A STUDY OF THE ACTION OF IODINE AND SILVER ACETATE ON FLAVANONES

BY A. C. JAIN, P. D. SARPAL AND T. R. SESHADRI, F.R.S.

(Department of Chemistry, University of Delhi, Delhi-7)

Received April 12, 1965

THE action of iodine and silver acetate on flavanones was first studied with a view to synthesize natural dihydroflavonols, several members of which were being discovered.[1-2] Since there is an active methylene group in the 3-position of flavanones as shown earlier by the formation of oximino derivatives with nitrous acid,[3] benzylidene derivatives with benzaldehyde in the presence of acids,[4] and by the formation of 3-bromo derivatives with bromine in the presence of U.V. light from several acetoxy-flavanones,[5] it was expected that iodine and silver acetate mixture would yield 3-acetoxy-flavanones which on careful hydrolysis could afford dihydroflavonols. The choice of silver acetate was made because it is less basic than sodium acetate and would promote acetoxylation of 3-iodo compound (if formed) rather than dehydroiodination as had been noticed earlier when a combination of iodine and sodium acetate was used.[6] In the last reaction which has subsequently been improved by using potassium acetate and acetic acid[7-9] it was considered that the first stage was iodination of the 3-position followed by dehydroiodination. The following results were reported in two earlier papers.[1,2] 5, 7-Dihydroxyflavanones such as pinocembrin, naringenin and hesperetin were reported to give 3-acetoxy compounds and on subsequent careful alkaline hydrolysis the corresponding dihydro-flavonols. On the other hand, methyl ethers of flavanones like 7, 4′-di-*O*-methyl naringenin and 7, 3′-di-*O*-methyl hesperetin and 5, 7-dimethoxyflavanone were reported to give the corresponding 3-iodo-derivatives which could, however, not be converted into dihydro-flavonols with alkali but formed different products.

This method did not give consistent results later in the hands of other workers in this laboratory. The earlier methods of characterisation of products based on melting points and colour reactions were not conclusive. A more critical study has, therefore, been found necessary and has now been carried out.

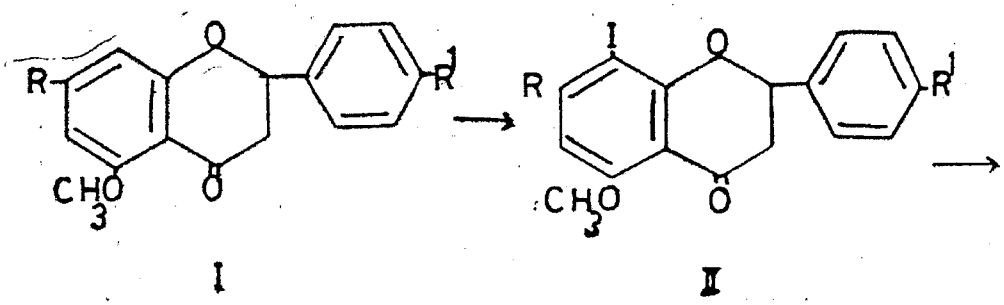
As a result of the study of a number of cases under a variety of conditions, it has been found that refluxing in ethanolic medium[1,2] does not allow complete conversion of the substrate into products even though the

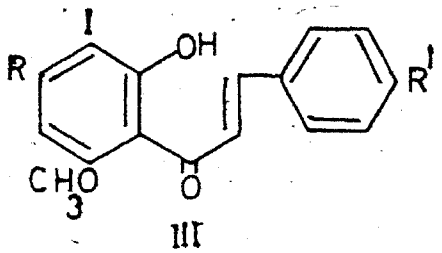
reaction definitely takes place. Better solvent media are (1) glacial acetic acid and (2) chloroform; in the case of (1), the reaction can be carried out at room temperature but in the case of (2), the reaction mixture has to be refluxed for several hours.

Under several conditions examined, the following flavanones did not react with iodine and silver acetate: simple flavanone, all flavanones substituted only in the 7-position in the ring A by groups like hydroxy, methoxy and acetoxy groups, 5, 7-diacetoxyflavanones and 5, 7-dihydroxyflavanones. The reaction products from naringenin and pinocembrin were examined in the crude state by I.R. spectroscopy to see if some 3-acetoxy-flavanones were formed. But no acetoxyl bands could be seen in the carbonyl region. Flavanones which led to definite products with iodine and silver acetate are discussed below:

1. *Reactions of fully methylated flavanones*

Naringenin trimethyl ether[10] (I *a*), being readily available, was examined first. In acetic acid medium, the only product isolated in good yields was found to be the 8-iodo derivative (II *a*). Its identity was established by treatment with 4% ethanolic potash when 2'-hydroxy-3'-iodo-4, 4', 6'-trimethoxychalkone (III *a*) was obtained agreeing with the description given by Chen *et al.*[11] It showed the right spectrum of a chalkone in the U.V. region. That nuclear iodination occurred only in the 8-position and not in the 6-position is also supported by the recent experiment on iodination of 5, 7, 4'-tribenzyloxyflavone when 8-iodo derivative was isolated.[11 a]





