

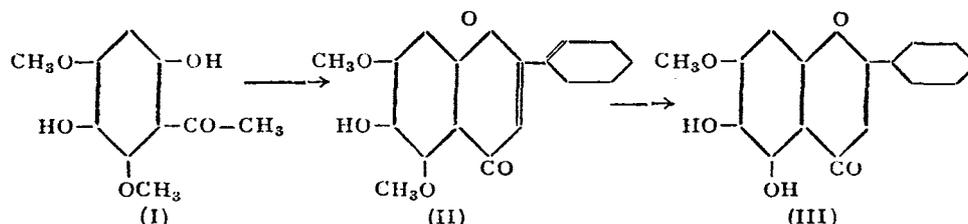
SYNTHESIS OF 5:6:7-HYDROXYFLAVONES AND THEIR DERIVATIVES—PART II

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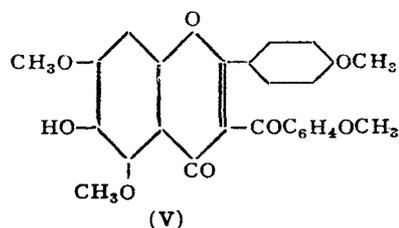
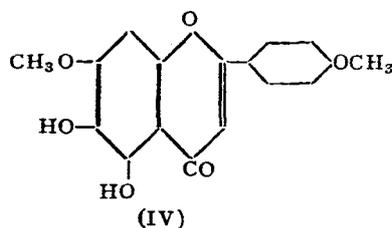
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In continuation of the work described in Part I,¹ an attempt has been made to prepare partially methylated derivatives of baicalein and scutellarein. For this purpose 2:5-dihydroxy-4:6-dimethoxy acetophenone (I) is subjected to the Allan-Robinson condensation using the anhydride and sodium salt of (1) benzoic acid and of (2) anisic acid. In the first case the product is 5:7-dimethoxy-6-hydroxyflavone (II). On methylation it yields 5:6:7-trimethoxy flavone, baicalein-trimethyl ether, identical with the sample prepared by the Baker-Venkataraman method.¹ Partial demethylation could be effected using aluminium chloride under mild conditions yielding 7-methoxy-5:6-dihydroxyflavone (baicalein-7-methyl ether III).



In its properties and reactions it is markedly different from croxylin-A² which is considered to be the 6-methyl ether of baicalein. The mixed melting point with a sample of the latter obtained from the root bark of *Oroxylum indicum* is depressed. The comparison is brought out in the following table:

	Oroxylin-A	7-Methyl ether of Baicalein
Appearance ..	Yellow needles	Thick rhombohedral prisms (Yellow)
M.p. of the substance ..	230-31°	219-20°
" acetate ..	131-32°	239-40°
Alcoholic FeCl ₃ ..	Red-violet	Green
Aq. NaOH ..	Yellow solution	Greenish-brown precipitate
Na Amalgam ..	Yellow solution	Blue solution, and a brown precipitate after an interval



The condensation of the above dihydroxy ketone (I) with anisic anhydride and sodium anisate gives rise to two products which could be separated by fractional crystallisation from alcohol. The less soluble component is a dimethyl ether whose colour reactions are very similar to those of the 7-methyl ether of baicalein. On methylation it yields the tetra-methyl ether of scutellarein and hence it is considered to be the 7:4'-dimethyl ether of scutellarein (IV). Its formation should be due to partial demethylation taking place during the Allan-Robinson condensation. Such demethylation has been noted in many other similar cases.

The second product obtained in very poor yields resembles in its reactions 5:7-dimethoxy-6-hydroxyflavone (II). Its methyl ether is, however, different from scutellarein tetramethyl ether. Hence it is not 5:7:4'-tetramethoxy-6-hydroxyflavone. The analytical results agree with the requirements for the 3-anisoyl derivative (V).

