SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

Part XLIII. Preparation of 3-Hydroxy Flavanones

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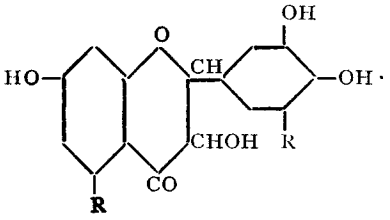
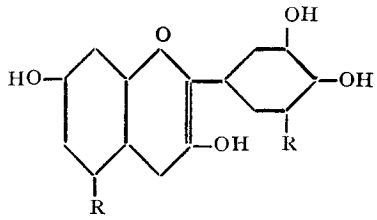
Several members of the new group of 3-hydroxy flavanones also called flavanolones have been recently discovered mainly in heartwoods. From the point of view of biogenesis they seem to occupy an important place in the evolution of anthoxanthins. They may be considered to be hydrated flavones or hydrogenated flavonols or hydroxylated flavanones. Actually they are accompanied by related members of the flavonol group in the plant sources, *e.g.*, fustin (I) is accompanied by fisetin (II) in the wood of *Rhus succedanea*;[1] ampelopsin (III) by myricetin (IV) in *Ampelopsis meliæfolia*.[2] Further the conversion of the flavanolones or their methyl ethers into the corresponding flavonols by dehydrogenation has been reported by several workers.[3, 4]



I, R=H
III, R=OH



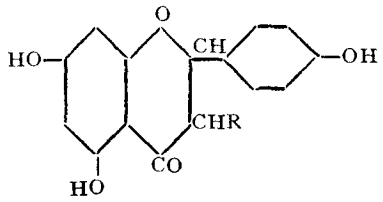
II, R=H
IV, R=OH

Among methods investigated in the past for the synthesis of 3-hydroxy flavanones, the most convenient would appear to be the bromination of the corresponding flavanones which is found to take place in the 3-position and subsequent exchange of the bromine atom for an acetate and eventually a hydroxyl group. Zemplen and Bognar[5] employed the acetate of hydroxy flavanones which were brominated in presence of ultra-violet light to yield 3-bromo flavanones. Earlier Kostanecki[6] used the flavanone methyl ether; in this case chances of nuclear bromination cannot altogether be avoided. A more readily available method for the synthesis of this important group

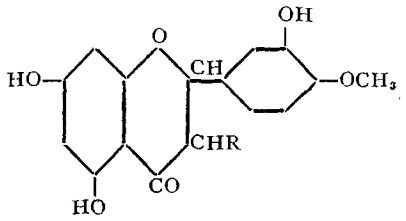
of compounds seemed to be desirable and hence the work reported in this communication.

In an earlier publication[7] on a new synthesis of flavones we employed the combined action of iodine and sodium acetate in alcoholic solution on a number of flavanones and this provided a convenient method of synthesis of flavones containing a hydroxyl in the 5-position. If however, instead of using sodium acetate, silver acetate is employed, the intermediate stages originally postulated for the iodine oxidation can be obtained. 3-Hydroxy flavanones constitute the important products in certain cases and their transformations can be studied (see Seshadri[8]). However there are differences in the course of the reaction depending upon the nature of the flavanone used as the starting material. Typical examples are discussed in the following paras.

Naringenin (V) and hesperetin (VI) are polyhydroxy flavanones and have been chosen first for the present study. They yield 3-acetoxy compounds by the action of iodine and silver acetate and these can be hydrolysed to the 3-hydroxy compounds. Among these products 3-hydroxy naringenin (V *a*), has been reported as a natural product.[3] But the synthetic compound differs from the natural one in its properties because the former is necessarily racemic and the latter optically active. 3-Hydroxy-hesperetin (VI *a*) has earlier been prepared by Zemplen and Bognar[5] using the 3-bromo compound as an intermediate and there is fair agreement between their product and ours.



