A NEW SYNTHESIS OF FLAVONES

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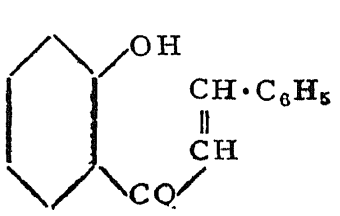
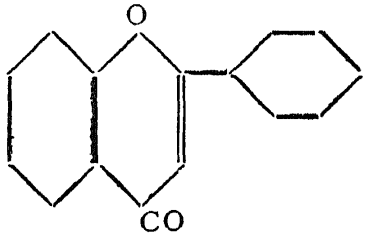
Received July 4, 1949

A number of related groups of compounds having the 15 carbon system, such as anthocyanins and anthoxanthins, occur in nature. The differences between them depend upon the state of oxidation of the oxygen containing ring. Though a large volume of evidence indicates that they have a parallel origin from a common precursor[1] the possibility of one type changing into another does not seem to be altogether excluded. Consequently methods of interconversion have some interest in biogenesis besides their value for the study of structural relations and for the easy synthesis of compounds.

The earliest method of synthesis of flavones employed chalkones (I) as starting materials.[2] This had very limited applicability and alternative methods were therefore preferred. But repeatedly efforts have been made with some success to improve it. The chief defect in the original method of Kostanecki using bromine and chalkones, is the possibility of nuclear bromination and of the predominent tendency to form benzalcoumara-



(I)



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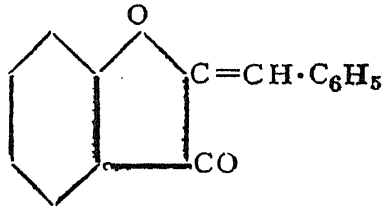
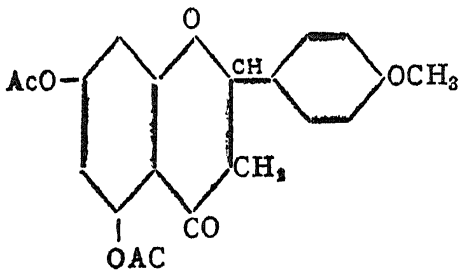


(III)

nones[3] (III) instead of flavones (II). A marked improvement is the direct dehydrogenation of chalkones or flavanones by means of selenium dioxide.[4] But it has been found to be satisfactory only in a few simple cases and it seems to fail when the chalkone contains a number of free hydroxyl groups.

In the use of his bromine method Kostanecki[5] met with greater success when he employed flavanones as their methyl ethers. A recent improvement is that of Zemplen and Bognar[6] who have submitted acetates of hydroxyflavanones (IV) to bromination in the presence of ultraviolet light whereby the bromine atom enters the 3-position alone (V). This is subsequently

eliminated as hydrogen bromide by means of alcoholic potash. One of their examples employing isosakuranetin diacetate is given below.



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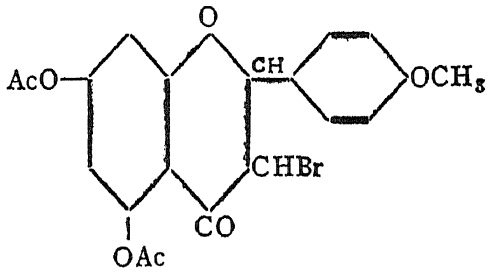

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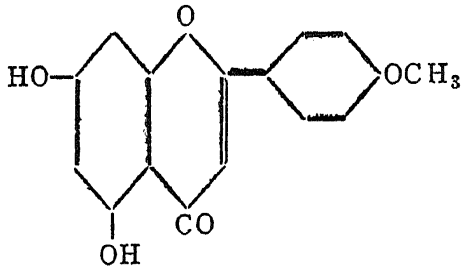
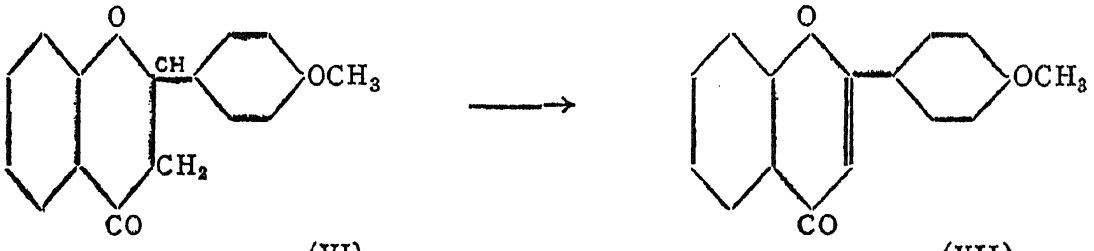


