STEREOCHEMISTRY OF 3-HYDROXY FLAVANONES*

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A number of 3-hydroxy flavanones (flavanolones) (I) have been isolated from natural sources and several have been obtained synthetically by methods enumerated below:—

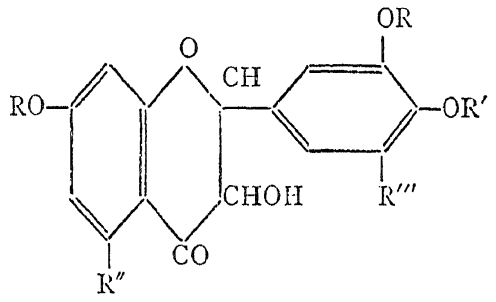
(1) *Reduction of the corresponding flavonol* (*II*).—The preparation of dihydroquercetin (I *b*) and dihydrokæmpferol (IV *c*) by this method using alkaline sodium hydrosulphite was carried out by Pew[1] and dihydromyricetin (I *d*) by Kotake, Kubota and Ichikawa.[2] The method was improved by Geissman and Lischner[3] and Shimizu and Yoshikawa.[4] Geissman *et al.*, also obtained small quantities of 2-hydroxy-2-benzyl coumaranones as by-products.

(2) *Ring closure starting from chalkones* (*III*).—Murakami and Irie[5] first used for this purpose alkaline hydrogen peroxide under controlled conditions. A detailed study of this reaction was made later by Reichel and Steudel[6] and more recently by Guider, Simpson and Thomas[7]. Oyamada[8] converted 2-acetoxy-4: 3′: 4′-trimethoxy chalkone (III) *via* its dibromide, diacetate and subsequent hydrolysis to fustin trimethyl ether (I *c*). More recently Marathe, Chandorkar and Limaye[9] have shown that chalkone dibromides yield 3-hydroxy flavanones (I) by heating with aqueous acetone and sodium carbonate.

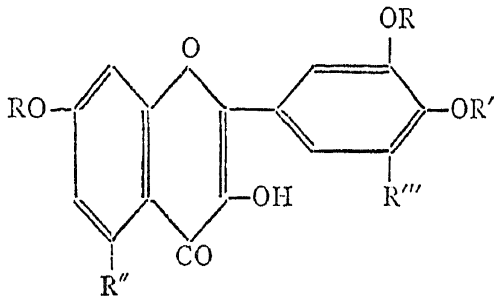
(3) *Substitution in the* 3*-position of flavanones* (*IV*).—In the earliest method of Zemplen and Bognar[10] bromination in the 3-position was effected in the presence of ultra-violet light, and the bromine atom replaced in two steps by a hydroxyl. Cavill *et al.*[14] applied this method to 7-methoxy flavanone and obtained only the flavone at the end. During the course of the present work when 3-bromo naringenin triacetate (IV *f*) was boiled with acetic anhydride and silver acetate it yielded apigenin acetate (V *h*) as the major product and dihydrokæmpferol tetra-acetate (IV *d*) as the minor product. It would appear that a mixture of flavone and flavanolone are generally produced, the proportions varying with conditions and in earlier work only the major

* Naturally occurring 3-hydroxy flavanones are specified by their trivial names and the synthetic ones by the method of preparation.

product might have been isolated after purification. Goel, Narasimhachari and Seshadri[11] employed iodine and silver acetate in absolute alcohol whereby in several cases the 3-acetoxy flavanones were produced. The action of lead tetra-acetate on flavanones has been observed by a number of workers.[12-14] to give a small yield of 3-acetoxy flavanones along with flavones and isoflavones. More recently Mahesh and Seshadri[15] have found that the action of Fenton's reagent on flavanone acetates (IV *h*) provides a convenient method for hydroxylation in the 3-position. This and the iodine-silver acetate method of Goel *et al.*[11] seem to effect simple substitution and are therefore considered to be typical examples.

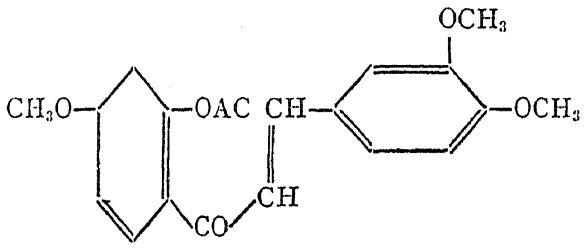


(I)



(II)

a R=R'=R''=R'''=H
b R=R'=R'''=H; R''=OH
c R=R'=CH_3; R''=R'''=H
d R=R'=H; R''=R'''=OH
e R=R'=CH_3; R''=R'''=OCH_3
f R=R'''=H; R'=CH_3; R''=OH



(III)

There seemed to exist appreciable differences between various samples of 3-hydroxy flavanones (I) obtained from natural sources and by different synthetic methods. These should be capable of explanation based on the stereochemistry of these structures. Among their transformations (*a*) dehydrogenation and (*b*) dehydration are the most important. The former gives rise to flavonols while the latter gives flavones.

(*a*) A number of methods have been used for dehydrogenation.

(i) *Catalytic.*—Kotake and Kubota[16] heated ampelopsin (I *d*) with cinnamic acid in the presence of P*d*-charcoal at 170° and obtained myricetin (II *d*). Later Lindstedt[17] used this method for the dehydrogenation of pinobanksin (IV *a*).