The above mentioned 7:4'-dimethyl ether of scutellarein is different in its properties from the isomeric 6:4'-dimethyl ether prepared by Wessely and Moser³ and considered to be identical with the dimethyl ether occurring in the flowers of *Linaria vulgaris*.⁴ The differences are shown below:

	7:4'-dimethyl ether of scutellarein	6:4'-dimethyl ether
Appearance	.. Yellow rectangular plates	Fine yellow needles
Melting point	.. 211-12°	201°, 219°
Aq. NaOH	.. Slowly forms a greenish yellow solution and a greenish brown precipitate is deposited	Yellow solution
FeCl ₃ reaction	.. Stable green	Dark brown

EXPERIMENTAL

5:7-Dimethoxy-6-hydroxyflavone (II).—2:5-Dihydroxy-4:6-dimethoxyacetophenone (1 g.), benzoic anhydride (5 g.) and sodium benzoate (2 g.) were intimately mixed and heated under diminished pressure at 180-85° (oil-bath) for 4 hours. After cooling, the hard brown mass was broken up, alcohol (50 c.c.) added and the mixture refluxed on the water-bath for 10

minutes. A solution of potassium hydroxide (4 g.) in water (6 c.c.) was then gradually introduced during the course of 15 minutes and the refluxing continued for a further 20 minutes. After distilling the alcohol under reduced pressure, the greenish-brown residue was dissolved in water (100 c.c.) and the solution filtered to remove any insoluble matter. On saturating it with carbon dioxide, the crude flavone separated as a brown solid which was filtered and crystallised twice from alcohol (animal charcoal). Yield 0.2 g. By another crystallisation from the same solvent, the dimethoxyflavone was obtained as pale yellow thick cubical crystals whereas it came down as fine needles when quickly crystallised. It melted at 212–13° and a further crystallisation did not raise the melting point.

It was moderately soluble in alcohol and more easily in acetone and glacial acetic acid. It dissolved in aqueous sodium hydroxide to give a bright yellow solution. In alcoholic solution it gave a weak brown colouration with ferric chloride and its solution in concentrated sulphuric acid was yellow without any fluorescence in daylight. (Found: C, 68.6; H, 4.9; $C_{17}H_{14}O_5$ requires C, 68.5; H, 4.7%.)

The substance (0.1 g.) was acetylated by refluxing (oil-bath) with acetic anhydride (5 c.c.) and fused sodium acetate (1 g.) for 3 hours. The acetate was crystallised from dilute acetic acid when it was obtained as colourless stout plates melting at 218–19°. It did not dissolve in cold aqueous alkali and gave no ferric reaction. (Found: C, 66.9; H, 4.9; $C_{19}H_{16}O_6$ requires C, 67.1; H, 4.7%.)

5:6:7-Trimethoxyflavone (Baicalein trimethyl ether).—The dimethoxy flavone (0.15 g.) was methylated in dry acetone (25 c.c.) using anhydrous potassium carbonate (2 g.) and dimethyl sulphate (1 c.c.) and boiling for 12 hours. The crude methyl ether separated as a practically colourless crystalline solid and it crystallised from dilute alcohol as colourless elongated rectangular prisms, melting at 165–66°. It was identical with baicalein trimethyl ether already reported¹ and the mixed melting point was undepressed. (Found: C, 68.9; H, 5.4; $C_{18}H_{16}O_5$ requires C, 69.2; H, 5.1%.)

7-Methoxy-5:O-dihydroxyflavone (7-O-methyl baicalein).—The partial demethylation of the above dimethyl ether (II) had to be effected under carefully controlled conditions. Excess of aluminium chloride and high temperature resulted in the reaction going too far producing baicalein.

To a solution of the dimethoxyflavone (0.25 g.) in nitrobenzene (25 c.c.) was added finely powdered anhydrous aluminium chloride (0.5 g.) and the mixture kept at the laboratory temperature for 24 hours. On the addition of petroleum ether, a yellow solid was precipitated, which was collected and

washed with a further quantity of petroleum ether to remove adhering nitrobenzene. The solid was added to water (50 c.c.) containing concentrated hydrochloric acid (2 c.c.) and glacial acetic acid (5 c.c.) and the mixture heated on the boiling water-bath for 15 minutes. The solution was then cooled and further diluted with water when the 7-methyl ether separated as a yellow crystalline solid. It was filtered, washed and crystallised twice from alcohol. Yield 0.15 g. On recrystallisation from absolute alcohol, it was obtained as thick rhombohedral prisms and melted at 219–20°. The melting point was depressed on admixture with an equal quantity of oroxylin-A. The dihydroxyflavone was moderately soluble in alcohol and acetone, and gave a stable green colouration with ferric chloride in alcoholic solution. With aqueous sodium hydroxide the crystals developed an orange-red colour and then changed into a dark greenish-brown precipitate. On treatment with sodium amalgam in absolute alcohol (Bargellini's test), the dihydroxyflavone gave an orange yellow solution which rapidly changed through green to blue in colour; a brown precipitate was obtained after some time. With lead acetate in alcoholic solution it gave an orange yellow precipitate. The yellow solution in concentrated sulphuric acid exhibited no fluorescence. (Found: C, 67.5; H, 4.4; OCH₃, 10.3; C₁₆H₁₂O₅ requires C, 67.6; H, 4.3; OCH₃, 10.9%.)