III

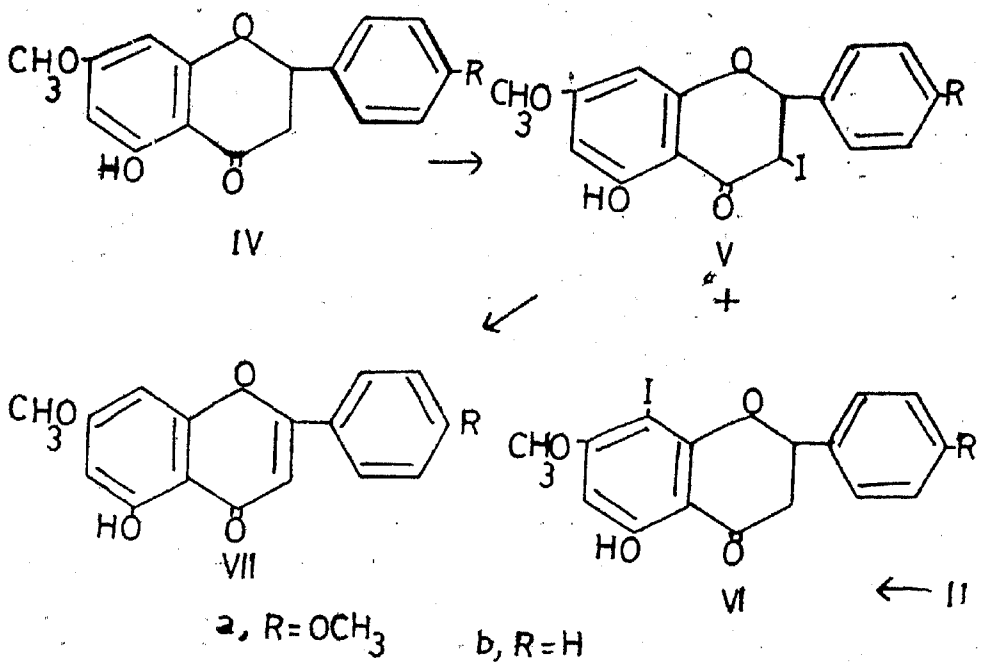
a, R = R' = CH3O
b, R = CH3O, R' = H
c, R = R' = H

5, 7-Dimethoxyflavanone[12] (I *b*) was next tested under the conditions of Goel *et al.*[2] The product was found to be mixed up with the unchanged flavanone and was difficult to purify. This may explain the lower m.p. recorded by Goel *et al.* When acetic acid was used as solvent, the product was obtained pure and in good yields. The iodo compound remained unaffected with pyridine and it gave with alkali only 2′-hydroxy-3′-iodo-4′, 6-′-dimethoxychalkone[11] (III *b*). The formation of the 3′-iodo-chalkone showed that iodination had occurred in the 8-position of the flavanone yielding (II *b*). While the above experiments were in progress, a paper by Keogh *et al.*[13] appeared on the above reaction. These results are in accord with ours.

Since 7-methoxyflavanone did not undergo any change with iodine and silver acetate but 5, 7-dimethoxyflavanone reacted, it appeared that the presence of 5-methoxyl was essential. Therefore, 5-methoxyflavanone (I *c*)[14] was examined. In fact it did undergo reaction and the product was only a single entity. That iodination did not take place in the pyranone ring was proved by the fact that it was recovered unchanged by the action of pyridine. Of the two aromatic positions 6 and 8 available for iodination, 8 is preferred in analogy with the earlier observation that bromination of 5-hydroxy flavone gives only 8-bromo compound.[14a] That methoxy flavanones undergo nuclear halogenation finds support also from the reaction with *N*-bromo-succinimide when nuclear brominated compounds result.[15–17]

2. *Reactions of 5-hydroxy-7-methoxyflavanones*

Partial methyl ethers of flavanones with free 5-hydroxyl are found to behave differently. 7, 4′-Di-*O*-methyl naringenin[18] (IV *a*) was first subjected to the iodination reaction in acetic acid medium. The product was found to be a mixture of two compounds separable by crystallisation. Both of them had iodine. The major component was identified as 3-iodo-5-hydroxy-7, 4′-dimethoxyflavanone (V *a*) since it yielded 7, 4′-di-*O*-methyl apigenin (VII *a*)[19] on treatment with dry pyridine. The minor product was found to contain idoine in the 8-position because it remained unchanged with pyridine. Its structure as 8-iodo-5-hydroxy-7, 4′-dimethoxyflavanone (VI *a*) was established by direct comparison with the synthetic compound obtained from (II *a*) by partial demethylation with anhydrous aluminium chloride in dry ether medium,