(ii) *Oxidation in alkaline solution.*—Murakamiand Irie[5] first showed that 3-hydroxy flavanones (I) obtained by synthetic method (2) underwent dehydrogenation to flavonols (II) with alkaline hydrogen peroxide. In the course of the present work using this reagent pinobanksin (IV *a*) obtained from the wood of *Pinus excelsa* has been dehydrogenated to galangin (V*a*). Oyamada[18] showed that fustin (I *a*) underwent similar oxidation in alkali in presence of air to yield fisetin (II *a*). These two processes have been applied to a number of synthetic (Method 2) dihydroflavonols also by Reichel and Steudel.[6]

(iii) *Disproportionation.*—Marathe *et al.*[9] have reported dehydrogenation by disproportionation on heating simple dihydroflavonol [synthetic method (2)] with alcoholic sodium hydroxide in absence of air or by simple thermal disproportionation. It has also been observed by Cavill *et al.*[14] that 3-acetoxy flavanones prepared by the action of lead tetra-acetate on flavanones undergo hydrolysis accompanied by dehydrogenation when treated with alcoholic NH_3 at 0°.

It may be noted that in alkaline solutions the opening of the pyranone ring is an important feature and may be responsible for by-products such as 2-hydroxy-2-benzyl coumaran-3-ones,[19, 20] 3-benzal coumaran-2-ones,[9, 19, 21] 2-benzyl[22] and 2-benzal[23, 24] coumaran-3-ones.

(iv) *During methylation.*—Kubota[25] observed that the use of aqueous alkali and methyl sulphate converted ampelopsin pentamethyl ether (I *e*) into myricetin hexamethyl ether. A similar observation was made by Lindstedt[17] and Goel *et al.*[11] using methyl sulphate and anhydrous potassium carbonate in acetone solution. The former showed that pinobanksin (IV *a*) first yielded its dimethyl (IV *g*) ether which finally changed into galangin trimethyl ether (V *i*) in small yields. The latter reported similar results with 3-hydroxy naringenin (IV *c*) natural as well as synthetic [method (3)]. The dehydrogenation could be brought about even by simply boiling with acetone and potassium carbonate.[11]

(v) *Bismuth acetate.*—More recently Guider *et al.*[7] have used bismuth acetate for the conversion of synthetic 3-hydroxy flavanones (I) obtained by method (2) into flavonols (II). This reagent is specific for the oxidation of $-CHOH$ to $-CO$ and is considered to function here in this manner. In the course of the present work it has been used to oxidise taxifolin (I *b*) and 3-hydroxy naringenin (IV *c*) prepared by Fenton's oxidation and is found to work very satisfactorily. Other methods of dehydrogenation are discussed later.

(*b*) *Dehydration.*—By boiling with acetic anhydride the natural as well as synthetic flavanolones (I) made by method (3) undergo dehydration yielding the corresponding flavone acetates (V *h*) though the yields are variable. In general the natural samples give much poorer yields.

The methods discussed above are not of value for the study of the stereochemistry of the 3-hydroxy flavanones since the use of high temperatures and strong reagents are involved and the use of alkali also opens the pyranone ring. The results yielded by the following methods seem to be, however, significant since they represent mild treatments.

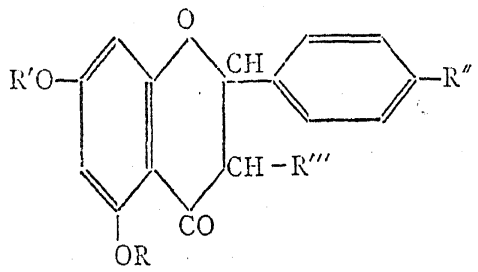
(i) *Dilute sulphuric acid in the presence of air.*—Pew[1] observed dehydrogenation of taxifolin (I *b*) by this method giving good yields of quercetin (II *b*). Cavill *et al.*[14] report that 3-hydroxy flavanones (I) obtained by lead tetracetate method behave in a similar way. During the course of the present work a similar observation has been made using a sample of dihydroquercetin (I *b*) prepared by method (1), dihydrorhamnocitrin (IV *e*) by method (2) and 3-hydroxy naringenin (IV *c*) by Zemplen's method. On the other hand Goel *et al.*[11] observed that under this treatment 3-hydroxy naringenin (IV *c*) prepared by the iodine-silver acetate method undergoes dehydration to apigenin (V *b*); Fenton's oxidation products also are now found to suffer dehydration in the same way.

(ii) *Iodine oxidation.*—Iodine in the presence of alcoholic sodium acetate has been employed earlier by Narasimhachari and Seshadri[26] for the conversion of flavanones (IV *b*) into flavones (V *b*). Its action on 3-hydroxy flavanones has now been studied. Pinobanksin (IV *a*), pinobanksin-7-methyl ether (IV *j*), aromadendrin (IV *c*), taxifolin (I *b*) and dihydroquercetin (I *b*) prepared by method (1) are found to undergo smooth dehydrogenation to give good yields of galangin (V *a*), izalpinin (V *j*), kæmpferol (V *c*) and quercetin (II *b*) respectively. A sample of 3-hydroxy naringenin (IV *c*) obtained by synthetic method (3), however, behaves differently and yields small amounts of kæmpferol (V *c*) along with a major yield of an iodo compound, and a considerable portion of the original substance is recovered which could be made to react again to yield more of the iodo compound but not kæmpferol (V *c*). The iodo compound decomposes rather readily and when refluxed with pyridine yields kæmpferol (V *c*). A sample of 3-hydroxy hesperetin (I *f*) prepared by the same synthetic method gave similar results.