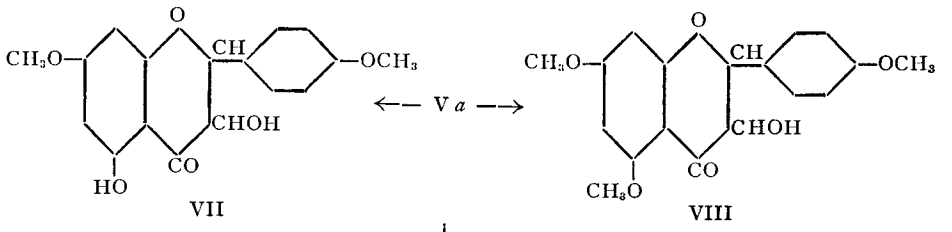
V, R=H
V *a*, R=OH



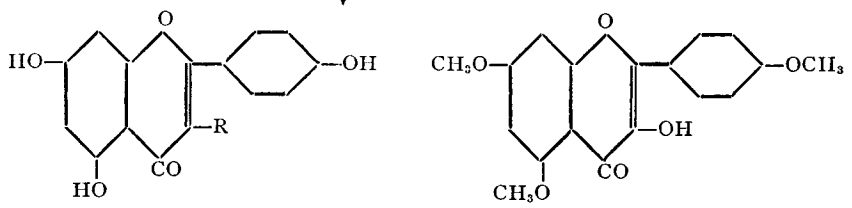
VI, R=H
VI *a*, R=OH

Besides optical activity there seems to be considerable difference between natural and synthetic compounds in their action towards alcoholic sulphuric acid. Using a natural sample of 3-hydroxy naringenin provided by Dr. Pew and isolated from the bark of Douglas fir wood[3] it has now been possible to prepare its dimethyl (VII) and trimethyl (VIII) ethers. The latter underwent dehydrogenation in acid solution to yield kæmpferol 5:7:4′-trimethyl ether (IX) whose properties agreed with the records found in the literature.[9] Pew reported similar dehydrogenation of the natural 3-hydroxy naringenin

in 2 normal sulphuric acid when a current of air was passed.[3] On the other hand synthetic 3-hydroxy naringenin underwent only dehydration under the same experimental conditions giving rise to apigenin (X *b*). The dehydration could be effected by simply refluxing with 4% alcoholic sulphuric acid for 24 hours.



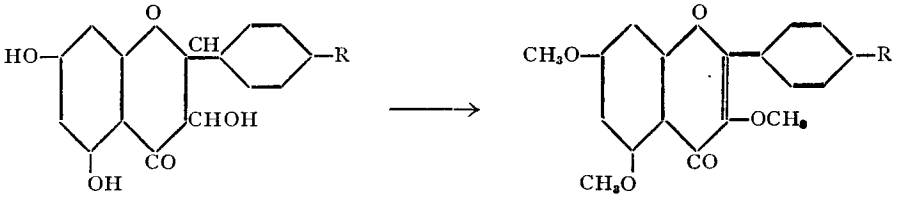
VII ← V *a* → VIII



X *a*, R=OH
X *b*, R=H

IX

There seems to be, however, agreement in the behaviour of the natural and synthetic 3-hydroxy flavanones towards methylating agents. Complete methylation of pinobanksin (XI) by Lindstedt using excess of methyl sulphate and anhydrous potassium carbonate in acetone solution was reported to be accompanied by dehydrogenation yielding galangin trimethyl ether (XII) in low yield.[10] Synthetic 3-hydroxy-naringenin (V*a*) has now been found to behave similarly and give a small yield of O-tetramethyl kæmpferol (XIII). Dehydrogenation seems to be the earlier stage and the methylation of the 3-hydroxyl group (enol) a later stage since otherwise the secondary alcoholic hydroxyl group of the flavanonols would be unaffected. This has been

