438. *Bromination and Nitration of 5-Hydroxyflavone.*

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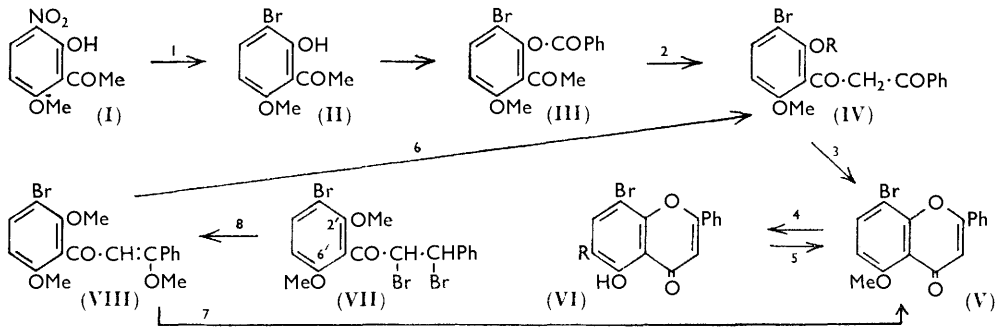
The product of monobromination of 5-hydroxyflavone is shown to be the 8-substituted derivative (VI; R = H). Mononitration also occurs normally in the 8-position.

Bromo-5-hydroxyflavones.—It has recently been shown [1] that nuclear bromination of 2'-hydroxy-4',6'-dimethoxychalcones occurs in the 3'- and not as previously thought in the 5'-position. Little work has been carried out on the bromination of flavones. Naik [2] reported that monobromination of 7-hydroxyflavone occurs in the 8-position but failed to monobrominate 5-hydroxyflavone. In a study of the action of electrophilic reagents on 5-substituted flavones it has now been found that bromination and probably nitration occur in the 8-position.

8-*Bromo-5-hydroxyflavone.*—Bromination of 5-hydroxyflavone at room temperature gave 8-bromo-5-hydroxyflavone (VI; R = H) identical with a sample prepared from 2-hydroxy-6-methoxy-3-nitroacetophenone [3] as shown in the formulæ (I—VI; R = H).



Reagents: 1, Reduction, diazotisation, and Sandmeyer. 2, Baker–Venkataraman. 3, NaOAc–AcOH. 4, $AlCl_3$–C_6H_6. 5, Me_2SO_4–$COMe_2$. 6, HCl. 7, HBr. 8, NaOMe.

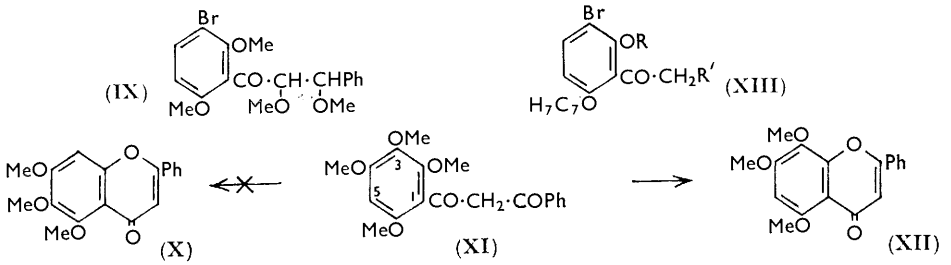
Another route to the product (VI; R = H) was by way of 3'-bromo-2',6'-dimethoxychalcone dibromide (VII) which with sodium methoxide formed the expected [4] trimethoxychalcone (VIII) and a second compound A (see below) which is possibly the tetramethoxy-compound (IX). Hydrolysis of the ether (VIII) removed only the enolic methyl group and gave 1-(3-bromo-2,6-dimethoxyphenyl)-3-phenylpropane-1,3-dione (IV; R = Me). With hydrogen bromide in acetic acid, compound (VIII) afforded 8-bromo-5-methoxyflavone (V) (mixed m. p.), and since no other flavone was formed in this reaction the 2'-methoxyl group is more vulnerable than the 6'-substituent to acid hydrolysis. This result agrees with previous findings on the course of selective dealkylation in the formation of xanthones from unsymmetrically substituted benzophenones.[5] In 1919 Bargellini,[6] using hydriodic acid, monodemethylated and coincidentally cyclised the diketone (XI). He assumed demethylation to have occurred at the least hindered methoxyl group, forming 5,6,7-trimethoxyflavone (X). Experiment now shows that the product was, however, 5,7,8-trimethoxyflavone (XII).[7]

