771. *Rearrangement in the Demethylation of 2'-Methoxyflavones.*

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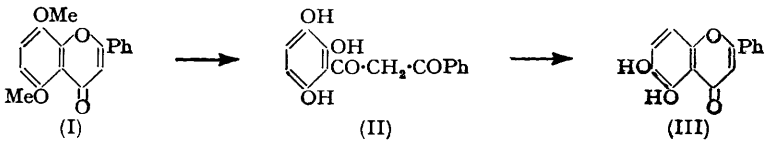
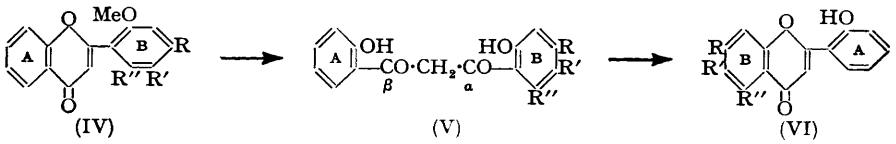
Certain 2'-methoxyflavones rearrange during demethylation by hydriodic acid under sufficiently drastic conditions, to give the related 2'-hydroxyflavones in which the 2-phenyl group and the fused aromatic ring of the original flavone are interchanged. Demethylation by aluminium chloride does not produce rearrangement. The more stable of each pair of related 2'-hydroxyflavones investigated is that in which the 2-phenyl side chain contains the smaller number of hydroxyl groups.

Shah, Mehta, and Wheeler (*J.*, 1938, 1555) suggested that a diketone of the benzoyl-γ-resorcyloylmethane type (II) was intermediate in the production of 5 : 6-dihydroxyflavones, *e.g.*, (III), by demethylation by hydriodic or hydrobromic acid of 5 : 8-dimethoxyflavones, *e.g.*, (I) (see Wessely and Moser, *Monatsh.*, 1930, **56**, 97). In agreement with this mechanism of decyclisation to a diketone, and recyclization on a second *o*-hydroxyl group, it has now



been found (see Philbin and Wheeler, *Chem. and Ind.*, 1952, 449) that some 2'-methoxyflavones (IV), when demethylated by hydriodic acid under sufficiently drastic conditions, yield by rearrangement the corresponding 2'-hydroxyflavones (VI) with, presumably, intermediate formation of a diketone of the disalicyloylmethane type (V). The methoxyflavones corresponding to (VI) did not rearrange under similar conditions.



	R	R′	R″
(IV*a*) 2' : 5'-Dimethoxyflavone...	H	OMe	H
(IV*b*) 2' : 4'- „ ...	OMe	H	H
(IV*c*) 2' : 6'- „ ...	H	H	OMe
(IV*d*) 2' : 4' : 6'-Trimethoxyflavone	OMe	H	OMe

5'-Bromo- and 5'-chloro-2' : 4'-dimethoxyflavone rearranged to (VI*b*) on demethylation by hydriodic acid under suitable conditions.

	R	R′	R″
(VI*a*) 6 : 2'-Dihydroxyflavone...	H	OH	H
(VI*b*) 7 : 2'- „ ...	OH	H	H
(VI*c*) 5 : 2'- „ ...	H	H	OH
(VI*d*) 5 : 7 : 2'-Trihydroxyflavone	HO	H	OH

The corresponding methoxyflavones did not rearrange when demethylated by hydriodic acid.

Preparation of 2'-Methoxyflavones.—Authentic specimens of 2'-methoxyflavones corresponding to (IV) and (VI) were prepared for the demethylation experiments. The majority of them were obtained by the Baker–Venkataraman method from the appropriate *o*-aroyloxyacetophenones with the usual satisfactory yields. 2' : 6'-Dimethoxyflavone (IV*c*) and 2' : 4' : 6'-trimethoxyflavone (IV*d*) were synthesised by debenzylation and cyclisation of the related *O*-benzylsalicyloyl-di- or -tri-methoxybenzoylmethane. 2' : 4'-Dimethoxyflavone (IV*b*) was prepared from the corresponding chalkone by treatment with selenium dioxide (Mahal, Rai, and Venkataraman, *J.*, 1935, 866); the action of phosphorus pentachloride on the flavanone, as employed by Hattori (*Acta Phytochim., Tokyo*, 1932, **6**, 152) gave, in our hands, 5'-chloro-2' : 4'-dimethoxyflavone. The structure of this flavone was established by analogy with 5'-bromo-2' : 4'-dimethoxyflavone, which was obtained by the action of ethanolic potassium cyanide on 2-acetoxyphenyl 1 : 2-dibromo-2-(5-bromo-2 : 4-dimethoxyphenyl)ethyl ketone (see Hutchins and Wheeler, *J.*, 1939, **91**).

The position of the bromine atom was determined by alkaline hydrolysis of the flavone which yielded 5-bromo-2 : 4-dimethoxybenzoic acid.

Demethylation by Aluminium Chloride.—The 2'-methoxyflavones, with the exceptions discussed below, were smoothly demethylated by aluminium chloride in benzene to the corresponding hydroxyflavones (Narasimhachari, Sastri, and Seshadri, *Proc. Indian Acad. Sci.*, 1949, **29***A*, 404). The absence of rearrangement during such demethylation was established by remethylation to the original methoxyflavone. Nitrobenzene was used in place of benzene as a solvent with 6 : 2'-dimethoxyflavone. Reaction was sluggish, and 6-hydroxy-2'-methoxyflavone was found with the dihydroxyflavone in the product. The structure of the hydroxymethoxyflavone was established by alkaline hydrolysis, which gave *o*-anisic acid, and by an unambiguous synthesis, using the Baker–Venkataraman method, from 2 : 5-di-*o*-anisoyloxyacetophenone.