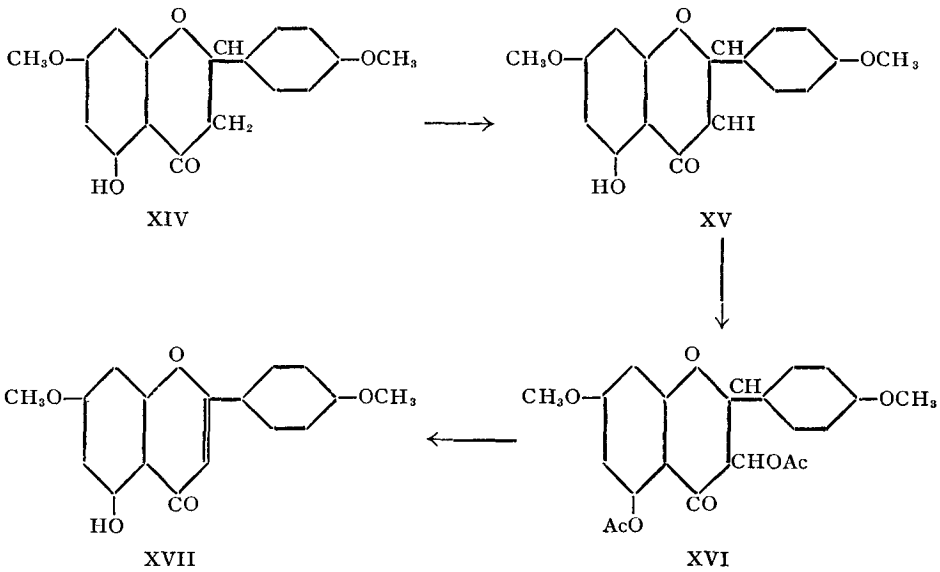


XI, R=H
V *a*, R=OH

XII, R=H
XIII, R=OCH_3

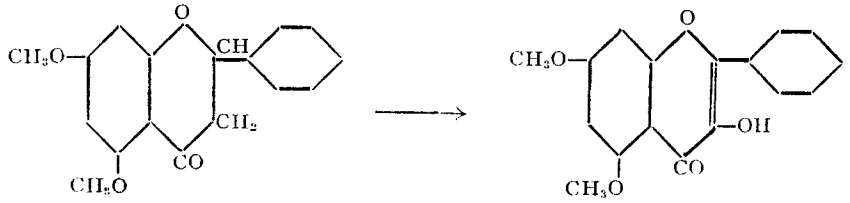
confirmed by boiling the natural 3-hydroxy naringenin (V*a*) with anhydrous potassium carbonate alone in acetone solution omitting dimethyl sulphate when kæmpferol (X *a*) could be obtained as the product.

An interesting result has been obtained in the reaction of naringenin 7:4′-dimethyl ether (XIV) which has only one free hydroxyl group in the 5-position; the product obtained on heating an alcoholic solution of the compound with iodine and silver acetate is found to be a mono iodo compound. This should be the 3-iodo compound (XV) the intermediate postulated in the mechanism of iodine oxidation;[7] the reaction stops here. However, when the iodo compound is refluxed in acetic anhydride solution with silver acetate it forms 3:5-diacetoxy-7:4′-dimethoxy flavanone (XVI). It could not be successfully crystallised and was therefore directly refluxed for 20 hours with alcoholic sulphuric acid. It underwent simultaneous hydrolysis and dehydration yielding apigenin dimethyl ether (XVII). This seems to be the first example of successful iodination of the 3-position of a flavanone ring using iodine and silver acetate. The 3-iodo compound on treatment with aqueous sodium hydroxide or alcoholic sodium acetate gave apigenin 7:4′-dimethyl ether (XVII).



5:7-Dimethoxy flavanone (XVIII) having no free hydroxyl groups gave different results when subjected to the same course of reactions. This also formed a 3-iodo derivative as the first stage. But when it was boiled with alcoholic potassium hydroxide for five minutes the resulting compound was found to be soluble in aqueous alkali, and acidification of the alkali

solution yielded a bright yellow compound. It gave a deep reddish brown colour with ferric chloride and melted at 178–80° and thus agreed with the description of 5: 7-dimethoxy-3-hydroxy flavone (XIX) described in the literature.[11] Acetylation yielded an acetate also agreeing with the earlier description.[11] The 3-iodo flavanone could be converted into the corresponding 3-acetoxy derivative by refluxing with acetic anhydride and silver acetate. Attempts to deacetylate this product using alcoholic potash (2%) yielded only the alkali-soluble galangin dimethyl ether (XIX) identical with the one obtained directly from the 3-iodo-compound. This is rather remarkable and is explicable on the basis that the 3-hydroxy compound which may be formed first undergoes ready dehydrogenation in alkaline medium. Such dehydrogenations are recorded in earlier literature also.[14]



XVIII XIX

EXPERIMENTAL

3-*Acetoxy hesperetin*

Hesperetin required for this purpose was obtained using the method of Gupta *et al.*[12]