Compound A (m. p. 70—72°), when heated under reduced pressure, formed the enol

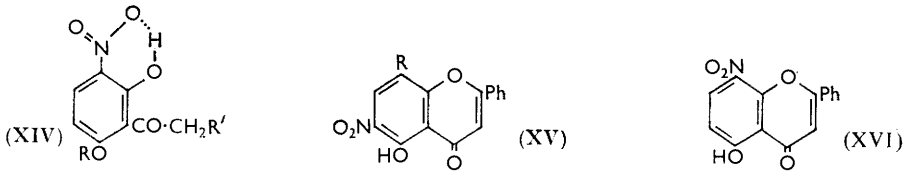
[1] Donnelly, *Tetrahedron Letters*, 1959, No. 9, 1.
[2] Naik, *J. Sci. Ind. Res., India*, 1961, **20**, *B*, 339.
[3] Naik, Thakor, and Shah, *Proc. Indian Acad. Sci.*, 1953, **37**, *A*, 765.
[4] Cf. Bhagwat and Wheeler, *J.*, 1939, 94.
[5] Swirski, Philbin, and Wheeler, *J.*, 1956, 4455.
[6] Bagellini, *Gazzetta*, 1919, **49**, 47; *Chem. Abs.*, 1920, **14**, 1527.
[7] Sastri and Seshadri, *Proc. Indian Acad. Sci.*, 1946, **24**, *A*, 243.

ether (VIII; m. p. 135—136°) and might have been regarded as that compound containing a molecule of methanol of crystallisation, but this is not so since the enol ether (VIII) recrystallised unchanged from methanol; compound (A) has perhaps structure (IX) though molecules of this type have not hitherto been reported.

Bromination of 2-hydroxy-6-methoxyacetophenone [8] yielded the 3-bromo-derivative (II). Similarly bromination of 2-benzyloxy-6-hydroxyacetophenone [9] gave the ketone (XIII; R = R′ = H), as established by the production of 8-bromo-5-hydroxyflavone when this ketone was subjected to the reactions shown for the conversion of ketone (II)



into compound (VI; R = H). Condensation of 6-benzyloxy-3-bromo-2-methoxyacetophenone (XIII; R = Me, R′ = H) with methyl benzoate to produce the diketone (XIII; R = Me, R′ = Bz) and subsequent debenzylation was envisaged as a route to 6-bromo-5-methoxyflavone since normally debenzylation occurs more readily than demethylation. However, condensation of the ketone (XIII; R = Me, R′ = H) with the benzoate was accompanied by demethylation and the phenolic diketone (XIII; R = H, R′ = Bz) was formed.



5-Hydroxyflavone or its 8-bromo-derivative (VI; R = H) was further brominated to yield 6,8-dibromo-5-hydroxyflavone (VI; R = Br), identical with a sample prepared from 3,5-dibromo-2,6-dihydroxyacetophenone [10] by Allan–Robinson benzoylation followed by mild hydrolysis. The dibromoflavone (VI; R = Br) had m. p. 250—251°, and formed an acetate, m. p. 187—189°, and a monomethyl ether, m. p. 226—228°. For the dibromoflavone (VI; R = Br) as well as these two derivatives Naik [2] reported m. p. 242°.

Treatment of 8-bromo-5-hydroxyflavone (VI; R = H) with nitric acid below 100° gave 8-bromo-5-hydroxy-6-nitroflavone (VI; R = NO_2). Rearrangement during this nitration is excluded since 8-bromo-5-hydroxyflavone was recovered ucnchanged when refluxed for some hours with 70% sulphuric acid.

5-Hydroxynitroflavones.—The compounds assigned [11] the constitution 5-hydroxy-6- and -8-nitroflavone have not been fully authenticated. These assignments rely on the assumption that owing to chelation in 2,6-dihydroxy-3-nitroacetophenone (XIV; R = R′ = H) the flavone obtained by the Allan–Robinson method with this ketone was the 5-hydroxy-6-nitro-derivative (XV; R = H).[11a] Mononitration of 5-hydroxyflavone [11b]

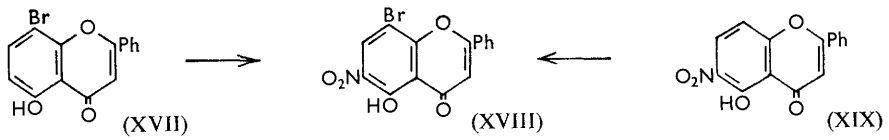
[8] Baker, *J.*, 1939, 956.
[9] Baker, Brown, and Scott, *J.*, 1939, 1922.
[10] Naik and Sethna, *J. Indian Chem. Soc.*, 1952, **29**, 493.
[11] (*a*) Naik and Thakor, *Proc. Indian Acad. Sci.*, 1953, **37**, *A*, 774; (*b*) Naik, Mehta, Thakor, Jadhav, and Shah, *ibid.*, 1953, **38**, *A*, 31.

gave a flavone which differed from that previously prepared and was therefore designated 5-hydroxy-8-nitroflavone (XVI). Further nitration of either of these nitroflavones yielded 5-hydroxy-6,8-dinitroflavone (XV; R = NO_2). Of these three nitroflavones, only the compound regarded as 5-hydroxy-6-nitroflavone failed to form an acetate. Later workers [12] accepted these assignments and used the mononitroflavones as reference compounds. They found that the 5-hydroxymononitroflavone obtained from 2′,6′-dihydroxy-3′-nitrochalcone *via* the flavanone and 3-bromoflavanone was identical with that prepared by Naik and his co-workers [11a] from the ketone (XIV; R = R′ = H) by the Allan–Robinson method and they concluded that it was 5-hydroxy-6-nitroflavone (XV; R = H). The resistance of this flavone to acetylation showed, they stated, the hindered nature of the 5-hydroxyl group. This evidence was not significant as 5-hydroxy-6,8-dinitroflavone had been acetylated.[11b] There were discrepancies in the melting points reported by the two schools.[11,12]

We sought unsuccessfully to prepare directly unambiguous samples of 5-hydroxy-6- and -8-nitroflavone. However, by using 8-bromo-5-hydroxy-6-nitroflavone (VI; R = NO_2) as a reference compound the structures previously assigned [11] to these nitroflavones were confirmed.

