

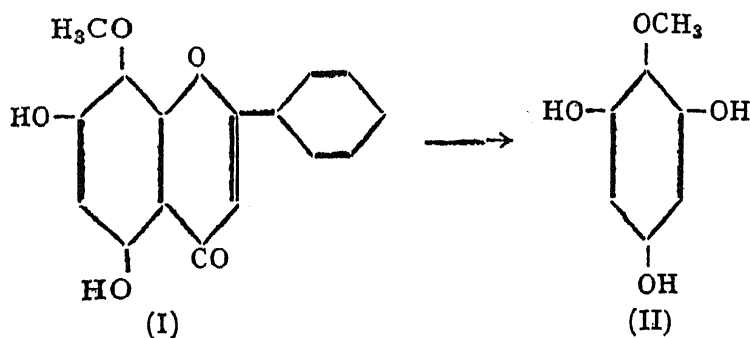
SYNTHESIS OF 5:7:8-HYDROXYFLAVONES AND THEIR DERIVATIVES

BY V. D. NAGESWARA SASTRI AND T. R. SESHADRI, F.A.Sc.

(From the Department of Chemistry, Andhra University)

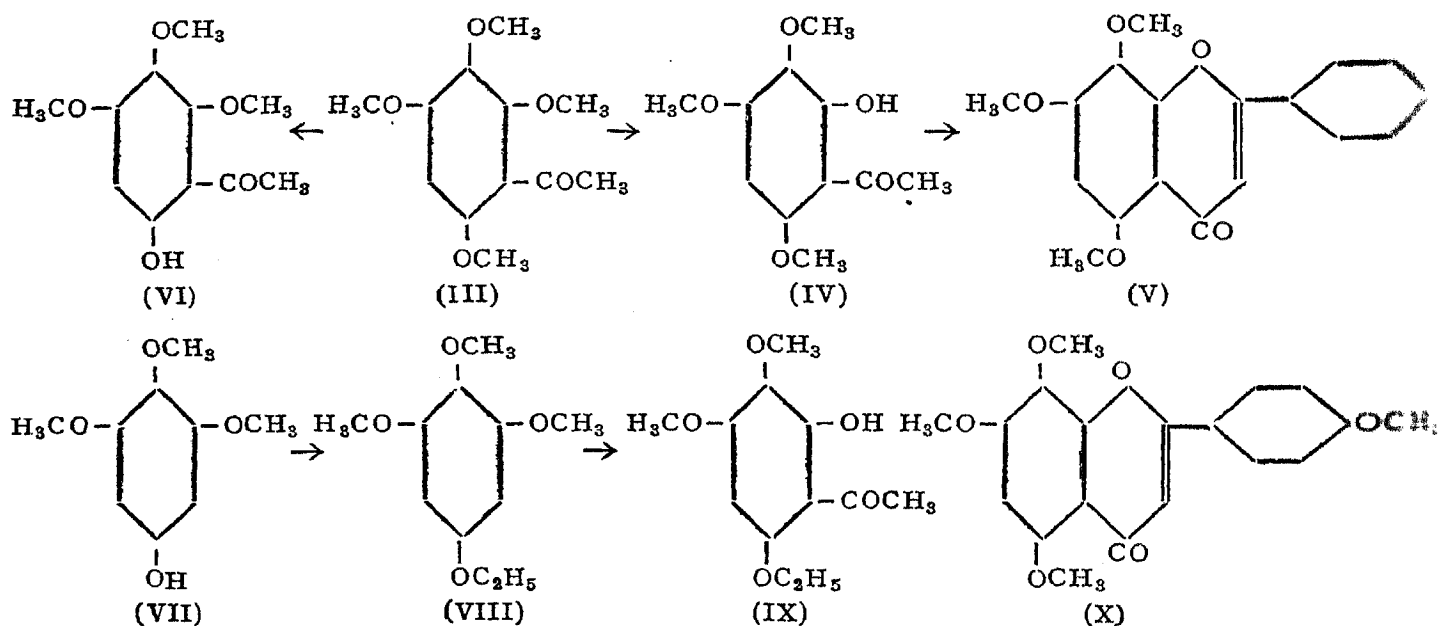
Received May 6, 1946

THOUGH a number of flavonols with the 5:7:8-arrangement of hydroxyl groups have been isolated from plants, only one member of the corresponding flavone series has so far been found in them and that is wogonin. It was first isolated by Takahashi¹ from the roots of *Scutellaria baicalensis* in which it occurs along with baicalein. Its constitution was first investigated by Shibata, Iwata and Nakamura² and later by Hattori.³ It was found to have the formula $C_{16}H_{12}O_5$ and a methoxyl group. By fission with alkali, benzoic acid and acetophenone were obtained. These indicated that it was a flavone with the side phenyl nucleus unsubstituted. Diazomethane effected only partial methylation and the monomethyl ether formed thereby gave reactions for the presence of a free hydroxyl group in the 5-position. Complete methylation could be carried out by means of dimethyl sulphate and alkali and the product, O-dimethyl wogonin, was found to be different from baicalein trimethyl ether. Further the trihydroxy-compound obtained by the demethylation of wogonin was not identical with baicalein. Consequently wogonin was considered to be a monomethyl ether of 5:7:8-trihydroxyflavone. From a study of the absorption spectrum Hattori³ fixed the position of the methoxyl group as 8 (Formula I). The isolation of iretol (II) from the products of alkali degradation of wogonin (Hattori and Hayashi⁴) further supported the above conclusion.



