

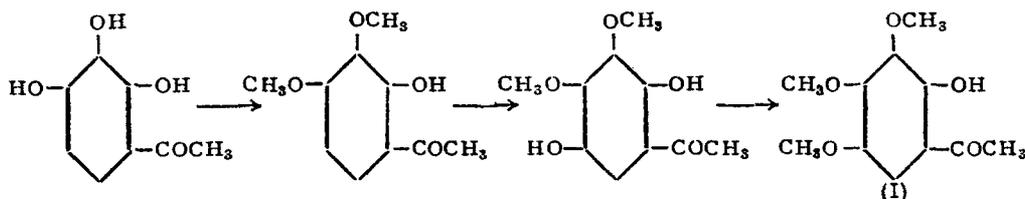
SYNTHESIS OF 6:7:8-HYDROXY-FLAVONES

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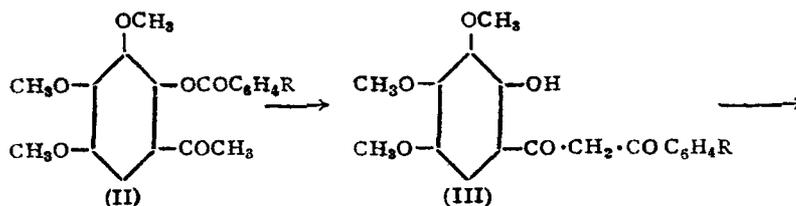
(From the Department of Chemistry, Andhra University)

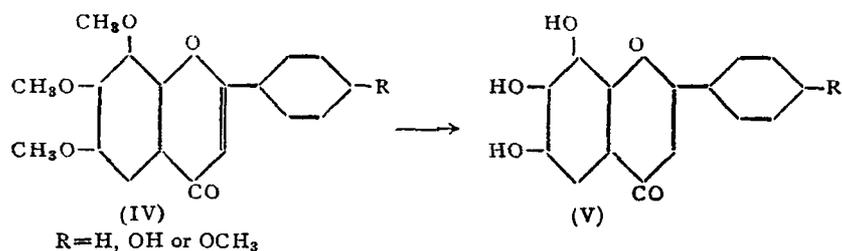
Received January 17, 1946

FLAVONES and flavonols derived from 1:2:3:4-tetra-hydroxy-benzene have not yet been isolated from natural sources. But they form a series having three contiguous hydroxyl groups (6:7:8) in the benzo-pyrone part somewhat parallel to those derived from 1:2:3:5-tetra-hydroxy-benzene with the 5:6:7-arrangement of hydroxyls. The difference in properties and reactions which this difference in structure may give rise to, is of interest and this information was required in connection with the study of plant pigments in progress in these laboratories. For purposes of comparative study the flavones of this type isomeric with baicalein and scutellarein have been synthesised and their properties described in this paper. The starting material for the present synthesis is 2-hydroxy-3:4:5-trimethoxyacetophenone (I) prepared according to the method of Baker.¹



The conversion into the flavones is effected by adopting the Baker-Venkataraman procedure.² The *O*-benzoyl or anisoyl compounds (II) are converted into the corresponding diketones (III) by means of sodamide and the final ring closure to the methoxyflavones (IV) carried out by heating with sodium acetate and acetic acid. Demethylation with hydriodic acid yields the hydroxyflavones (V). They have also been characterised by the preparation of their acetates.

