid separated which was repeatedly extracted with ether (total vol. 200 c.c.). After evaporating the ether the residue was crystallised from aqueous alcohol yielding flesh coloured rhombohedral prisms (0.18 g.), m.p. 238–40° (*d*). It agreed in m.p. and colour reactions with an authentic sample of 3-hydroxy naringenin obtained by Fenton's oxidation⁴ and the mixed m.p. was un-depressed.

3-Iodo-naringenin-7:4'-dimethyl ether (IV a)

Naringenin-dimethyl ether (0.6 g.) was subjected to iodine treatment using the above procedure when it yielded the 3-iodo-derivative (0.6 g.), m.p. 164–66°, which agreed in melting point and colour reactions with the compound obtained by Goel *et al.*¹

Action of alcoholic potash

It (0.6 g.) was treated with alcoholic potash (15 c.c.; 4%) for ten minutes. The solution was acidified and the solid that separated was filtered and crystallised from alcohol to yield almost colourless needles of apigenin-7:4'-dimethyl ether, m.p. 170–71°.

3-Iodo-hesperetin-dimethyl ether (IV b)

Hesperetin-dimethyl ether (1 g.) dissolved in absolute alcohol (80 c.c.) was treated with silver acetate (2 g.) and iodine (0.85 g. in 20 c.c.) as in the case of O-dimethyl-naringenin. The 3-iodo-compound was crystallised from ethyl acetate petroleum ether mixture to yield pale yellow crystals (1 g.),

m.p. 155–56°. It gave a violet colour with alcoholic ferric chloride (Found: C, 47.8%; H, 4.0%; $C_{18}H_{18}O_6I$ requires C, 47.3%; H, 3.9%).

(a) *Action of alcoholic potash.*—The above compound (0.2 g.) after refluxing with alcoholic potash (25 c.c., 4%) for ten minutes was acidified and the solid obtained was crystallised from ethanol yielding luteolin trimethyl ether, as pale yellow needles, m.p. 160–61°.

(b) *Action of pyridine.*—3-Iodo-hesperetin-dimethyl ether (0.1 g.) was treated with pyridine (10 c.c.) and the solution heated over a boiling water-bath for two hours. The reaction mixture was poured into water (50 c.c.), the solid that separated was washed with dilute hydrochloric acid and subsequently with cold water. On crystallisation from ethanol it yielded luteolin-trimethyl ether (50 mg.), m.p. 160–61°.

3-Iodo-5:7-dimethoxy flavanone (III b)

5:7-Dimethoxy-flavanone (1.0 g.) was subjected to iodine oxidation as in the above cases. The 3-iodo-compound thus obtained separated from alcohol as colourless needles (0.8 g.), m.p. 183–84°.¹

(a) *Treatment with alcoholic potash*

3-Iodo-5:7-dimethoxy flavanone (1 g.) was heated with alcoholic potash (20 c.c., 4%) for ten minutes on a boiling water-bath. The alcohol was removed under reduced pressure; the solution was diluted, acidified and extracted with ether. The ether solution was washed successively with 0.5% and 10% sodium hydroxide solutions.

(i) 0.5% *Sodium hydroxide soluble fraction.*—The solution on acidification yielded a yellow solid (100 mg.) which on crystallisation from aqueous alcohol yielded yellow prisms, m.p. 178–80°, alone or mixed with galangin 5:7-dimethyl ether (VI a), synthesised earlier by Kostanecki and Tambor.⁵ It gave a reddish brown colour with alcoholic ferric chloride.

Its acetate prepared by heating it with acetic anhydride and pyridine crystallised from alcohol to yield colourless stout rectangular prisms melting at 184–86°. It agreed with the description of 3-acetoxy-5:7-dimethoxy flavone.⁵

(ii) 10% *Sodium hydroxide soluble fraction.*—On acidification of the alkaline solution a colourless solid was obtained (400 mg.) which crystallised from methanol, chloroform and light petroleum mixture to give colourless needles, m.p. 170–71°. It gave no colour with alcoholic ferric chloride and also with magnesium and hydrochloric acid. Its properties agreed with

those of 2-hydroxy-2-benzyl-4:6-dimethoxy-coumaranone⁶ (VII) and the mixed m.p. with a synthetic sample was undepressed.

The above compound (50 mg.) was treated with concentrated sulphuric acid (5 c.c.) at 0° C. and the temperature was raised to 20° during half an hour. It was then poured into water when 4:6-dimethoxy-benzal coumaranone, m.p. 151–52°, was obtained.

(iii) The ether solution which was freed from alkali-soluble fractions gave on evaporation chrysin-dimethyl ether (100 mg.), m.p. 115–17°.

(b) *Action with pyridine.*—The above iodo-compound (III b) (0.4 g.) was heated with pyridine (40 c.c.) on a boiling water-bath for two hours and the reaction mixture poured in water (100 c.c.). The solid that separated was washed with dilute hydrochloric acid and crystallised from ethanol to yield pale yellow plates of chrysin-dimethyl ether, m.p. 115–17°.

Iodine oxidation of hesperetin-dimethyl ether (II b)

Hesperetin-dimethyl ether (0.2 g.) was dissolved in glacial acetic acid (5 c.c.) and fused potassium acetate (0.5 g.) added. Iodine (0.2 g.) in glacial acetic acid (5 c.c.) was slowly added to the boiling mixture during one hour. The acetic acid was removed under reduced pressure and saturated sulphur dioxide solution (25 c.c.) added. The solid thus obtained was filtered, washed with cold water and dried in a vacuum desiccator. It was then repeatedly extracted with boiling ethyl acetate and the solution concentrated to about 15 c.c. To this was added petroleum ether (40–60°), when a yellow precipitate settled down. By controlled precipitation with petroleum ether all the yellow compound was precipitated. The solution was filtered (Filtrate F) and the yellow residue was crystallised from ethyl acetate yielding pale yellow crystals (40 mg.), m.p. 155–56°, undepressed when mixed with a sample of 3-iodo-hesperetin-dimethyl ether described already. On heating the above sample of iodo-compound with pyridine (2 c.c.) on a boiling water-bath for two hours and working up as mentioned above it gave luteolin-trimethyl ether, m.p. 160–61°. It contained no iodine and had R_f (circular) 0.82 in acetic acid water (3:2) at 23°, the same as given by an authentic sample of luteolin 7:3':4'-trimethyl ether.

The filtrate (F) was evaporated when a colourless solid (50 mg.), m.p. 160–61°, identical in colour reactions and m.p. with luteolin-trimethyl ether was obtained.

SUMMARY

A modified procedure for the action of iodine and silver acetate gives rise to purer products. Agreeing with earlier observations, hesperetin gives a good yield of 3-acetoxy hesperetin and hesperetin 7:3'-dimethyl ether yields the 3-iodo-compound. The iodoflavanones invariably yield the corresponding flavones by the action of pyridine. In the treatment with alcoholic potash, those which have a free 5-hydroxyl, e.g., 3-iodo naringenin 7:4'-dimethyl ether and 3-iodo hesperetin 7:3'-dimethyl ether yield only the corresponding flavones; whereas 3-iodo-5:7-dimethoxy flavanone having no free 5-hydroxyl group gives a mixture of products, containing the flavone, the flavonol and the 2-hydroxy-2-benzyl 4:6-dimethoxy coumaranone. The difference seems to depend on the stability of the oxygen ring.

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