In order to provide synthetic evidence in confirmation of the constitution of wogonin, Hattori³ proceeded as follows. 2:3:4:6-Tetramethoxyacetophenone (III) was treated with aluminium chloride and the product, considered to be 2-hydroxy-3:4:6-trimethoxyacetophenone (IV), was fused

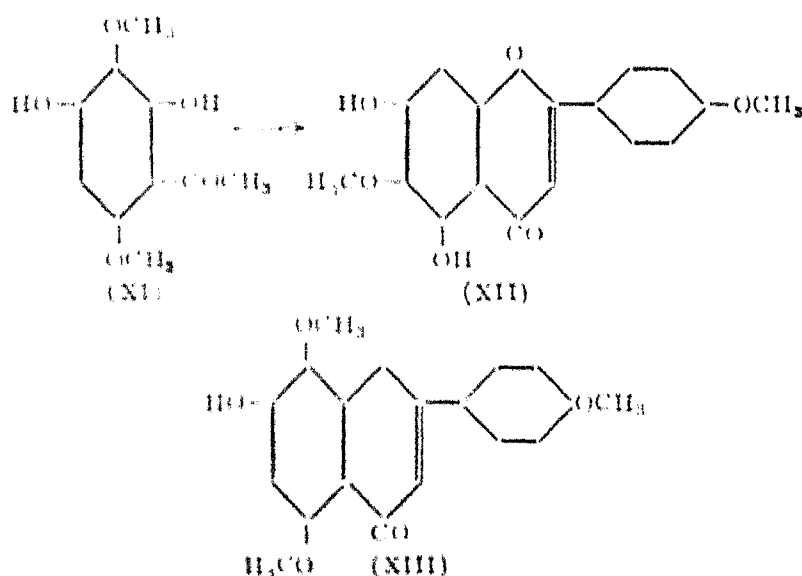
with benzoic anhydride and sodium benzoate according to the method of Allan and Robinson. The trimethoxy flavone thus obtained was identical with wogonin dimethyl ether (V) and it yielded on demethylation a trihydroxyflavone different from baicalein and identical with norwogonin. The constitution of the ketone was, however, indefinite since demethylation with aluminium chloride could take place in either of the two ortho-positions. Further Nierenstein⁵ claimed to have obtained the acetophenone (IV) with a different melting point. As a matter of fact Shibata and Hattori⁶ at one time felt that the substance was in reality the isomeric 2-hydroxy-4:5:6-trimethoxyacetophenone (VI). Subsequently, however, Hattori⁷ supplied indirect evidence in support of the earlier constitution (IV) for the ketone by the following series of reactions. Antiarol (VII) was transformed into its ethyl ether (VIII) which underwent conversion into 2-hydroxy-3:4-dimethoxy-6-ethoxyacetophenone (IX) by the action of acetyl chloride and aluminium chloride. The analogy is based on the assumption that the ethoxy and methoxy groups can be dealkylated with equal ease.