Attempts to prepare an authentic specimen of 5-methoxy-8-nitroflavone by (i) Allan–Robinson benzoylation of 2-hydroxy-6-methoxy-3-nitroacetophenone (I) followed by hydrolysis, or (ii) cyclisation of the diketone (XIV; R = Me, R′ = Bz) by sodium acetate in acetic acid, produced demethylation. The 5-hydroxymononitroflavone, m. p. 237—238°, obtained in each case was identical with that obtained by Allan–Robinson fusion of 2,6-dihydroxy-3-nitroacetophenone (XIV; R = R′ = H). This 5-hydroxymononitroflavone on bromination yielded 8-bromo-5-hydroxy-6-nitroflavone (XVIII), identical with that prepared by nitrating 8-bromo-5-hydroxyflavone (XVII) as already described.

The flavone produced by Allan–Robinson benzoylation of compound (XIV; R = R′ = H) is therefore 5-hydroxy-6-nitroflavone (XIX) as assumed on theoretical grounds.[11]



(XVII) (XVIII) (XIX)

Contrary to previous findings this flavone forms an acetate. An independent proof that the 5-hydroxymononitroflavone had structure (XIX) was provided when on catalytic reduction it gave 6-amino-5-hydroxyflavone identical with a sample prepared by rearrangement of 8-amino-5-hydroxyflavone with hydrochloric acid.[13]

When nitration of 5-hydroxyflavone was carried out in the presence of sulphuric acid [11a] inseparable mixtures, probably due to overnitration, were produced. Eventually a procedure based on that of Seshadri and Trivedi [12] was employed. This method, although not always reliable (sometimes no pure product could be isolated), afforded 5-hydroxy-8-nitroflavone (XVI) in yields of up to 6%.

Wessely–Moser Rearrangement.—Flavonoids containing a 5-hydroxyl or 5-alkoxyl group and substituted in the 6- or 8-position are of interest in relation to the Wessely–Moser rearrangement.[14] Treatment of 8-bromo-5-hydroxyflavone (VI; R = H) with hydriodic acid produced dehalogenation to yield 5-hydroxyflavone. When the bromoflavone was refluxed with hydrobromic acid in acetic anhydride, 6,8-dibromo-5-hydroxyflavone was unexpectedly the only product isolated. To ensure that the reaction mixture did not contain free bromine the experiment was repeated with formic acid as solvent.

[12] Seshadri and Trivedi, *J. Org. Chem.*, 1958, **23**, 1735.
[13] Iyer and Venkataraman, *Proc. Indian Acad. Sci.*, 1953, **37**, *A*, 629.
[14] Wessely and Moser, *Monatsh.*, 1930, **56**, 97; Wheeler and Philbin, " Les Heterocycles Oxygénés," *Colloq. Cent. nat. de la Recherche sci.* (*Paris*), 1957, **64**, 55.

The product was again the dibromoflavone (VI; R = Br), in about 7% yield. A similar result was obtained by Nicolet [15] who found, for example, that 4-acetamido-3-bromotoluene when refluxed with hydrochloric acid gave some 3,5-dibromotoluidine. In the present case no halogen-free product was identified. While no rearrangement occurred when the 8-bromo-compound was refluxed for 3 hours with sulphuric acid, 5-hydroxy-8-nitroflavone readily rearranged in sulphuric acid to 5-hydroxy-6-nitroflavone (XIX); compound (XIX) was itself recovered unchanged after similar treatment.

In one experiment the product of nitration of 5-hydroxyflavone was the 6- and not the 8-nitro-derivative. Whether its formation is due to the ready isomerisation which 5-hydroxy-8-nitroflavone undergoes in acid conditions or whether the 6-nitro-derivative is formed in small quantities during the nitration remains undecided.

Experimental

Crystallisation was from ethanol unless otherwise stated.

8-Bromo-5-hydroxyflavone (VI; R = H).—(*a*) *From 5-hydroxyflavone.* Bromine (0·1 ml.) in chloroform (10 ml.) was added to a stirred solution of 5-hydroxyflavone [16] (0·5 g.) in chloroform (50 ml.) during 1 hr., and the solvent was allowed to evaporate. The residue, 8-bromo-5-hydroxyflavone, crystallised from acetic acid in yellow needles (0·1 g.), m. p. 179—180° (acetate, m. p. 212—214°) identical with an authentic sample prepared as described under (*b*).

(*b*) *By Baker–Venkataraman transformation.* Two methods (i) and (ii) are reported for the production of the required 3-bromo-2-hydroxy-6-methoxyacetophenone (II).