Two anomalous results were obtained by aluminium chloride demethylation. 2' : 4' : 6'-Trimethoxyflavone (IV*d*) gave with this reagent, in benzene, 2' : 4' : 6'-trihydroxy-3' : 5'-diphenylflavone. The structure assigned to this diphenyl compound is based on the following considerations : (1) its analysis and the analysis of the triacetate; (2) the absence of a 5-hydroxyl group (no colour with ethanolic ferric chloride)—this shows that no rearrangement to a 5 : 7 : 2'-trihydroxyflavone occurred on demethylation with aluminium chloride; (3) the compound yielded salicylic acid on alkaline hydrolysis, showing that these hydroxyl and the two phenyl groups are in the one nucleus. The production of diphenyl compounds by intermolecular dehydrogenation under the action of aluminium chloride in benzene has previously been observed (see Thomas, " Anhydrous Aluminium Chloride in Organic Chemistry," Reinhold Publ. Corp., New York, 1941, pp. 658, 712). Normal demethylation was effected with mesitylene as a solvent. This hydrocarbon is, presumably, sterically hindered from condensation. The use of nitrobenzene as a solvent did not give satisfactory results.

Again, 5'-bromo-2' : 4'-dimethoxyflavone gave 2' : 4'-dihydroxyflavone by treatment with aluminium chloride in benzene. Examples of such debromination with formation of bromobenzene are known (Thomas, *op. cit.*, p. 693).*

Demethylation by Hydriodic Acid.—2' : 5'-Dimethoxyflavone (IV*a*), when heated with hydriodic acid in phenol under pressure, gave 6 : 2'-dihydroxyflavone (VI*a*). The identity of the product was confirmed by examination of its ultra-violet absorption spectrum and by preparation of the diacetate and dimethyl ether. Less drastic conditions of demethylation yielded mixtures of 2' : 5'- and 6 : 2'-dihydroxyflavone. Treatment with sulphuric acid (70%) at the boiling point (cf. Ozawa, Okuda, Kawanishi, and Fujii, *J. Pharm. Soc. Japan*, 1951, **71**, 1178) converted 2' : 5'-dimethoxyflavone into 6 : 2'-dihydroxyflavone. 2' : 5'-Dihydroxyflavone rearranged with hydriodic acid under the same conditions as its dimethyl ether, while 6 : 2'-dimethoxyflavone was demethylated without rearrangement. Kostanecki and Seifart (*Ber.*, 1900, **33**, 2510) obtained 6 : 2'-diethoxyflavone in a pure state by re-ethylation of 6 : 2'-dihydroxyflavone prepared by the action of boiling hydriodic acid on an impure specimen of the diethyl ether.

2' : 4'-Dimethoxyflavone (IV*b*) and the 5'-chloro- and the 5'-bromo-derivative rearranged to yield 7 : 2'-dihydroxyflavone (VI*b*) when demethylated under pressure at above 200°. Under milder conditions, 2' : 4'-dihydroxyflavone was obtained. The 7 : 2'-dimethyl ether did not rearrange when demethylated under pressure. Kostanecki and Salis (*Ber.*, 1899, **32**, 1034) re-ethylated 7 : 2'-dihydroxyflavone which they had prepared from an impure specimen of the diethyl ether by treatment with boiling concentrated hydriodic acid, and obtained 7 : 2'-diethoxyflavone in a pure state.

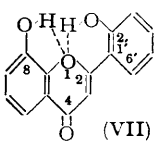
2' : 6'-Dimethoxyflavone (IV*c*) and 2' : 4' : 6'-trimethoxyflavone (IV*d*) rearranged completely on demethylation, even at atmospheric pressure, to yield the hydroxyflavones (VI*c*) and (VI*d*), respectively. The methyl ethers of the last two hydroxyflavones did not rearrange.

Discussion of Results.—This work shows that, for the compounds examined, the more stable of each flavone pair related to a diketone of the type (V) is that in which the 2-

* [Added, Oct. 13th, 1953.] See Fairbrother and Scott (*Chem. and Ind.*, 1953, 998).

phenyl side chain contains the smaller number of hydroxyl groups. This result agrees with earlier work on the cyclisation of disalicyloylmethane dialkyl ethers. Kostanecki and Webel (*Ber.*, 1901, **34**, 1454) found that *O*-ethylsalicyloyl-2 : 4 : 6-trimethoxybenzoylmethane yielded 5 : 7 : 2′- and not 2′ : 4′ : 6′-trihydroxy-flavone on treatment with hydriodic acid. Hattori (*Acta Phytochim., Tokyo*, 1932, **6**, 147) showed that *o*-anisoyl-2 : 4-dimethoxybenzoylmethane gave similarly 7 : 2′- and not 2′ : 4′-dihydroxyflavone. Cyclisation of (V) is equivalent to esterification and requires enolisation of one of the keto-groups (see Nowlan, Slavin, and Wheeler, *J.*, 1950, 340); this will be hindered at $C_{(\alpha)}$ in (V) by the proximity of ring B which contains anionoid (hydroxyl) groups; cyclisation will, therefore, occur preferentially, though not necessarily exclusively, on $C_{(\beta)}$.