Hesperetin (1 g.) was dissolved in absolute alcohol (25 c.c.) and pure powdered silver acetate (1·5 g.) added to it. The mixture was boiled and a boiling solution of iodine in absolute alcohol (0·85 g. in 20 c.c.) added to it. After refluxing for 4 hours it was filtered, the silver salts washed with hot alcohol and alcohol distilled off from the filtrate. The oily residue which solidified on cooling was twice crystallised from ethyl acetate-petrol mixture. It was obtained in the form of aggregates of pale yellow tiny prisms melting at 146–47°. It gave a violet colour with ferric chloride (Found: C, 58·9; H, 4·4; $C_{18}H_{16}O_8$, $\frac{1}{2}$ H_2O requires C, 58·5; H, 4·6%). Yield 0·6 g.

3-*Hydroxy-hesperetin* (*VI a*)

The 3-acetoxy compound (0·5 g.) given above was treated with aqueous sodium hydroxide (10 c.c., 2%) and the solution warmed on a water-bath for five minutes, cooled and acidified with ice-cold hydrochloric acid. The sticky mass that separated was filtered and washed with water. It was crystallised from boiling aqueous alcohol when it separated as tiny prisms

melting at 214–16° (Zemplen and Bognar[8] reported the m.p. as 202°). Yield of the pure product was 0·32 g. (70%). It gave a violet colour with ferric chloride and was easily soluble in aqueous sodium carbonate. Its alcoholic solution gave a brilliant red colour with magnesium and hydrochloric acid and a pink colour with zinc and hydrochloric acid (Found: C, 58·9; H, 4·4; $C_{16}H_{14}O_7$, $\frac{1}{2}$ H_2O requires C, 58·7; H, 4·6%).

3-Hydroxy naringenin (V a)

A mixture of naringenin (1 g.) and silver acetate (1·2 g.) in boiling absolute alcohol (20 c.c.) was treated with a boiling solution of iodine in the same solvent (0·85 g. in 20 c.c.) and the mixture refluxed for 4 hours. The product was worked up as in a previous experiment. 3-Acetoxy naringenin crystallised from dilute alcohol in the form of colourless tiny prisms melting at 226–28° (decomp.); yield 0·6 g. It gave a bright scarlet colour when treated with magnesium and hydrochloric acid and a pink colour with zinc dust and hydrochloric acid in alcoholic solution.

3-Acetoxy naringenin (0·25 g.) was hydrolyzed with aqueous sodium hydroxide (10 c.c., 2%) under mild conditions as described in the earlier experiment. It crystallised from boiling aqueous alcohol as almost colourless stout prisms melting at 238–40° (decomp.) with darkening at 230°; yield 0·16 g. Its alcoholic solution developed a reddish violet colour with ferric chloride, a scarlet red colour with magnesium and hydrochloric acid and a pink colour with zinc and hydrochloric acid. It thus agreed in its reactions with those described for 3-hydroxy naringenin. However the mixed melting point with the natural sample supplied by Dr. Pew was considerably depressed because they were different stereo isomers (Found: C, 58·9; H, 4·5; $C_{15}H_{12}O_6$, H_2O requires C, 58·8; H, 4·6%).

Methylation of 3-hydroxy naringenin

(a) Synthetic sample to kæmpferol tetramethyl ether (XIII)

3-Hydroxy naringenin (0·5 g.) was refluxed in dry acetone solution (200 c.c.) with dimethyl sulphate (0·7 c.c., excess) and anhydrous potassium carbonate (2 g.) for 24 hours. The mixture was filtered, the potassium salts washed with hot acetone and the solvent removed by distillation. The oily mass solidified on keeping with a little alcohol for a few days in the refrigerator. It was filtered and crystallised thrice from alcohol when it was obtained as colourless needles melting at 164–65°. Further crystallisation did not raise the melting point. It gave no colour with ferric chloride, was insoluble in aqueous alkali and developed a bright red colour when its alcoholic solution was treated with magnesium and hydrochloric acid. It

agreed in its properties and reactions with kæmpferol tetramethyl ether and a mixed melting point with an authentic sample was undepressed (Found: C, 66·2; H, 5·5; $C_{19}H_{18}O_6$ requires C, 66·6; H, 5·5%).

