

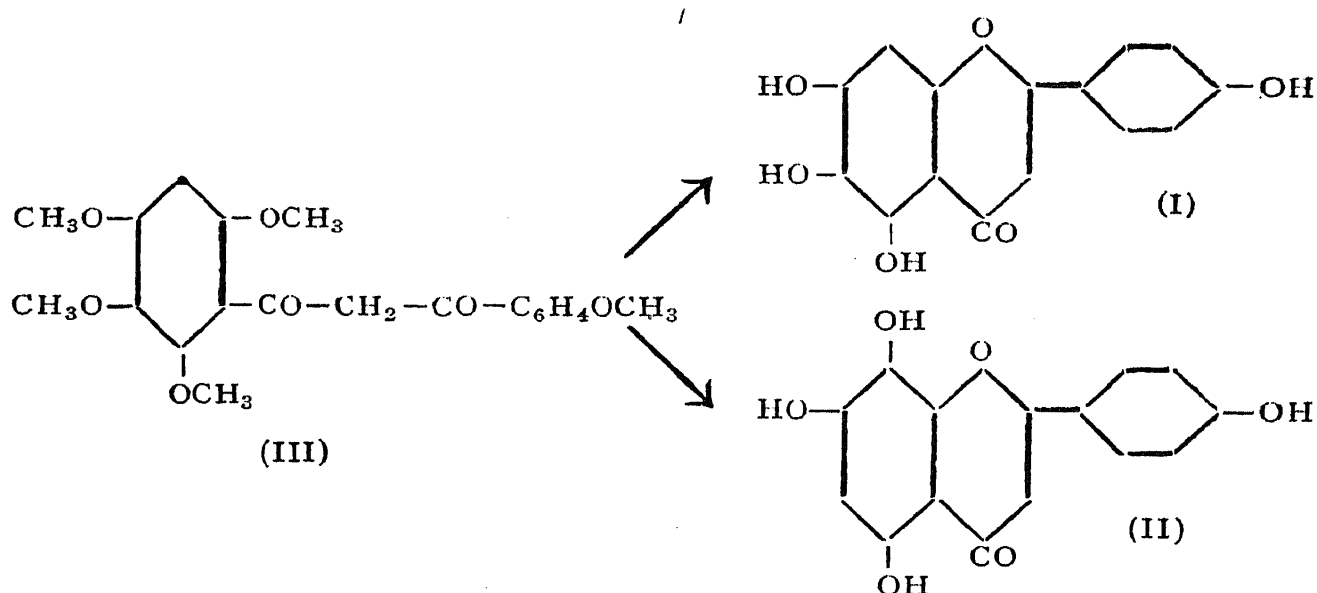
# SYNTHESIS OF 5:6:7- HYDROXYFLAVONES AND THEIR DERIVATIVES—PART I

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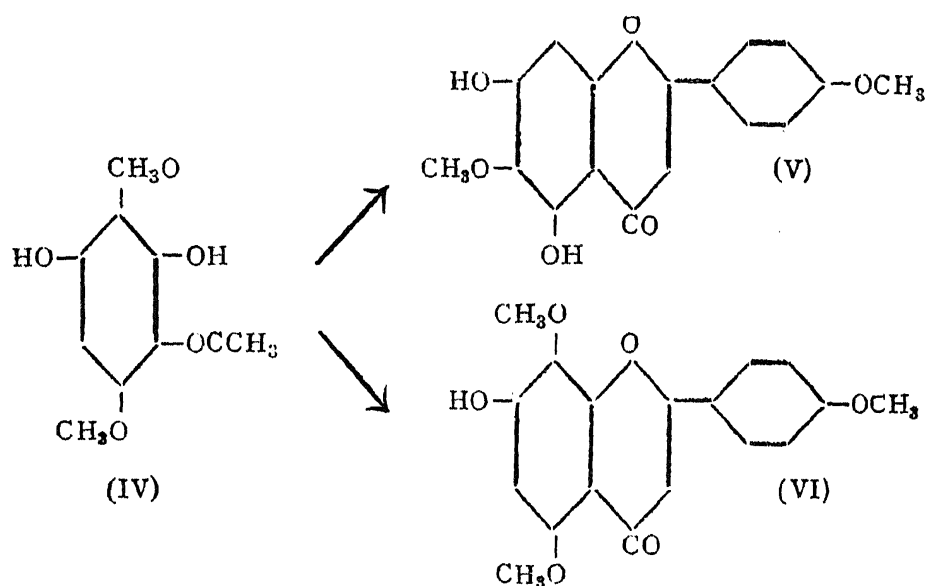
OF the possible flavones with the 5:6:7-arrangement of hydroxyls in the benzopyrone part only two are so far known to occur in nature either free or combined. They are baicalein and scutellarein. The latter was the first to be discovered and studied. It was isolated by Molisch and Goldschmiedt<sup>1</sup> from the leaves and flowers of *Scutellaria altissima*; it has also been found in the leaves and flowers of *S. baicalensis*. Its constitution was investigated by Goldschmiedt and Zerner<sup>2</sup> who concluded that it should be either 5:6:7:4'-(I) or 5:7:8:4'-tetrahydroxy flavone (II). This was confirmed by the synthesis of Bargellini<sup>3</sup> who submitted pentamethoxy-dibenzoyl-methane (III) to the action of hydriodic acid. The reaction could proceed in two ways, but actually scutellarein alone was obtained. This synthesis, however, did not enable the choice to be made between the two alternatives.