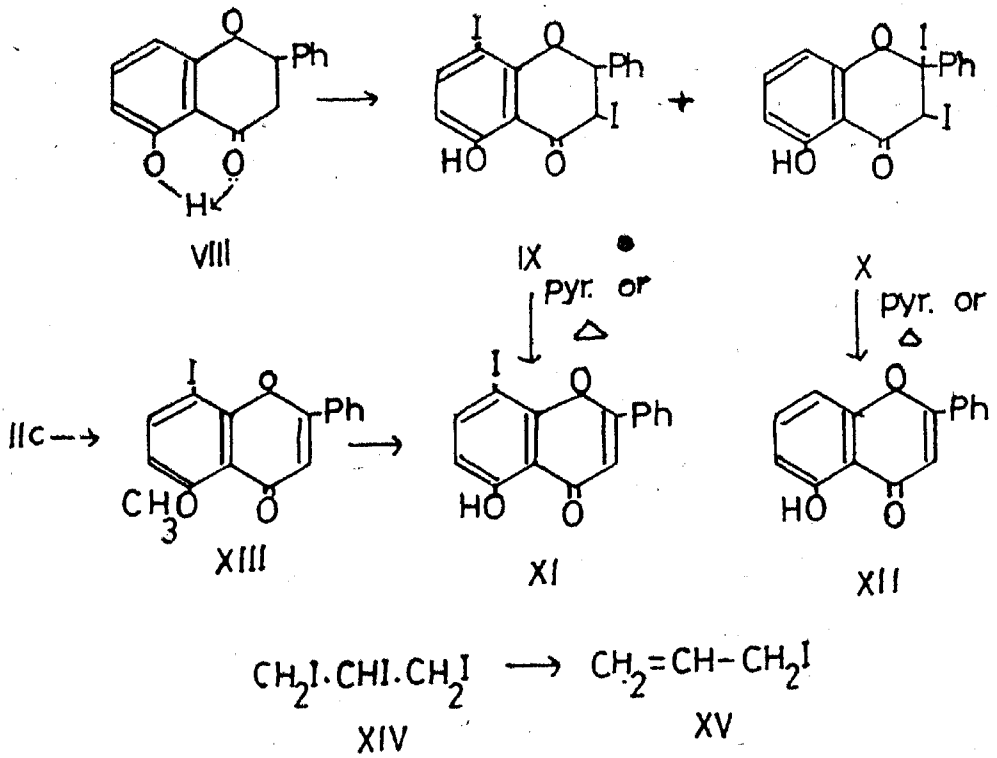
When the above experiment of iodination was repeated in ethanolic solution according to the conditions of Goel *et al.*, the same mixture was obtained as mentioned above. Earlier they recorded only one product, *viz.*, 3-iodo-compound but it should have been contaminated by the 8-iodo-compound as shown by the difference in melting point.

Similar results were obtained in the case of 5-hydroxy-7-methoxyflavanone (IV *b*).[20] Thus a mixture of 3-iodo-(V *b*) and 8-iodo-(VI *b*) derivatives was obtained; the former was identified by its conversion into 5-hydroxy-7-methoxyflavone[21] (VII *b*) and the latter by direct comparison with a synthetic sample obtained from (II *b*).

3. *Reaction with 5-hydroxyflavanone (VIII)*

The above results revealed the importance of a free 5-hydroxyl in flavanones for iodination to take place in the 3-position. To test this point, simple 5-hydroxyflavanone[18] (VIII) was studied. It afforded a mixture of two di-iodo compounds in almost equal amounts. One of them proved to be 3, 8-di-iodo compound (IX) because the action of pyridine yielded 8-iodo-5-hydroxyflavone (XI) identical with the synthetic sample obtained by dehydrogenation and subsequent demethylation of 8-iodo-5-methoxyflavanone (II *c*). The other compound had both the iodine atoms in the pyranone ring since reaction with pyridine gave 5-hydroxyflavone[22] (XII), identical with an authentic sample. Since iodine sublimes at its m.p., two

iodine atoms could be in 2 and 3 positions and the iodinated product would have structure (X). Such iodination in the 2-position seems to be possible because of activation by the phenyl ring. The facile 2, 3 deiodination finds analogy in the formation of allyl iodide from glycerol and hydriodic acid where 1, 2, 3-tri-iodopropane (XIV) is the intermediate product, and the quantitative formation of ethylene and iodine from di-iodo-ethane in aqueous alcoholic solution containing potassium iodide.[23]