Decyclisation to the corresponding diketone (II or V) of a flavone containing a hydroxyl group in the 8- or 2′-position (see VII) may be promoted by formation of hydrogen bonds between the oxygen atom 1, and those linked at 8 and 2′. The following facts are in line with this suggestion : (*a*) Demethylation precedes decyclisation since the hydroxyflavone is obtained without rearrangement if the conditions of demethylation are sufficiently mild. (*b*) The distances between the oxygen atoms involved are of the order of the hydrogen-bond length. (*c*) The presence of a second hydroxyl group in the 6′-position (see VII) increases the statistical probability of hydrogen bonding; reference has already been made to the ready rearrangement obtained with 2′ : 6′-dimethoxyflavones. (*d*) Rearrangement of a 5 : 8-dihydroxy- or of a 2′-hydroxy-flavone has so far been obtained only in presence of hydrogen ions; that is, with hydrobromic, hydriodic, or aqueous sulphuric acid. The action of pyridine hydrochloride on 5 : 8-dimethoxyflavone yielded 5 : 8-dihydroxyflavone without rearrangement (observation by Mr. M. Doporto working in this laboratory); attempts to demethylate 2′ : 5′-dimethoxyflavone using hydrogen iodide in acetic anhydride gave only tars. The decyclisation reaction is, therefore, analogous to the acid-catalysed hydrolysis of an ester with acyl–oxygen fission [fission of bond 1 : 2 in (VII); see Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686]. It will be promoted by the proton attack involved in hydrogen-bond formation on the ether-oxygen atom 1. The cationoid activity of the carbon atom at position 2 may be still further increased by proton attack on the oxygen atom at position 4. (*e*) Dr. T. H. Simpson (see Simpson and Garden, *J.*, 1952, 4638; Shaw and Simpson, *ibid.*, p. 5027), to whom we are indebted for comments and suggestions, has kindly informed us that a survey of the chromatographic properties of a number of 2′-hydroxyflavones suggests that in simple compounds significant hydrogen bonding occurs between the 2′-hydroxyl group and the pyrone-oxygen atom at position 1.


(VII)

It should be mentioned that while an ether-oxygen atom can form hydrogen bonds (see Murty and Seshadri, *Proc. Indian Acad. Sci.*, 1942, **16***A*, 50) the bonds postulated above are weaker than those involved in the resonance chelation occurring in flavones between the carbonyl oxygen at position 4 and the 5-hydroxyl group. Jain, Seshadri, and Thiruvengadam, *ibid.*, 1952, **36**, *A*, 217) found that the 2′-hydroxyl group in flavonols, unlike the 5-hydroxyl group in flavones, showed no particular resistance to methylation; on the other hand, the 2′-hydroxyl group in flavanones is strongly chelated to the pyranone ether-oxygen atom (Narasimhachari, Rajagopalan, and Seshadri, *ibid.*, p. 231). The difference between the dry and the wet melting points of a series of hydroxyflavones has now been found to be : 5-hydroxy- (chelated), 12°; 7-hydroxy- (no possibility of hydrogen bonding), 50°; 8-hydroxy-, 48°; 2′-hydroxy-, 32°; 2′ : 4′ : 6′-trihydroxy, 65°; 2′ : 4′ : 6′-trihydroxy-3′ : 5′-diphenylflavone, 50°. These depressions show chelation in 5-hydroxyflavone only (see Ferguson, " Electron Structures of Organic Molecules," Prentice-Hall, Inc., New York, 1952, p. 66).

While internal hydrogen bonding is considered to promote hydrolytic fission of the pyrone ring in 8- and 2′-hydroxyflavone, it may not be essential for such fission, as rearrangement has been observed with 5-hydroxy-6- and -8-methylchromones. The results, however, differ from those obtained with 5 : 6- and 5 : 8-dihydroxychromones. For instance, Schmid and Bolleter (*Helv. Chim. Acta*, 1950, **33**, 917) found that 5-hydroxy-7-methoxy-2 : 6-dimethylchromone gave 5 : 7-dihydroxy-2 : 8-dimethylchromone on treat-

ment with hydriodic acid; here the 8-methyl derivative is more stable. Whalley (*Chem. and Ind.*, 1953, 277) obtained some 5 : 7 : 2'-trihydroxy-6-methyl*iso*flavone by the action of aluminium chloride on 5 : 7 : 2'-trimethoxy-8-methyl*iso*flavone. It may be that here direct migration of a methyl group is involved. This is believed to be the only reported instance of aluminium chloride's causing rearrangement of a chromone (Donnelly, Philbin, and Wheeler, *ibid.*, p. 567).

Experimental

Ethanol was employed for crystallisation if no solvent is mentioned.

Preparation of 2'-methoxyflavones, and of the corresponding 2'-hydroxyflavones by demethylation by aluminium chloride.

(1) 2' : 5'-*Dihydroxyflavone.*—o-(2 : 5-*Dimethoxybenzoyloxy*)*acetophenone*, which was prepared by the pyridine–acid chloride method (see Nowlan, Slavin, and Wheeler, *J.*, 1950, 342), crystallised in plates, m. p. 72—73° (Found : C, 67·9; H, 5·5; OMe, 20·6. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3; 2OMe, 20·7%). This ester was shaken in pyridine with powdered potassium hydroxide (1·5 mols.) for 3 hr. and the product was poured on ice and hydrochloric acid. 2 : 5-*Dimethoxybenzoylsalicyloylmethane*, which separated, crystallised in yellow needles (90%), m. p. 84—85° (Found : C, 67·8; H, 5·5; OMe, 20·7%. Required : as for the ester), and gave a green colour with ethanolic ferric chloride. The hydroxydiketone was boiled for 3 min. with glacial acetic acid containing a few drops of hydrochloric acid. 2' : 5'-*Dimethoxyflavone* (IV*a*) was precipitated by controlled addition of water. It crystallised in needles (70%), m. p. 120° (Found : C, 72·1; H, 4·8; OMe, 22·1. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0; 2OMe, 22·0%). This flavone was refluxed ($CaCl_2$ guard) in benzene for 1·5 hr. with anhydrous aluminium chloride (6 parts), and the insoluble residue was treated with ice and dilute hydrochloric acid (10%). After 5 min. the mixture was heated on a steam-bath for 15 min. and cooled. 2' : 5'-*Dihydroxyflavone* crystallised in yellow needles (60%), m. p. 284—285°, which gave a faint green fluorescence in concentrated sulphuric acid (Found : C, 71·1; H, 3·6. $C_{15}H_{10}O_4$ requires C, 70·9; H, 3·9%). The *diacetate* (prepared by sodium acetate–acetic anhydride) crystallised in colourless needles, m. p. 148° (Found : C, 67·2; H, 4·3. $C_{19}H_{14}O_6$ requires C, 67·5; H, 4·1%). For remethylation to confirm the structure, the dihydroxyflavone was refluxed in acetone for 6 hr. with methyl sulphate (10% excess) and potassium carbonate. The mixture was filtered, and the crystals which separated on concentration of the filtrate were extracted with boiling aqueous ethanol. The methoxyflavone which separated (80% yield) did not depress the m. p. of an authentic sample of 2' : 5'-dimethoxyflavone.