The trihydroxy flavone, baicalein was obtained from the roots of *S. baicalensis* by Shibata, Iwata and Nakamura<sup>4</sup> and it has also been found to be present in the root and stem barks of *Oroxylum indicum*.<sup>4</sup> It resembles scutellarein closely in its properties. The substance had already been synthesised by Bargellini<sup>5</sup> following the method adopted by him for scutellarein. Of the two possible isomers only one was again obtained

and that was given the 5:6:7-constitution. The main point mentioned in favour of this was that the product was not identical with hydroxy-chrysin obtained by Nierenstein<sup>6</sup> by the oxidation of chrysin and considered by him to be 5:7:8-trihydroxy flavone. Since Nierenstein's claim was later shown to be wrong, this support lost its significance. Hattori<sup>7</sup> who later repeated the above synthesis of Bargellini was not able to confirm the older observations regarding the exclusive formation of scutellarein from the diketone (III). Similar results were obtained by him even with regard to the baicalein synthesis. Consequently the previous synthetic support for the constitution of these compounds could not be considered definite.

Wessely and Moser<sup>8</sup> attempted to supply more definite evidence for the constitution of scutellarein by the synthesis of 5:7:8:4'-tetrahydroxy flavone in an unambiguous manner. For this purpose 2:4-dihydroxy-3:6-dimethoxy acetophenone (IV) was heated with the anhydride and sodium salt of anisic acid according to the method of Allan and Robinson. The product was, however, found to be a dimethyl ether of scutellarein (V) and this extraordinary result was attributed to initial demethylation in the ortho-position of the ketonic group and subsequent ring closure favouring the 5:6:7-arrangement. Thus even in this method complications were found to exist. In one of the large number of experiments, however, such demethylation did not occur and the normal condensation product, 7-hydroxy-5:8:4'-trimethoxy flavone (VI) was produced.