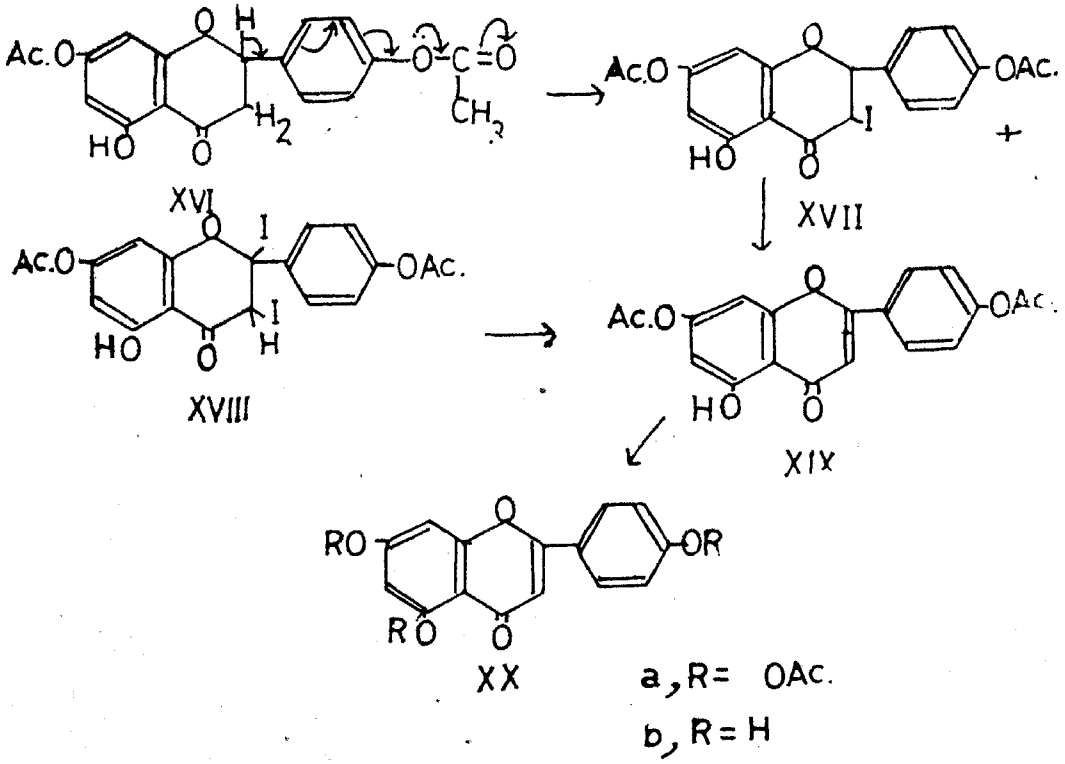
$$CH_2I.CHI.CH_2I \longrightarrow CH_2=CH-CH_2I$$

XIV XV

4. *Reaction of* 7, 4′-di-*O-acetyl naringenin* (*XVI*)

From the above experiments, it became clear that a free 5-hydroxyl is necessary for iodination in the pyranone ring of the flavanone molecule. Since nuclear iodination could be inhibited by protecting other hydroxyls of ring A by acetylation, it was expected that 7, 4′-di-*O*-acetyl naringenin (XVI)[24] could give compounds iodinated exclusively in the pyranone ring. Indeed it has been found to be the case. Chloroform and acetic acid were used separately as solvents; the latter was found to give better yields but some caution had to be taken in the working up of the product. The reaction mixture should be diluted with water rather than concentrated, since the heating introduced further changes.

The product from 7, 4′-di-*O*-acetyl naringenin (XVI) was a mixture of two iodo compounds. The major product analysed for a di-iodoflavanone derivative and on treatment with pyridine, it gave 7, 4′-di-*O*-acetyl apigenin (XIX)[25] which was unambiguously characterised by preparing its complete acetate (XX *a*),[16] by deacetylation to apigenin[16] (XX *b*) and partial methylation to 7, 4′-di-*O*-methyl apigenin[19] (VII *a*). This showed that both the iodine atoms had entered the hetero ring and just as in the case of 5-hydroxyflavanone (VIII), two iodine atoms could be in the 2, 3-positions (*see* XVIII). Iodination in the 2-position is more facile here than in other cases because of the influence of the 4′-acetoxyl group which is electron withdrawing [*see* formula (XVI)]. The minor fraction in the above reaction was identified as 3-iodo-7, 4′-di-*O*-acetyl naringenin (XVII) because it yielded the same 7, 4′-di-*O*-acetyl apigenin (XIX) on treatment with pyridine as in the above case.



DISCUSSION

From the above experiments, it may be inferred that iodine and silver acetate constitute a source of iodonium ions as shown in the equation given below and the reaction with flavanones is very much dependent on

the substituents present. No reaction occurs if there is no substituent at all in the ring A and if 7-position alone is substituted by any group. But iodination occurs if 5-hydroxy and 5-methoxy groups are present. Even here no reaction occurs if 7-hydroxyl is also present free. Probably the 7-hydroxyl being markedly acidic forms the silver salt and subsequently reduces all the reactivity, aromatic as well as of the pyranone ring. Aromatic iodination is promoted by a 5-methoxyl group in the ring A. 5-Hydroxy-7-methoxy compounds yield mixtures containing both aromatic and pyranone substitution. Aromatic iodination can be avoided if partial acetates are taken just as in 7-acetoxy-5-hydroxyflavanone. The favourable influence of the 5-hydroxyl for the iodination of pyranone ring seems to be the chelation which increases methylene reactivity in the 3-position (*see* XVI).

Perhaps this is the first time that electrophilic substitution of the 2-position in a flavanone has been met with. But this takes place only after the 3-position has undergone earlier substitution. Though even in the original flavanone the effect of the phenyl group may activate the 2-position (benzylic position), this is obviously not enough particularly because of the existing oxygen substitution. The presence of iodine in 3-position seems to increase the activity of the 2-position sufficiently to produce iodination. As already mentioned an acetoxyl in the 4-position has also a favourable effect.

$$I_2 + AgOAC \longrightarrow I^+ + (OAC)^- + AgI.$$

Experimental

Unless otherwise stated, U.V. spectra were measured in absolute ethanolic solution and I.R. spectra using nujol mull; m.p.'s are uncorrected; light petroleum used had the boiling range 40–60°.