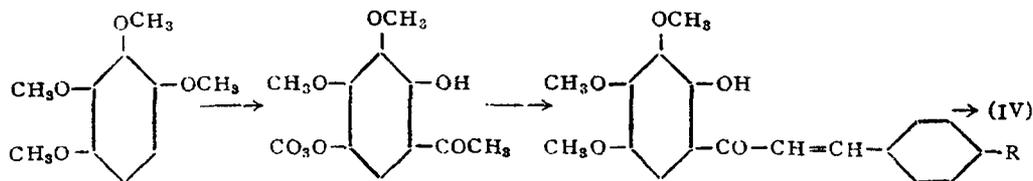




Structurally the new flavones have a hydroxyl in the 8-position in the place of the one present in the 5-position of baicalein and scutellarein. Regarding fluorescence in concentrated sulphuric acid the two pairs resemble and they give very little emission. The hydroxy compounds exhibit no fluorescence; among the ethers there is feeble emission only from 6:7:8:4'-tetramethoxy-flavone. In alcoholic solution neither the hydroxy compounds nor the methyl ethers give any fluorescence. This is in accordance with expectations; it has been noted³ that the 8-position in coumarins and flavylum salts is as inhibitive of fluorescence as the 5-position.

The isomeric compounds differ markedly in alkali colour reactions. Baicalein and scutellarein give bright green colour, the former yielding also a precipitate. The 6:7:8-hydroxy-compounds are more easily soluble and give a yellow colour in sodium carbonate and orange-red in sodium hydroxide solution. The ferric chloride colour is also different. The 6:7:8-compounds give a deep-green colour rapidly changing to greenish blue, whereas baicalein and scutellarein give a greenish-brown, the green colour not being prominent. The reaction of the new flavones with sodium amalgam in alcoholic solution (Bargellini's test) is also somewhat different.

After the above work was completed, an abstract of a paper by Bargellini and Oliviero on the synthesis of 6:7:8-hydroxyflavones and flavonols appeared in the *British Chemical Abstracts*.⁴ They adopted a different method as indicated below. The melting points of the final products and their derivatives as recorded by them agree with ours.



EXPERIMENTAL

2-Benzoyloxy-3:4:5-trimethoxyacetophenone (II, R = H).—2-Hydroxy-3:4:5-trimethoxyacetophenone (I, 2.5 g.) was treated with dry pyridine

(10 c.c.) and benzoyl chloride (2 c.c.) and shaken well for 10 minutes. The mixture was then heated on the water-bath for 20 minutes and added to ice-water containing a few c.c. of dilute hydrochloric acid. The benzoyl derivative separated as an oil which quickly solidified to a brown solid on stirring. It was filtered, washed with very dilute hydrochloric acid and then dissolved in sufficient quantity of ether. The ether solution was successively washed with dilute hydrochloric acid, aqueous sodium carbonate and sodium hydroxide to remove benzoic acid and unchanged ketone. It was once again washed with dilute hydrochloric acid and water and dried over calcium chloride. Distillation of the solvent yielded the benzoyl derivative as a colourless crystalline solid which was collected and recrystallised from alcohol and benzene. It was obtained as stout irregular prisms and melted at 127–28°. Yield, 2.0 g. The substance gave no colour with ferric chloride in alcoholic solution and was insoluble in cold aqueous sodium hydroxide (Found: C, 65.3; H, 5.3; $C_{18}H_{18}O_6$ requires C, 65.5; H, 5.5%).

2-Hydroxy-3:4:5-trimethoxydibenzoylmethane (III, R = H).—A solution of the above compound (2 g.) in dry toluene (20 c.c.), was treated with sodamide (8 g.) finely powdered under toluene. The mixture which rapidly turned yellow, was vigorously stirred for ten minutes and heated on the boiling water-bath for 4-5 hours with frequent shaking. The yellow solid product was then filtered, washed well with warm benzene and cautiously added with stirring to crushed ice. When the unreacted sodamide was completely decomposed, the yellow solution was filtered to remove any insoluble matter and saturated with carbon dioxide. The dibenzoylmethane separated as a bright yellow oil. A further small quantity of it was obtained by extracting the toluene filtrate with 5% aqueous alkali and saturating the alkaline solution with carbon dioxide. Both the lots were taken together in ether and the clear ether solution dried over sodium sulphate. The solvent was then distilled when it left an oily product which did not solidify even when allowed to stand in the refrigerator for 24 hours. It was therefore directly used for conversion into the trimethoxy-flavone. Yield, 0.6 g. It dissolved in aqueous sodium hydroxide to give a bright yellow solution and its solution in alcohol developed a bluish-green colouration with a drop of ferric chloride.