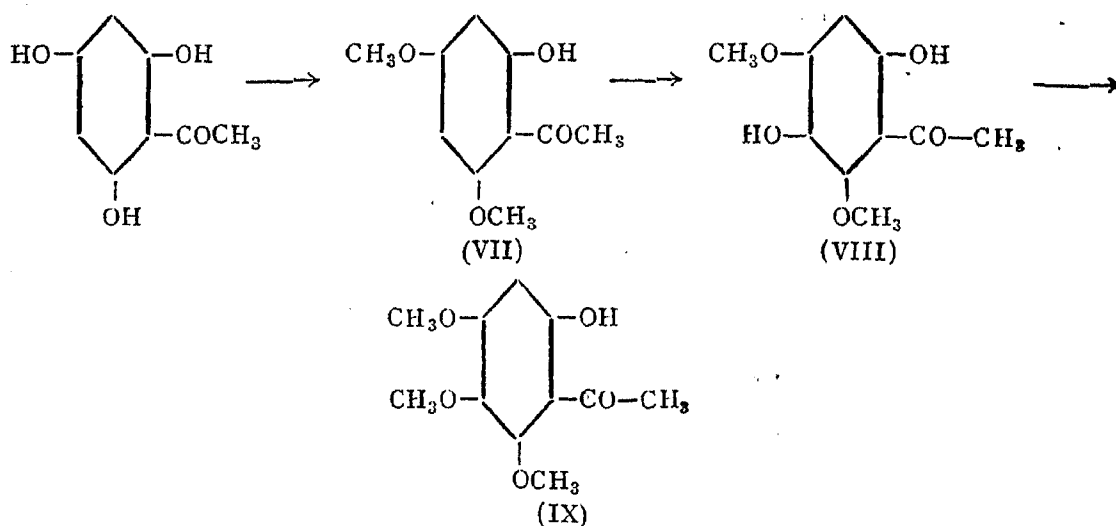


An unequivocal proof for the constitution of scutellarein was provided by Robinson and Schwarzenbach<sup>9</sup> who synthesised its tetramethyl ether by a novel method in which the 4-aminoderivative of the corresponding flavylum salt was an intermediate. This method, however, involves the preparation of

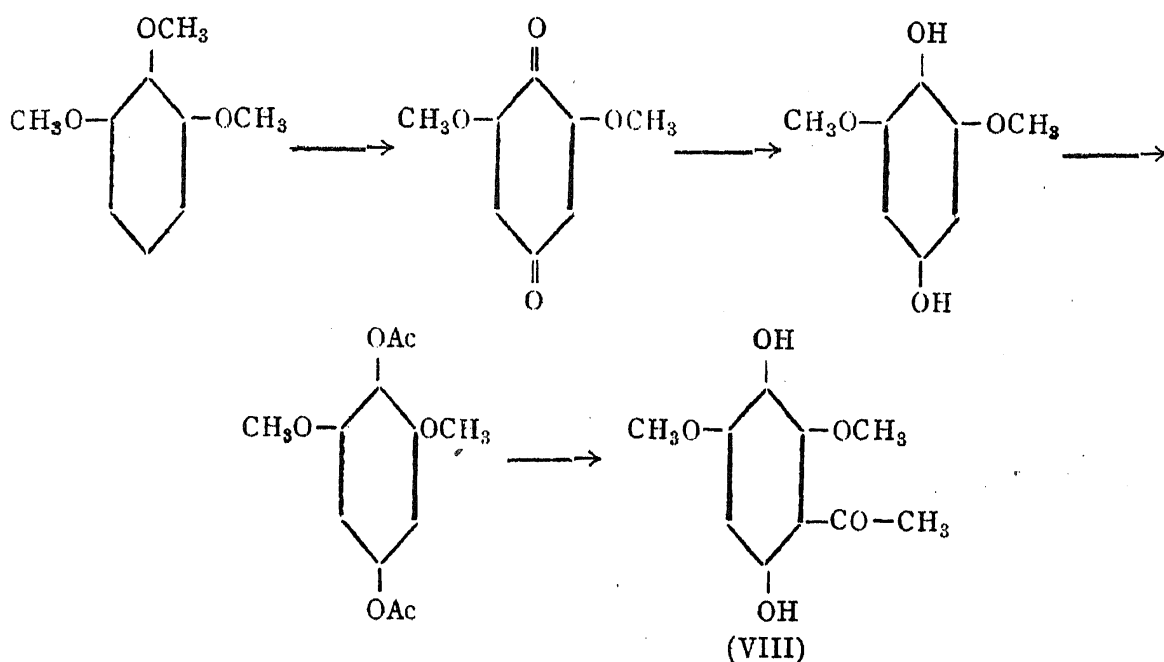
aroyl-pyruvamides which are not easily accessible and hence has not been generally employed for the synthesis of flavones.

In view of the position reviewed above, a simple and at the same time unambiguous method of synthesis of the 5:6:7-hydroxyflavones seemed to be needed. One such method which will also be useful for the study of the partial methyl ethers of baicalein and scutellarein has now been worked out. The required ortho-hydroxy ketone has been prepared by an unambiguous method and converted into the flavones by adopting the Baker-Venkataraman<sup>10</sup> procedure which is free from complications. The constitution of the products are therefore free from doubt and the work reported in this paper therefore provides unequivocal confirmation of the constitutions of baicalein and scutellarein.

