

# SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

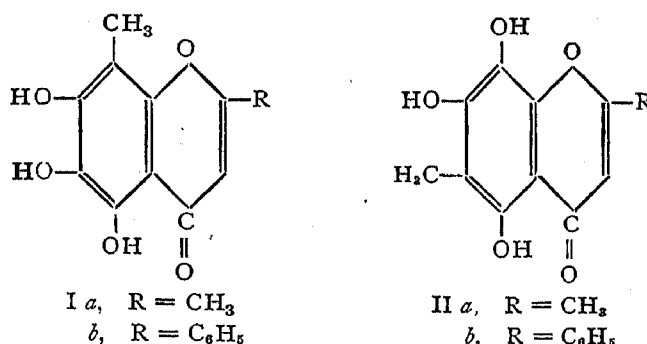
## Part LXVI. Relative Stability of Isomeric 6-Methyl and 8-Methyl-Trihydroxy Flavones

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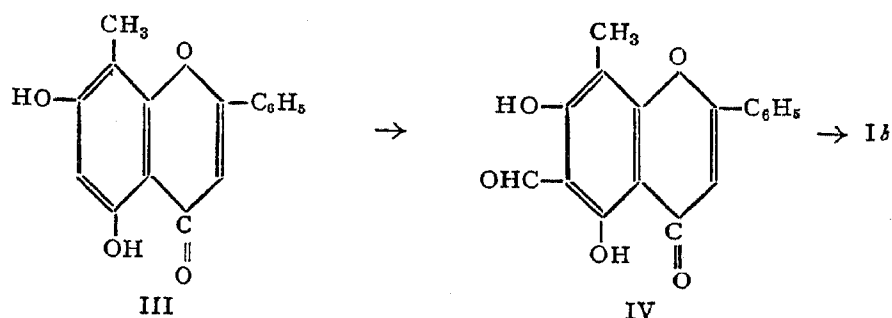
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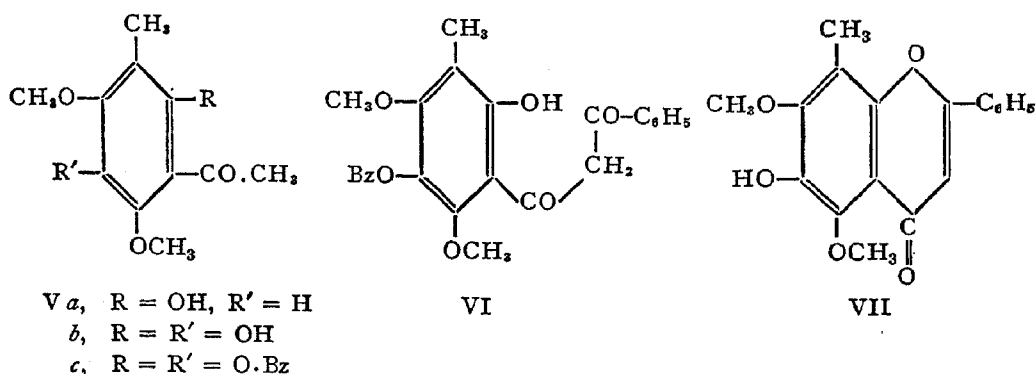
IN a recent publication<sup>1</sup> Mukerjee, Rajagopalan and Seshadri reported the preparation of 2:8-dimethyl-5:6:7-trihydroxy (I *a*) and 2:6-dimethyl-5:7:8-trihydroxy (II *a*) chromones and their derivatives. They subjected their methyl ethers to demethylation with hydriodic acid; the methyl ether of (I *a*) underwent only demethylation and no isomeric change whereas the methyl ether of (II *a*) underwent demethylation and complete isomerisation. This showed that for maximum stability the 6-position for the hydroxyl and the 8-position for methyl are the most favourable. In order to test the validity of the conclusion to other groups of compounds a similar study has now been made using analogous flavone derivatives, *i.e.*, 5:6:7-trihydroxy-8-methyl flavone (I *b*) and 5:7:8-trihydroxy-6-methyl flavone (II *b*).



The most convenient method for the preparation of flavone (I *b*) is to start with 8-methyl chrysin (III) whose preparation has already been described.<sup>2</sup> It is converted into the corresponding 6-aldehyde (IV) by the hexamine method and subsequent Dakin oxidation in tetramethyl ammonium hydroxide solution<sup>3</sup> yields 8-methyl baicalein (I *b*). Methylation under appropriate conditions gives its 6:7: di- and 5:6:7-trimethyl ethers. These suffer demethylation with hydriodic acid under ordinary conditions giving solely 8-methyl baicalein and there is no isomeric change.