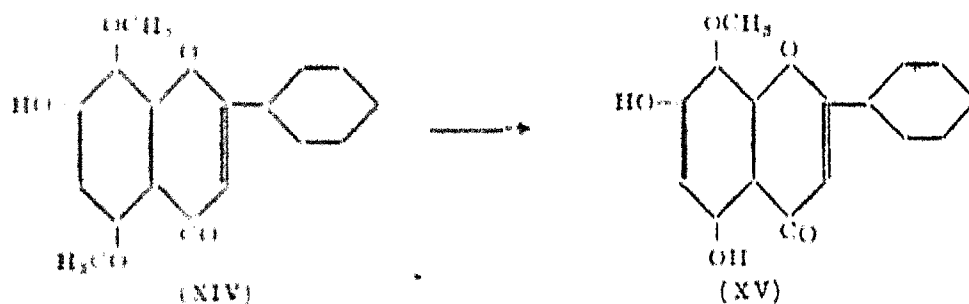
The Allan-Robinson method was also used for the synthesis of the higher member of the flavone series and Hattori⁷ claimed the synthesis of 5:7:8:4'-tetramethoxyflavone (X) by the anisoylation of the ketone (IV).

Wessely and Moser⁸ employed for their synthetic work 2:4-dihydroxy-3:6-dimethoxyacetophenone (XI), a ketone with a definite constitution. However, the Allan-Robinson condensation using anisic anhydride and sodium anisate took an unexpected course resulting in partial demethylation and the formation of the dimethyl ether of scutellarein (XII); the expected

5:7:8-compound (XIII) was obtained in only one experiment out of a large number. This result was confirmed by Wessely and Kallab⁹ who, however, noticed that the acylation of the ketone (IV) led to the formation of the 5:7:8-compound (X) in agreement with the observation of Hattori,⁷ no demethylation interfering in this case with the normal course of the reaction.



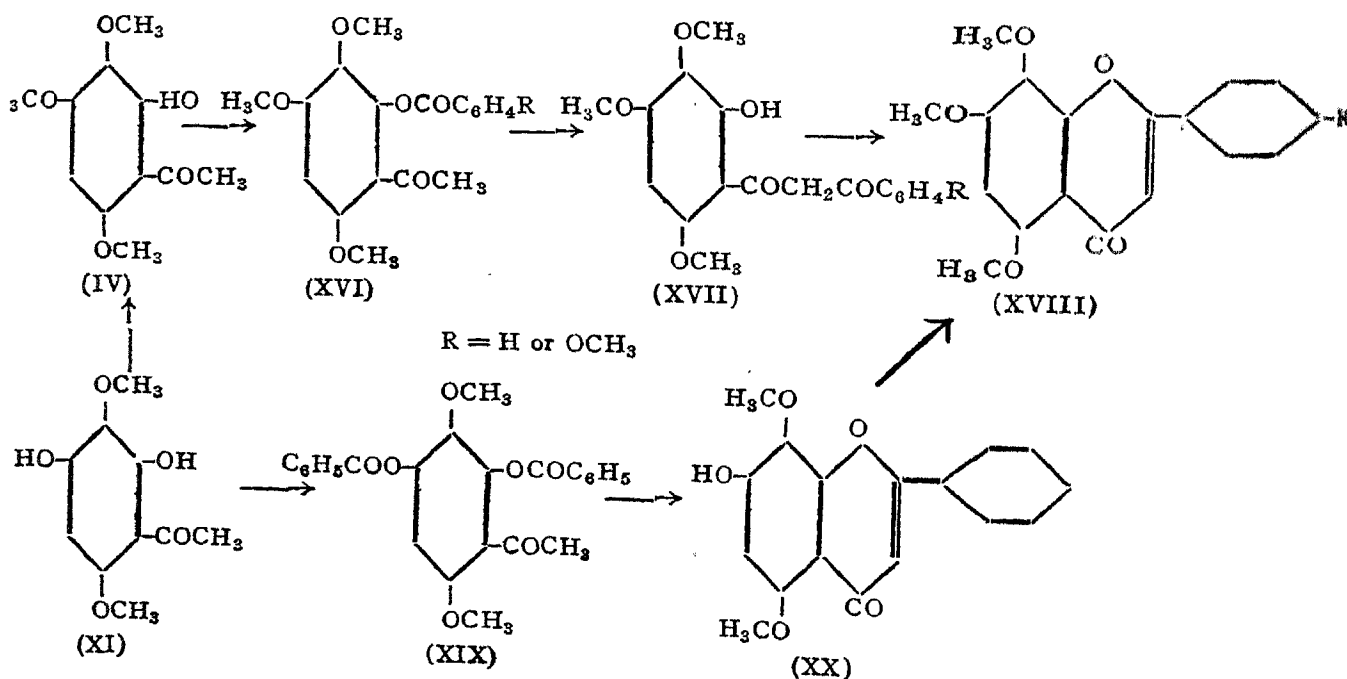
Contrary to the results of Wessely and Moser,⁸ Furukawa and Tamaki¹⁰ claimed that the acylation of the above dihydroxyketone (XI) proceeded normally to yield 5:8:4-trimethoxy-7-hydroxy flavone (XII). The benzoylation was also reported to give the normal product (Shah, Mehta and Wheeler¹¹) which in this case was 5:8:dimethoxy-7-hydroxy-flavone (XIV). Wogonin (XV) was obtained from it by partial demethylation and wogonin dimethyl ether by methylation.