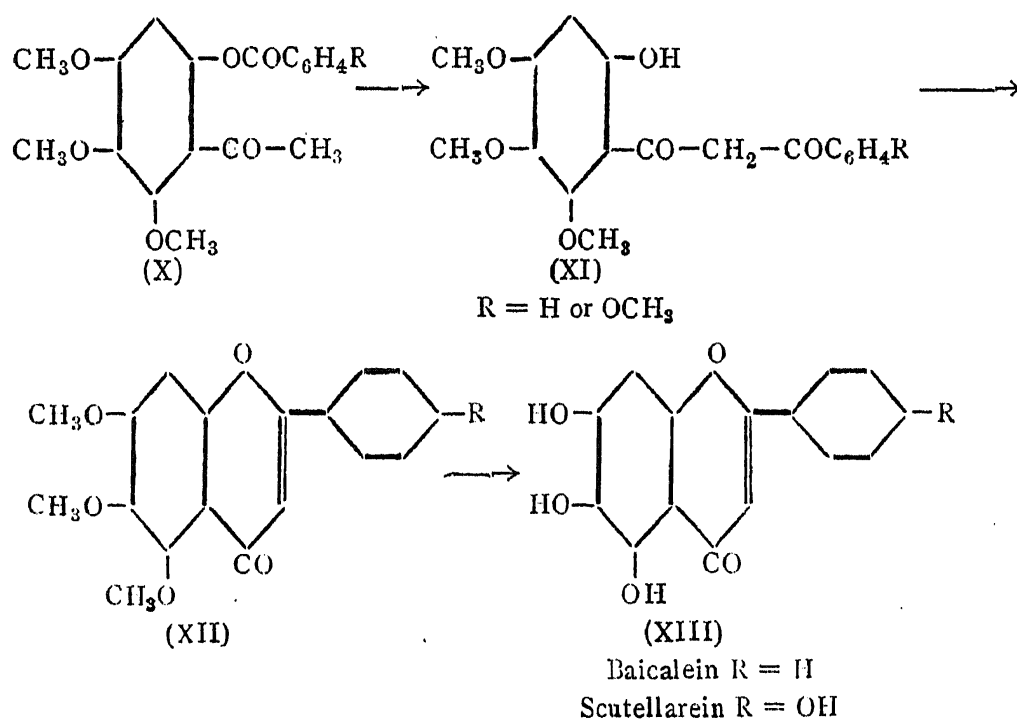
2-Hydroxy-4:5:6-trimethoxyacetophenone (IX) has now been prepared starting from phloroacetophenone and passing through the stages indicated below. Phloroacetophenone is subjected to partial methylation using the requisite amounts of dimethyl sulphate and potassium carbonate. The 4:6-dimethyl ether (VII) is obtained in good yield. This compound was originally made by Kostanecki and Tambor<sup>11</sup> by the partial demethylation of phloroacetophenone trimethyl ether and was subsequently obtained by Canter, Curd and Robertson<sup>12</sup> along with the *p*-hydroxy isomer by the Hoesch condensation of phloroglucinol dimethyl ether with acetonitrile.



Phloroacetophenone-dimethyl ether (VII) undergoes smooth oxidation with potassium persulphate in alkaline solution to give the 2:5-dihydroxy compound (VIII) in good yield. The constitution of this ketone is arrived at not only from analogy with a large number of similar cases<sup>13</sup>, but is supported by its reactions. This compound was obtained earlier by Mauthner<sup>14</sup> starting from pyrogallol trimethyl ether and proceeding as indicated below:



The new method of preparation seems to be definitely better. The final stage is partial methylation converting the dihydroxy ketone (VIII) into (IX).<sup>13</sup> Its benzoyl and anisoyl derivatives (X) undergo rearrangement into the ortho-hydroxy diketones (XI) in the presence of sodamide in toluene solution and ring closure to the flavones (XII) is effected by heating with glacial acetic acid and sodium acetate. Demethylation with boiling hydriodic acid yields baicalein and scutellarein (XIII).



The hydroxy compounds and the methyl ethers have all the properties recorded for baicalein, scutellarein and their derivatives. The synthetic baicalein and its derivatives have been compared with samples obtained from *Oroxylum indicum* and found to be identical. The following important

points may be noted. Neither the hydroxy flavone nor their methyl ethers develop any fluorescence in alcoholic or concentrated sulphuric acid solution. The two hydroxy compounds resemble each other in their reaction with alcoholic ferric chloride, lead acetate and sodium amalgam and differ in their behaviour with sodium hydroxide. While baicalein yields rapidly bluish-green flocks on the addition of aqueous alkali, scutellarein dissolves to give a greenish yellow solution which rapidly turns deep green.