The procedure for the hydroxyflavones described at (2), (3), (7), (9), (11) was, unless otherwise stated, as given for 2' : 5'-dihydroxyflavone.

(2) 6 : 2'-*Dihydroxyflavone* (VI*a*).—2-o-*Anisoyloxy*-5-*methoxyacetophenone*, plates, m. p. 82—83° [Found : C, 67·7; H, 5·4; OMe, 20·6. Cf. (1)], o-*anisoyl*-5-*methoxysalicyloylmethane*, pale yellow plates, m. p. 89—91° (ethanolic ferric colour, olive green) (Found: C, 68·1; H, 5·5; OMe, 20·8. Required: as for the ester), and 6 : 2'-*dimethoxyflavone*, needles, m. p. 146° [Found : C, 72·4; H, 4·9; OMe, 21·9. Cf. (1)], were prepared.

The dimethoxyflavone was heated in nitrobenzene with aluminium chloride (1 part) on a steam-bath for 1 hr. The mixture was poured on ice and hydrochloric acid, and nitrobenzene was removed in steam. The precipitate from the aqueous residue was extracted with xylene in a hot Soxhlet apparatus. 6 : 2'-Dihydroxyflavone, which remained as an insoluble residue, crystallised (charcoal) in pale yellow plates, m. p. 300—304°; its diacetate had m. p. 148—149° (Found : C, 67·3; H, 4·1. Calc. for $C_{19}H_{14}O_6$: C, 67·5; H, 4·1%) (Kostanecki and Seifart, *Ber.*, 1900, **33**, 2512; Vyas and Shah, *Proc. Indian Acad. Sci.*, 1951, **33***A*, 114). This dihydroxyflavone and its diacetate showed a brilliant green fluorescence in concentrated sulphuric acid. On remethylation as described at (1) it gave 6 : 2'-dimethoxyflavone (mixed m. p.). The yield of dihydroxyflavone from the dimethoxyflavone was increased by using 5 parts of aluminium chloride and extending the time of heating to 5 hr.

The material soluble in xylene, which was 6-*hydroxy*-2'-*methoxyflavone* [see (3) below], crystallised in needles (25% yield), m. p. 230—232° (Found : C, 71·3; H, 4·5; OMe, 10·9. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5; OMe, 11·6%). To determine its structure, the flavone was refluxed with ethanolic sodium ethoxide until a sample of the reaction mixture did not exhibit a green fluorescence in concentrated sulphuric acid. Ethanol was removed in steam, and the residue was acidified and steam-distilled. *o*-Anisic acid (mixed m. p.) separated from the distillate.

(3) 6-*Hydroxy*-2'-*methoxyflavone*.—2 : 5-*Di*-o-*anisoyloxyacetophenone*, m. p. 98—100° (Found: C, 68·6; H, 4·8; OMe, 14·7. $C_{24}H_{20}O_7$ requires C, 68·6; H, 4·8; 2OMe, 14·8%), and o-*anisoyl*-(5-o-*anisoyloxysalicyloyl*)*methane*, yellow needles, m. p. 123—125° (ethanolic ferric colour, green) (Found: C, 68·3; H, 4·8; OMe, 14·8. Required: as for the ester), were obtained. In one preparation of this diketone in which the mixture of ester, potassium hydroxide, and pyridine was heated on a steam-bath for a few minutes before being shaken at room temperature, it was found necessary to dissolve the crude product in benzene and extract the diketone from the solution by dilute aqueous sodium hydroxide. 6-o-*Anisoyloxy*-2'-*methoxyflavone*, plates, m. p. 160—162° (Found: C, 71·5; H, 4·7; OMe, 15·5. $C_{24}H_{18}O_6$ requires C, 71·6; H, 4·5; 2OMe 15·4%), remained in the benzene solution. This flavone which was also obtained by cyclisation of the above *o*-hydroxy-diketone (m. p. 123—125°) as described at (1), was refluxed for 10 min. with acetic acid containing 25% (by vol.) of concentrated hyrochloric acid. The precipitate which was obtained on dilution of the acid mixture with water was extracted with aqueous sodium hydroxide (2%). Acidification of the filtered solution gave 6-hydroxy-2'-methoxyflavone [see above at (2)], m. p. 230—232°, not depressed by addition of the material soluble in xylene obtained in the demethylation by aluminium chloride in nitrobenzene of 6 : 2'-dimethoxyflavone. 6-*Acetoxy*-2'-*methoxyflavone* was dimorphous, crystallising in needles which melted at 135° and 142° (Found: C, 69·7; H, 4·5: OMe, 9·5. $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·5; OMe, 10·0%). The samples of 6-hydroxy-2'-methoxyflavone obtained by the Baker–Venkataraman method [see (3)] and by partial demethylation of 6 : 2'-dimethoxyflavone [see (2)] gave the same acetate (mixed m. p.).