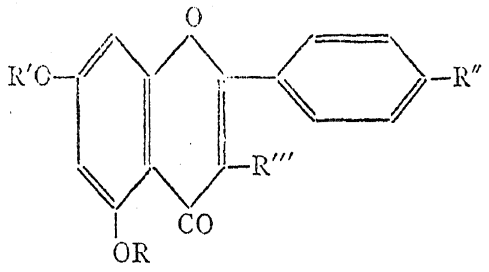
A similar though somewhat different result has been obtained using boiling glacial acetic acid and fused potassium acetate instead of alcohol for this reaction. Slightly better yields of quercetin (II *b*) are obtained from taxi-

folin (I *b*). In the case of synthetic 3-hydroxy naringenin (IV *c*) obtained by method (3) the yield of kæmpferol (V *c*) and the iodo compound was higher and there was no recovery of unchanged material.

In view of the peculiar behaviour of these synthetic compounds the action of 4% alcoholic sulphuric acid on 3-hydroxy naringenin (IV *c*) obtained by method (3) has been reinvestigated. The major product was apigenin (V *b*) and could be readily obtained pure by crystallisation from alcohol. When the mother liquor was subjected to circular paper chromatography two rings corresponding to those of kæmpferol (V *c*) (weak) and apigenin (V *b*) (strong) were obtained. The behaviour of these samples will be discussed in detail later on.



(IV)



(V)

a R=R′=R″=H; R‴=OH
b R=R′=R‴=H; R″=OH
c R=R′=H; R″=R‴=OH
d R=R′=Ac; R″=R‴=OAc
e R=H; R′=CH_3; R″=R‴=OH
f R=R′=Ac; R″=OAc; R‴=Br
g R=R′=CH_3; R″=H; R‴=OH
h R=R′=Ac; R″=OAc; R‴=H
i R=R′=CH_3; R″=H; R‴=OCH_3
j R=R″=H; R′=CH_3; R‴=OH

An explanation of the above observations could be sought from a study of the conformation of the simple flavanone and 3-hydroxy flavanone structures. In molecular models of flavanones, carbon atoms 2 and 3 of the pyranone ring (A, see Formula VI) are not in the same plane as the other atoms of this ring and of the condensed benzene ring, though the deviation is not much. Of the non-ring bonds of each of these two carbon atoms, one is axial and the other is equatorial. The equatorial bonds are *cis* to each other. There are two ways in which the axial bonds could be arranged (i) axial bond in the 2-position (α,....) and axial bond in the 3-position (β,___) (VI *a*) and (ii) the reverse (VII *a*). These would represent mirror-image forms. In the case of simple flavanones the 2-phenyl should be allotted the equatorial bond by virtue of its bulk; consequently the C_2-hydrogen should be axial and the bond can be α or β representing the (+) or (−) form. A number of optically active flavanones are now known and they are mostly (−) in rotation.

3-HYDROXY FLAVANONES

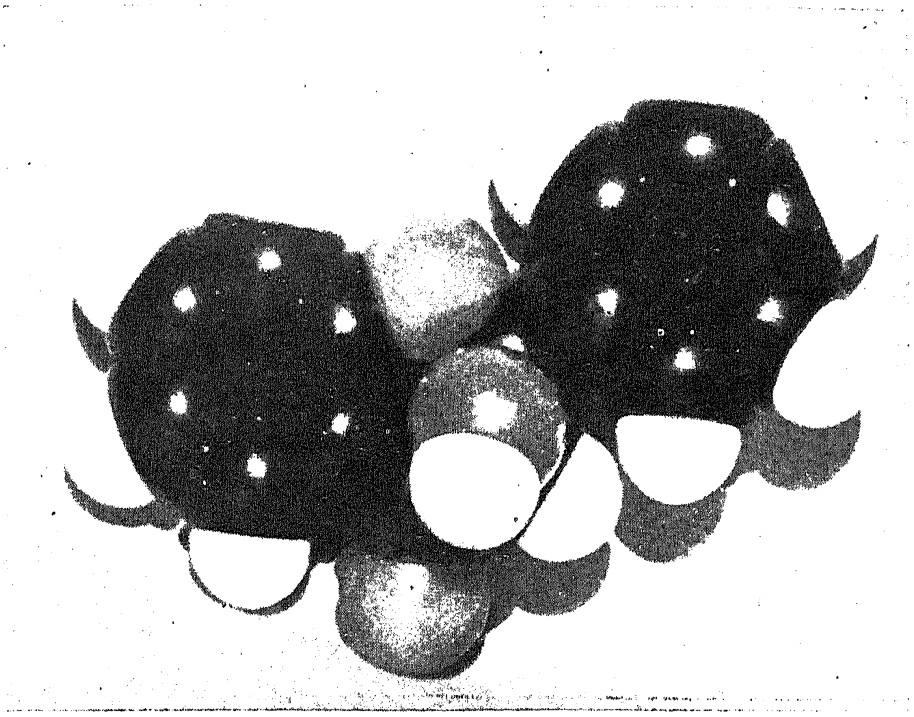


FIG. 1. Front view.