For the dehydrogenation of a flavanone to flavone there is also mention of the use of phosphorus pentachloride. Hattori[7] treated 4′-methoxy flavanone (VI) with phosphorus pentachloride in boiling benzene solution and recorded the preparation of 4′-methoxy flavone (VII). This method has now been repeated by us using 7-methoxy flavanone and the corresponding flavone obtained, the yield being fairly satisfactory. It seemed to be possible that the slow liberation of chlorine from phosphorus pentachloride, at the temperature of boiling benzene employed for this purpose, brought about the dehydrogenating action; but this reagent cannot be used for hydroxy compounds and even in the case of ethers considerable amount of resin formation takes place.

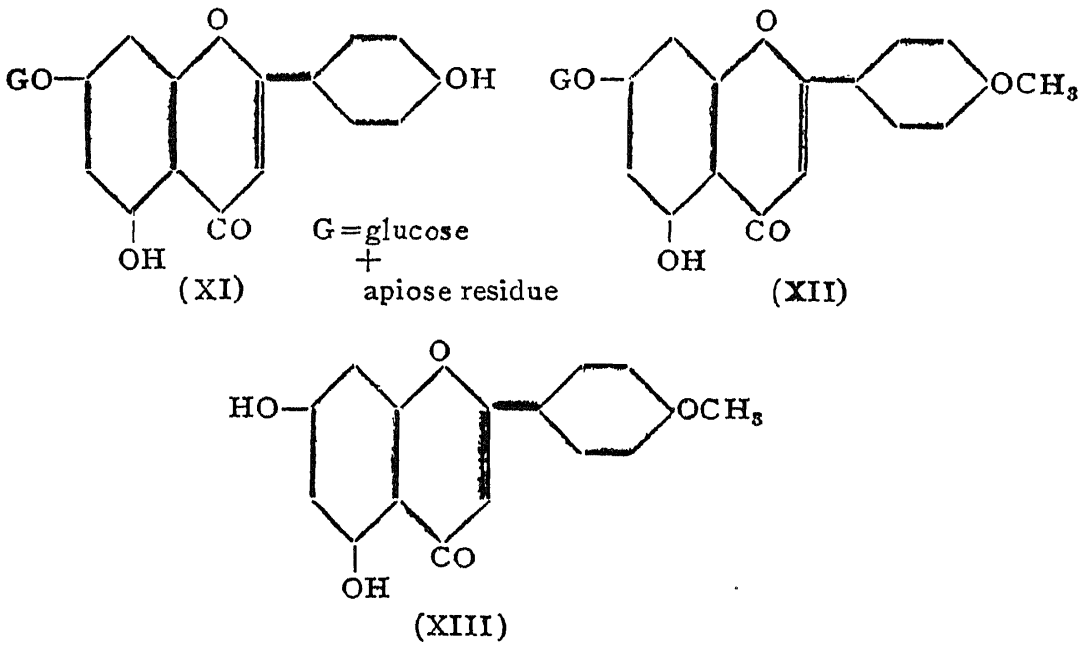


(VI) (VII)

In view of the points discussed above, it appeared that iodine would be a more convenient dehydrogenating agent and it would be free from the defects of nuclear halogenation and resin formation. Actually this reagent has been used earlier for the conversion of rotenone into dehydro-rotenone,[8] but its application has not so far been extended outside the rotenone group, a possible reason being that the discovery was empirical and was made at a time when the existence of a pyranone ring in rotenone was not recognised. It has now been found to be an extremely convenient method of

converting hydroxy flavanones into flavones. In boiling alcoholic solution and in the presence of excess of sodium acetate, iodine brings about smooth dehydrogenation and very good yields of flavones are obtained. Naringenin, isosakuranetin, naringenin dimethyl ether, hesperetin and its dimethyl ether have thus been oxidised and the corresponding flavones prepared and characterised.