(i) A mixture of 2-hydroxy-6-methoxy-3-nitroacetophenone [3] (7·2 g.), stannous chloride (20 g.), and concentrated hydrochloric acid (70 ml.) was refluxed for ½ hr., then poured into boiling water (500 ml.); the hot solution was treated with hydrogen sulphide and the resulting precipitate discarded. The filtrate, made alkaline with aqueous ammonia, yielded to chloroform *3-amino-2-hydroxy-6-methoxyacetophenone* which crystallised from light petroleum (b. p. 60—80°) in red needles (3 g.), m. p. 66° (Found: C, 60·1; H, 6·3; N, 7·1. $C_9H_{11}NO_3$ requires C, 59·7; H, 6·1; N, 7·7%). The amine (0·2 g.) in 20% aqueous sulphuric acid (2·5 ml.) at 0° was diazotised with 12·5% aqueous sodium nitrite (2 ml.) and added to freshly prepared cuprous bromide (0·4 g.) in 10% hydrobromic acid (7 ml.) at 100°; heating was continued for 10 min. The mixture yielded to ether *3-bromo-2-hydroxy-6-methoxyacetophenone* which formed yellow prisms (0·05 g.), m. p. 99—100° (Found: C, 44·1; H, 3·6; Br, 32·4; OMe, 12·5. $C_9H_9BrO_3$ requires C, 44·1; H, 3·7; Br, 32·6; OMe, 12·7%).

(ii) 2-Hydroxy-6-methoxyacetophenone [8] (9 g.) in chloroform (80 ml.) was treated with bromine (3 ml.) and kept for 3 hr. at room temperature. Removal of the solvent and crystallisation of the residue gave 3-bromo-2-hydroxy-6-methoxyacetophenone (9 g.), m. p. and mixed m. p. 99—100°.

Benzoylation of 3-bromo-2-hydroxy-6-methoxyacetophenone (8 g.) in pyridine gave the *2-benzoate*, prisms (9 g.), m. p. 99—100° (Found: C, 55·1; H, 4·0; Br, 22·2; OMe, 9·1. $C_{16}H_{13}BrO_4$ requires C, 55·0; H, 3·7; Br, 22·9; OMe, 8·9%). A mixture of the ester, m. p. 99—100° (10 g.), dry pulverised potassium hydroxide (17 g.), and pyridine (100 ml.) was heated at 100° for 0·5 hr. and acidified. *1-(3-Bromo-2-hydroxy-6-methoxyphenyl)-3-phenylpropane-1,3-dione*, which separated, formed orange-yellow prisms (8 g.), m. p. 142—144° (Found: C, 55·0; H, 3·7; Br, 22·8; OMe, 9·0. $C_{16}H_{13}BrO_4$ requires C, 55·0; H, 3·7; Br, 22·9; OMe, 8·9%). A mixture of the diketone (7 g.), anhydrous sodium acetate (15 g.), and acetic acid (100 ml). was refluxed for 1·5 hr. and diluted with water. The precipitated *8-bromo-5-methoxyflavone* formed needles (6 g.), m. p. 189—190° (Found: C, 58·1; H, 3·3; Br, 23·8; OMe, 9·5. $C_{16}H_{11}BrO_3$ requires C, 58·0; H, 3·3; Br, 24·2; OMe, 9·4%). A mixture of this flavone (1 g.), aluminium chloride (4 g.), and benzene (25 ml.) was refluxed for 1·5 hr. The solvent was removed and the residue heated with 10% hydrochloric acid (25 ml.) at 100° for 20 min. *8-Bromo-5-hydroxyflavone*, which separated, crystallised from acetic acid in yellow needles (0·6 g.), m. p. 179—180° (Found: C, 56·7; H, 2·9; Br, 25·1. $C_{15}H_9BrO_3$ requires C, 56·8; H, 2·8; Br, 25·2%). The ethanolic ferric reaction colour was black-violet. Remethylation of the

[15] Nicolet, *J. Amer. Chem. Soc.*, 1921, **43**, 2081.
[16] Rajagopalan, Rao, and Seshadri, *Proc. Indian Acad. Sci.*, 1947, **25**, *A*, 432.

demethylated flavone (acetone–potassium carbonate–methyl sulphate) gave 8-bromo-5-methoxyflavone, m. p. and mixed m. p. 189—190°. The *acetate*, obtained by using acetic anhydride–perchloric acid, formed needles, m. p. 212—214° (Found: C, 56·9; H, 3·3; Br, 22·1. $C_{17}H_{11}BrO_4$ requires C, 56·8; H, 3·1; Br, 22·3%).

(*c*) *By way of 3′-bromo-2′,6′-dimethoxychalcone dibromide* (VII). 50% Aqueous sodium hydroxide (50 ml.) was added to a solution of 2,6-dimethoxyacetophenone [17] (5 g.) and benzaldehyde (4·5 g.) in ethanol (100 ml.). The mixture was kept at room temperature for 12 hr. and then acidified. *2′,6′-Dimethoxychalcone*, which separated, formed plates (5 g.), m. p. 124—125° (Found: C, 76·3; H, 6·1; OMe, 23·3. $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0; OMe, 23·1%). Bromine (1 ml.) was added to a solution of the chalcone (2·5 g.) in acetic acid (25 ml.); the mixture was kept protected from light overnight. *3′-Bromo-2′,6′-dimethoxychalcone dibromide* separated as a powder (3 g.), m. p. 142—144°, unchanged by crystallisation from acetic acid (Found: C, 40·2; H, 3·1; Br, 46·8; OMe, 12·3. $C_{17}H_{15}Br_3O_3$ requires C, 40·2; H, 3·0; Br, 47·3; OMe, 12·2%).