#### EXPERIMENTAL

*2-Hydroxy-4:6-dimethoxyacetophenone* (VII).—Phloracetophenone (4.2 g.) dried in an air-oven at  $120^{\circ}$ , was dissolved in dry acetone (15 c.c.); to the clear solution was added dry benzene (75 c.c.), freshly ignited potassium carbonate (15 g.) and dimethyl sulphate (6.5 g.; 2.2 mols.) and the mixture refluxed on the water-bath for 12 hours with occasional shaking. The inorganic salts were then filtered and washed with hot benzene. The filtrate was washed twice with water, (20 c.c.) each time, and then extracted with 5% aqueous sodium hydroxide four times. The united alkaline extract was poured into ice-cold dilute hydrochloric acid when 2-hydroxy-4:6-dimethoxyacetophenone was precipitated as a practically colourless crystalline mass. It was filtered and thoroughly macerated with 5% aqueous sodium carbonate to remove any monomethyl ether that might have been formed, and again filtered and washed well with water. (The filtrate did not yield any crystalline solid on acidification). Yield, 3.2 g. On crystallisation from dilute alcohol it was obtained as colourless irregular prisms melting at  $82-83^{\circ}$  (Canter, Curd and Robertson<sup>10</sup> give m.p.  $81-82^{\circ}$ ). It dissolved in aqueous alkali to an yellow solution and gave a brownish-red ferric reaction in alcoholic solution.

The substance (0.5 g.) was acetylated by heating with acetic anhydride (5 c.c.) and freshly fused sodium acetate (1.0 g.) on the boiling water-bath for two hours. The acetyl derivative crystallised from ethyl acetate as stout rhombic prisms and melted at  $106-107^{\circ}$  (Canter, Curd and Robertson<sup>12</sup> give m.p.  $106-7^{\circ}$ ).

*2:5-Dihydroxy-4:6-dimethoxy-acetophenone* (VIII).—2-Hydroxy-4:6-dimethoxy-acetophenone (15 g.) was dissolved in aqueous sodium hydroxide (20 g. in 200 c.c. of water), the solution cooled to a temperature of  $15-20^{\circ}$  and kept continuously stirred. A solution of potassium persulphate (22 g.; 1.1 mol.) in water (300 c.c.) was then introduced dropwise during the course of 4 hours, the temperature being maintained at  $15-20^{\circ}$  throughout the reaction. After allowing to stand for 24 hours, the dark reddish-brown

reaction mixture was rendered distinctly acid to litmus by the addition of concentrated hydrochloric acid. The unreacted original ketone which was precipitated as a dark brown crystalline solid, was filtered and washed with a small quantity of water. The clear aqueous filtrate was treated with sodium sulphite (5 g.) and animal charcoal (3 g.) and again filtered after stirring well for about 5–10 minutes. Concentrated hydrochloric acid (150 c.c.) was then added and the solution heated on the boiling water-bath for  $\frac{1}{2}$  hour. On cooling it rapidly deposited a brownish yellow crystalline mass which was collected, and washed with water. Yield, 5 g. The filtrate was twice extracted with ether and the solvent distilled when a further quantity (1 g.) of the dihydroxy-compound was obtained. If the solution should be heated on the water-bath for a longer duration (1 hour) for the hydrolysis, the product obtained was very deep brown in colour and was difficult to purify. When twice crystallised from aqueous alcohol using animal charcoal the substance was obtained as stout yellow rhombic prisms melting at 164–65° (Mauthner<sup>14</sup> gives m.p. 162–63°). It was moderately soluble in hot water, more so in alcohol and acetone, but sparingly soluble in light petroleum. Its solution in aqueous sodium hydroxide was bright yellow and turned deep reddish-brown on keeping. In alcoholic solution the substance gave a transient green colouration with ferric chloride which rapidly became reddish-brown either on keeping or on the addition of a slight excess of the reagent. No precipitate was obtained with lead acetate in alcoholic solution. (Found: C, 56.8; H, 5.4;  $C_{10}H_{12}O_5$  requires C, 56.6; H, 5.7%.)

*2:5-Dibenzoyloxy-4:6-dimethoxy acetophenone.*—Dry pyridine (8 c.c.) and benzoyl chloride (1.5 g.) were added to the above *p*-dihydroxy acetophenone (1.0 g.) and the mixture heated on the boiling water-bath for 20 minutes. It was added to ice-cold water containing a few c.c. of hydrochloric acid and the precipitated brown solid collected, washed with water and crystallised twice from alcohol in which it was moderately soluble. The dibenzoate was thus obtained as colourless thick aggregates of micaceous plates and it melted at 153–54°. The substance did not dissolve in cold aqueous alkali and gave no colour with ferric chloride in alcoholic solution. (Found: C, 68.4; H, 5.1;  $C_{24}H_{20}O_7$  requires C, 68.6; H, 4.8%.)