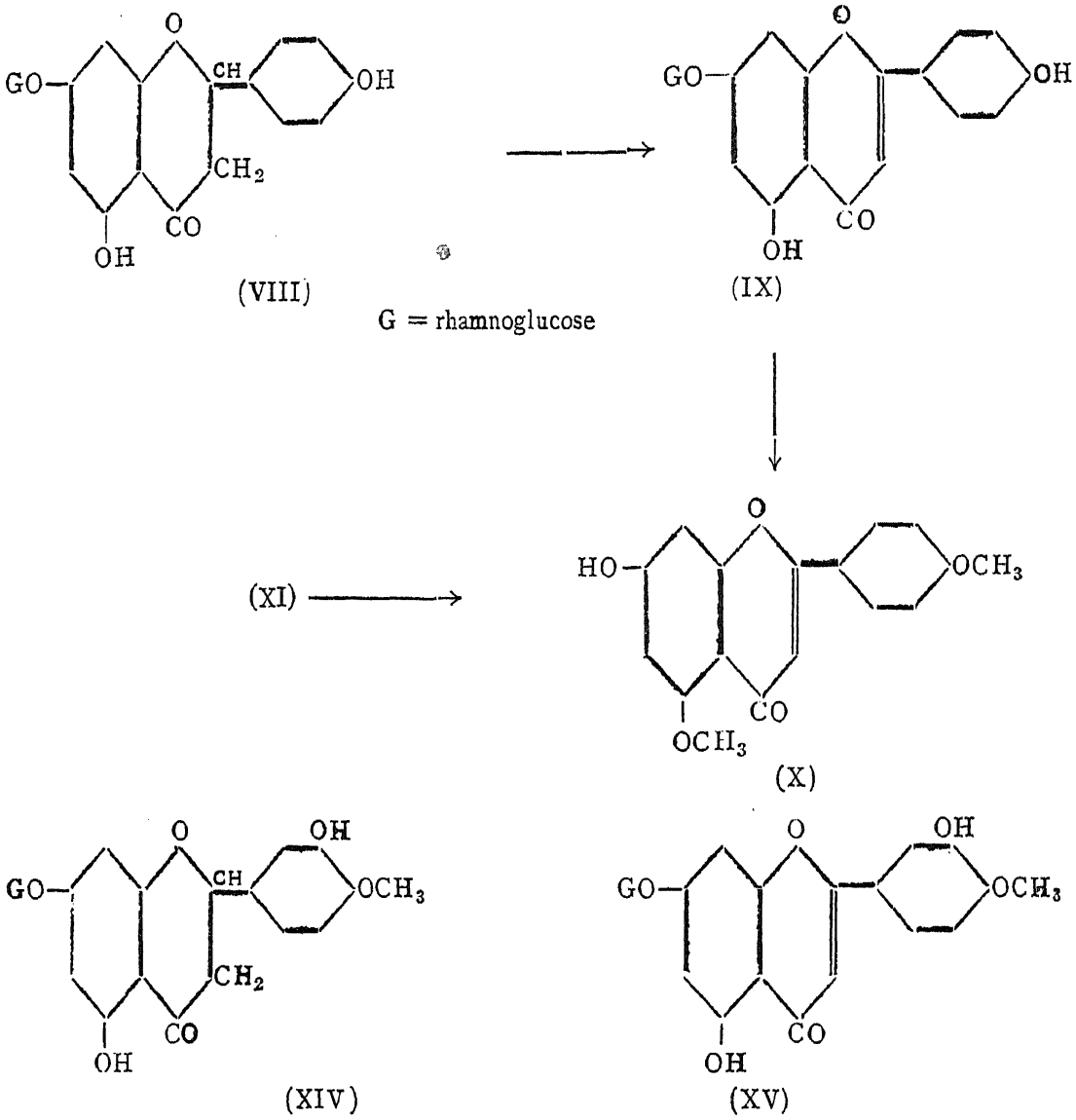
The method is suitable also for the oxidation of hydroxyflavanone glycosides. In this connection naringin (VIII), its 4′-monomethyl ether and hesperedin have been used. The first yields a new apigenin-7-glycoside (IX) which when subjected to methylation and hydrolysis gives rise to 7-hydroxy-5: 4′-dimethoxy flavone (X). This is a useful reference compound for establishing the constitution of the 7-glycosides of apigenin; apiin (XI) has now been examined in this connection. Apiin was methylated by Von Gerichten[9] using sodium methoxide and methyl iodide in alcoholic solution. The product was a monomethyl ether (XII) of the glycoside. On hydrolysis it produced a monomethyl ether of apigenin whose constitution was not established by him. Perkin and Horsefall[10] however expressed the opinion that it was probably identical with acacetin (XIII). Accepting this and taking into consideration that the 5-hydroxyl of a flavone is rather resistant to methylation it could be inferred that apiin is a 7-glycoside (XI), the changes being represented as given below.