The dihydroxyflavone (0.1 g.) was acetylated by refluxing (oil-bath) with acetic anhydride (5 c.c.) and sodium acetate (1 g.) for two hours. The diacetate was crystallised twice from ethyl acetate when it was obtained as shining elongated hexagonal plates melting at 239–40°. (Found: C, 65.1; H, 4.6; C₂₀H₁₆O₇ requires C, 65.2; H, 4.3%.)

5:6-Dihydroxy-7:4'-dimethoxyflavone (7:4'-O-dimethyl scutellarein).—An intimate mixture of the dihydroxyacetophenone (I, 2 g.), anisic anhydride (12 g.) and sodium anisate (4 g.) was heated under diminished pressure at 180–85° (oil-bath) for 6 hours. The hydrolysis was effected by refluxing with alcohol (100 c.c.) and a solution of potassium hydroxide (10 g.) in water (10 c.c.) and the product worked up in the usual manner. The crude product obtained on saturating the alkaline solution with carbon dioxide was filtered and washed with water. Yield, 0.25 g. It gave two fractions on crystallisation from alcohol. When the hot alcoholic solution was cooled, a sparingly soluble yellow solid first separated. It was collected and crystallised twice from the same solvent when 5:6-dihydroxy-7:4'-dimethoxyflavone was obtained as yellow rectangular plates, melting at 211–13° with sintering at 208°. Yield, 0.15 g. Further crystallisation did not raise the melting point. The substance was moderately soluble in acetone but not so

readily in alcohol. Its solution in concentrated sulphuric acid was yellow and exhibited no fluorescence. In alcoholic solution it gave a stable green colouration with ferric chloride. When treated with dilute aqueous sodium hydroxide, the substance first became orange-red, then turned into greenish-blue flakes and dissolved to give a greenish-yellow solution; on allowing to stand, a greenish-brown precipitate was subsequently deposited. (Found: C, 65.0; H, 4.7; OCH₃, 19.0; C₁₇H₁₄O₅ requires C, 65.0; H, 4.5; OCH₃, 19.7%.)

The dihydroxyflavone (0.1 g.) was methylated using dry acetone (30 c.c.), anhydrous potassium carbonate (1 g.) and acid-free dimethyl sulphate (0.5 c.c.). The methyl ether was crystallised from dilute alcohol when it was obtained as colourless stout cubical crystals melting at 161–62° and identical with scutellarein tetramethyl ether.

5:7:4'-trimethoxy-6-hydroxy-3-anisoyl-flavone.—The alcoholic mother-liquor obtained after filtering off the above compound, was concentrated and allowed to cool. A pale greenish-yellow solid separated which after two crystallisations from dilute alcohol came out as pale yellow narrow rectangular plates and melted at 224–26°. Yield, 75 mg. It dissolved in aqueous sodium hydroxide to give an yellow solution. Its solution in alcohol gave a weak brown colouration with ferric chloride. (Found: C, 67.7; H, 4.9; OCH₃, 26.4; C₂₆H₂₂O₈ requires C, 67.5; H, 4.7; OCH₃, 26.8%.)

SUMMARY

Employing 2:5-dihydroxy-4:6-dimethoxyacetophenone and the Allan-Robinson method, the 5:7-dimethyl ether of baicalein is obtained and from it by partial demethylation the 7-methyl ether. This is definitely different from oroxylin-A. The use of anisic anhydride in the above condensation yields two products, (1) 7:4'-dimethyl ether of scutellarein and (2) 5:7:4'-trimethyl ether of 3-anisoyl-scutellarein. The former is different from the 6:4'-dimethyl ether obtained from natural sources.

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