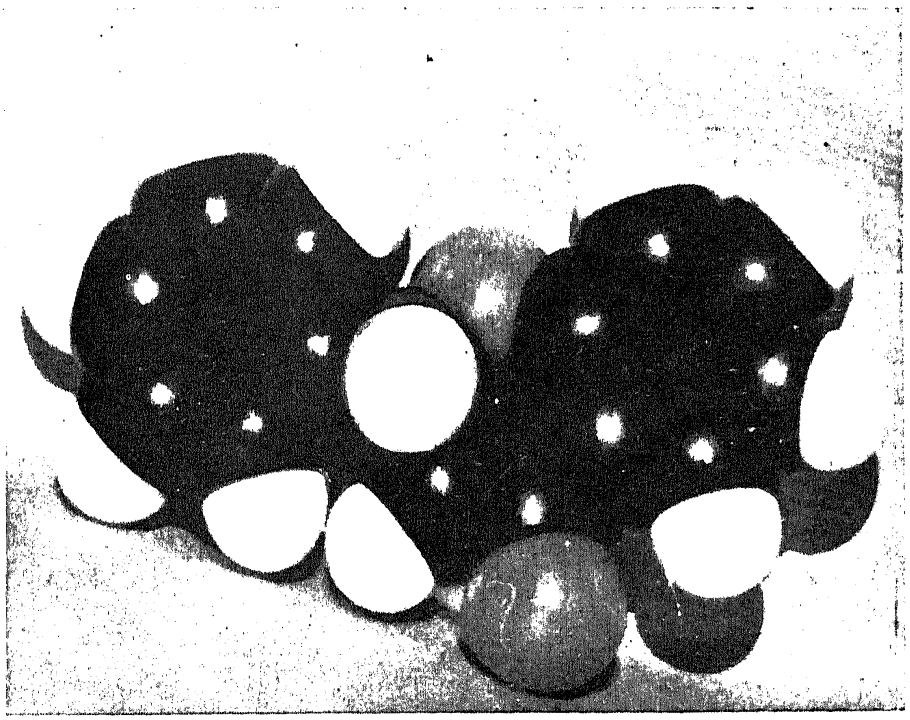


FIG. 2. Back view.

FIGS. 1 and 2. Side phenyl in the 2-position and hydrogen atom in the 3-position are equatorial. Axial hydrogen in the 2-position (Fig. 2) and axial hydroxyl in the 3-position (Fig. 1) are visible.

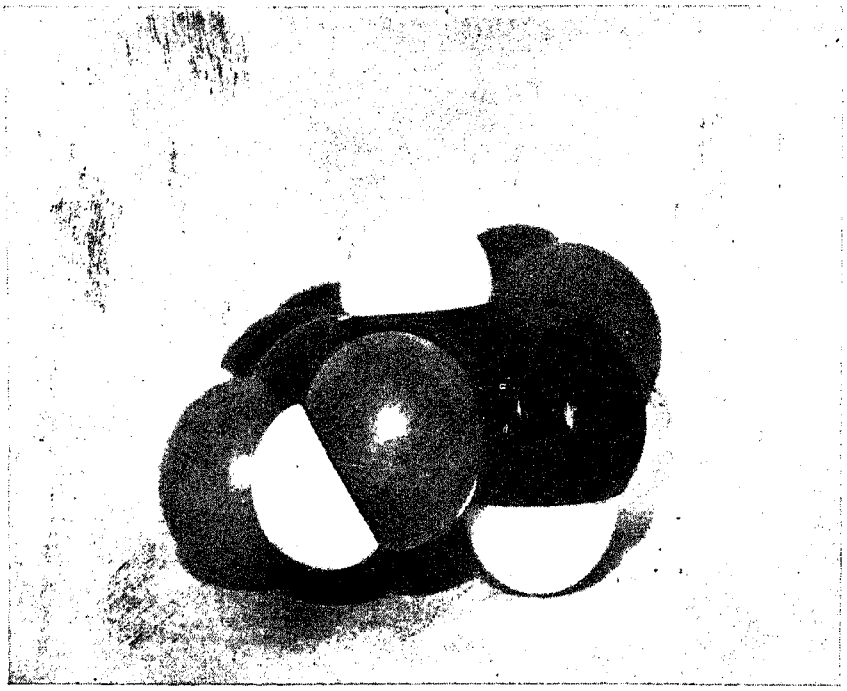


FIG. 3. Side view: side phenyl omitted.

FIG. 3. Hydrogen atoms in 2 and 3-positions are axial and trans while hydroxyl in the 3-position is equatorial.