(XI) (XII) (XIII)

Apiin (XI) has now been subjected to complete methylation and hydrolysis and the product found to be identical with 5: 4′-dimethyl apigenin (X) obtained from naringin as described above. Since the constitution of naringin (VIII) has already been established unequivocally by complete methylation[11] and since the above experiments establish the relationship

between the two glycosides, they provide confirmation of the constitution of apiin. The concerned transformations are represented by the formulæ given below. Though there is no naturally occurring flavone glycoside corresponding to naringin or 4′-methyl-naringin, hesperedin (XIV) gives on oxidation diosmin (XV). This conversion was brought about earlier by Zemplen and Bognar[6] by using their modified bromine method.

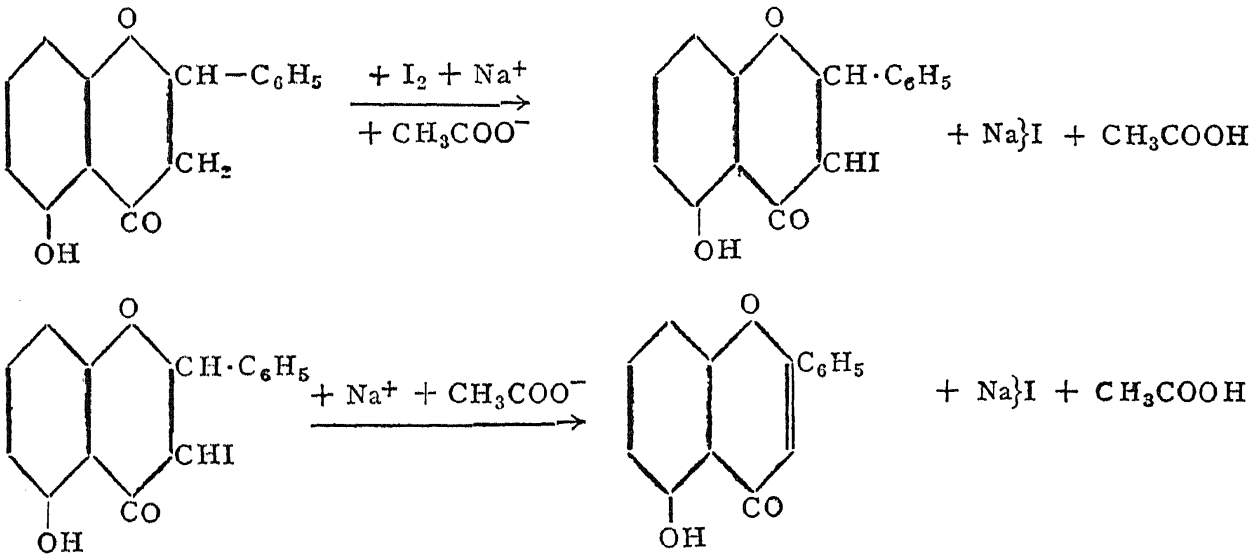


The iodine method of oxidation works most smoothly with all flavanones having a free hydroxyl in the 5-position. If this should be absent or should have been methylated a mixture of products is formed which is sometimes rather difficult to separate unless fairly large quantities are employed. From the mixture some quantity of the chalkone corresponding to the original flavanone could be dissolved out by means of dilute alkali. The remainder contains besides the flavone, the isomeric benzal-coumaranone also. The reason for this difference seems to be the stabilising influence of the 5-hydroxy group on the flavanone structure[11] at the temperature and the mild alkaline conditions employed. It is obvious that with 5-hydroxy compounds

the stable flavanone structure undergoes the normal reaction whereas in the absence of this group, change into the isomeric chalkone is the cause of complications. The influence of temperature is also marked; in the cold more of the flavone is produced and it could be successfully isolated, whereas at the boiling point of alcohol benzalcoumaranone is produced predominantly. This is obvious because of the greater instability of the pyronone ring at the higher temperature.