*2-Hydroxy-4:5:6-trimethoxy acetophenone (IX).*—The 2:5-dihydroxy-compound (2 g.) was dissolved in a mixture of dry acetone (10 c.c.) and dry benzene (75 c.c.) and to this solution were added acid-free dimethyl sulphate (1 c.c.; 1.1 mol.) and freshly ignited potassium carbonate (6 g.). The mixture was heated under reflux for 12 hours, the inorganic salts filtered and washed with a small quantity of hot benzene. The benzene filtrate was

washed with 5% aqueous sodium carbonate in order to remove any un-methylated dihydroxy-compound and then extracted with 10% aqueous sodium hydroxide. The united alkaline extracts were acidified with ice-cold (1:1) hydrochloric acid when the partially methylated ether was obtained as a reddish-brown oil. It was taken in ether, the ether solution dried over sodium sulphate and the solvent distilled. The residue was then treated with light petroleum (b.p. 40-60°) when the last traces of unchanged dihydroxy compound were precipitated. After allowing to stand for an hour, the petroleum ether solution was carefully decanted and the solvent was distilled off; 2-hydroxy-4:5:6-trimethoxy acetophenone was left behind as a yellow oil. Yield, 1.5 g. It dissolved in aqueous sodium hydroxide to a yellow solution and gave a deep violet brown colour with ferric chloride in alcoholic solution (*cf.* Baker<sup>13</sup>).

*2-Benzoyloxy-4:5:6-trimethoxy acetophenone (X, R = H).*—The above compound (2 g.) was dissolved in dry pyridine (10 c.c.) and treated with benzoyl chloride (1.5 c.c.). After shaking well for five minutes, the mixture was heated on the water-bath for  $\frac{1}{2}$  hour and then added to ice-water containing hydrochloric acid. The benzoyl derivative which separated as an oil was taken in ether, the ether solution washed successively with dilute hydrochloric acid, and aqueous sodium hydroxide. After a final washing with water, the solution was dried over calcium chloride and the solvent distilled. The solid product was crystallised first from alcohol, then from benzene and finally from benzene-alcohol mixture. The benzoyl derivative was thus obtained as broad rectangular plates and prisms and melted at 87-88°. Yield, 2 g. The substance gave no ferric reaction and did not dissolve in cold aqueous alkali. (Found: C, 65.6; H, 5.8;  $C_{18}H_{18}O_6$  requires C, 65.5; H, 5.5%.)

*2-Hydroxy-4:5:6-trimethoxydibenzoylmethane (XI, R = H).*—To a solution of the above benzoyl derivative (2 g.) in dry toluene (30 c.c.) was added sodamide (8 g.) which had been finely powdered under toluene. The mixture was well stirred for 10 minutes and then heated on the boiling water-bath for 4 hours with frequent shaking. The yellow solid product was filtered, washed well with hot benzene, dried and carefully added to ice-cold water. The resulting yellow solution was filtered and saturated with carbon dioxide. The dibenzoylmethane separated as a deep orange-red oil which turned into a deep-yellow solid when left in the refrigerator for two days. It was collected, washed with water, dried and crystallised from benzene, light petroleum mixture. Yield, 1.2 g. After a second crystallisation from the same solvent the diketone was obtained as golden yellow rectangular

plates and prisms and melted at 99–100°. It was easily soluble in alcohol, acetone and benzene and dissolved in aqueous sodium hydroxide to a bright yellow solution. Its alcoholic solution gave a deep brownish-green colour with ferric chloride. (Found: C, 65.3; H, 5.8;  $C_{18}H_{18}O_6$  requires C, 65.5; H, 5.5%.)