(*b*) *Natural Sample :* (i) 7 : 4′-*Dimethyl ether* (*VII*).—3-Hydroxy naringenin (0·3 g.) kindly supplied by Dr. Pew was dissolved in dry acetone (20 c.c.), dimethyl sulphate (0·22 c.c., 2 moles) and anhydrous potassium carbonate (0·5 g.) added and the mixture refluxed for 6 hours. On filtering and distilling off acetone from the filtrate, a colourless crystalline solid was obtained. It crystallised from alcohol as colourless clusters of needles melting at 189–90°. It gave a red colour with ferric chloride, a bright red colour with magnesium and hydrochloric acid and a pink colour with zinc dust and hydrochloric acid. It was sparingly soluble in aqueous alkali, the solution developing a yellow colour gradually (Found: C, 64·1; H, 5·0; $C_{17}H_{16}O_6$ requires C, 64·6; H, 5·1%).

(ii) 5 : 7 : 4′-*Trimethyl ether* (*VIII*).—The natural sample of 3-hydroxy naringenin (0·3 g.) was methylated with 3 moles of dimethyl sulphate (0·33 c.c.) by refluxing in acetone solution with anhydrous potassium carbonate (1 g.) for 10 hours. The methylated product crystallised from alcohol as aggregates of colourless rectangular tablets melting at 142–43°. It gave no colour with ferric chloride in alcohol and was insoluble in dilute aqueous alkali (Found: C, 64·0; H, 6·0; loss on drying 2·7; $C_{18}H_{18}O_6$, $\frac{1}{2}H_2O$ requires C, 63·7; H, 5·7%; loss on drying 2·5%). It thus agreed in its properties with 5 : 7 : 4′-trimethoxy-3-hydroxy flavanone.

Conversion to kæmpferol 5 : 7 : 4′-*trimethyl ether* (*IX*)

The above methylation product (trimethyl ether) (0·15 g.) was refluxed with alcoholic sulphuric acid (20 c.c., 4%) for 25 hours on a water-bath. It was concentrated to 10 c.c. under reduced pressure and diluted with an equal volume of water. The yellow solid that separated was filtered and crystallised from alcohol. It formed yellow needles melting at 149–50°. It gave a deep brown colour with ferric chloride and was soluble in aqueous alkali giving a yellow solution. With concentrated sulphuric acid it gave a greenish yellow fluorescence (Found: C, 62·5; H, 5·5; $C_{18}H_{16}O_6$, H_2O requires C, 62·4; H, 5·2%). Kostanecki and Tambor[9] reported earlier this compound as a monohydrate and gave m.p. 149–50°.

Conversion of natural sample to kæmpferol (*X a*)

The natural sample of 3-hydroxy naringenin was refluxed in acetone solution in the presence of anhydrous potassium carbonate for 16 hours when the solution gradually turned yellow. It was then filtered and acetone

removed by distillation. The yellow solid when crystallised from alcohol was found to be a mixture (m.p. 210–20°) and crystallisation did not effect a separation. The mixture developed a greenish yellow fluorescence with concentrated sulphuric acid thus showing the presence of kæmpferol, the original compound gave only a bright yellow solution. Paper chromatography using phenol saturated with water as the irrigating solvent gave a bright yellow ring corresponding to kæmpferol (circular Rf. at 0·78) compared with the ring developed by an authentic specimen.[13]

Iodination of naringenin 7: 4′-dimethyl ether to 3-iodo naringenin dimethyl ether (XV)

Naringenin 7: 4′-dimethyl ether (1 g.) was refluxed in absolute alcoholic solution with iodine (0·8 g. in alcohol 20 c.c.) and silver acetate (2 g.) for 4 hours. The mixture was then filtered, alcohol distilled off from the filtrate and the colourless solid twice crystallised from alcohol. It was obtained as colourless long prisms and prismatic needles melting at 164–66°. It gave a positive test for iodine. It gave a red colour with ferric chloride and was sparingly soluble in alkali (Found: C, 47·6; H, 3·9; $C_{17}H_{15}O_5I$ requires C, 47·9; H, 3·5%).

