

## Synthesis of Biflavonoids. Part-I

M. S. Y. KHAN\*, S. U. KHAN, CH. I. Z. KHAN and M. R. PARTHASARATHY\*\*

Department of Medicinal Chemistry, Institute of History of Medicine and Medical Research,  
Hamdard Nagar, New Delhi-110 062

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Syntheses of the methyl ether derivatives of 6,6''-biapigenin (4), 6,6''-bisoflavone (11), 6,6''-bisdihydroflavonol (12) and 5,5''-bisaurone (13) (all new compounds) were done by using 5,5'-linked dimer of 4,6-dimethyl ether of phloracetophenone (2). The structures of these compounds were established on the basis of their spectral properties.

**O**XIDATION of phloracetophenone dimethyl ether (1) was reported earlier<sup>1</sup>, to yield 5,5'-linked dimer (2). The proof for its linkage was furnished by its conversion to hexa-*o*-methyl 6,6''-biapigenin (4) differing from the common 8,8''-linked cupressuflavone hexamethyl ether. Availability of the dimeric ketone (2) in good yield prompted us to synthesise a few more flavonoids with the object of pharmacological screening (flavonoids in recent years have been reported to have important pharmacological actions)<sup>2-4</sup>.

In the present paper we report the syntheses of several new biflavonoids and their intermediate products (Chart A). Although the synthesis of biapigenin hexamethyl ether (4) had already been carried out earlier<sup>1</sup>, but the yield was poor. It was therefore, synthesised by another route using Baker Venkataraman rearrangement, which gave the product in better yields. Modification of conditions during B-V reaction led to 7 which could be cyclised to give 8. The synthesis of bisoflavone tetramethyl ether (11) was carried out successfully by preparing the dibenzyl bischalcone (9) and then treating it with H<sub>2</sub>O<sub>2</sub> to give an epoxide, 10 and finally reacting this epoxide with BF<sub>3</sub> etherate. During the process of BF<sub>3</sub> treatment the two methoxyl groups at 5,5''-positions of the expected bisoflavone hexamethyl ether got demethylated to give 11. So far, as the authors are aware, no bisoflavone has ever been synthesised or isolated as yet from any natural source and we are reporting its synthesis for the first time.

The synthesis of bisdihydroflavonol hexamethyl ether (12) and bisaurone hexamethyl ether (13) is also being reported which was carried out by reacting the bischalcone (3) with H<sub>2</sub>O<sub>2</sub>.

### Experimental

All melting points were determined in open capillaries in a paraffin bath and are uncorrected.

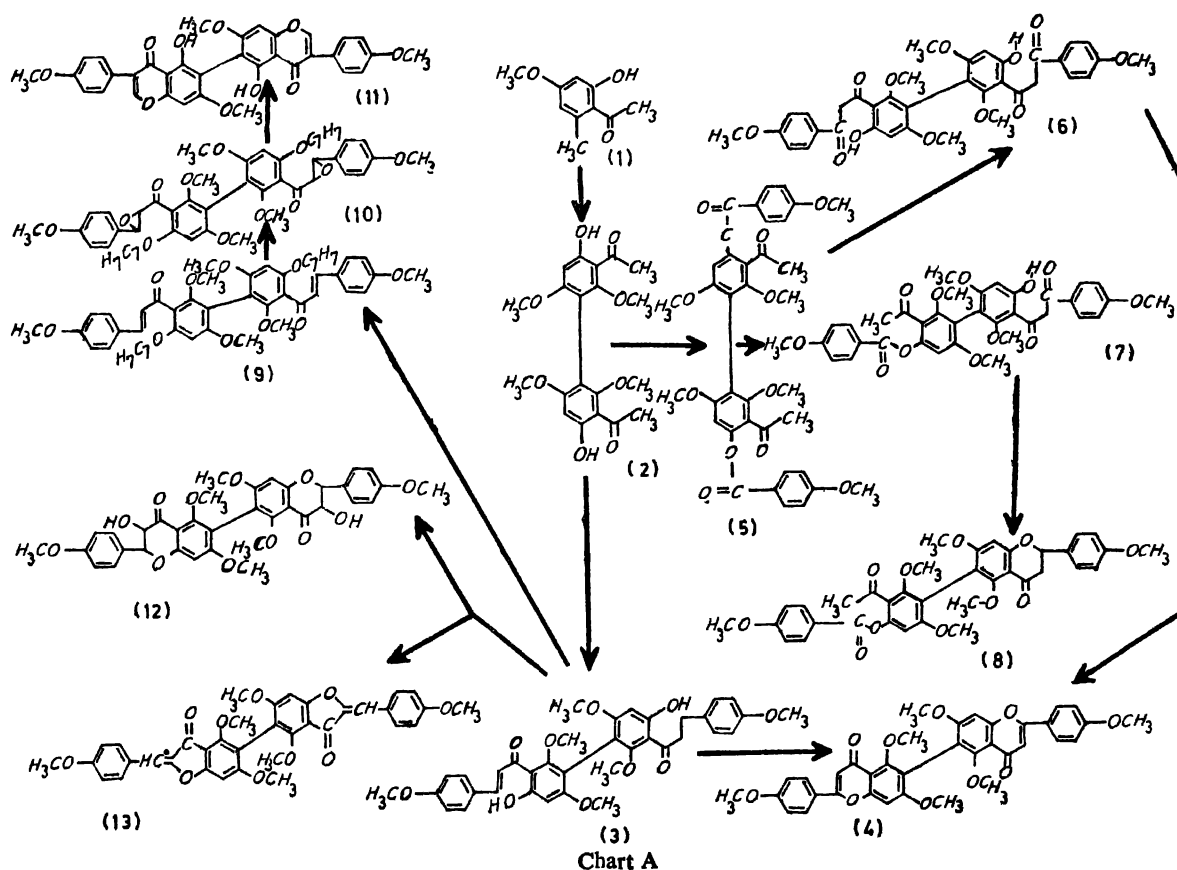
Uv spectrum was recorded in ethanol, ir spectrum in KBr, and nmr in CDCl<sub>3</sub>, a drop of TFA was added where the solubility in CDCl<sub>3</sub> was poor. Satisfactory elemental analyses were obtained for all the compounds.