Reaction of 5, 7, 4′-*trimethoxyflavanone* (*I* a) *to yield* 8-*iodo*-5, 7, 4′-*trimethoxyflavanone* (*II* a)

The flavanone[10] (I *a*, 0·5 g.) was dissolved in glacial acetic acid (20 ml.) and fine, powdered and dried silver acetate (1 g.) added. The mixture was treated with a solution of iodine (0·42 g.) in glacial acetic acid (30 ml.) at room temperature with constant stirring and product allowed to stand overnight. Silver salts were filtered and the filtrate concentrated under reduced pressure when a pale yellow solid (0·6 g.) separated. It crystallised from ethyl acetate-light petroleum mixture as colourless silky needles (0·45 g.),

m.p. 205–06°, $\lambda_{max.}$ 286, 325 mμ (log ε 4·17, 4·07 respectively) (Found: C, 48·9; H, 4·2. $C_{18}H_{17}IO_5$ requires: C, 49·1; H, 3·9%).

The above iodoflavanone (II *a*, 0·2 g.) was heated with ethanolic potash (5 ml.; 4%) for 10 min. on a boiling water-bath, cooled and acidified. The precipitate was filtered and crystallised from ethanol when 2′-hydroxy-3′-iodo-4, 4′, 6′-trimethoxychalkone (III *a*) separated as orange-yellow needles (0·15 g.), m.p. 180–81° (lit.[11], m.p. 178–79°); purple brown ferric reaction, $\lambda_{max.}$ 371 mμ (log ε 4·56) (Found: C, 48·9; H, 4·0. Calculated for $C_{18}H_{17}IO_5$: C, 49·1; H, 3·9%).

Reaction of 5, 7-*dimethoxyflavanone* (*I* b) *to yield* 8-*iodo*-5, 7-*dimethoxyflavanone* (*II* b)

(*a*) *Using ethanol.*—The flavanone[12] (I *b*; 0·5 g.) was reacted under the conditions reported by Goel *et al.*[2] The product (m.p. 140–60°) was fractionally crystallised from ethanol. The first crop (mother liquor A) separated as colourless needles (0·15 g.), m.p. 198–99° (Keogh *et al.*[13] reported 198–200° as the m.p. for the 8-iodo derivative, II *b*). Potash treatment yielded 2′-hydroxy-3′-iodo-4′, 6′-dimethoxy chalkone (III *b*) as yellow needles, m.p. 170–71° (lit.[11], m.p. 170°). The mother liquor (A) yielded unchanged 5, 7-dimethoxyflavanone (I *b*) (0·3 g.), m.p. 141°.

(*b*) *Using acetic acid.*—When the flavanone (I *b*; 0·5 g.) was reacted with iodine and silver acetate in acetic acid medium as mentioned for tri-*O*-methyl naringenin, the product was entirely 8-iodo-5, 7-dimethoxyflavanone (II *b*; 0·45 g.), m.p. and mixed m.p. with the above sample 198–99°.

Reaction of 5-*Methoxyflavanone* (*I* c) *to Yield* 8-*Iodo*-5-*Methoxyflavanone* (*II* c)

The flavanone[14] (I c; 1 g.) was treated with iodine (0·85 g.), silver acetate (2 g.) and glacial acetic acid (100 ml.). The product was crystallised from ethyl acetate-light petroleum mixture when 8-iodo-5-methoxyflavanone (II *c*) separated as colourless broad prisms (0·9 g.), m.p. 151–52° (Found: C, 50·7; H, 3·6. $C_{16}H_{13}IO_3$ requires: C, 50·5; H, 3·4%). When it (0·2 g.) was heated with pyridine (10 ml.) on a boiling water-bath for 2 hr., it was recovered unchanged.

Reactions of 5-*hydroxyflavanones.* (*i*) *Reaction of* 7, 4′-*di*-O-*methyl naringenin* (*IV* a) *to yield* 3-*iodo*-(*V* a) *and* 8-*iodo*-(*VI* a)-7, 4′-*dimethyl naringenins*

(*a*) *Using acetic acid.*—The flavanone[18] (IV *a*) (0·7 g.) in glacial acetic acid (20 ml.) was treated with silver acetate (1·4 g.) and iodine (0·65 g.)

in glacial acetic acid. The product (0·8 g.) melted between 120–135° and was a mixture and the separation was brought about by boiling with methanol (40 ml.). The insoluble residue (0·3 g.) (Methanolic mother liquor A) crystallised from ethyl acetate-light petroleum yielding the 8-iodo derivative (VI *a*) as colourless prisms (0·2 g.), m.p. 177–78°; violet ferric reaction (Found: C, 47·5; H, 3·5. $C_{17}H_{15}IO_5$ requires: C, 47·9; H, 3·5%). An authentic sample of 8-iodo-7, 4′-di-*O*-methyl naringenin was prepared as follows:

8-Iodo-5, 7, 4′-trimethoxyflavanone (II *a*; 0·3 g.) was suspended in dry ether (25 ml.) and treated with a solution of anhydrous aluminium chloride (1·5 g.) in ether (25 ml.). The solution was kept at room temperature with occasional shaking. Ether was removed and the complex decomposed with dilute hydrochloric acid. The solid (100 mg.) crystallised from ethyl acetate-light petroleum mixture as colourless prisms (60 mg.), m.p. 177-78°, undepressed by the above sample obtained by iodination.