A solution of the dibromide (4·5 g.) and sodium methoxide (from 1 g. of sodium) in methanol (100 ml.) was refluxed for 3 hr. and poured into water. The mixture yielded to ether an oil which on trituration with warm light petroleum (b. p. 40—60°) gave a solid; evaporation of the supernatant petroleum afforded an oil (A). The solid was *3′-bromo-2′,6′,β-trimethoxychalcone* (VIII) which crystallised from light petroleum (b. p. 100—120°) or methanol in prisms (0·6 g.), m. p. 135—136° (Found: C, 57·8; H, 4·6; Br, 21·6; OMe, 24·9. $C_{18}H_{17}BrO_4$ requires C, 57·3; H, 4·5; Br, 21·2; OMe, 24·7%); the oil was possibly *1-(3-bromo-2,6-dimethoxyphenyl)-2,3-dimethoxy-3-phenylpropan-1-one* (IX); it crystallised from light petroleum (b. p. 80—100°; cooled with methanol–solid carbon dioxide) in needles (0·7 g.), m. p. 70—72° (Found: C, 55·7; H, 5·1; Br, 19·9; OMe, 29·7. $C_{19}H_{21}BrO_5$ requires C, 55·7; H, 5·1; Br, 19·6; OMe, 30·3%). After 3 months the m. p. had fallen to 62—68°. Compound (A) yielded compound (VIII) (m. p. and mixed m. p.) when heated in a drying pistol at the b. p. of acetone for 4 hr. at 2 mm. in the presence of " Anhydron." With ethanolic ferric chloride, compound (A) gave no immediate colour but a red colour instantly on boiling; compound (VIII) afforded no colour immediately or on boiling, but a red colour developed in about 5 hr. at room temperature.

Heating 3′-bromo-2′,6′,β-trimethoxychalcone (0·2 g.) in a 12·5% solution (4 ml.) of hydrogen bromide in acetic acid at 55° for 12 hr., pouring the mixture into aqueous sodium carbonate, and extraction with ether gave 8-bromo-5-methoxyflavone (0·05 g.), m. p. and mixed m. p. 189—190°.

3′-Bromo-2′,6′,β-trimethoxychalcone (0·5 g.) and concentrated hydrochloric acid (0·5 ml.) in methanol (40 ml.) were refluxed for 5 min. The sticky solid which separated on cooling was dissolved in ethanol at 60° and mixed with saturated ethanolic copper acetate. The *copper*(II) *derivative* of 1-(3-bromo-2,6-dimethoxyphenyl)-3-phenylpropane-1,3-dione which was precipitated crystallised from benzene–light petroleum (b. p. 80—100°) in green needles (0·3 g.), m. p. 226—228° (Found: C, 51·7; H, 3·8; Cu, 7·9; OMe, 15·6. $C_{34}H_{28}Br_2CuO_8$ requires C, 51·8; H, 3·6; Cu, 8·1; OMe, 15·8%).

(*d*) *By way of the diketone* (XIII; R = H, R′ = Bz). 1-(6-Benzyloxy-3-bromo-2-hydroxyphenyl)-3-phenylpropane-1,3-dione was prepared by two methods. (*a*) Bromine (1·6 ml.) was added to a solution of 2-benzyloxy-6-hydroxyacetophenone [9] (7·5 g.) in acetic acid (75 ml.), and the mixture was kept for 12 hr. Treatment with water then gave a solid which on crystallisation gave *6-benzyloxy-3-bromo-2-hydroxyacetophenone* in yellow needles (5·8 g.), m. p. 125—126° (Found: C, 55·9; H, 4·2; Br, 24·3. $C_{15}H_{13}BrO_3$ requires C, 56·1; H, 4·1; Br, 24·9%). This ketone (1·1 g.) in pyridine (15 ml.) was heated with benzoyl chloride (0·5 ml.) at 60° for 2 min., allowed to cool, and kept for 2 hr. The solid which was formed on acidification by dilute hydrochloric acid crystallised from acetone–ethanol, to yield *2-benzoyloxy-6-benzyloxy-3-bromoacetophenone* (1·3 g.), m. p. 146—147° (Found: C, 61·8; H, 4·1; Br, 18·9. $C_{22}H_{17}BrO_4$ requires C, 62·1; H, 4·0; Br, 18·8%). A mixture of the ester (1·0 g.), pyridine (25 ml.), and pulverised potassium hydroxide (1·5 g.) was heated at 60° for 1 min. and then kept at room temperature for 2 hr. Acidification afforded *1-(6-benzyloxy-3-bromo-2-hydroxyphenyl)-3-phenylpropane-1,3-dione* which formed yellow needles (0·6 g.), m. p. 177—179° (Found: C, 62·1; H, 4·2; Br, 18·3. $C_{22}H_{17}BrO_4$ requires C, 62·1; H, 4·0; Br, 18·8%).