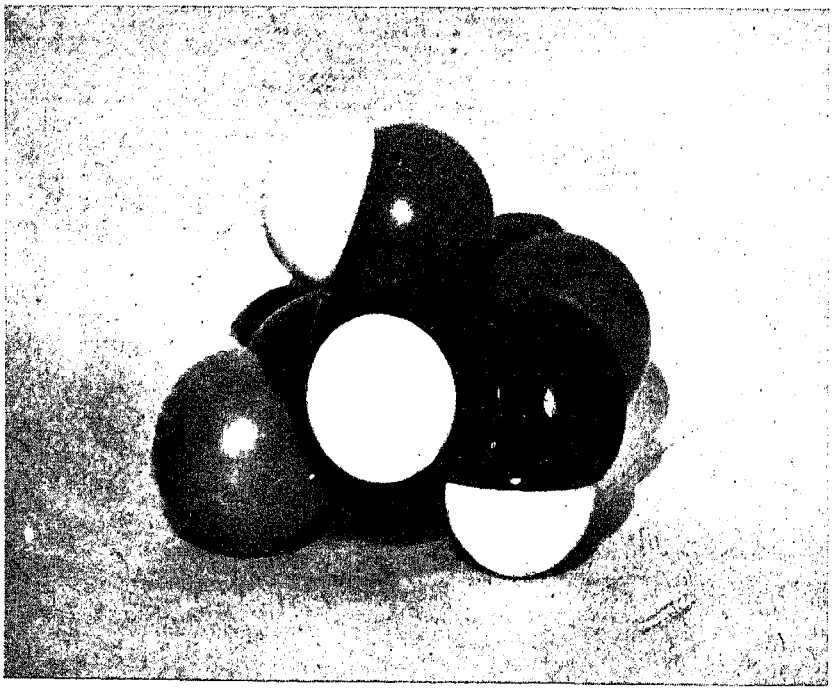
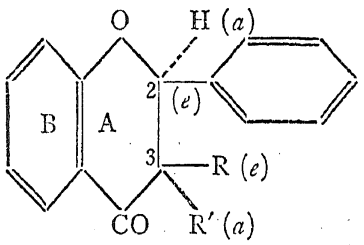
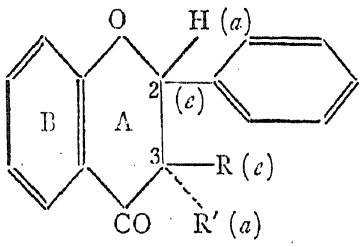


FIG. 4. Side view.: side phenyl omitted.

FIG. 4. Hydrogen atom in the 2-position and hydroxyl in the 3-position are axial and trans while hydrogen in the 3-position is equatorial.



(VI)



(VII)

a R=R'=H
b R=OH; R'=H
c R=H; R'=OH

(*d*) axial
(*e*) equatorial
— *β* orientation
--- *α* orientation

In the case of 3-hydroxy flavanones more forms can arise depending on the dispositions of the hydroxyl in the 3-position. In a stable naturally occurring from it would be reasonable to expect that the bulkier hydroxyl group would occupy the equatorial position (C-OH equatorial) leaving the C-H bond axial being α or β. Since each of these restricts automatically the disposition of the C-H axial bond in the 2-position, there can be only two stereoisomeric naturally occurring flavanolones. In them the two C-H bonds in the 2 and 3-positions being axial and trans (VI *b* and VII *b*), the requirements for ready elimination of hydrogen atoms are satisfied[27] and they readily yield the corresponding flavonols under mild conditions as already explained.

Among the synthetic methods the first method may be expected to yield racemates having the same configuration as the natural compounds because in the original flavonol structure (planar) the phenyl and the hydroxyl groups are necessarily linked by equatorial bonds and since they are bulky groups the introduction of hydrogen by reduction will not alter their equatorial arrangement. This is supported by the behaviour of dihydroquercetin (I *b*) (obtained by the reduction of quercetin) which undergoes ready dehydrogenation by boiling with dilute sulphuric acid. The second method involves ring closure. Here too the bulkier groups, *i.e.*, phenyl and hydroxyl would naturally be expected to take up the equatorial positions and the properties of the compounds are in agreement. The conditions seem to be different in the case of the third method of synthesis involving substitution by means of iodine and silver acetate[11] and by Fenton's reagent.[15]. The behaviour of the products, that is ready dehydration would suggest that the hydroxyl group in the 3-position is now linked by an axial bond (VI *c* and VII *c*) and this along with the C_2-H (axial) suffers trans elimination as water. Even the behaviour of these samples with iodine and sodium or potassium acetate would suggest this orientation of the hydroxyl group. It then follows that in substitution reactions of simple flavanones the axial hydrogen in the 3-position (VI *a* and VII *a*) is more reactive and this should be attributed to steric factors.

In the flavanone structure the axially linked atoms are less sterically hindered as compared to the equatorial ones. In this respect these structures differ from cyclohexane derivatives in which the axially linked positions are sterically hindered[28] and are not readily available for substitution reactions.

Examining the details of the behaviour of these 3-hydroxy flavanones obtained by substitution (method 3) it appears that they consist predominently of the type (VI *c*) and (VII *c*) with C-OH axial. In their reactions with sulphuric acid, besides flavones only very small amounts of the corresponding flavonols seem to be formed. This may mean that the synthetic product was a mixture having as a very minor component the more stable variety with the C-OH equatorial or it may be that the sample consisted only of one entity (C-OH axial) and a small transformation into the more stable (C-OH) equatorial variety took place during the course of treatment with sulphuric acid. A similar explanation could be given for the behaviour of these compounds with regard to iodine and sodium acetate in alcohol or acetic acid solutions. This reaction is very slow obviously due to the difficulty of an elimination reaction in which an equatorial hydrogen is involved and hence considerable quantity of the unchanged compound is recovered from the alcoholic solution. The iodo compound which is the major product may have involved substitution of the less accessible equatorial C-H in the 3-position, and its subsequent elimination is not easy and requires treatment with pyridine. There is another possibility which should not be overlooked. Because of the peculiar conditions of the hydroxy flavanone structure with C-OH bond axial, the C_2-H (axial) group (VI *c* and VII *c*) may undergo substitution comparatively more easily. Even here the subsequent elimination will be difficult and would require pyridine for its removal along with the equatorial hydrogen of the carbon atom 3.