The methanolic mother liquor A on concentration and cooling yielded a second product which was filtered. It crystallised from ethyl acetate-light petroleum mixture yielding 3-iodo-7, 4′-di-*O*-methyl naringenin (V *a*) as pale yellow needles (0·46 g.), m.p. 148–49°, purple ferric reaction. (Found: C, 47·9; H, 3·9. $C_{17}H_{15}IO_5$ requires: C, 47·9; H, 3·5%.)

The above 3-iodoflavanone (0·1 g.) was heated with pyridine (5 ml.) on a boiling water-bath for 2 hr., diluted with water (50 ml.) and the solid product filtered and washed first with dilute hydrochloric acid and then with water. When crystallised from ethanol it yielded apigenin-7, 4′-dimethyl ether (VII *a*; 50 mg.) as very pale yellow needles, m.p. 170–71° (lit.[19], m.p. 173°).

(*b*) *Using absolute ethanol.*—When the above iodination was carried out using absolute ethanol according to the procedure of Goel, Mahesh and Seshadri,[2] the product was the same mixture yielding 8-iodo (VI *a*, 0·15 g.) and 3-iodo-compounds (V *a*; 0·3 g.).

(*ii*) *Reaction of 5-hydroxy-7-methoxyflavanone* (*IV* b) *to yield 3-iodo* (*V* b) *and 8-iodo-*(*VI* b) *derivatives*

The flavanone[20] (IV *b*, 0·8 g.) when treated with iodine (0·7 g.) and silver acetate (1·6 g.) in glacial acetic acid (100 ml.) gave a product melting in the range 80–115°. This mixture was separated by boiling with methanol (30 ml.). The insoluble residue crystallised from ethyl acetate-light petroleum mixture yielding 8-iodo-5-hydroxy-7-methoxyflavanone (VI *b*; 0·3 g.)

as colourless needles, m.p. 155–56°; purple violet ferric reaction (Found: C, 48·4; H, 3·5. $C_{16}H_{13}IO_4$ requires: C, 48·5; H, 3·3%). An authentic sample was prepared from 8-iodo-5, 7-dimethoxyflavanone (II *b*; 0·3 g.) which was subjected to partial demethylation using anhydrous aluminium chloride (1·5 g.) and ether (50 ml.). 8-Iodo-5-hydroxy-7-methoxyflavanone separated as colourless needles (0·1 g.), m p. 155–56°, undepressed by the above sample obtained by iodination.

The methanolic solution when concentrated and cooled yielded 3-iodo-5-hydroxy-7-methoxyflavanone (V *b*) which crystallised from ethyl acetate-light petroleum mixture as pale yellow needles (0·25 g.), m.p. 125–26°, deep purple ferric reaction (Found: C, 48·3; H, 3·4. $C_{16}H_{13}IO_4$ requires: C, 48·5; H, 3·3%). This iodoflavanone (0·1 g.) was heated with pyridine (5 ml.) on a boiling water-bath for 2 hr. and diluted with water (50 ml.). The product crystallised from ethanol giving tectochrysin (VII *b*) as pale yellow needles (50 mg.), m.p. 165–66° (lit.[21], m.p. 163°), $\lambda_{max.}$ 269 mμ (log ε 4·21).

(*iii*) *Reaction of 5-hydroxyflavanone (VIII) to yield 2, 3-di-iodo (X) and 3, 8-di-iodo (IX)-5-hydroxyflavanones*

5-Hydroxyflavanone[18] (VIII; 1 g.) was treated with iodine (0·8 g.) and silver acetate (2 g.) and glacial acetic acid (100 ml.). The product melted between 100–135° and was separated by boiling with benzene (25 ml.). The insoluble residue (0·5 g.) crystallised from ethyl acetate-light petroleum mixture yielding 3, 8-di-iodo derivative (IX) as colourless needles (0·4 g.), m.p. 207–08°, purple ferric reaction (Found: C, 36·4; H, 2·2. $C_{15}H_{10}I_2O_3$ requires: C, 36·6; H, 2·0%).

The benzene mother liquor on concentration and cooling yielded a solid which was filtered and crystallised from ethyl acetate-light petroleum mixture yielding pale yellow needles of 2, 3-di-iodo-5-hydroxyflavanone (X) (0·3 g.), m.p. 110–11°, purple-violet ferric reaction (Found: C, 36·5; H, 2·2. $C_{15}H_{10}I_2O_3$ requires: C, 36·6; H, 2·0%).