Conversion to apigenin dimethyl ether (XVII)

(i) The above iodo compound (0·1 g.) was heated on a water-bath with aqueous alcoholic sodium hydroxide (4 c.c., 2%) for 10 minutes. The mixture was then diluted and acidified with dilute hydrochloric acid. The product crystallised from alcohol as almost colourless needles melting at 170–71° identical with apigenin 7: 4′-dimethyl ether. Yield 0·06 g. On acetylation using acetic anhydride and pyridine it yielded the acetate which crystallised from alcohol as colourless prismatic needles melting at 193–4° identical with the 5-acetate of apigenin 7: 4′-dimethyl ether.

(ii) The 3-iodo compound (0·1 g.) was heated with acetic anhydride (5 c.c.) and silver acetate (0·2 g.) at 140° for 8 hours. The silver salts were separated by filtration and the acetic anhydride decomposed by putting in ice pieces and leaving overnight. Water was then decanted off and the sticky mass washed with water twice by decantation. Attempts to crystallise it were not successful and hence it was directly used for further reaction.

It was refluxed with alcoholic sulphuric acid (4%) for 16 hours, and the alcoholic solution was then concentrated under reduced pressure. The solid that separated on cooling, when recrystallised from alcohol melted at 170–71° agreeing with apigenin dimethyl ether and also gave an acetate

identical with 5-acetoxy 7: 4′-dimethoxy flavone (m.p. and mixed m.p. 193–94°).

(iii) The 3-iodo compound was boiled with sodium acetate (1 g.) in alcoholic solution (50 c.c.). Even from the boiling solution a yellow crystalline substance separated. It was filtered and washed with hot alcohol. It appeared as yellow needles melting at 260–61°. The alcoholic filtrate on complete removal of the solvent gave a little of a pale yellow solid. On recrystallisation from the minimum amount of alcohol it melted at 170–71° and was identical with apigenin dimethyl ether.

Iodination of 5: 7-*dimethoxy flavanone to* 3-*iodo*-5: 7-*dimethoxy flavanone*

To a boiling absolute alcoholic solution of 5: 7-dimethoxy flavanone (1 g. in 20 c.c.) was added silver acetate (1·5 g.) and a boiling solution of iodine (0·8 g.) in the same solvent. The colour of iodine gradually disappeared in the course of 30 minutes. The mixture was refluxed for 4 hours, then filtered and alcohol distilled from the filtrate. The colourless residue when crystallised from excess of alcohol separated as colourless needles melting at 183–84°. It gave no colour with ferric chloride and was insoluble in aqueous alkali (Found: C, 49·6; H, 4·0; $C_{17}H_{15}O_4I$ requires C, 49·8; H, 3·7%).

Conversion to galangin-5: 7-*dimethyl ether* (*XIX*)

The 3-iodo compound (0·2 g.) was heated on a water-bath with absolute alcoholic potash (6 c.c., 4%) for 10 minutes, alcohol removed under reduced pressure, the residue dissolved in water and the solution acidified after cooling. The yellow solid was collected, washed with water and crystallised from alcohol. It was obtained as yellow prisms melting at 178–80°; it gave a deep reddish brown colour with ferric chloride and was soluble in aqueous alkali. It thus agreed with the properties of galangin 5: 7-dimethyl ether described in literature.[11]

Its acetate prepared by heating it with acetic anhydride and pyridine crystallised from alcohol as colourless stout rectangular prisms melting at 184–86°. It agreed with the description of 3-acetoxy 5: 7-dimethoxy flavone found in literature.[11]

SUMMARY

The action of iodine and silver acetate varies with the type of flavanones employed, and yields the intermediate stages postulated in the new flavone synthesis using iodine and sodium acetate. The polyhydroxyflavanones, naringenin and hesperetin form directly the 3-acetates which can be hydrolysed to the 3-hydroxy compounds. On the other hand from naringenin

7:4′-dimethyl ether and 5:7-dimethoxy flavanone, the 3-iodo compounds can be isolated as the first intermediates. The behaviour of the 3-hydroxy flavanones in acid and alkaline conditions also varies; either dehydrogenation to flavonol or dehydration to flavone taking place.

Our thanks are due to Dr. Pew of the Forest Products Laboratory, Madison, U.S.A., for the generous supply of 3-hydroxy naringenin used in this work.

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