Obviously slight and ununderstood changes in the experimental conditions seem to bring about these differences in the nature of the products and the Allan-Robinson reaction has not yielded, in the case of these flavones, as consistent results as with the corresponding series of flavonols.¹² Since authentic samples of the 5:7:8-hydroxyflavones and their derivatives were required in connection with the study of plant colouring

matters in progress in these laboratories, it was found necessary to synthesise them by the Baker-Venkataraman method starting with a ketone of unambiguous constitution.

2-Hydroxy-3:4:6-trimethoxyacetophenone (IV) has now been prepared by a direct method which is free from ambiguity. It involves partial methylation of 2:4-dihydroxy-3:6-dimethoxyacetophenone (XI). The product is, however, found to be identical with the sample obtained by the nuclear acetylation of 1:2:3:5-tetramethoxybenzene according to the improved method of Baker¹³ which involves partial demethylation. The preparation of the dihydroxy ketone itself has now been simplified. It is obtained directly from 1:4-dimethoxy-2:6-dibenzoyloxybenzene by the Hoesch reaction using acetonitrile, debenzoylation and condensation taking place in one operation. Its benzoate (XVI) undergoes smooth rearrangement in the presence of sodamide to form 2-hydroxy-3:4:6-trimethoxydibenzoylmethane (XVII) which subsequently yields 5:7:8-trimethoxyflavone (XVIII) when heated with acetic acid and sodium acetate. This agrees in its properties with the dimethyl ether of wogonin.³ The higher member of this series, 5:7:8:4'-tetramethoxyflavone (XVIII, R = OCH₃) has also been prepared in a similar way using the O-anisoyl derivative of the ketone.



The dihydroxy ketone (XI) has also been directly used for this synthesis. The dibenzoate (XIX) undergoes migration and subsequent ring-closure to 5:8-dimethoxy-7-hydroxyflavone (XX) though the yields are poor. This

compound corresponds in its properties to the product obtained by Shah, Mehta and Wheeler¹¹ by adopting the Allan-Robinson method. Its constitution is definite since it has yielded 5:7:8-trimethoxyflavone (wogonin dimethyl ether) (XVIII) on methylation.

Discordant results have been reported in regard to the action of hydriodic acid on the methyl ethers of the 5:7:8-hydroxyflavones. Hattori⁹ and Furukawa and Tamaki¹⁰ claimed to have obtained the normal products of demethylation from wogonin, wogonin dimethyl ether, 5-ethoxy-7:8-dimethoxyflavone and 7-hydroxy-5:8:4'-trimethoxyflavone. On the other hand Wessely and coworkers^{8,9} noticed isomeric change into the 5:6:7-hydroxy compounds. Shah, Mehta and Wheeler¹¹ also met with this difficulty in the use of hydriodic acid and hence they effected demethylation using aluminum chloride which was found to be free from this defect. At a later stage Hattori¹² reviewing the whole position, explained that these discrepancies were due to the different conditions used by the different workers and reported that, when employed under controlled conditions, hydriodic acid does not bring about isomeric change. Our experiments using wogonin dimethyl ether indicate that by boiling for two hours with hydriodic acid, as is usually done in ordinary demethylations, almost complete conversion into baicalein takes place and this is obtained in a pure condition on crystallising the product. It has also been characterised by the preparation of the acetate. Though under the milder conditions prescribed by Hattori¹² the product consists essentially of norwogonin, the melting point is frequently found to be low even after repeated crystallisation and only under exceptional circumstances is a pure sample obtained. It would appear that though the isomeric change is considerably minimised, it is not altogether avoided. Under these mild conditions sometimes the demethylation is not complete. The behaviour of the higher member (tetramethoxy flavone) is quite similar. Shah, Mehta and Wheeler¹¹ employed anhydrous aluminum chloride in nitrobenzene for the demethylation of 5:8-dimethoxy-7-hydroxy flavone and obtained norwogonin. For the demethylation of wogonin dimethyl ether we have now employed this reagent in benzene medium since a methoxyl in the 7-position of flavones is best demethylated in this solvent.¹³ Norwogonin thus obtained is a golden yellow crystalline solid melting at 257-59° and yielding an acetate melting at 225-6°. Its properties are quite different from those of baicalein, the reactions with alkali, ferric chloride and *p*-benzoquinone being quite characteristic.