(4) 2' : 4'-*Dihydroxyflavone*.—2-Hydroxyphenyl 2 : 4-dimethoxystyryl ketone (Hattori, *loc. cit.*, p. 152) was refluxed in pentanol with selenium dioxide (1 part) for 12 hr. The product was filtered, and the filtrate and pentanol washings were steam-distilled. 2' : 4'-Dimethoxyflavone (IV*b*) remained as a paste, which crystallised in yellow needles (25%), m. p. 131° (Found: C, 68·0, 68·2; H, 5·4, 5·6; OMe,20·4. Calc. for $C_{17}H_{14}O_4,H_2O$: C, 68·0; H, 5·3; 2OMe, 20·7%) (cf. Hattori, *loc. cit.*). Demethylation with aluminium chloride in benzene [see at (1)] gave 2' : 4'-dihydroxyflavone, which crystallised in yellow plates, m. p. 285—286°, and exhibited a bright blue fluorescence in concentrated sulphuric acid (Found: C, 70·7; H, 4·2. Calc. for $C_{15}H_{10}O_4$: C, 70·9; H, 3·9%). Hattori (*loc. cit.*) gives m. p. 268—270°. Remethylation as described at (1) yielded the original dimethoxyflavone (mixed m. p.). 2' : 4'-*Diacetoxyflavone*, m. p. 144°, crystallised in needles (Found: C, 68·1; H, 4·4. $C_{19}H_{14}O_6$ requires C, 67·5; H, 4·1%).

(5) 5'-*Chloro*-2' : 4'-*dihydroxyflavone*.—2' : 4'-Dimethoxyflavanone (Hattori, *loc. cit.*) (4 g.) was heated, with shaking, in benzene (80 ml.) containing phosphorus pentachloride (10 g.) until 5'-*chloro*-2' : 4'-*dimethoxyflavone* separated. It crystallised in needles (1 g.), m. p. 198° (Found: C, 64·6; H, 4·1; Cl, 10·8; OMe, 19·7. $C_{17}H_{13}O_4Cl$ requires C, 64·5; H, 4·1; Cl, 11·2; 2OMe, 19·6%).

Demethylation with aluminium chloride gave 5'-*chloro*-2' : 4'-*dihydroxyflavone*, which crystallised in yellow plates, m. p. >300° (Found: C, 58·9, 59·2; H, 3·5, 3·6; Cl, 11·8. $C_{15}H_9O_4Cl,H_2O$ requires C, 58·7; H, 3·6; Cl, 11·6%). The structure was confirmed by remethylation to the original chlorodimethoxyflavone. 2' : 4'-*Diacetoxy*-5'-*chloroflavone* crystallised in needles, m. p. 144° (Found: C, 61·2; H, 3·5; Cl, 10·1. $C_{19}H_{13}O_6Cl$ requires C, 61·2; H, 3·5; Cl, 9·5%).

(6) 5'-*Bromo*-2' : 4'-*dihydroxyflavone*.—2-*Acetoxyphenyl* 2 : 4-*dimethoxystyryl ketone*, which was prepared by acetylation (sodium acetate–acetic anhydride) of the corresponding chalkone (Hattori, *loc. cit.*), crystallised in yellow prisms, m. p. 78—80° (Found: C, 69·9; H, 5·3. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·5%). A suspension of the acetoxychalkone (4 g.) in glacial acetic acid was treated at room temperature with bromine (3 ml.) and after some hours the mixture was diluted with water. The precipitate, 2-*acetoxyphenyl* 1 : 2-*dibromo*-2-(5-*bromo*-2 : 4-*dimethoxyphenyl*)*ethyl ketone*, separated from ligroin as a yellow powder (6 g.), m. p. 181—182° (Found: C, 40·9; H, 2·7; Br, 42·1. $C_{19}H_{17}O_5Br_3$ requires C, 40·4; H, 3·0; Br, 42·5%). This acetoxyketone (1·2 g.) was refluxed in alcohol (25 ml.) with potassium cyanide (0·6 g.) for 3 hr. (see Hutchins and Wheeler, *J.*, 1939, 91). 5'-*Bromo*-2' : 4'-*dimethoxyflavone*, which separated when the solution was kept at 0°, crystallised in aggregates (0·6 g.), m. p. 196° (Found: C, 56·3; H, 3·8; Br, 22·4. $C_{17}H_{13}O_4Br$ requires C, 56·5; H, 3·6; Br, 22·2%).

Demethylation of 5'-bromo-2' : 4'-dimethoxyflavone by aluminium chloride in benzene yielded 2' : 4'-dihydroxyflavone, m. p. 285—286°; the product gave 2' : 4'-diacetoxyflavone [mixed m. p.; see (4)]. In some experiments, in which the time of demethylation was curtailed, products with less bromine than 5'-bromo-2' : 4'-dihydroxyflavone were obtained. To determine its structure, 5'-bromo-2' : 4'-dimethoxyflavone (1 g.) was refluxed with sodium ethoxide

(from 2 g. of sodium) in ethanol (50 ml.) for 7 hr. The solution was diluted with water, saturated with carbon dioxide, extracted with ether without filtration, and acidified. The precipitate thus obtained crystallised in pale yellow needles, m. p. 196°. This m. p. was not depressed by addition of an authentic sample of 5-bromo-2 : 4-dimethoxybenzoic acid (Rice, *J. Amer. Chem. Soc.*, 1926, **48**, 3126) (Found : C, 41·7; H, 3·6; Br, 31·3; OMe, 23·1. Calc. for $C_9H_9O_4Br$: C, 41·4; H, 3·4; Br, 30·7; 2OMe, 23·8%) prepared by methylation of 5-bromo-2 : 4-dihydroxybenzoic acid by methyl sulphate and aqueous sodium hydroxide.