Deviations have, however, been observed when using Zemplen's method[10] or lead tetra-acetate[14] for the synthesis of 3-hydroxy flavanones (I) by substitution. As already mentioned these methods are found to yield a mixture of 3-hydroxy flavanone and flavone. The simplest and the most satisfactory explanation appears to be that as an initial step a 3-acetoxy (axial) compound is produced by the ready substitution of C_3-H (axial) of the flavanone. Because of the higher temperature and the solvents employed, (trans) elimination of acetic acid takes place readily to yield flavone and at the same time there is partial configurational change to produce C_3-acetoxy (equatorial) flavanone. When subjected to treatment with dilute sulphuric acid and air the resulting 3-hydroxy flavanones undergo dehydrogenation to yield flavonols as observed.

In view of the abovementioned possibility of change in configuration by treatment with reagents, a sample of 3-hydroxy naringenin (IV *c*) obtained by the synthetic method (3) was treated with alcoholic sodium acetate which is known to be good for bringing about enolisation[29] as a preliminary to configurational change. The product was found to behave similar to the natural compounds and underwent ready dehydrogenation with sulphuric acid. Hence the possibility of the configurational change from the less stable C_3-OH (axial) to the more stable C_3-OH (equatorial) form is confirmed. This seems to take place even in the presence of potassium carbonate in acetone solution and may account for the partial dehydrogenation to flavonol brought about by this reagent even with 3-hydroxy flavanones prepared by Fenton's oxidation[15] or iodine and silver acetate method.[11]

Experimental

Oxidation of pinobanksin (IV a) *with alkaline hydrogen peroxide*

Pinobanksin (200 mg.) was dissolved in methanolic potash (20 c.c.; 4%), hydrogen peroxide (2 c.c.; 100 vol.) added and the mixture allowed to stand at room temperature for 24 hours. On dilution with water to 200 c.c. and acidification, a yellow solid separated and it crystallized from aqueous alcohol as yellow prismatic rods, m.p. 214–15°. It gave a reddish brown colour with ferric chloride, an orange colour with magnesium and hydrochloric acid and a pale yellow colour with zinc and hydrochloric acid. Its m.p. agreed with that of galangin (V *a*) and the mixed m.p. was undepressed. Yield 100 mg.

Dehydrogenation using bismuth acetate

(*a*) *Taxifolin* (*I* b).—Taxifolin (300 mg.) was added to a mixture of basic bismuth carbonate (500 mg.), acetic acid (5 c.c.) and amyl alcohol (50 c.c.) and refluxed at 140° for 1½ hours. The solvents were removed under reduced pressure and the residue extracted with aqueous borax solution. On acidifying the solution a deep yellow solid separated which crystallised as yellow needles from aqueous alcohol m.p. 306–08°. It gave a greenish brown colour with alcoholic ferric chloride, red colour with magnesium and hydrochloric acid and a mixed m.p. with quercetin (II *b*) was undepressed. Yield 200 m.g.

(*b*) 3-*Hydroxy naringenin* (*IV* c) *obtained by method* (3)[15].—3-Hydroxy naringenin (50 mg.) was oxidised by bismuth acetate as in the above case and it yielded kæmpferol (V *c*) (25 mg.).

Dehydration with acetic anhydride

(*a*) *Pinobanksin* (*IV a*).—Pinobanksin (100 mg.) was refluxed with acetic anhydride (1 c.c.) for 2 hours and the reaction mixture poured on crushed ice (50 g.). The resinous solid was first purified by the use of ethyl acetate, light petroleum mixture. It then crystallised from aqueous alcohol as colourless needles, m.p. 190° agreeing with chrysin diacetate. Yield 25 mg.

(*b*) *Synthetic* 3 : 5 : 7-*trihydroxy flavanone* (*IV* a) *prepared by method* (3)[15] —The compound (100 mg.) was subjected to dehydration with acetic anhydride as in the case of pinobanksin and it yielded chrysin diacetate (60 mg.).

Action of 2*N sulphuric acid*

(*a*) *On dihydroquercetin* (*I* b), *prepared by method* (1)[3]: 2N sulphuric acid (50 c.c.) was added to dihydroquercetin (200 mg.) and heated on a water-bath. The solution turned yellow after 3 hours and a yellow substance started separating after about 12 hours. After 30 hours the mixture was extracted with ether, the ether removed and the residue crystallised from aqueous alcohol, m.p. 308–10°. It gave a greenish brown colour with alcoholic ferric chloride, red colour with magnesium and hydrochloric acid and the mixed m.p. with quercetin was undepressed. Yield 120 mg.