EXPERIMENTAL

2:4-Dihydroxy-3:6-dimethoxyacetophenone (XI).—

2:6-Dibenzyloxy-1:4-dimethoxybenzene¹² (3.5 g.) was treated with anhydrous ether (50 c.c.), freshly distilled acetonitrile (1.5 c.c.) and finely powdered fused zinc chloride (1 g.). A rapid stream of dry hydrogen chloride was passed through the mixture during the course of 5 hours, the reaction flask being cooled in ice-salt mixture. The ketimine hydrochloride began to separate as a dark brown semi-solid mass and the reaction was completed by keeping the tightly corked flask in a refrigerator for two days. The ether was then decanted and the residue of the ketimine hydrochloride washed twice with 20 c.c. portions of dry ether. It was dissolved in water (50 c.c.) and the hydrolysis effected by heating the solution on the boiling water-bath for $\frac{1}{2}$ hour. On cooling, it deposited the crude ketone as a practically colourless crystalline mass with a small quantity of resinous matter. It was filtered, washed and crystallised twice from hot water (charcoal) when the dihydroxy ketone was obtained as bunches of long colourless needles which melted at 128–129° (Wessely and Moser⁸ give m.p. 129°): Yield, 1.5 g. It was freely soluble in alcohol and dissolved with a pale yellow colour in aqueous sodium hydroxide and aqueous sodium carbonate. Its alcoholic solution developed a violet-brown colouration with a drop of ferric chloride. (Found: C, 56.7; H, 5.9; C₁₀H₁₂O₅ requires C, 56.6; H, 5.7%).

2-Hydroxy-3:4:6-trimethoxyacetophenone (IV).—

A mixture of the above dihydroxyacetophenone (1 g.), dry acetone (5 c.c.), dry benzene (50 c.c.), anhydrous potassium carbonate (3 g.) and acid-free dimethyl sulphate (0.5 c.c.) was refluxed on the water-bath for 12 hours. The inorganic salts were then filtered off and washed with a small quantity of warm benzene. The benzene filtrate was washed twice with water and then extracted with 5% aqueous sodium hydroxide. On acidification with hydrochloric acid, the alkaline extract yielded the partially methylated ether as a pale brown solid. It was filtered, washed with water and crystallised twice from dilute alcohol. Yield, 0.8 g. It was obtained as pale yellow stout rectangular prisms melting at 113–114°. It dissolved in aqueous sodium hydroxide to a pale yellow solution and gave a reddish brown colour with ferric chloride in alcoholic solution. (Found: C, 58.6; H, 6.5; C₁₁H₁₄O₅ requires C, 58.4; H, 6.2%). For the substance obtained by the nuclear acetylation of 1:2:3:5-tetramethoxybenzene Baker¹³ gave the melting point of 103–105°. Its melting point could now be raised to 113–114° by repeated crystallisation and it is identical with the sample described above.

2-Benzoyloxy-3:4:6-trimethoxyacetophenone (XVI, R = H).—

2-Hydroxy-3:4:6-trimethoxyacetophenone (2 g.) was dissolved in dry pyridine (10 c.c.) and treated with benzoyl chloride (1.5 c.c.). The mixture was heated on a boiling water-bath for 30 minutes and then added to ice-water containing a little dilute hydrochloric acid; the oil that first separated solidified to a crystalline solid on stirring. It was filtered off, washed with very dilute hydrochloric acid and water and dissolved in sufficient quantity of ether. The ether solution was washed with 5% aqueous sodium carbonate and 5% aqueous sodium hydroxide to remove any acid and unchanged hydroxyketone. After a final washing with water it was dried over calcium chloride and the solvent distilled. The colourless crystalline solid residue was recrystallised from alcohol and alcohol-benzene mixture when the benzoyl derivative was obtained as rhombohedral prisms and melted at 124–125°. Yield, 2.5 g. It was insoluble in aqueous alkali and gave no colour with ferric chloride in alcoholic solution. (Found: C, 65.4; H, 5.5; $C_{19}H_{18}O_6$ requires C, 65.5; H, 5.5%).