(7) 7 : 2'-*Dihydroxyflavone* (VI*b*).—2-o-*Anisoyloxy*-4-*methoxyacetophenone*, needles, m. p. 77—78° (Found : C, 68·0; H, 5·5; OMe, 20·0. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3; 2OMe, 20·7%), and o-*anisoyl*-4-*methoxysalicyloylmethane*, yellow prisms, m. p. 117° (ethanolic ferric colour, dark red) (Found: C, 68·2; H, 5·3; OMe, 20·7. Required: as for the ester), were prepared. The diketone, on cyclisation, gave 7 : 2'-dimethoxyflavone (m. p. 176—177°) previously prepared by Hattori (*loc. cit.*, p. 148) by treatment of *o*-anisoyl-2 : 4-dimethoxybenzoylmethane with hydriodic acid. 7 : 2'-Dihydroxyflavone, m. p. >300° (Hattori, *loc. cit.*; Kostanecki and Salis, *Ber.*, 1899, **32**, 1033), was obtained by demethylation of the dimethoxyflavone by aluminium chloride; its structure was confirmed by remethylation; 7 : 2'-diacetoxyflavone formed needles, m. p. 104° (Kostanecki and Salis, *loc. cit.*, give m. p. 105°) (Found : C, 67·5; H, 4·3. Calc. for $C_{19}H_{14}O_6$: C, 67·5; H, 4·1%).

(8) 2' : 6'-*Dihydroxyflavone*.—A mixture of 2 : 6-dimethoxyacetophenone (5 g.), methyl *O*-benzylsalicylate (10 g.), and sodamide (2·2 g.) was heated at 140—150° in an atmosphere of nitrogen for 2 hr. The product was cooled and added to water, and the resulting mixture was acidified with dilute hydrochloric acid and extracted with ether. O-*Benzylsalicyloyl*-2 : 6-*dimethoxybenzoylmethane* was removed from the ethereal extract with aqueous sodium hydroxide (5%) and recovered by acidification. It crystallised in prisms (2·7 g.), m. p. 90°, and gave a red ethanolic ferric colour (Found : C, 73·6; H, 5·6; OMe, 15·5. $C_{24}H_{22}O_5$ requires C, 73·8; H, 5·6; 2OMe, 15·9%). The diketone (2·3 g.) was heated for 1 hr. at 100° with acetic acid (50 ml.) and concentrated hydrochloric acid (25 ml.). 2' : 6'-*Dimethoxyflavone* (IV*c*) which separated when the liquid was poured into water crystallised in plates (1·5 g.), m. p. 145—147° (Found : C, 72·4, H, 4·9; OMe 21·1. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0; 2OMe, 22·0%). Demethylation with aluminium chloride gave 2' : 6'-*dihydroxyflavone*, plates, m. p. 274—278° (Found: C, 71·3; H, 4·4. $C_{15}H_{10}O_4$ requires C, 70·9; H, 3·9%); the *diacetate* (prepared by acetic anhydride–perchloric acid) formed prisms, m. p. 141—142° (Found : C, 67·9; H, 4·4. $C_{19}H_{14}O_6$ requires C, 67·5; H, 4·1%). This flavone did not fluoresce in sulphuric acid. On remethylation, 2' : 6'-dimethoxyflavone was obtained.

(9) 5 : 2'-*Dihydroxyflavone* (VI*c*).—2-o-*Anisoyloxy*-6-*methoxyacetophenone* formed prisms, m. p. 98—100° (Found : C, 67·5; H, 5·2; OMe, 20·5. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3; 2OMe, 20·7%), and o-*anisoyl*-6-*methoxysalicyloylmethane* yellow plates, m. p. 80—90° {the compound partly cyclised on heating [see (11) below]; ethanolic ferric colour, greenish-brown} (Found: C, 67·8; H, 5·4; OMe 20·5. Required: as for the ester); 5 : 2'-*dimethoxyflavone* formed prisms, m. p. 179—180° (Found : C, 72·4; H, 5·3; OMe, 21·9. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0; 2OMe, 22·0%). Demethylation by aluminium chloride gave 5 : 2'-*dihydroxyflavone*, pale yellow needles, m. p. 268—269°; the structure was confirmed by remethylation (Found : C, 71·0; H, 4·1. $C_{15}H_{10}O_4$ requires C, 70·9; H, 3·9%).

(10) 2' : 4' : 6'-*Trihydroxyflavone*.—A mixture of 2 : 4 : 6-trimethoxyacetophenone (4 g.) and methyl *O*-benzylsalicylate (7 g.) was refluxed with sodium powder (0·8 g.) in xylene (20 ml.) for 45 min. The product when cold was treated with damp ether and with aqueous sodium hydroxide (2%). O-*Benzylsalicyloyl*-2 : 4 : 6-*trimethoxybenzoylmethane* which separated from the alkaline solution on acidification gave a red ethanolic ferric colour and crystallised in needles (3 g.), m. p. 129—131° (Found : C, 70·9; H, 5·5. $C_{25}H_{24}O_6$ requires C, 71·4; H, 5·7%). The diketone (1·5 g.) was refluxed for 30 min. with acetic acid (10 ml.) and hydrochloric acid (5 ml.). 2' : 4' : 6'-*Trimethoxyflavone* (IV*d*), which separated when the product was poured into water, crystallised in prisms (0·3 g.), m. p. 159—160°, from ligroin and methanol (Found : C, 69·1; H, 5·2; OMe, 29·3. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·1; 3OMe, 29·8%). Demethylation of this flavone (0·6 g.) with aluminium chloride (3·0 g.), as described at (1) except that benzene was replaced by mesitylene (15 ml.) to prevent nuclear arylation (see 2' : 4' : 6'-trihydroxy-3' : 5'-diphenylflavone below), gave 2' : 4' : 6'-trihydroxyflavone, which separated from ethyl acetate in pale yellow plates (0·3 g.), m. p. 280—284° (decomp.), and exhibited a deep blue fluorescence in sulphuric acid. The ethanolic ferric reaction was negative (Found : C, 66·7; H, 3·8. $C_{15}H_{10}O_5$ requires C, 66·7; H, 3·7%). Remethylation gave the original trimethoxyflavone. 2' : 4' : 6'-*Triacetoxyflavone*, when repeatedly crystallised from methanol, separated in prisms,