*5:6:7-Trimethoxy-flavone (Baicalein trimethyl ether, XII, R = H).—*The dibenzoylmethane (1 g.) was dissolved in glacial acetic acid (10 c.c.) and to the solution was added fused sodium acetate (2 g.). The mixture was gently boiled over a wire-gauze for 4 hours and then diluted with water (100 c.c.). When allowed to stand for two or three hours, the solution deposited a practically colourless crystalline solid which was collected, washed, and crystallised from aqueous alcohol. Yield, 0.6 g. On recrystallisation from dilute alcohol the trimethoxyflavone was obtained as colourless elongated rectangular prisms (mostly rods) and melted at 165–66° (Hattori<sup>1</sup> gives m.p. 163–64°). It was insoluble in aqueous sodium hydroxide and gave no colour with ferric chloride. Its solution in concentrated sulphuric acid was yellow without any fluorescence in daylight. With magnesium and concentrated hydrochloric acid its alcoholic solution developed an orange-yellow colour. (Found: C, 69.1; H, 4.9;  $C_{18}H_{16}O_5$  requires C, 69.2; H, 5.1%.)

*5:6:7-Trihydroxy-flavone (Baicalein, XIII, R = H).—*The foregoing methoxy flavone (0.3 g.) was dissolved in acetic anhydride (5 c.c.) and cautiously treated with hydriodic acid (*d.* 1.7; 5 c.c.) and the mixture heated at 135–40° for two hours (oil-bath). On pouring the cooled reaction mixture into water saturated with sulphur dioxide, the trihydroxy flavone separated as an yellow solid, which was collected, boiled with water and crystallised twice from alcohol. It formed yellow coloured narrow rectangular plates and melted at 264–65° (Shibata, Iwata and Nakamura<sup>4</sup> give m.p. 264–65°).

The trihydroxy flavone was moderately soluble in alcohol, more so in acetone and glacial acetic acid, but sparingly soluble in petroleum ether. Its solution in concentrated sulphuric acid was deep yellow and exhibited no fluorescence. In alcoholic solution it gave an orange-yellow precipitate with lead acetate, and a brown colour with a tinge of green with ferric chloride. When added to aqueous ammonia, the crystals developed an orange-red colour and dissolved to give a bright-yellow solution. The flavone dissolved with difficulty in aqueous sodium carbonate to a greenish-yellow solution which gave a dark greenish-brown precipitate on keeping. In 10% aqueous sodium hydroxide the crystals turned deep red in colour and subsequently changed into greenish-brown flocks. When treated with



sodium amalgam in absolute alcohol, it immediately gave green flocks (Bargellini's test). (Found: C, 66.6; H, 4.0;  $C_{15}H_{10}O_5$  requires C, 66.7; H, 3.7%.)

*Baicalein triacetate*.—The triacetate was prepared by treating the flavone (0.1 g.) with acetic anhydride (5 c.c.) and fused sodium acetate (1 g.) and boiling the mixture for two hours. When crystallised twice from ethyl acetate, it was obtained as short, colourless rectangular rods and it melted at 194–95° with slight sintering at 190° (Shibata, Iwata and Nakamura<sup>4</sup> give m.p. 191–92°).

2 - Anisoyloxy - 4 : 5 : 6 - trimethoxyacetophenone (*X*,  $R = OCH_3$ ).—2-Hydroxy-4 : 5 : 6-trimethoxyacetophenone (IX) (2 g.) was anisoylated by heating with anisoyl chloride (2 c.c.) and dry pyridine (10 c.c.), for  $\frac{1}{2}$  hour on the boiling water-bath and the product worked up as in the case of the benzoyl derivative. The colourless crystalline solid, obtained on removal of the ether, was crystallised from alcohol, benzene and finally from benzene-light petroleum mixture. The anisate was thus obtained as (colourless) stout prisms and it melted at 112–13°. It did not dissolve in cold aqueous sodium hydroxide and gave no ferric reaction. (Found: C, 63.3; H, 5.2;  $C_{19}H_{20}O_7$  requires C 63.3; H, 5.6%.)

2-Hydroxy-4 : 5 : 6 : 4'-tetramethoxydibenzoylmethane (*XI*,  $R = OCH_3$ ).—A solution of the above *O*-anisoyl derivative (2 g.) in dry toluene (30 c.c.) was treated with finely powdered sodamide (8 g.). The mixture which rapidly turned yellow was heated on the boiling water-bath for 5 hours and the yellow solid collected, washed with hot benzene, dried and added to ice-water. The yellow solution was saturated with carbon dioxide and the dibenzoylmethane which first separated as an oil, solidified on leaving in the refrigerator for two days. The solid was then collected, dried and crystallised from benzene-light petroleum mixture when it was obtained as bright yellow rectangular prisms melting at 114–15°. Yield, 1.2 g. It was readily soluble in alcohol, acetone and benzene but less so in petroleum ether. It dissolved in aqueous alkali to give a bright yellow solution and gave an olive green colour with ferric chloride in alcoholic solution. (Found: C, 63.5; H, 5.9;  $C_{19}H_{20}O_7$  requires C, 63.3; H, 5.6%.)