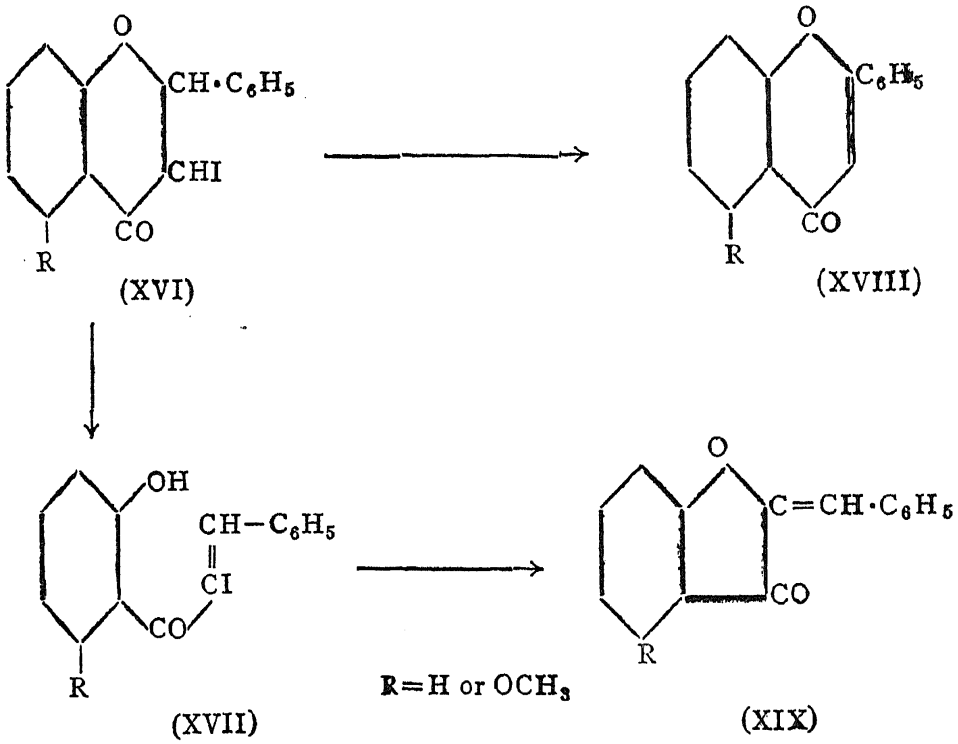
Mechanism of the reaction.—LaForge and Smith[8] considered the dehydrogenation of rotenone as due to iodination and subsequent elimination of hydrogen iodide. This was supported by the fact that they obtained in their experiments only 35% yield of dehydrorotenone the remainder being the acetate of rotenolone. In our experiments on flavanones the yield of flavones was much higher (60–70%). As a by-product small quantities of lower melting substances were found to be formed which appear to be flavanolone acetates thus supporting the general mechanism given by the above authors. These products are being studied in detail and will be reported later.

In considering the details of this chemical reaction it is necessary to emphasise the part played by the unstable and reactive acetate ion, both in the iodination of the reactive CH_2 and subsequent elimination of hydrogen iodide. The stages can be pictured as given below.



In the absence of a hydroxyl group in the 5-position of the flavanone as already mentioned, complicated changes take place due to the instability of the oxygen ring. Some amount of the corresponding chalkone is produced and it does not undergo any iodination; this point was independently tested using 2-hydroxy-4:6:4′-trimethoxy-chalkone which was unaffected by iodine. But the flavanone that has undergone iodination (XVI) can

take part in the next stage of the reaction either as such or after the opening of the ring to form the corresponding iodinated chalkone (XVII). In the first case flavone (XVIII) is produced and in the second alternative benzal-coumaranone (XIX) is produced when hydrogen iodide is eliminated.