m. p. 147—148° (Found: C, 64·1; H, 3·9. $C_{21}H_{16}O_8$ requires C, 63·6; H, 4·0%). Treatment of this trimethoxyflavone (0·4 g.) with aluminium chloride (2 g.) in benzene (20 ml.) as described at (1) gave 2′ : 4′ : 6′-*trihydroxy*-3′ : 5′-*diphenylflavone* which crystallised from ethanol and acetic acid in plates (0·35 g.), m. p. 298—302° (decomp.), and exhibited a green fluorescence in sulphuric acid. It gave no colour with ethanolic ferric chloride (absence of 5-hydroxyl group) (Found: C, 75·2, 75·2; H, 4·4, 4·4. $C_{27}H_{18}O_5,\frac{1}{2}H_2O$ requires C, 75·2; H, 4·4%). The *triacetate* crystallised in plates, m. p. 160—162° (shrink at 154°) (Found: C, 71·9; H, 4·5. $C_{33}H_{24}O_8$ requires C, 72·3; H, 4·4%).

To determine its structure the diphenylflavone was hydrolysed with ethanolic sodium ethoxide as described at (2). Ethanol was removed in steam, and the residue was acidified, steam-distilled, and extracted with ether. The ethereal extract yielded salicylic acid, m. p. and mixed m. p. 156—157°, to sodium carbonate solution.

(11) 5 : 7 : 2′-*Trihydroxyflavone* (VI*d*).— 2-o-*Anisoyloxy*-4 : 6-*dimethoxyacetophenone* formed plates, m. p. 102° (Found: C, 65·5; H, 5·7; OMe, 28·3. $C_{18}H_{18}O_6$ requires C, 65·5; H, 5·5; 3OMe, 28·2%), and o-*anisoyl*-4 : 6-*dimethoxysalicyloylmethane* yellow plates, m. p. 98—100° (indefinite; the compound cyclised on heating; see below) (ethanolic ferric colour, olive-green) (Found: C, 65·7; H, 5·4; OMe, 27·8 Required: as for the ester). When the diketone was heated for 20 min. at 115°, there remained after extraction of the product with aqueous 2% sodium hydroxide a white residue, which did not give an ethanolic ferric colour and on crystallisation did not depress the m. p. of 5 : 7 : 2′-*trimethoxyflavone* * prepared by cyclisation of the above diketone with acetic acid containing a trace of hydrochloric acid [see (1) above]; it formed needles, m. p. 174—176° (Found: C, 69·3; H, 5·2; OMe, 29·5. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·1; 3OMe, 29·8%). Demethylation by aluminium chloride in benzene gave 5 : 7 : 2′-trihydroxyflavone (VI*d*), needles, m. p. 278°, raised by addition of an authentic sample of the trihydroxyflavone, m. p. 281° (Kostanecki and Webel, *Ber.*, 1901, **34**, 1455); the 5 : 7 : 2′-triacetate, plates, had m. p. 178° (lit., 178°) (Found: C, 64·0; H, 4·0. Calc. for $C_{21}H_{16}O_8$: C, 63·6, H, 4·0%). The structure of this trihydroxyflavone which gave a green colour with ethanolic ferric chloride was confirmed by remethylation.

Demethylation of 2′-methoxyflavones by hydriodic acid.

Formation of 6 : 2′-*Dihydroxyflavone from* 2′ : 5′-*Dimethoxyflavone*.—2′ : 5′-Dimethoxyflavone (1·2 g.) was heated with hydriodic acid (12 ml.; *d* 1·7) and phenol (12 ml.) in a sealed tube at 170° for 2 hr., and the product was poured into saturated aqueous sodium hydrogen sulphite. The precipitate on repeated crystallisation formed pale yellow plates (0·2 g.) (A), m. p. 298—300° [6 : 2′-dihydroxyflavone has m. p. 304—305°; Kostanecki and Seifart, *loc. cit.* at (2) above]. The ultra-violet absorption spectrum in ethanol of (A) (max. at 270, 296, and 335 mμ; log ε 4·26, 4·01, and 4·23) was identical with that of 6 : 2′-dihydroxyflavone and differed from that of 2′ : 5′-dihydroxyflavone (max. at 248, 296, and 365 mμ; log ε 4·24, 4·14, and 3·92). The diacetate of (A) was identical with 6 : 2′-diacetoxyflavone [m. p. and mixed m. p. 148°; mixed m. p. with 2′ : 5′-diacetoxyflavone (m. p. 148°), 120°]. Methylation of (A) by methyl sulphate and potassium carbonate in acetone gave 6 : 2′-dimethoxyflavone, m. p. and mixed m. p. 146° [mixed m. p. with 2′ : 5′-dimethoxyflavone (m. p. 120°), 100—110°]. The 6 : 2′-derivatives mentioned showed the characteristic green fluorescence in sulphuric acid.

Demethylation of 2′ : 5′-dimethoxyflavone with hydriodic acid in phenol under less drastic conditions, *e.g.*, for 5 hr. at atmospheric pressure at 160—170° in an atmosphere of carbon dioxide, gave mixtures of 2′ : 5′- and 6 : 2′-dihydroxyflavone. Fractionation of the product from ethanol, in which 6 : 2′-dihydroxyflavone is the more soluble, was controlled by observation of the ultra-violet fluorescence of a sulphuric acid solution. That exhibited by the 6 : 2′-compound is more intense. The identity of the purified hydroxyflavone was confirmed by acetylation and methylation. 2′ : 5′-Dihydroxyflavone underwent rearrangement to 6 : 2′-dihydroxyflavone under the same conditions as the dimethoxy-derivative. 6 : 2′-Dimethoxyflavone was demethylated without rearrangement when treated with hydriodic acid in phenol at 170—180° in a sealed tube for 5 hr. The product was identified as 6 : 2′-dihydroxyflavone by acetylation and methylation.