(*b*) 6-Benzoyloxy-3-bromo-2-hydroxyacetophenone (8·0 g.) with methyl sulphate and potassium carbonate in benzene yielded an oil, b. p. 196°/2 mm., which later solidified and on

[17] Cartwright, Jones, and Marmion, *J.*, 1952, 3499.

crystallisation from light petroleum (b. p. 60—80°; cooled in methanol–solid carbon dioxide) gave 6-*benzyloxy*-3-*bromo*-2-*methoxyacetophenone* as needles (6·0 g.), m. p. 48—50° (Found: C, 57·2; H, 4·5; Br, 23·2; OMe, 9·3. $C_{16}H_{15}BrO_3$ requires C, 57·3; H, 4·5; Br, 23·9; OMe, 9·3%). 6-Benzyloxy-3-bromo-2-methoxyacetophenone (0·7 g.) in toluene (20 ml.) was refluxed for 30 min. with methyl benzoate (1·1 ml.) and pulverised sodium (0·14 g.). The alkali-soluble portion of the product proved to be 1-(6-benzyloxy-3-bromo-2-hydroxyphenyl)-3-phenylpropane-1,3-dione, m. p. 177—179° alone or mixed with the diketone prepared as described under (*a*).

Cyclisation of the diketone (0·3 g.) by sodium acetate and acetic acid as described above gave 5-*benzyloxy*-8-*bromoflavone* (0·25 g.), m. p. 166—167° (Found: C, 65·1; H, 3·7; Br, 18·9. $C_{22}H_{15}BrO_3$ requires C, 64·9; H, 3·7; Br, 19·6%), which with aluminium chloride in benzene (cf. above) produced 8-bromo-5-hydroxyflavone, m. p. and mixed m. p. 179—180°.

5,7,8-*Trimethoxyflavone* (XII). A solution of 2,5-dihydroxy-4,6-dimethoxyacetophenone [18] (5·5 g.) in 20% aqueous sodium hydroxide (35 ml.) was heated under nitrogen with methyl sulphate (13 ml.) at 100° for 1 hr. 20% Aqueous sodium hydroxide (30 ml.) was added to the mixture which was then extracted with ether. Crystallisation of the ether-soluble material gave 2,3,4,6-tetramethoxyacetophenone as plates (3·0 g.), m. p. 55—57° (lit.,[6] m. p. 43—45°). Condensation of the acetophenone with methyl benzoate, by using sodium in xylene, afforded 1-(2,3,4,6-tetramethoxyphenyl)-3-phenylpropane-1,3-dione, m. p. 111—112° (lit.,[6] 110—112°). A mixture of this diketone (0·1 g.) and a 50% w/w solution (6 ml.) of hydrogen bromide in acetic acid was kept for 12 hr. at 40° and then poured into aqueous sodium carbonate. The solid which separated was washed with aqueous sodium sulphite and crystallised from aqueous ethanol. Recrystallisation from light petroleum (b. p. 60—80°) gave 5,7,8-trimethoxyflavone, as needles, m. p. 163—166°. A mixed m. p. determination with 5,7,8-trimethoxyflavone, m. p. 166—167°, prepared as described by Sastri and Seshadri [7] showed m. p. 165—166°, and a similar determination with an authentic specimen of 5,6,7-trimethoxyflavone,[18] m. p. 163—164°, gave m. p. 134—146°.

6,8-*Dibromo*-5-*hydroxyflavone* (VI; R = Br).—(*a*) 3,5-Dibromo-2,6-dihydroxyacetophenone [10] (0·4 g.), sodium benzoate (1 g.), and benzoic anhydride (4 g.) were heated under nitrogen at 160—170° for 10 hr. Ethanol (100 ml.) and 50% aqueous potassium hydroxide (12 ml.) were added; the mixture was refluxed for 30 min. and poured into dilute hydrochloric acid. A portion (0·1 g.) of the precipitated solid, ethanol (35 ml.), and 50% aqueous potassium hydroxide (2 ml.) were refluxed together for 40 min.; the cooled mixture was acidified by dilute hydrochloric acid. The mixture yielded, to chloroform, 6,8-dibromo-5-hydroxyflavone which crystallised from acetic acid in yellow needles (0·03 g.), m. p. 250—251° (lit.,[2] m. p. 242°) (Found: C, 45·9; H, 2·0; Br, 40·5. Calc. for $C_{15}H_8Br_2O_3$: C, 45·5; H, 2·0; Br, 40·4%). Methylation afforded 6,8-dibromo-5-methoxyflavone m. p. 226—228° (lit.,[2] m. p. 242°) (Found: C, 47·2; H, 2·4; OMe, 7·8. Calc. for $C_{16}H_{10}Br_2O_3$: C, 46·8; H, 2·4; OMe, 7·6%). 5-Acetoxy-6,8-dibromoflavone had m. p. 187—189° (lit.,[2] 242°) (Found: C, 46·1; H, 2·4; Br, 36·7. Calc. for $C_{17}H_{10}Br_2O_4$: C, 46·6; H, 2·3; Br, 36·5%).