EXPERIMENTAL

Iodine oxidation of hydroxy flavanones

1. *Naringenin dimethyl ether.*—Naringenin 7 : 4′-dimethyl ether which was prepared by the partial methylation of naringenin[11] (0·5 g.) and sodium acetate (2 g.) were dissolved in hot alcohol (10 c.c.) and the solution kept gently boiling over a small flame. To this a boiling solution of iodine (0·4 g.) in alcohol (8 c.c.) was added slowly. Iodine was rapidly decolourised in the beginning and when the addition was complete there was permanent colour. Even from the hot solution a pale yellow solid separated out. The solution was allowed to cool slowly when more of the compound crystallised out. It was filtered and washed with water. Yield 0·3 g. The product was almost pure and melted at 170–1° with slight sintering at 165°. It crystallised from alcohol in the form of pale yellow prisms melting at 170–1°.[12] It agreed in its properties with apigenin 7 : 4′-dimethyl ether and the mixed melting point with an authentic sample obtained by the partial methylation of genkwanin[13] was undepressed.

2. *Naringenin.*—A boiling solution of naringenin (1 g.) and sodium acetate (3 g.) in alcohol was treated with an alcoholic solution of iodine (0·8 g.) and the solution concentrated on a water-bath till crystals appeared.

The pale yellow solid that separated on cooling was filtered and washed with water. It crystallised from dilute alcohol as almost colourless leaflets melting at 340–42° and was identical in all its properties with apigenin.[12] Yield 0·65 g.

On methylation with excess of dimethyl sulphate and anhydrous potassium carbonate in dry acetone solution, it gave trimethyl apigenin which crystallised from ethyl acetate as colourless rectangular tablets melting at 152–4°[14] and the mixed melting point with a sample obtained by the methylation of genkwanin (described below) was undepressed.

Genkwanin[13] (0·5 g.) was refluxed in acetone solution with dimethyl sulphate (0·5 c.c.) and anhydrous potassium carbonate (2 g.) for 12 hours. It was then filtered and acetone distilled off. The product, genkwanin dimethyl ether, crystallised from ethyl acetate as colourless rectangular tablets melting at 152–4° and was identical with apigenin trimethyl ether.

3. *Isosakuranetin.*—Isosakuranetin which was prepared from naringin by partial methylation and hydrolysis[11] gave acacetin m.p. 258–60°. The mixed melting point with an authentic sample prepared by the Allan-Robinson method[15] was undepressed.

4. *Hesperetin* yielded diosmetin m.p. 256–7°.[16] Its identity was confirmed by preparing the acetate which melted at 193–4°.

5. *Hesperetin dimethyl ether.*—Hesperetin dimethyl ether,[17] prepared by methylating hesperetin with dimethyl sulphate (2·2 mols.) in acetone solution for 8 hours, was treated with iodine as in the case of naringenin dimethyl ether. The solid that separated on cooling the alcoholic solution was filtered and washed with water. It crystallised from alcohol in the form of pale yellow prisms melting at 169–70°. The mixed melting point with the sample of luteolin trimethyl ether described by Rao, Seshadri and Viswanadham[15] was undepressed.

Iodine oxidation of hydroxy flavanone glycosides

1. *Naringin* (VIII) *to Apigenin 7-rhamnoglucoside* (IX).—Naringin (2 g.) was dissolved in alcohol (10 c.c.), sodium acetate (2 g.) added and the solution boiled over a small flame. To this a boiling solution of iodine in alcohol (10 c.c.) was slowly added during the course of 10 minutes. At first there was rapid decolourisation and in the end there was a permanent colouration due to iodine. The solution was then concentrated over a water-bath, diluted with water and saturated with ether. After 24 hours a pale yellow crystalline solid separated out. This was filtered, washed with water and crystallised from alcohol when it came out in the form of

pale yellow flat needles and rectangular plates melting at 198–200°. Its alcoholic solution gave a reddish violet colour with ferric chloride and a deep red colour when reduced with magnesium and hydrochloric acid. (Found: C, 51·1; H, 5·6; $C_{27}H_{30}O_{14}$, $3H_2O$ requires C, 51·3; H, 5·7%.) This was hydrolysed by boiling with 7% aqueous sulphuric acid for 2 hours. The clear solution deposited on cooling apigenin as a pale yellow crystalline solid. It crystallised from alcohol as almost colourless leaflets melting at 340–2° alone or in admixture with the sample obtained from naringenin.