(*b*) *On dihydrorhamnocitrin* (*IV* e), *prepared by method* (2)[7].—Dihydrorhamnocitrin (100 mg.) was heated with 2 N sulphuric acid for 30 hours. A yellow solid separated which crystallised as yellow needles from alcohol, m.p. 220–22°. It gave a green colour with ferric chloride, a red colour with magnesium and hydrochloric acid and a green fluorescence with concentrated sulphuric acid. Its m.p. and colour reactions thus agreed with those of rhamnocitrin (V *e*). Yield 60 mg. With acetic anhydride and pyridine it yielded 3 : 5 : 4′-triacetoxy-7-methoxy flavone, m.p. 200–01°.

(*c*) *On* 3-*hydroxy naringenin* (*IV* c), *made by Fenton's oxidation.*[15]— 3-Hydroxy naringenin (50 mg.) was heated with 2 N sulphuric acid as in the above case. A pale yellow solid separated which crystallised as pale yellow needles from alcohol, m.p. 338–42°. It gave a violet colour with alcoholic ferric chloride, a red colour with magnesium and hydrochloric acid and agreed in m.p. and mixed m.p. with apigenin.

The alcoholic mother liquor was subjected to circular paper chromatography using phenol-water mixture (upper layer) as the irrigating solvent. A yellow ring was observed having R*f* value of 0·24. On spraying with ammonia the original yellow ring turned orange-red and a fresh yellow ring with R*f* value of 0·44 was observed. An authentic sample of kæmpferol under the same condition gave an R*f* value of 0·24 while apigenin gave an

Rf value of 0·44. Thus the mother liquor was found to contain a mixture of apigenin (major component) and kæmpferol (minor component).

Iodine oxidation: (i) *alcohol and sodium acetate*

(*a*) *Natural 3-hydroxy flavanones.*—To a boiling solution of the compound (200 mg.) in rectified spirit (5 c.c.) was added dropwise a solution of iodine (160 mg.) and sodium acetate (1 g.) in rectified spirit (10 c.c.) during half an hour. Refluxing was continued for another 30 minutes, the alcohol distilled off and the residue treated with sulphur dioxide water. The pale yellow solid was first purified by the precipitation of coloured impurities from an ethyl acetate solution using light petroleum and finally crystallised from aqueous alcohol. The compounds thus obtained were characterised by positive magnesium and hydrochloric acid colour, m.p. and mixed m.p. with authentic samples. They also yielded orange to orange-red coloured lead salts. The results are given below:

	Oxidation product	Approximate Yield
Pinobanksin (IV *a*)	Galangin (V *a*)	45%
Pinobanksin-7-methyl ether (IV *j*) ..	Izalpinin (V *j*)	40%
Taxifolin (I *b*)	Quercetin (II *b*)	60%
Aromadendrin (IV *c*)	Kæmpferol (V *c*)	60%

(*b*) *Dihydro-quercetin* (*I* b) *prepared by method* (1).—Dihydroquercetin for this purpose was prepared by Geissman and Lichner's[3] modification of Pew's method. On oxidation with iodine and sodium acetate as in the above experiments it yielded quercetin (II *b*) in about 60% yields.

(*c*) 3-*Hydroxy naringenin* (*IV* c), *prepared by iodine and silver acetate method*[11].—The compound (200 mg.) was subjected to iodine oxidation according to the above procedure. The crude orange coloured solid product was first purified by the use of ethyl acetate, light petroleum mixture and then dissolved in methanol (0·5 c.c.) and allowed to stand in the refrigerator for 2 days. A solid separated which crystallised from aqueous alcohol as yellow needles, m.p. 276–78°. It gave a red colour with magnesium and hydrochloric acid and agreed in m.p. and mixed m.p. with an authentic sample of kæmpferol (V *c*). Yield 20 mg.

The alcoholic mother liquor was evaporated and the residue dried. It was then dissolved in 20 c.c. of boiling ethyl acetate and allowed to cool. After standing for about 24 hours in a refrigerator a small amount of pale yellow crystals appeared which turned black on filtration. Even after a recrystallisation the crystals turned brownish-black as soon as the solvent

dried up. The black solid responded to qualitative tests for iodine and decomposed even below 60°. Yield 40 mg. On concentration of the ethyl acetate mother liquor a solid was obtained which crystallised from aqueous alcohol as stout prisms, m.p. 238–40° agreeing with the original sample of 3-hydroxy naringenin. Yield 60 mg. This recovered 3-hydroxy naringenin was again subjected to iodine oxidation when it yielded 20 mg. of the iodo compound but no kæmpferol.

The iodo compound mentioned above (50 mg.) was dissolved in dry pyridine (0·5 c.c.) and heated on a boiling water-bath for 2 hours. Dilute hydrochloric acid (15%; 10 c.c.) was added and the solution extracted with ether. After evaporating the ether solution the residue was crystallised from aqueous alcohol yielding yellow needles melting at 276–78°. Its colour reactions, m.p. and mixed m.p. showed identity with kæmpferol (V *c*). Yield 20 mg. 3-Hydroxy naringenin obtained by Fenton's oxidation also behaved in a similar way.