6:7:8-Trimethoxy-flavone (IV, R = H).—The crude dibenzoylmethane (0.5 g.) was dissolved in glacial acetic acid (8 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, cooled and diluted with water (80 c.c.). A small quantity of the trimethoxy-flavone separated as a crystalline solid. It was filtered and the filtrate extracted with ether. The ether extract was carefully shaken with 5% aqueous sodium carbonate to remove acetic acid and then

washed with water. On distilling off the solvent, more of the flavone was obtained as a colourless crystalline solid. The combined product was crystallised from dilute alcohol. After a further crystallisation from ethylacetate-light petroleum mixture, the trimethoxy flavone was obtained as aggregates of prismatic rods and melted at 144–45° (Bargellini and Oliviero⁴ give m.p. 146°). Yield, 0.3 g. It was readily soluble in the common organic solvents and gave an orange-yellow colour with magnesium and concentrated hydrochloric acid in alcoholic solution. Its solution in concentrated sulphuric acid was yellow and exhibited no fluorescence (Found: C, 69.0; H, 5.3; C₁₈H₁₆O₅ requires C, 69.2; H, 5.1%).

6:7:8-Trihydroxyflavone (*V*, *R* = *H*).—A solution of the trimethoxy flavone (0.25 g.) in acetic anhydride (5 c.c.) was treated with hydriodic acid (*d*, 1.7; 5 c.c.) and the mixture heated at 130–35° in an oil-bath for 2 hours. It was then cooled and poured into water containing sulphurous acid. The precipitated yellow solid was collected, boiled with water and crystallised from alcohol. Yield, 0.15 g. On recrystallisation from alcohol the trihydroxyflavone was obtained as straw-coloured rectangular micaceous plates and melted at 280–282° with slight decomposition (Bargellini and Oliviero⁴ give m.p. 280° decomp.). Its alcoholic solution developed a greenish-blue colouration on the addition of a drop of ferric chloride; with excess of the reagent a brown precipitate was deposited slowly. It dissolved in concentrated sulphuric acid to an yellow solution which exhibited no fluorescence. With lead acetate in alcoholic solution it gave a bright orange-yellow precipitate, and with magnesium and hydrochloric acid its alcoholic solution developed an orange colouration. When treated with sodium amalgam in absolute alcohol the trihydroxyflavone gave a green solution and a flocculent green precipitate which slowly turned brown (Bargellini's test). It dissolved in aqueous alkali to give a brownish-orange solution which gradually faded in colour; no green flocks separated. With dilute ammonia it gave an yellow solution (Found in a sample dried at 120° for 2 hours *in vacuo*: C, 66.5; H, 3.9. C₁₅H₁₀O₅ requires C, 66.7; H, 3.7%).

The triacetate was prepared by heating the above hydroxy-flavone (0.1 g.) with acetic anhydride (5 c.c.) and fused sodium acetate (1 g.) for two hours. It was crystallised twice from ethylacetate and was obtained as stout flat needles melting at 207–08° with previous sintering at 202° (Bargellini and Oliviero⁴ give m.p. 197–98°) (Found: C, 63.7; H, 4.3. C₂₁H₁₆O₈ requires C, 63.6; H, 4.1%).

2-Anisoyloxy-3:4:5-trimethoxy-acetophenone (*II*, *R* = *OCH*₃).—The hydroxyketone (*I*, 2.5 g.) was treated with dry pyridine (10 c.c.) and anisoyl

chloride (2 c.c.) and the mixture heated on the boiling water-bath for 30 minutes. The product was worked up in the same way as described for the benzoyl derivative. The crude *O*-anisoyl compound was a colourless solid which was purified by crystallisation from alcohol and then alcohol-benzene mixture. Yield, 2.0 g. A final crystallisation from alcohol yielded elongated rectangular plates and prisms melting at 114–15°. It did not dissolve in cold dilute aqueous sodium hydroxide and gave no colour with ferric chloride in alcoholic solution (Found: C, 63.1; H, 5.8. $C_{19}H_{20}O_7$ requires C, 63.3; H, 5.6%).