5 : 6 : 7 : 4'-Tetramethoxy flavone (*Scutellarein tetramethyl ether*, (*XII*,  $R = OCH_3$ ).—A mixture of the above dibenzoylmethane (1 g.), glacial acetic acid (10 c.c.) and fused sodium acetate (2 g.) was gently boiled for 4 hours and diluted with water (100 c.c.). The aqueous solution was extracted with ether and the ether solution carefully shaken with 5% aqueous sodium carbonate to remove acetic acid and then washed with water. On

distilling off the solvent, a colourless crystalline solid was obtained which was recrystallised from dilute alcohol. Yield, 0.8 g. It was readily soluble in the common organic solvents and on recrystallisation from aqueous alcohol, scutellarein tetramethylether was obtained as colourless stout cubical crystals and melted at 162–63° (Goldschmiedt and Zerner<sup>2</sup> give m.p. 158–60°). It was insoluble in aqueous alkali and gave no colour with ferric chloride in alcoholic solution. It dissolved in concentrated sulphuric acid to give an yellow solution which exhibited no fluorescence. (Found in a sample dried *in vacuo* at 130° for two hours; C, 66.8; H, 5.5; C<sub>19</sub>H<sub>18</sub>O<sub>6</sub> requires C, 66.7; H, 5.3%.)

*5:6:7:4'-Tetra-hydroxy flavone (Scutellarein, XIII, R = OH)*—The demethylation of the tetramethoxy flavone (0.2 g.) was effected by heating (oil-bath) at 135–40° with acetic anhydride (5 c.c.) and hydriodic acid (*d.* 1.7; 5 c.c.). The tetrahydroxy flavone was twice crystallised from alcohol when it was obtained as short, yellow needles. Yield, 0.15 g. It turned brown at about 300° and did not melt down below 340° (Goldschmiedt and Zerner<sup>2</sup> found that it becomes dark at about 300° and does not melt or decompose below 330°). The substance dissolved in alcohol, acetone and ethyl acetate with difficulty but more readily in glacial acetic acid. Its solution in concentrated sulphuric acid was yellow without any fluorescence. With lead acetate in alcoholic solution it gave an orange yellow precipitate and with ferric chloride it developed a green colour which turned brown with a tinge of green. The substance dissolved in ammonia to give a bright yellow solution which subsequently turned orange-brown; in aqueous sodium carbonate it gave an yellow colour which rapidly turned green. In aqueous sodium hydroxide it formed a deep greenish-yellow solution which immediately became pure green in colour; no precipitate was obtained even on keeping the solution for 24 hours. When the substance was treated with sodium amalgam in absolute alcohol, there was an immediate formation of green flocks (Bargellini's test). (Found: C, 63.0; H, 3.8; C<sub>15</sub>H<sub>10</sub>O<sub>6</sub> requires C, 62.9; H, 3.5%.)

*Scutellarein tetraacetate*.—The tetraacetate prepared by heating (oil-bath) the hydroxy flavone (0.1 g.) with acetic anhydride (5 c.c.) and fused sodium acetate (1 g.) was crystallised twice from acetic acid-alcohol mixture. It was obtained as long fine needles and melted at 240–41° (Goldschmiedt and Zerner<sup>2</sup> give m.p. 235–37°; Wessely and Moser<sup>8</sup> give m.p. 238°).

#### SUMMARY

A simple and at the same time unambiguous method of synthesis of the 5:6:7-hydroxyflavones, baicalein and scutellarein and their derivatives is

described. It starts from phloracetophenone which is partially methylated to the 4:6-dimethyl ether. Oxidation of this ether with potassium persulphate yields the 2:5-dihydroxy compound which on partial methylation produces 2-hydroxy-4:5:6-trimethoxyacetophenone. Using the benzoyl and anisoyl derivatives of this ketone and adopting the Baker-Venkataraman procedure, the trimethyl ether of baicalein and the tetramethyl ether of scutellarein have been prepared and from them the hydroxyflavones and their acetates.

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