(*b*) A solution of 5-hydroxyflavone or 8-bromo-5-hydroxyflavone (0·03 g.) and bromine (0·1 ml.) in acetic acid (2 ml.) was heated to the b. p., kept at room temperature for 1 hr., and then boiled to remove the excess of bromine. On cooling, 6,8-dibromo-5-hydroxyflavone separated in yellow needles (0·03 g.), m. p. 250—251° alone or mixed with the preceding sample.

5-*Hydroxy*-6-*nitroflavone* (XV; R = H).—(*a*) Benzoylation of 2-hydroxy-6-methoxy-3-nitroacetophenone [3] (3 g.) in pyridine gave 2-*benzoyloxy*-6-*methoxy*-3-*nitroacetophenone*, plates (4 g.), m. p. 128—130° (Found: C, 61·2; H, 4·1; N, 4·0; OMe, 10·1. $C_{16}H_{13}NO_6$ requires C, 61·0; H, 4·2; N, 4·4; OMe, 9·8%). A mixture of the ester (1·5 g.), dry pulverised potassium hydroxide (2 g.), and pyridine (30 ml.) was shaken for 2 hr. and poured into dilute acetic acid. 1-(2-*Hydroxy*-6-*methoxy*-3-*nitrophenyl*)-3-*phenylpropane*-1,3-*dione*, which separated, formed yellow needles (0·5 g.), m. p. 116—119° (Found: C, 60·8; H, 4·1; N, 5·1; OMe, 10·5. $C_{16}H_{13}NO_6$ requires C, 61·0; H, 4·2; N, 4·4; OMe, 9·8%). A mixture of this diketone (2·3 g.), anhydrous sodium acetate (6 g.), and acetic acid (50 ml.) was refluxed for 1 hr. and then allowed to cool. 5-Hydroxy-6-nitroflavone, which separated, crystallised from acetic acid in yellow needles (1·5 g.), m. p. 237—238° (Found: C, 63·6; H, 3·1; N, 5·7. Calc. for $C_{15}H_9NO_5$: C, 63·6; H, 3·2; N, 5·0%). The ethanolic ferric reaction colour was red. The *acetate*, which had not previously been obtained,[11a,12] was prepared by use of acetic anhydride–sodium acetate and

[18] Sastri and Seshadri, *Proc. Indian Acad. Sci.*, 1946, **23**, *A*, 262.

formed pale yellow needles, m. p. 190—191° (shrinking at 185°) which gave no colour with ethanolic ferric chloride (Found: C, 63·1; H, 3·7; N, 4·2. $C_{17}H_{11}NO_6$ requires C, 62·8; H, 3·4; N, 4·3%).

(*b*) 2-Hydroxy-6-methoxy-3-nitroacetophenone [3] (3 g.), benzoic anhydride (15 g.), sodium benzoate (4 g.), and pyridine (0·5 ml.) were heated under nitrogen at 150—160° for 9 hr. Ethanol (100 ml.) and 50% aqueous potassium hydroxide (20 ml.) were added; the mixture was refluxed for 40 min. and the ethanol was removed under reduced pressure. The residue was treated with water (500 ml.); insoluble material was collected and on crystallisation from acetic acid gave 5-hydroxy-6-nitroflavone in yellow needles (1·5 g.), m. p. 237—238° not depressed by addition of a sample prepared as described at (*a*).

(*c*) The Allan–Robinson benzoylation of 2,6-dihydroxy-3-nitroacetophenone carried out by Naik and Thakor [11a] and by Seshadri and Trivedi [12] was repeated, with 1 g. of the acetophenone. 3-Benzoyl-5-hydroxy-6-nitroflavone (0·55 g.), m. p. 236—238° (lit.,[11a] 235—236°), was obtained as the ethanol-insouble fraction; the ethanol-soluble fraction, previously taken to be 5-hydroxy-6-nitroflavone (lit.,[11a] m. p. 209° raised [12] on further crystallisation from chloroform to 230—232°) gave, on crystallisation from acetic acid a mixture of a yellow powder (B) and red needles (C). The powder (B) was 5-hydroxy-6-nitroflavone which crystallised from acetone–methanol in yellow needles (0·05 g.), m. p. and mixed m. p. with a sample prepared as above 237—238°. The needles (C) gave, on crystallisation from acetic acid, pink-brown needles, m. p. 214—217° not raised by further crystallisation from acetone–methanol. Depressions in m. p.s to about 190—200° were observed when this compound was mixed with 3-benzoyl-5-hydroxy-6-nitroflavone, m. p. 236—238°, 5-hydroxy-6-nitroflavone, m. p. 237—238°, or 5-hydroxy-8-nitroflavone, m. p. 225—226° (see below). This product, m. p. 214—217°, of which insufficient for analysis was obtained, may be 3-benzoyl-5-hydroxy-8-nitroflavone.

(*d*) Debenzoylation, with alkali, of 3-benzoyl-5 hydroxy-6-nitroflavone [11a] was performed with a dilute solution of the 3-benzoylflavone (0·15 g.) in 4% ethanolic potassium hydroxide (80 ml.) to avoid separation of unchanged material. The 5-hydroxy-6-nitroflavone thus obtained formed needles, m. p. and mixed m. p. 237—238°.