2-Hydroxy-3:4:5:4'-tetramethoxy-dibenzoylmethane (III, R = OCH₃).—The above *O*-anisoyl derivative (2 g.) in dry toluene (20 c.c.) and sodamide (8 g.) were used for the rearrangement. The diketone was obtained as a heavy oil (0.7 g.) which showed no tendency to solidify even when kept in the refrigerator for 24 hours and was therefore directly used for conversion into the tetramethoxyflavone. The substance dissolved in aqueous sodium hydroxide to give a deep yellow solution. In alcoholic solution it gave a greenish-blue colour with ferric chloride.

6:7:8:4'-Tetramethoxyflavone (IV, R = OCH₃).—Ring closure of the above diketone (0.5 g.) was effected by heating with glacial acetic acid (5 c.c.) and fused sodium acetate (1 g.) according to the procedure already described for the simpler case. The crude tetramethoxyflavone was twice crystallised from dilute alcohol when the pure compound was obtained as long colourless flat needles and melted at 179–80° (Bargellini and Oliviero⁴ give m.p. 175–78°). Yield, 0.3 g. It was readily soluble in the common organic solvents and its alcoholic solution developed an orange-yellow colour with magnesium and hydrochloric acid. It dissolved in concentrated sulphuric acid to give an orange-yellow solution with a weak green fluorescence (Found: C, 66.9; H, 5.5; $C_{18}H_{18}O_6$ requires C, 66.7; H, 5.3%).

6:7:8:4'-Tetrahydroxyflavone (V, R = OH).—The demethylation of the above tetramethoxy flavone (0.2 g.) was effected by boiling it for two hours with acetic anhydride (8 c.c.) and hydriodic acid (*d*, 1.7; 8 c.c.). The yellow solid obtained on dilution with water containing sulphurous acid was collected and boiled with water and recrystallised twice from alcohol. The tetrahydroxyflavone was thus obtained as aggregates of pale yellow needles and narrow rectangular plates. Yield, 0.15 g. It became orange red at 245°, dark brown at 300° and did not melt down below 330° (Bargellini and Oliviero⁴ give m.p. 250° with decomposition). It was moderately soluble in alcohol and acetone, and dissolved more easily in glacial acetic acid. Its alcoholic solution gave a greenish-blue colour with a drop of ferric chloride

and deposited a brown precipitate with a slight excess of the reagent. Its solution in concentrated sulphuric acid was yellow and exhibited no fluorescence. When treated with sodium amalgam in absolute alcoholic solution (Bargellini's test), a greenish-brown precipitate was slowly formed. The flavone dissolved in ammonia to give a yellow solution and in aqueous sodium hydroxide to give an orange-red solution which gradually faded in colour (Found in a sample dried *in vacuo* at 120–25° for two hours: C, 62.7; H, 3.8. $C_{15}H_{10}O_6$ requires C, 62.9; H, 3.5%).

The tetraacetate was prepared by heating the above compound (0.1 g.) with acetic anhydride (5 c.c.) and fused sodium acetate (2 g.) for two hours. It was crystallised twice from acetone-ethyl-acetate mixture when it was obtained as thin long needles melting at 254–55° with slight sintering at 248° (Bargellini and Oliviero⁴ give m.p. 249°) (Found: C, 61.0; H, 4.3; $C_{23}H_{18}O_{10}$ requires C, 60.8; H, 4.0%).

SUMMARY

6:7:8-Trihydroxy and 6:7:8:4'-tetrahydroxyflavones and their derivatives (methyl ethers and acetates) have been prepared starting with 2-hydroxy-3:4:5-trimethoxyacetophenone and adopting the Baker-Venkataraman procedure. Their properties and reactions have been studied and compared with those of the isomeric compounds, baicalein and scutellarein.

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