Action of pyridine

(*i*) *On 2, 3-di-iodo flavanone (X).*—The di-iodo flavanone (X; 0·2 g.) was heated with pyridine (10 ml.) on a boiling water-bath for 2 hr. The product was crystallised from ethyl acetate-light petroleum mixture when 5-hydroxyflavone (XII) separated as pale yellow needles (0·1 g.), m.p. 157° (lit.[22], m.p. 156-57°) $\lambda_{max.}$ 270 mμ (Found: C, 75·5; H, 4·4. Calculated for $C_{15}H_{10}O_3$: C, 75·6; H, 4·2%).

(*ii*) *On* 3, 8-*di-iodo compound* (*IX*).—The product obtained by treating the di-iodoflavanone (IX) with pyridine (10 ml.) crystallised from ethyl acetate-light petroleum mixture as lemon-yellow needles, m.p. 240–42°, $\lambda_{max.}$ 274 mμ (Found: C, 49·3; H, 2·5. $C_{15}H_9IO_3$ requires: C, 49·5; H, 2·5%). It agreed with 8-iodo-5-hydroxyflavone, an authentic sample of which was prepared as given below.

A solution of 5-methoxy-8-iodoflavanone (II C; 200 mg.) in glacial acetic acid (15 ml.) was refluxed with anhydrous potassium acetate (0·5 g.) and iodine (0·1 g.) for 2 hr. Acetic acid was distilled under reduced pressure and sulphurous acid (20 ml.) added. The resulting mixture was extracted with ether; ether residue yielded after crystallisation from ethyl acetate-light petroleum mixture colourless needles of (XIII) (100 mg.), m.p. 110–12°, $\lambda_{max.}$ 229, 294 mμ (log ϵ 4·27, 4·29 respectively) (Found: C, 50·7; H, 3·0. $C_{16}H_{11}IO_3$ requires: C, 50·8; H, 2·9%). It (50 mg.) was subjected to partial demethylation using anhydrous aluminium chloride (0·5 g.) and ether (50 ml.) and the product crystallised from ether-light petroleum mixture when 5-hydroxy-8-iodoflavone (XI) separated as pale yellow needles, m.p. 240–42°.

Reaction of naringenin-7, 4′-diacetate (*XVI*) *to yield* 3-*iodo-*(*XVII*) *and* 2, 3-*di-iodo* (*XVIII*) *naringenin* 7, 4′-*diacetates*

The flavanone diacetate[24] (XVI, 1 g.) was treated with iodine (0·85 g.), silver acetate (2 g.) and glacial acetic acid (100 ml.). Water was added to precipitate the reaction products instead of distilling off the solvent under vacuum. The mixture (0·8 g.) was subjected to fractional crystallisation using ethyl acetate. The first crop gave pale yellow prisms (0·6 g.) which proved to be 2, 3-di-iodo derivative (XVIII), m.p. 218–19°, $\lambda_{max.}$ 285, 350 mμ (log ϵ 3·88, 3·83 respectively), $\nu_{max.}$ 1750 (acetate C=0), 1650 cm.$^{-1}$ (chelated C = 0) (Found: C, 37·8; H, 2·6. $C_{19}H_{14}I_2O_7$ requires: C, 37·5; H, 2·3%).

The ethyl acetate mother liquor on concentration gave the 3-iodo compound (XVII; 0·1 g.), m.p. 181–82°, $\lambda_{max.}$ 285, 335 mμ (log ϵ 3·82, 3·95 respectively), $\nu_{max.}$ 1750 (acetate C = 0) and 1650 cm.$^{-1}$ (chelate C = 0) (Found: C, 47·2; H, 3·2. $C_{19}H_{15}IO_7$ requires: C, 47·2; H, 2·8%).

The above iodoflavanones (0·2 g.) were separately heated with pyridine (10 ml.) on boiling water-bath for 2 hr. The product was the same in both cases. It was crystallised first from ethyl acetate-light petroleum mixture and then from methanol when apigenin-7, 4′-diacetate (XIX) appeared as

pale yellow needles (0·1 g.), m.p. 207–08° (lit.[25], 192–93°), $\lambda_{max.}$ 270, 325 mμ (log ε 3·9, 2·56 respectively), $\nu_{max.}$ 1760 (acetate C = 0) and 1660 cm.$^{-1}$ (chelated C = 0) (Found: C, 64·5; H, 4·0. $C_{19}H_{14}O_7$ requires: C, 64·3; H, 4·0%).

The diacetate (XIX; 20 mg.) was acetylated completely by boiling with acetic anhydride (3 ml.) and pyridine (2 drops) for 1 hr. and the product crystallised from ethanol when apigenin triacetate (XX *a*) separated as colourless needles, m.p. 185–86° (lit.[16], m.p. 186–87°), no ferric reaction (Found: C, 63·6; H, 4·3. Calculated for $C_{21}H_{16}O_8$: C, 63·6; H, 4·1%).

The diacetate (XIX) was deacetylated by boiling with ethanolic hydrochloric acid (2 hr.) when apigenin (XX *b*) crystallised as yellow needles, m.p. 349–51° (d.) (lit.[16], m.p. 350–52° d.) purple ferric reaction.

Apigenin (XX *b*) as obtained above was methylated by boiling with 2 moles of dimethyl sulphate in the presence of potassium carbonate and acetone for 6 hr. Apigenin 7, 4′-dimethyl ether (VII *a*) crystallised as lemon-yellow needles, m.p. 170–71° (lit.[19], m.p. 173°).