8-Methyl baicalein can also be prepared by an alternative method starting from 2-hydroxy-3-methyl-4:6-dimethoxy acetophenone<sup>4</sup> (V *a*); the steps are indicated in the following formulæ. It may be mentioned in this connection that this is the first instance of the successful application of Baker-Venkataraman isomerisation (Wheeler modification<sup>5</sup>) to a quinol derivative.

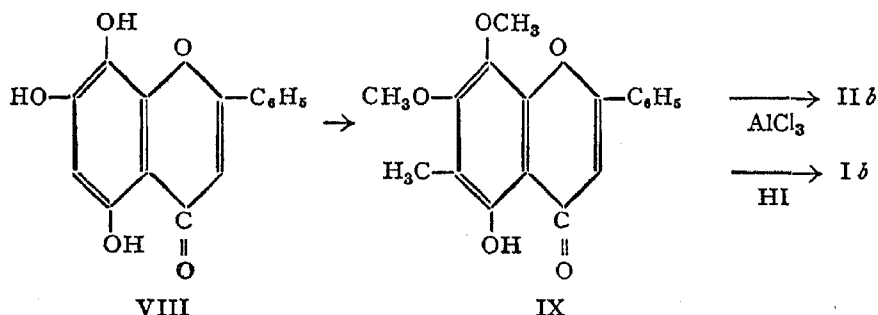


For the preparation of the isomeric 6-methyl-5:7:8-trihydroxy flavone (II *b*), norwogonin (VIII) was subjected to nuclear methylation whereby 5-hydroxy-7:8-dimethoxy-6-methyl flavone (IX) was obtained along with a larger amount of 5-hydroxy-7:8-dimethoxy flavone; the two could be separated by chromatography over alumina or 'magnesol'. When subjected to demethylation with hydriodic acid, (IX) suffers demethylation and complete isomeric change into 8-methyl baicalein (I *b*). Thus the flavone derivatives behave very similar to the corresponding chromones. However, for the preparation of 6-methyl norwogonin (II *b*) demethylation of the dimethyl ether (IX) with aluminium chloride in benzene solution was found to be suitable. Attempts to prepare this compound by the nuclear oxidation of 6-methyl chrysin with alkaline persulphate were unsuccessful.

#### EXPERIMENTAL

*5:7-Dihydroxy-8-methyl flavone-6-aldehyde* (IV).—5:7-Dihydroxy-8-methyl flavone (III) required for this work was prepared according to the procedure of Mukerjee and Seshadri<sup>2</sup>; in the isomerisation of 2-benzoyloxy-3-methyl-4:6-dimethoxy acetophenone to the diketone, the pyridine-potash

method of Wheeler was found to be more convenient and gave better yields than the sodamide-toluene method.



A mixture of 8-methyl chrysin (1.2 g.) in glacial acetic acid (100 c.c.) and hexamine (4 g.) was heated in a boiling water-bath for 6 hours. The deep red solution was treated with concentrated hydrochloric acid (20 c.c.) and the heating continued for another 20 minutes when a pale yellow solid separated. The mixture was diluted with a large volume of water and left overnight in the refrigerator. The aldehyde crystallised from benzene or glacial acetic acid as pale yellow, soft, flat needles (0.7 g.), m.p. 255–56°; mixed m.p. with 8-methyl chrysin, 220° (Found: C, 68.7; H, 4.2;  $\text{C}_{17}\text{H}_{12}\text{O}_5$  requires C, 68.9 and H, 4.1%). The aldehyde is sparingly soluble in alcohol, acetone and ethyl acetate but more soluble in hot benzene and hot glacial acetic acid. It is not readily soluble in aqueous sodium hydroxide and on warming formed a yellow, sparingly soluble sodium salt. It gave a red-brown ferric reaction. The *dinitrophenyl hydrazone* of the aldehyde formed orange-red tiny needles, m.p. 330° (decomp.).

The aldehyde gave the *tetra-acetate* on acetylation in the cold with acetic anhydride and a drop of concentrated sulphuric acid; colourless plates (from acetone), m.p. 236–37° (gas evolution) (Found: C, 62.6; H, 4.9;  $\text{C}_{25}\text{H}_{22}\text{O}_{10}$  requires C, 62.2 and H, 4.6%).