(*d*) 3-*Hydroxy hesperetin* (*I* f), *prepared by iodine and silver acetate method*[11].—The compound (200 mg.) was subjected to iodine oxidation and the product worked up as in the above experiment. A small amount of a substance (15 mg.) separated from alcohol, m.p. 259–60°. It gave a red colour with magnesium and hydrochloric acid, an olive brown colour with alcoholic ferric chloride and agreed in m.p. with quercetin-4′-methyl ether (II*f*); mixed m.p. with an authentic sample prepared earlier by Gupta and Seshadri[30] was undepressed. An iodo compound (40 mg.) was also obtained along with the unreacted product (75 mg.). The recovered product was again subjected to iodine oxidation and just as in the previous case only an iodo compound was obtained which when heated with dry pyridine also yielded quercetin-4′-methyl ether.

(ii) *Glacial acetic acid and fused potassium acetate*

(*a*) *Taxifolin* (*I* b).—To a solution of taxifolin (500 mg.) in glacial acetic acid (10 c.c.) was added fused potassium acetate (2 g.) and iodine (420 mg.) in glacial acetic acid (5 c.c.). The mixture was refluxed for $2\frac{1}{2}$ hours, acetic acid removed under reduced pressure and water added. The brownish yellow solid product was first purified by the precipitation of coloured impurities from an ethyl acetate solution using light petroleum and finally crystallised from aqueous alcohol. It agreed in its colour reactions, m.p. and mixed m.p. with quercetin. Yield 350 mg.

(*b*) 3-*Hydroxy naringenin* (*IV* c) *prepared by method* (3)[15].—3-Hydroxy naringenin (100 mg.) was subjected to iodine oxidation in acetic acid solution. The reaction products were purified and separated as in the oxidation using

alcohol and sodium acetate; kæmpferol (25 mg.) and iodo compound (35 mg.) were obtained. No unreacted product could, however, be isolated.

Attempts to prepare 3-hydroxy naringenin (IV c) by Zemplen's method.— Naringenin triacetate (1 g.) was dissolved in chloroform (20 c.c.) and bromine (0·41 g.) in chloroform (10 c.c.) was added dropwise with cooling. The mixture was exposed to ultra-violet light for 2 hours, during which hydrobromic acid was evolved. The chloroform solution was washed with water, dried over anhydrous sodium sulphate and the chloroform removed under reduced pressure. The pale yellow oil thus obtained contained bromine and could not be crystallised. It (1·1 g.) was refluxed at 140° with acetic anhydride (15 c.c.) in the presence of silver acetate (1·0 g.) for $1\frac{1}{2}$ hours, filtered and poured into water. The white solid thus obtained crystallised as colourless needles from aqueous alcohol and melted over a range of 15° and could not be conveniently purified further. This acetate (600 mg.) was refluxed with alcoholic hydrochloric acid (1 : 1; 30 c.c.) for 30 minutes. On cooling an yellow solid separated (300 mg.) which crystallised from alcohol as pale yellow needles, m.p. 338–42°. It gave a yellow colour with concentrated hydrochloric acid, a violet colour with alcoholic ferric chloride and a red colour with magnesium and hydrochloric acid and agreed with apigenin (V *b*), mixed m.p. undepressed.

The alcoholic mother liquor was evaporated under reduced pressure and the residue extracted repeatedly with ether. After evaporating the combined ether extract the residue was crystallised from dilute methanol when it separated as colourless rectangular prisms m.p. 239–40° (*d.*). It gave a red colour with zinc and hydrochloric acid and magnesium and hydrochloric acid and a violet colour with alcoholic ferric chloride. Yield 50 mg. It (40 mg.) was heated with 2 N sulphuric acid (30 c.c.) for 30 hours. A yellow solid separated which crystallised as yellow needles from aqueous alcohol, m.p. 276–78°. It gave a bluish green colour with ferric chloride, a red colour with magnesium and hydrochloric acid and no colour with zinc and hydrochloric acid. It thus agreed in m.p. with kæmpferol and mixed m.p. was undepressed. Yield 25 mg.

Isomerisation of 3-hydroxy naringenin (IV c) obtained by Fenton's oxidation[15].—3-Hydroxy naringenin (100 mg.) obtained by Fenton's oxidation was dissolved in alcohol (25 c.c.) and sodium acetate (15 g.) in water (10 c.c.) was added. The mixture was allowed to stand at room temperature for 24 hours, alcohol removed under reduced pressure and the remaining solution extracted repeatedly with ether. After evaporating the combined ether extract, the residue was crystallised from dilute methanol when

it separated as colourless rectangular prisms m.p. 239–40° (*d.*). It gave a pink to red colour with zinc and hydrochloric acid, a red colour with magnesium and hydrochloric acid and a violet colour with alcoholic ferric chloride. Yield 80 mg. It (70 mg.) on refluxing with 2 N sulphuric acid yielded kæmpferol (V *c*). Yield 35 mg.

SUMMARY

A number of 3-hydroxy flavanones occur in nature and several have been obtained using a number of synthetic methods. Though they behave generally in the same way when subjected to drastic methods of dehydrogenation or dehydration, those obtained by substitution of flavanones in the 3-position seem to differ markedly from others in their reactions towards mild reagents such as dilute sulphuric acid and iodine. This is attributed to stereochemical differences. In this particular synthetic method the 3-hydroxyl is axial (H_2O elimination easy) whereas in the others it is equatorial (H_2 elimination easy). In flavanones substitution of the axially disposed C-H is the favoured one because it is sterically unhindered.

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