SUMMARY

For the action of iodine and silver acetate on flavanones to take place, the nature and position of substituents are important. The presence of either a 5-hydroxyl or a 5-methoxyl is essential for any reaction to occur. A free hydroxyl in the 7-position is inhibitory even for iodination of 5-hydroxyflavanone derivatives. Complete methyl ethers yield 8-iodo-compounds; whereas 5-hydroxy-7-methoxyflavanones afford a mixture of 3-iodo and 8-iodo derivatives. Simple 5-hydroxy-flavanone forms 3, 8-di-iodo and 2, 3-di-iodo-5-hydroxy flavanones. 5-Hydroxy-7, 4′-diacetoxy-flavanone undergoes iodination only in the pyranone part to yield 2, 3-di-iodo and 3-iodo derivatives; substitution in the benzene ring is inhibited. It is suggested that the 5-hydroxyl by chelation with the carbonyl increases the activity of the methylene group in the 3-position.

REFERENCES

1. Goel, O. P., Narasimhachari, N. and Seshadri, T. R. — *Proc. Ind. Acad. Sci.*, 1954, **39** A, 254.
2. Goel, R. N., Mahesh, V. B. and Seshadri, T. R. — *Ibid.*, 1958, **47** A, 184.

3. Kostanecki, S. von and Lampe, V. — *Ber. Dtsch. Chem. Ges.*, 1904, **37**, 773, 1402.
4. Ryan, H. and Cru ess-Callaghan, G. — *Proc. Royal Irish Acad.*, 1929, **39 B**, 124.
5. Zemplen, G. and Bognar, R. — *Ber. Dtsch. Chem. Ges.*, 1943, **76**, 452.
6. Narasimhachari, N. and Seshadri, T. R. — *Proc. Ind. Acad. Sci.*, 1949, **30 A**, 151.
7. Mahesh, V. B. and Seshadri, T. R. — *Ibid.*, 1955, **41 A**, 210.
8. Goel, R. N. and Seshadri, T. R. — *Ibid.*, 1958, **47 A**, 191.
9. ———— .. — *Tetrahedron*, 1959, **5**, 91.
10. Kostanecki, S. von, Lampe, V. and Tambor, J. — *Ber. Dtsch. Chem. Ges.*, 1904, **37**, 2096.
11. Chen, F. C., Chang, C. T. and Chen, T. S. — *J. Org. Chem.*, 1962, **27**, 85.
11*a*. Nakazawa, K. and Ito, M. — *Chem. Pharm. Bull.*, 1963, **11**, 283.
12. Rao, K. V. and Seshadri, T. R. — *Proc. Ind. Acad. Sci.*, 1946, **23 A**, 213.
13. Keogh, E. J., Philbin, E. M., Ushioda, S. and Wheeler, T. S. — *J. Chem. Soc. London*, 1963, p. 5271.
14. Seshadri, T. R. and Venkateswarlu, V. — *Proc. Ind. Acad. Sci.*, 1947, **26 A**, 189.
14*a*. Mc Cusker, P. E., Philbin, E. M. and Wheeler, T. S. — *J. Chem. Soc. London*, 1963, p. 2374.
15. Bannerji, N. R. and Seshadri, T. R. — *Proc. Ind. Acad. Sci.*, 1952, **36 A**, 134.
16. Looker, J. H. and Holm, J. M. — *J. Org. Chem.*, 1959, **24**, 567.
17. Chen, T. S., Liu, Y. S. and Chen, F. C. — *Formosan Sci.*, 1962, **16**, 31; *Chem. Abst.*, 1963, **59**, 2759.
18. Aiyer, S. N., Dass, I. and Seshadri, T. R. — *Proc. Ind. Acad. Sci.*, 1957, **46 A**, 238.
19. Hasegawa, M. and Shirato, T. — *J. Amer. Chem. Soc.*, 1955, **77**, 3557.
20. Narasimhachari, N. and Seshadri, T. R. — *Proc. Ind. Acad. Sci.*, 1948, **27 A**, 234.

21. Hasegawa, M. — *J. Amer. Chem. Soc.*, 1958, **79**, 1738.

22. Rao, K. V., Rajagopalan, S. and Seshadri, T. R. — *Proc. Ind. Acad. Sci.*, 1947, **25** A, 436.

23. Slator, A. .. — *J. Chem. Soc.*, 1904, **85**, 1697.

24. Mahesh, V. B., Neelakantan, S. and Seshadri, T. R. — *J. Sci. and Ind. Res. (India)*, 1956, **15 B**, 287.

25. Simokoriyama, M. .. — *Bull. Chem. Soc. Japan*, 1941, **16**, 284.

26. Nesmeyanov, N. A. and Reutov, O. A. — *Tetrahedron*, 1964, **20**, 2803.

655–65. Printed at The Bangalore Press, Mysore Road, Bangalore City, by K. V. Varadarajan, Manager, and Published by B. S. Venkatachar, Editor, "Proceedings of the Indian Academy of Sciences," Bangalore