Methylation and hydrolysis to 7-hydroxy-5 : 4′-dimethoxy flavone (X).—The above oxidation product, apigenin glycoside (0·5 g.), was finely suspended in dry acetone (50 c.c.), dimethyl sulphate (0·5 c.c.) and anhydrous potassium carbonate (2 g.) were added and the mixture refluxed for 24 hours. It was then filtered and the potassium salts (R) washed with hot acetone. On evaporating the solvent, a viscous mass was obtained which was insoluble in cold aqueous alkali and gave no colour with ferric chloride in alcohol. It was directly hydrolysed by boiling with 7% aqueous sulphuric acid for 2 hours when a pale yellow solid separated out. It crystallised from alcohol as pale yellow rectangular prisms melting at 265–7°. It dissolved in aqueous sodium hydroxide and carbonate giving a yellow solution. Its alcoholic solution gave no colour with ferric chloride but gave an orange red colour with magnesium and hydrochloric acid.

The potassium salts residue (R) was found to contain further quantities of methylated glycoside. On dissolving it in water and adding sufficient quantity of sulphuric acid, not only to neutralise the carbonate but also to raise the acid concentration to 7% and heating under reflux for 2 hours a crystalline solid was obtained. It melted at 264–6° and was identical with the above product. Total yield 0·15 g. (Found: C, 68·0; H, 4·9; OCH_3, 21·0; $C_{17}H_{14}O_5$ requires C, 68·4; H, 4·7, OCH_3, 20·8%.)

On methylation with dimethyl sulphate and anhydrous potassium carbonate in acetone it gave apigenin trimethyl ether, m.p. 152–4°, identical with the sample described already.

Methylation of apiin (XI) and hydrolysis.—A fine suspension of apiin (0·4 g.) in acetone was methylated by refluxing with excess of dimethyl sulphate and anhydrous potassium carbonate for 30 hours. After filtering and distilling off the solvent a pale yellow sticky mass separated which was insoluble in alkali and which gave no colour with ferric chloride in alcohol. It was hydrolysed with 7% sulphuric acid. The product crystallised from alcohol in the form of pale yellow (almost colourless) rectangular prisms and melted at 265–7°. It was identical in its properties and colour reactions

with 7-hydroxy 5:4'-dimethoxy flavone and a mixed melting point with the sample described above was undepressed. As mentioned in an earlier case some more of the product could be obtained by working up the carbonate residues. Total yield 0·1 g.

2. *Naringin-4'-methyl ether.*—This was obtained by partial methylation of naringin with dimethyl sulphate and anhydrous potassium carbonate in acetone.[11]

A solution of naringin-4'-methyl ether in alcohol was treated as before with iodine and sodium acetate. The oxidation product separated only as a semi-solid mass. It did not crystallise satisfactorily and hence was directly hydrolysed to acacetin, m.p. 258–9°. Mixed melting point with an authentic sample was not depressed.

3. *Hesperidin (XIV) to diosmin (XV).*—To a finely divided suspension of hesperidin (2 g.) in alcohol (20 c.c.) was added sodium acetate (3 g.) and the mixture kept gently refluxing over a wire-gauze. To this a boiling solution of iodine (0·8 g.) in alcohol was added and the refluxing continued for further 15 minutes. The solid slowly dissolved and an almost clear solution was obtained. This was filtered hot, and the filtrate concentrated, diluted with water and extracted with chloroform to remove any free iodine. The aqueous solution was then saturated with ether and left overnight. A white crystalline solid gradually separated. It was filtered and washed with water. It crystallised from aqueous pyridine in the form of colourless rectangular plates melting at 270° (decomp.). Its alcoholic solution gave an orange red colour with magnesium and hydrochloric acid. It agreed in all its properties with diosmin.[16]

Methylation and hydrolysis.—As in the previous case, the above oxidation product, diosmin, was methylated in fine suspension in acetone and the product worked up. The aglucone separated after hydrolysis as a pale yellow crystalline solid. It crystallised from alcohol as pale yellow stout rectangular prisms melting at 284–5°. Its alcoholic solution gave no colour with ferric chloride but with magnesium and hydrochloric acid a bright red colour. It agreed in its properties with 7-hydroxy 5:3':4'-trimethoxy flavone.[18]