*5:6:7-Trihydroxy-8-methyl flavone (Ib)*.—The foregoing aldehyde (1.0 g.) was suspended in pyridine (30 c.c.) and tetramethyl ammonium hydroxide (10%; 10 c.c.) added. The red solution was cooled in ice-water, nitrogen bubbled through it for 10 minutes and hydrogen peroxide (6%; 3 c.c.) was added dropwise with vigorous shaking; the solution turned dark brown. Nitrogen was passed for another 2 hours, the reddish-yellow solution heated to 50° and acidified with dilute sulphuric acid. The yellow solid crystallised from methanol as tiny yellow prisms (0.5 g.) turning brown at 220° and melting at 286–88° (decomp.) (Found: C, 67.3; H, 4.4;  $\text{C}_{16}\text{H}_{12}\text{O}_5$  requires C, 67.6 and H, 4.2%).

The compound gives a brown-black ferric reaction which turns brown on standing. With aqueous sodium hydroxide a bluish-green solution is obtained which turns green on shaking; on standing a dark green precipitate settles and the solution becomes colourless. Treatment with sodium amalgam in alcoholic solution yields a deep green solution from which a green precipitate separates gradually the solution becoming yellow (Bargellini's test).

The *triacetate* prepared by the acetic anhydride-sulphuric acid method crystallised from alcohol as colourless prisms, m.p. 214–15°.

*5-Hydroxy-6:7-dimethoxy-8-methyl flavone*.—8-Methyl baicalein (0.4 g.) was partially methylated by refluxing with dimethyl sulphate (0.3 c.c.) and potassium carbonate (5 g.) in dry acetone (50 c.c.) for 6 hours. The dimethyl ether crystallised from isopropyl alcohol (charcoal) as yellow, thin plates; m.p. 159–60°. It gave a deep green ferric reaction (Found: C, 69.7; H, 5.5;  $C_{18}H_{16}O_5$  requires C, 69.2 and H, 5.1%).

*5:6:7-Trimethoxy-8-methyl flavone*.—8-Methyl baicalein (0.6 g.) was completely methylated by refluxing with dimethyl sulphate (2 c.c.) and potassium carbonate (8 g.) in dry acetone (200 c.c.) for 32 hours. The methyl ether was purified by chromatography over alumina and elution with benzene. It crystallised from dilute methanol as colourless, small plates, m.p. 133–34° (Found: C, 69.6; H, 5.8;  $C_{19}H_{18}O_5$  requires C, 69.9 and H, 5.5%).

*2:5-Dihydroxy-3-methyl-4:6-dimethoxy acetophenone (V b)*.—Oxidation of 3-methyl phloracetophenone dimethyl ether<sup>3</sup> (2.1 g.) was carried out in a cold mixture of pyridine (50 c.c.) and aqueous potassium hydroxide (2.8 g. in 40 c.c. water) by the dropwise addition (mechanical stirring) of a solution of potassium persulphate (3.5 g. in 150 c.c. water). The quinol isolated as usual crystallised from benzene-petroleum ether as yellow small prisms (0.6 g.), m.p. 119–20° (Found: C, 58.5; H, 6.4;  $C_{11}H_{14}O_5$  requires C, 58.4 and H, 6.2%).

The quinol gave a transient green colour with alcoholic ferric chloride; the solution turned deep red with more of the reagent. It dissolved readily in aqueous sodium hydroxide to give a bright yellow solution; on shaking with air the colour faded, then became pale pink which gradually disappeared.

*2:5-Dibenzoyloxy-3-methyl-4:6-dimethoxy-acetophenone (V c)*.—The above quinol (2 g.) was heated with benzoyl chloride (4 c.c.) and dry pyridine (15 c.c.) for 2 hours on a boiling water-bath. Ice-water was added and after standing overnight the mixture was extracted with ethyl acetate, the extract

was washed with dilute soda, dilute acid and water. Removal of the solvent left a viscous oil which quickly solidified. The dibenzoate crystallised from alcohol as colourless, thick prisms, m.p. 175–76° (Found: C, 68.6; H, 5.4;  $C_{25}H_{22}O_7$  requires C, 69.1 and H, 5.1%).

*Isomerisation of the dibenzoate to the diketone (VI).*—The dibenzoate (1.5 g.) was dissolved in warm, dry pyridine (20 c.c.) and vigorously shaken with powdered potassium hydroxide (1 g.) with occasional warming on a water-bath. The mixture turned yellow and after 15 minutes a yellow salt separated. After shaking for one hour, acetic acid was added and then diluted with a large volume of water. The sticky material solidified on cooling and scratching and crystallised from ethanol as yellow, irregular prisms (0.7 g.), m.p. 135–36°. It gave a greenish-brown ferric reaction (Found: C, 69.7; H, 5.2;  $C_{25}H_{22}O_7$  requires C, 69.1 and H, 5.1%).