2-Hydroxy-3:4:6-trimethoxydibenzoylmethane (XVII, R = H).—

The O-benzoyl derivative (3 g.) was dissolved in dry toluene (30 c.c.) and treated with sodamide (10 g.) finely powdered under toluene. The mixture was heated on a steam-bath for five hours with frequent shaking and left overnight. The yellow solid was then collected, washed well with warm benzene, dried and added in small quantities to crushed ice. When all the unchanged sodamide was decomposed, the yellow solution was filtered to remove insoluble impurities and saturated with carbon dioxide. The dibenzoylmethane separated as a deep orange-yellow oil which solidified in the course of about an hour. It was collected, washed and crystallised from benzene-light petroleum mixture; yield, 1.5 g. On recrystallisation from the same solvent, the dibenzoylmethane was obtained as long, stout rectangular prisms and melted at 132–133°. It dissolved in aqueous sodium hydroxide to give a bright yellow solution and gave an intense reddish-brown colouration with ferric chloride in alcoholic solution. (Found: C, 65.7; H, 5.5; $C_{18}H_{18}O_6$ requires C, 65.5; H, 5.5%).

5:7:8-Trimethoxyflavone (wogonin dimethyl ether, XVIII, R = H).—

A mixture of the dibenzoylmethane (1 g.), glacial acetic acid (10 c.c.) and fused sodium acetate (2 g.) was gently boiled over a wire-gauze for 4 hours. On dilution with water the trimethoxyflavone separated as a colourless crystalline solid which was collected, washed and crystallised twice from dilute alcohol. It was obtained as colourless, long narrow rectangular plates

and prisms melting at 166–167°: yield, 0.7 g. (Hattori³ gives m.p. 167–168°). Its solution in concentrated sulphuric acid was yellow and exhibited no fluorescence. (Found in material dried at 120° for two hours *in vacuo*: C, 69.3; H, 5.4; C₁₈H₁₆O₅ requires C, 69.2; H, 5.1%).

2:4-Dibenzoyloxy-3:6-dimethoxyacetophenone (XIX).—

A mixture of the dihydroxyketone (XI, 2 g.), dry pyridine (10 c.c.) and benzoyl chloride (3 g.) was heated on the water-bath for 30 minutes and then added to water containing hydrochloric acid. The semi-solid product obtained, was worked up as in the previous benzylation. After crystallisation from alcohol, the dibenzoate was obtained as colourless prismatic rods and melted at 117–118°. It was insoluble in aqueous sodium hydroxide and gave no colour with ferric chloride in alcohol solution. (Found: C, 68.6; H, 5.0; C₂₄H₂₀O₇ requires C, 68.6; H, 4.8%).

Rearrangement of (XIX).—

Sodamide (6 g.) finely powdered under toluene, was added to the dibenzoate (2 g.) in toluene (30 c.c.) and the mixture heated on the water-bath for 4 hours. It was yellow in the initial stages and rapidly acquired a greenish tinge. The solid product was collected, washed with toluene, and dissolved in ice-water; the solution was filtered and saturated with carbon dioxide. Not much solid, however, was precipitated in this case, and the entire mixture was therefore extracted with ether. The ether solution, after drying over sodium sulphate, was distilled leaving an orange-yellow semi-solid which gradually solidified when left in the refrigerator for 24 hours. It was filtered and crystallised from benzene-light petroleum mixture when rhombic prisms were obtained: yield, 0.5 g. It melted between 117–125° and appeared to be a mixture of 2-hydroxy-4-benzoyloxy- and 2:4-dihydroxy-3:6-dimethoxy- ω -benzoylacetophenones; it was used directly for the next stage in the synthesis. It dissolved in aqueous sodium hydroxide to an yellow solution and gave a reddish-brown colouration with ferric chloride in alcoholic solution.