Demethylation of 2′ : 5′-*Dimethoxyflavone by Sulphuric Acid* (70%).—The dimethoxyflavone (1 g.) was refluxed with sulphuric acid (70%; 15 ml.) for 2 hr. and the product was poured into water. The crude flavone which was precipitated crystallised in pale-yellow plates (0·7 g.), exhibiting in sulphuric acid solution the brilliant green fluorescence characteristic of 6 : 2′-

* [Added, Oct. 13th, 1953.] Gupta and Seshadri (*Proc. Indian Acad. Sci.*, 1953, **37**, *A*, 615) give m. p. 176—177°.

dihydroxyflavone, and giving 6 : 2'-diacetoxy- and 6 : 2'-dimethoxy-flavone, respectively (mixed m. p.s) on acetylation and methylation.

Formation of 7 : 2'-*Dihydroxyflavone from* 2' : 4'-*Dimethoxyflavone.*—A mixture of 2' : 4'-dimethoxyflavone (0·2 g.), hydriodic acid (6 ml.; *d* 1·7) and phenol (3 ml.) was heated in a sealed tube at 210° for 0·5 hr. The product which separated when the mixture was poured into aqueous sodium hydrogen sulphite melted above 300° after crystallisation (yield, 0·12 g.), and gave 7 : 2'-dimethoxyflavone and 7 : 2'-diacetoxyflavone [mixed m. p.s; see (7) above], respectively, on methylation and acetylation. Treatment of 5'-chloro-2' : 4'-dimethoxyflavone and 5'-bromo-2' : 4'-dimethoxyflavone with hydriodic acid in phenol under pressure at 210° (0·5 hr.) gave 7 : 2'-dihydroxyflavone (mixed m. p.). The product from the chlorodimethoxyflavone gave 7 : 2'-diacetoxyflavone on acetylation.

Demethylation of 2' : 4'-dimethoxyflavone, and of the 5-bromo- and the 5-chloro-derivative, by hydriodic acid in phenol in an atmosphere of carbon dioxide at 160—170° for 2 hr. gave 2' : 4'-dihydroxyflavone; each product yielded 2' : 4'-diacetoxyflavone on acetylation.

7 : 2'-Dimethoxyflavone gave 7 : 2'-dihydroxyflavone (confirmation by acetylation) on treatment with hydriodic acid in phenol under pressure at 160° for 2 hr.

Formation of 5 : 2'-*Dihydroxyflavone from* 2' : 6'-*Dimethoxyflavone.*—The dimethoxyflavone (0·2 g.) [see (8) above] was refluxed with hydriodic acid (6 ml.; *d* 1·7) and phenol (3 ml.) in carbon dioxide for 2 hr. at 160°. The crude flavone which was precipitated when the product was poured into saturated aqueous sodium hydrogen sulphite crystallised in pale yellow needles, m. p. and mixed m. p. with 5 : 2'-dihydroxyflavone, 268—269°. Remethylation gave 5 : 2'-dimethoxyflavone (mixed m. p.); this flavone was demethylated without rearrangement under the above conditions.

Formation of 5 : 7 : 2'-*Trihydroxyflavone from* 2' : 4' : 6'-*Trimethoxyflavone.*—The trimethoxyflavone [see (10) above] was refluxed with hydriodic acid and phenol at atmospheric pressure for 2 hr., or with hydriodic acid alone (see preceding paragraph). The product when purified in the usual way did not depress the m. p. of 5 : 7 : 2'-trihydroxyflavone [see (11)]; its identity was confirmed by remethylation and acetylation. When 2' : 4' : 6'-trimethoxyflavone was heated with hydriodic acid (5 ml.; *d* 1·7) alone for 2 hr. a mixed product was obtained which on acetylation gave 5 : 7 : 2'-triacetoxyflavone (mixed m. p.) as a first crop from alcohol.

[*Added, Oct.* 13*th*, 1953.] After submission of this paper, Vol. **37**, *A* of the *Proc. Indian Acad. Sci.* up to May 1953 became available in Dublin, and our attention was directed to two papers by Seshadri and his collaborators (pp. 611 and 620) describing experiments on the demethylation of 2'-methoxyflavones suggested by the preliminary results of Philbin and Wheeler (*Chem. and Ind.*, 1952, 449). In their investigations the Indian workers prepared 5-hydroxy-2'-methoxyflavone (m. p. 190—191°), 5 : 2'-dimethoxyflavone (m. p. 134—135°), and 5 : 2'-dihydroxyflavone (m. p. 175—176°). As will be seen the m. p.s for the dimethoxy- and the dihydroxy-flavone differ markedly from those given above. We have also found that 5-*hydroxy*-2'-*methoxyflavone* prepared by partial methylation (methyl sulphate, potassium carbonate, and acetone) of 5 : 2'-dihydroxyflavone forms yellow plates, m. p. 140° (Found : C, 72·2; H, 4·3; OMe, 11·6. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5; OMe, 11·6%). It should be pointed out that Seshadri and his collaborators used aqueous sodium carbonate to de-anisoylate 3-*o*-anisoyl-5-hydroxy-2'-methoxyflavone obtained by the Allan–Robinson method, and that the de-anisoylated product was used to prepare the dihydroxy- and the dimethoxy-flavone. This method of removing a 3-aroyl group has been found unreliable in this laboratory (observation by Mr. G. McMahon). Analytical results for carbon and hydrogen will not differentiate between the 3-anisoylated and the de-anisoylated product involved.

Our (unpublished) results on the demethylation of methyl ethers of 5 : 7 : 2' : 4'-tetrahydroxyflavone agree with those of Gupta and Seshadri (*Proc. Indian Acad. Sci.*, 1953, **37**, *A*, 611).

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