Iodine oxidation of fully methylated flavanones:

1. (*a*) 5:7:3':4'-*Tetramethoxy flavanone.*—As in the above cases a boiling solution of 5:7:3':4'-tetramethoxy flavanone[19] (0·2 g.) and sodium acetate (1 g.) in alcohol was treated with iodine (0·15 g.). Even from the hot solution a bright yellow solid crystallised out. This was filtered after

cooling and washed with aqueous sodium hydroxide (10%) to remove the chalkone formed (*c*). The undissolved product crystallised from alcohol in the form of bright yellow rectangular rods melting at 171°. Yield 0·06 g. It gave a deep red colour with concentrated sulphuric acid and rapidly decolourised bromine in carbon tetrachloride. It agreed in its properties with 4:6:3′:4′-tetramethoxy benzalcoumaranone described by Geissman and Fukushima[20] and a mixed melting point with a sample obtained by their method was undepressed.

The sodium hydroxide washings (*c*) yielded on acidification the bright yellow chalkone which crystallised from alcohol as bright yellow prisms, m.p. 157–58° and the mixed m.p. with 2-hydroxy-4:6:3′:4′-tetramethoxy chalkone[19] was undepressed.

(*b*) The above reaction was repeated at the room temperature and the reaction mixture was kept constantly shaken for 4 hours. At the end alcohol was removed on a water-bath, the residue treated with hot aqueous alkali (10%), cooled and extracted with ether. On evaporating the ether a pale yellow solid was obtained. Two crystallisations from dilute aqueous alcohol gave the product in almost colourless needles melting at 190–2°. It gave a bright red colour with magnesium and hydrochloric acid in alcoholic solution and agreed in its properties with luteolin tetramethyl ether.[21]

To a boiling solution of 2-hydroxy-4:6:4′-trimethoxy-chalkone[11] (0·5 g.) and sodium acetate (2 g.) in alcohol, a solution of iodine in alcohol was added. The colour of iodine was not discharged even after boiling under reflux for two hours; the chalkone could be recovered unchanged.

2. *7-Methoxy flavanone.*—A solution of 7-methoxy flavanone (1 g.) in alcohol (10 c.c.) was treated with shaking with a solution of iodine (0·5 g.) and sodium acetate (2 g.) in alcohol at the room temperature and the product worked up as given in the above experiment. This was twice crystallised from dilute alcohol when it came out in the form of colourless needles melting at 110° and the mixed melting point with an authentic sample of 7-methoxy flavone was not depressed. Yield 0·3 g.

Oxidation with phosphorus pentachloride :

7-Methoxy flavanone.—7-Methoxy flavanone (0·5 g.) was dissolved in hot benzene (10 c.c.) and treated with phosphorus pentachloride (1 g.). The mixture was boiled for 10 minutes. There was a brisk evolution of hydrogen chloride in the beginning which subsided in the end. Benzene was then distilled off and the excess of phosphorus pentachloride was

decomposed with ice. The solid that separated out was filtered and washed with water. On crystallising it from alcohol 7-methoxy flavone was obtained in the form of colourless needles melting at 110–11° and the mixed melting point with an authentic sample was undepressed. Yield 0·15 g.

Summary

Iodine, in the presence of hot alcoholic sodium acetate, is shown to be a convenient reagent for the conversion of hydroxy flavanones into flavones. Naringenin, its 4′ and 4′: 7-dimethyl ethers, hesperetin and its dimethyl ether are thus oxidised smoothly into apigenin and its ethers and diosmetin respectively. The method is also suitable for glycosides; examples chosen are naringin, its monomethyl ether and hesperidin. The constitution of apiin is discussed and confirmed by correlation with that of naringin.

The method works smoothly in all cases where a free hydroxyl is present in the 5-position. In its absence a mixture is formed; by working in the cold the flavones can be obtained, whereas in the hot benzalcoumaranones could be isolated. In such cases the suitability of the phosphorus pentachloride method has been tested using 7-methoxy flavanone.

The reaction is considered to involve (1) iodination of the 3-position and (2) elimination of hydriodic acid and these are brought about smoothly with the help of the active and unstable acetate ions. If the second stage involves iodinated flavanone, flavone is obtained; on the other hand if the corresponding iodinated chalkone is present, benzal-coumaranone results.

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