7-Hydroxy-5:8-dimethoxyflavone (XX).—

The foregoing product (0.4 g.) was dissolved in glacial acetic acid (5 c.c.), freshly fused sodium acetate (1 g.) added and the whole gently boiled over a wire-gauze for 4 hours. The mixture was diluted with water (50 c.c.) and the precipitated pale-brown crystalline solid filtered and washed with a small quantity of water and alcohol. It was dissolved in 5% aqueous sodium hydroxide and the bright yellow solution filtered to remove some insoluble residue. The flavone was then reprecipitated by passing carbon

dioxide into the clear alkaline solution. It was filtered, washed with hot alcohol, acetone and ether, and finally crystallised from ethyl acetate. 7-Hydroxy-5:8-dimethoxy-flavone was then obtained as long rhombohedral plates and it melted at 286-287° (Shah, Mehta and Wheeler¹¹ record m.p. 287-288°): yield, 0.3 g. It was very sparingly soluble in the common organic solvents and dissolved in aqueous sodium hydroxide to a bright yellow solution. It gave no colour with ferric chloride in alcoholic solution and dissolved in concentrated sulphuric acid to an yellow solution without any fluorescence. (Found: C, 68.3; H, 4.8; C₁₇H₁₄O₅ requires C, 68.5; H, 4.7%).

To a suspension of the above hydroxyflavone (0.2 g.) in dry acetone (25 c.c.) were added acid-free dimethyl-sulphate (1 c.c.) and anhydrous potassium carbonate (2 g.). The mixture was heated under reflux for 12 hours, the potassium salts filtered and washed with warm acetone. The acetone filtrate was concentrated to small bulk and diluted with water. The precipitated methyl ether was crystallised from dilute alcohol when it was obtained as colourless narrow rectangular plates and prisms melting at 166-167° and identical with authentic 5:7:8-trimethoxyflavone already described.

5:7:8-Trihydroxyflavone (norwogonin).

Wogonin dimethyl ether (0.2 g.) was dissolved in dry benzene (12 c.c.) and freshly powdered anhydrous aluminium chloride (1.0 g.) added and the mixture gently refluxed on a water-bath kept at 80-85° for one hour. After cooling, the solvent was decanted and the orange coloured solid residue decomposed with ice and dilute hydrochloric acid. Finally, the mixture was diluted with water and heated on a boiling water-bath for 15 minutes. The colour of the solid turned golden yellow. It was filtered and washed. The product appeared crystalline and melted at 252-254° sintering a few degrees earlier. A recrystallisation from rectified spirits yielded golden yellow rectangular rods and prisms melting at 258-60°. Further recrystallisation did not raise the melting point. Shah *et al.*¹¹ gave the melting point as 250-51°. (Found: OCH₃, nil; C, 66.8; H, 4.0; C₁₅H₁₀O₅ requires C, 66.7; H, 3.7%). When to an alcoholic solution of the substance a drop of ferric chloride solution is added, a brown colour is obtained which intensifies to a deep reddish-brown on further addition. With a very dilute solution of the reagent and using just a drop it is possible to get a pale green colour, but further addition yields the deep reddish-brown. A similar deep reddish-brown solution results on adding an alcoholic solution of *p*-benzoquinone and a brown precipitate is slowly formed. With 2% aqueous alkali

it forms an immediate brownish-red solution which instantaneously changes into pale blue; this slowly fades to a very pale yellow. With a buffer solution of pH 12.2 an orange-yellow solution is obtained which fades rapidly to a pale yellow colour in the course of a few minutes.

The acetate of norwogonin was prepared by boiling the hydroxy-flavone with acetic anhydride and a drop of pyridine for 3 hours. It crystallised from ethyl acetate as colourless rectangular rods melting 225°–226°. Hattori⁷ gave the melting point as 216–17°. (Found: C, 63.5; H, 4.2; $C_{21}H_{16}O_8$ requires C, 63.6; H, 4.1%).

2-Anisoyloxy-3:4:6-trimethoxyacetophenone (XVI, R = OCH₃).—

A mixture of the acetophenone (IV, 2 g.), dry pyridine (10 c.c.) and anisoyl chloride (2 c.c.) was heated on the water-bath for 30 minutes. The pale-brown solid obtained by adding ice-water containing hydrochloric acid, was filtered, washed with very dilute hydrochloric acid and water, and treated thrice with 50 c.c. portions of cold ether to remove unchanged original ketone. After two crystallisations from alcohol the anisoyl derivative was obtained as rhombic prisms melting at 173–174°: Yield, 3.0 g. It was insoluble in aqueous sodium hydroxide and gave no ferric reaction. (Found: C, 63.3; H, 5.7; $C_{19}H_{20}O_7$ requires C, 63.3; H, 5.6%).