*6-Hydroxy-5:7-dimethoxy-8-methyl flavone (VII).*—Ring closure of the diketone to the flavone was effected by heating with fused sodium acetate in glacial acetic acid solution for 2 hours. The colourless solid obtained on dilution was dissolved in warm alkali and the alkaline solution acidified. The flavone crystallised from methyl alcohol as almost colourless small prisms, m.p. 227–28°. It did not give any colour with alcoholic ferric chloride (Found: C, 69.5; H, 5.5;  $C_{18}H_{16}O_5$  requires C, 69.2 and H, 5.1%).

Methylation of the hydroxy compound by the methyl sulphate-potassium carbonate-acetone method yielded *8-methyl-5:6:7-trimethoxy flavone* identical with the sample already described.

*Action of hydriodic acid on 8-methyl baicalein and its methyl ethers.*—A mixture of 8-methyl baicalein (0.8 g.), acetic anhydride (15 c.c.) and hydriodic acid (15 c.c., *d.* 1.7) was refluxed for 3 hours and then diluted with saturated sodium bisulphite solution. The yellow solid on crystallisation from alcohol melted at 286–88° (decomp.) and did not depress the m.p. of an authentic specimen of 8-methyl baicalein. Similar treatment of 8-methyl baicalein 6:7-di- and 5:6:7-trimethyl ethers also yielded 8-methyl baicalein identified by m.p., mixed m.p. and colour reactions.

*Nuclear methylation of norwogonin (VIII) to 5-hydroxy-7:8-dimethoxy-6-methyl flavone (IX).*—Norwogonin required for this experiment was prepared by the method of Sastri and Seshadri.<sup>6</sup> The only modification introduced was that the 2-benzoyloxy-3:4:6-trimethoxy acetophenone was converted into the diketone by the pyridine-potash method of Wheeler<sup>5</sup> which was convenient and the yields were good.

Norwogonin (1.0 g.) was dissolved in ice-cold absolute methanol (75 c.c.) containing sodium methoxide from 1.4 g. of sodium. The deep blue-green solution was treated with methyl iodide (10 c.c.) and the mixture was gently shaken for an hour. It was then refluxed for 4 hours on a water-bath during which period the colour of the solution became brown. Methanol was removed under reduced pressure, dilute hydrochloric acid added and the brown solid was filtered. It was extracted with hot benzene, and the benzene solution passed through 'magnesol' which was eluted with more benzene (100 c.c.). The benzene eluate on evaporation left a yellow residue which crystallised from ethyl alcohol as yellow, long needles (50 mg.), m.p. 256-57° (Found: C, 69.3; H, 5.1;  $C_{18}H_{16}O_5$  requires C, 69.2 and H, 5.1%). It gave a green ferric chloride colour.

Further elution with benzene-acetone (1:1) gave 5-hydroxy-7:8-dimethoxy flavone (0.3 g.), m.p. 176-77°.

*Action of hydriodic acid on (IX).*—5-Hydroxy-7:8-dimethoxy-6-methyl flavone (IX) (0.1 g.) was refluxed with acetic anhydride (2 c.c.) and hydriodic acid (2 c.c.; *d.* 1.7) for 3 hours. The product on crystallisation from methanol melted at 286-88° and did not depress the m.p. of an authentic sample of 8-methyl baicalein. It also showed the same colour reactions as the latter.

*5:7:8-Trihydroxy-6-methyl flavone (II b).*—5-Hydroxy-7:8-dimethoxy-6-methyl flavone (0.1 g.) was refluxed with aluminium chloride (0.3 g.) in dry benzene (5 c.c.) solution for 2 hours. On working up as usual 6-methyl norwogonin crystallised from alcohol as deep yellow long needles turning brown at 240° and melting at 265-67° (decomp.). It gave a greenish-brown ferric chloride colour which changed to brown on standing. On reduction with sodium amalgam in alcoholic solution a transient orange brown colour was produced and the solution quickly became colourless (Found: C, 67.2; H, 4.2;  $C_{16}H_{12}O_5$  requires C, 67.6 and H, 4.2%).

#### SUMMARY

8-Methyl baicalein has been made (1) from 8-methyl chrysin by the preparation of the 6-aldehyde and subsequent Dakin's reaction and (2) from C-methyl phloracetophenone dimethyl ether by steps involving persulphate oxidation and flavone ring closure. The isomeric 6-methyl compound has been obtained by the nuclear methylation of norwogonin and demethylation with aluminium chloride. The methyl ethers of the former undergo only demethylation when boiled with hydriodic acid whereas those of the latter undergo isomeric change besides demethylation.

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