8-*Bromo*-5-*hydroxy*-6-*nitroflavone*.—(*a*) Nitric acid (10 ml.; *d* 1·42) was added to a solution of 8-bromo-5-hydroxyflavone (0·25 g.) in acetic acid (20 ml.) at an initial temperature of 75°; after 5 hr. the mixture was diluted with water. The precipitated 8-*bromo*-5-*hydroxy*-6-*nitroflavone*, on crystallisation from acetic acid and from pyridine, formed pale brown prisms (0·1 g.), m. p. 251—253° (Found: C, 49·6; H, 2·2; Br, 22·4; N, 3·5. $C_{15}H_8BrNO_5$ requires C, 49·7; H, 2·2; Br, 22·1; N, 3·9%).

(*b*) Bromine (0·1 ml.) was added to a solution of 5-hydroxy-6-nitroflavone (0·2 g.) in chloroform (40 ml.); after 18 hr. the solvent was removed. The residue, on purification as in (*a*), formed brown prisms (0·1 g.), m. p. 258—260°, m. p. and mixed m. p. with the above product (m. p. 251—253°) 258—260°. Infrared spectra of the two products were identical.

6-*Amino*-5-*hydroxyflavone*.—5-Hydroxy-6-nitroflavone (0·2 g.) in acetone (100 ml.) was hydrogenated over saturated Raney nickel (0·5 g.) until 3 mol. of hydrogen had been absorbed (6 hr.). 6-Amino-5-hydroxyflavone, which remained after removal of catalyst and solvent, formed golden plates (0·15 g.), m. p. 182—183° alone or when mixed with the product (m. p. 182—183°) obtained [13] by rearrangement of 8-amino-5-hydroxyflavone.

Nitration of 5-*Hydroxyflavone*.—(*a*) 5-*Hydroxy*-8-*nitroflavone*. Nitric acid (50 ml.; *d* 1·42) was added to a solution of 5-hydroxyflavone [16] (0·5 g.) in acetic acid (6 ml.). 5-Hydroxy-8-nitroflavone, which separated from the solution during 1·5 hr., crystallised from acetic acid in pale brown needles (0·03 g.), m. p. 225—226° [Naik *et al.*[11b] give m. p. 225° (shrinking at 200°); Seshadri and Trivedi [12] give m. p. 215° (shrinking at 100°, softening at 190°)].

(*b*) 5-*Hydroxy*-6-*nitroflavone* (XIX). 5-Hydroxyflavone (1·5 g.) was added to a cooled mixture of acetic acid (40 ml.) and nitric acid (40 ml.; *d* 1·42); the mixture was kept below 15° for 2 hr. and diluted. The precipitate, on repeated crystallisation from acetic acid and from acetone–ethanol, formed yellow needles (0·04 g.), m. p. 233—235° raised to 234—236° by addition of a sample of 5-hydroxy-6-nitroflavone (m. p. 237—238°) prepared as described above.

The Stability of Flavones (XVI), (XV; R = H), *and* (VI; R = H) *in Presence of Acids*.—(*a*) *Formation of* 5-*hydroxy*-6-*nitroflavone from* 5-*hydroxy*-8-*nitroflavone*. A mixture of 5-hydroxy-8-nitroflavone (0·02 g.) and 70% aqueous sulphuric acid (3 ml.) was refluxed for ½ hr. and diluted with water. The precipitated 5-hydroxy-6-nitroflavone, on crystallisation from aqueous acetic acid and from acetone–ethanol, formed pale brown needles, m. p. 233—236°; a mixed

m. p. with the starting compound was 195—200° and with a sample of 5-hydroxy-6-nitroflavone prepared as above was 236—237°. The same product (m. p. 234—236°) was obtained after similar treatment of 5-hydroxy-6-nitroflavone.

(*b*) *Attempted rearrangement of 8-bromo-5-hydroxyflavone* (VI; R = H). (i) 8-Bromo-5-methoxyflavone gave 5-hydroxyflavone (mixed m. p.) on treatment with hydriodic acid.

(ii) A mixture of 8-bromo-5-methoxyflavone (0·6 g.), 60% hydrobromic acid (20 ml.), and acetic anhydride (16 ml.) was refluxed for 1 hr. 6,8-Dibromo-5-hydroxyflavone, which separated on cooling, formed on repeated crystallisation yellow needles (0·04 g.), m. p. 250—251° not depressed by addition of a sample prepared as above. Formation of the dibromoflavone (VI; R = Br) was not inhibited by the use of formic acid instead of acetic anhydride as solvent.

(iii) A mixture of 8-bromo-5-methoxyflavone (2 g.) and 70% aqueous sulphuric acid (60 ml.) was refluxed for 3 hr. and diluted with water. The precipitated yellow solid was collected, washed, dried, and steam-distilled at 180—190° for 45 min. Crystallisation of the volatile fractions gave no useful result; the residue was 8-bromo-5-hydroxyflavone, which on crystallisation from acetone and from aqueous acetic acid formed yellow needles (0·1 g.), m. p. 176—177° raised to 178—179° by addition of a sample prepared as above.

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