2-Hydroxy-3:4:6:4'-tetramethoxydibenzoylmethane (XVII, R = OCH₃).—

The O-anisoyl derivative (2.5 g.), dry toluene (30 c.c.) and finely powdered sodamide (8 g.) were used for the rearrangement. The dibenzoylmethane which was precipitated from the alkaline solution as a yellow solid, was crystallised twice from benzene-light petroleum mixture. It was thus obtained as yellow narrow rectangular plates melting at 155–156°: yield, 1.4 g. It dissolved in aqueous alkali to give an yellow solution and its alcoholic solution developed a reddish-brown colouration with ferric chloride. (Found: C, 63.3; H, 5.6; $C_{19}H_{20}O_7$ requires C, 63.3; H, 5.6%).

5:7:8:4'-Tetramethoxyflavone (XVIII, R = OCH₃).—

A mixture of the above dibenzoylmethane (1 g.), glacial acetic acid (10 c.c.) and sodium acetate (2 g.) was gently boiled over a wire-gauze for 4 hours, and then diluted with water; the tetramethoxyflavone was precipitated as a colourless crystalline solid. It was twice crystallised from alcohol when long needles and narrow rectangular plates melting at 209–210° were obtained: Yield, 0.8 g. (Wessely and Kallab⁹ give m.p. 208°; Hattori⁷ gives m.p. 207–208°). It was moderately soluble in

alcohol, more so in acetone and acetic acid. The yellow solution in concentrated sulphuric acid exhibited no fluorescence. (Found: in material dried at 120-125° *in vacuo* for two hours: C, 66.6; H, 5.5; C₁₉H₁₈O₆ requires C, 66.7; H, 5.3%).

SUMMARY

Since there was an element of uncertainty in the methods employed in the past for the synthesis of 5:7:8-hydroxyflavone derivatives, an unambiguous method has now been worked out. The required ketone, 2-hydroxy-3:4:6-trimethoxyacetophenone has been prepared by the partial methylation of 2:4-dihydroxy-3:6-dimethoxyacetophenone which is obtained directly from 1:4-dimethoxy-2:6-dibenzyloxybenzene by the Hoesch reaction. It has been converted into 5:7:8-trimethoxyflavone (wogonin-dimethyl ether) and 5:7:8:4'-tetramethoxyflavone by the Baker-Venkataraman procedure. Even the above dihydroxyketone could be used for this purpose fairly satisfactorily and it yields as an intermediate stage 5:8-dimethoxy-7-hydroxyflavone. Demethylation with hydriodic acid even under mild conditions is not satisfactory. Nor-wogonin is best obtained by employing anhydrous aluminium chloride in benzene solution for this reaction.

REFERENCES

1. Takahashi .. *Chem. Zentr.*, 1889, ii, 620.
2. Shibata, Iwata and Nakamura.. *Acta Phytochim.*, 1923, 1, 105.
3. Hattori .. *Ibid.*, 1930, 5, 99.
4. ——— and Hayashi .. *Ber.*, 1933, 66, 1279.
5. Nierenstein .. *J.C.S.*, 1917, 4.
6. Shibata and Hattori .. *J. Pharm. Soc. Japan*, 1931, 51, 15.
.. *Chem. Zentr.*, 1931, i, 3358.
7. Hattori .. *Acta Phytochim.*, 1931, 5, 219.
8. Wessely and Moser .. *Monatsh.*, 1930, 56, 97.
9. ——— and Kallab .. *Ibid.*, 1932, 60, 26.
10. Furukawa and Tamaki .. *Bull. Inst. Phy. Chem. Research (Tokyo)*, 1931, 10, 732.
11. Shah, Mehta and Wheeler .. *J.C.S.*, 1938, 1555.
12. Baker, Nodzu and Robinson.. *Ibid.*, 1929, 74.
Goldsworthy and Robinson .. *Ibid.*, 1938, 56.
Rao, Rao and Seshadri .. *Proc. Ind. Acad. Sci., A*, 1944, 19, 88.
13. Baker .. *J.C.S.*, 1941, 666.
14. Hattori .. *Ber.*, 1939, 72, 1914.
15. Krishnaswamy and Seshadri .. *Proc. Ind. Acad. Sci., A*, 1942, 15, 437.