**Bisester (5):** The dimer (2; 1.0 g) was dissolved in dry pyridine (6.0 ml) in a dry test tube under anhydrous conditions and then anisoyl chloride (1.5 g) was added to it. The mixture was heated on a boiling water bath for 3 h. The cooled reaction mixture was poured into dilute hydrochloric acid. A precipitate separated out which was filtered, washed with water and then with NaHCO<sub>3</sub> solution (10%) to remove the anisic acid formed during the work up. It was again washed with water and dried. On crystallisation from methanol it gave yellow needles of 5 (1.2 g), m.p. 160-61°;  $\delta$  2.42 (6H, s), 3.84 (18H, br s), 6.42 (2H, s); 6.92 (4H, d, *J* 9Hz) and 8.1 (4H, d, *J* 9Hz).

**Bisdiketone (6):** To a solution of the bisester (5; 500 mg) in dry pyridine (6.0 ml) was added powdered potassium hydroxide (500 mg). The reaction mixture was shaken with occasional warming. After 4 h, it was diluted with ice-cold water and the cooled aqueous solution was poured into dilute HCl when a yellow precipitate was obtained. It was filtered, washed with water and crystallised from methanol to give a yellow compound 6 (400 mg), m.p. 190°; gave a green colour with ferric chloride;  $\delta$  3.9 (18H, br s), 6.45 (2H, s), 6.96 (4H, d, *J* 9Hz) and 8.0 (4H, d, *J* 9Hz).

**Hexa-*O*-methyl-6,6''-biapigenin (4):** The above diketone (6; 500 mg) was dissolved in glacial acetic acid (10.0 ml) and freshly fused sodium acetate (900 mg) was added to it. The reaction mixture was refluxed on an oil bath for 4 h at 150-60°. The cooled solution was diluted with water. The precipitate so obtained was filtered, washed with

\*\*Department of Chemistry, Delhi University, Delhi-110 007.



water, dried and crystallised from methanol as yellow needles, 4 (400 mg), m.p. 220°; gave a deep pink colour with Mg/HCl and a negative test with ferric chloride; with one drop of TFA  $\delta$  3.92 (6H, s), 4.15 (6H, s), 4.21 (6H, s), 6.84 (2H, s), 7.02 (2H, s), 7.2 (4H, d,  $J$  9 Hz) and 8.12 (4H, d,  $J$  9 Hz).

**Monoester monoflavone 8:** The bisester (5; 500 mg) was dissolved in dry pyridine (60 ml) and powdered KOH (500 mg) was added to it. The reaction mixture was shaken for 3 h with occasional warming and then worked up as given above for 6. On crystallisation from methanol it gave a yellow compound (400 mg), m.p. 210–12°; gave a light brown colour with FeCl<sub>3</sub> and was characterised as 7;  $\delta$  2.6 (3H, s), 3.72 (3H, s), 3.76 (3H, s), 3.8 (6H, s), 4.0 (3H, s), 4.1 (3H, s), 6.78 (1H, s), 7.16 (1H, s), 6.88 (2H, d, *J* 9Hz), 7.06 (2H, d, *J* 9Hz), 7.95 (2H, d, *J* 9Hz) and 8.1 (2H, d, *J* 9Hz).

The above monoester diketone 7 (500 mg) was dissolved in glacial acetic acid (10.0 ml). Freshly fused sodium acetate (900 mg) was added to this solution and the reaction mixture was refluxed on an oil bath at 150-60° for 3 h. It was then cooled and diluted with water when a precipitate was obtained which was filtered, washed with water and crystallised from methanol as yellow needles (400 mg), m p. 175-76°; did not give any colour with ferric chloride, gave a pink colour on treat-

ment with Mg/HCl and was characterised as **8**;  $\delta$  2.55 (3H, s), 3.85 (3H, s), 3.90 (6H, s), 3.92 (s, 3H); 4.1 (6H, s); 6.45 (1H, s); 6.75 (1H, s); 6.95 (4H, d,  $J$  9 Hz); 7.10 (1H, s), 8.05 (2H, d,  $J$  9 Hz) and 8.08 (2H, d,  $J$  9 Hz).

**Dibenzyl bischalcone (9) :** A mixture of bischalcone (3 ; 500 mg), freshly distilled benzyl chloride (400 mg), anhydrous potassium carbonate (1.0 g) and potassium iodide (500 mg) in dry acetone was refluxed for 48 h, till it showed a negative  $\text{FeCl}_3$  test. The mixture was cooled, inorganic salts were filtered off and washed with hot acetone. The filtrate and the washings were combined together and evaporated to dryness. An oily mass was left which was carefully washed with petroleum ether several times. After sometime the oily mass solidified, which on crystallisation from methanol gave yellow cubic crystals (350 mg), m.p.  $144-45^\circ$ ; did not give any ferric colour reaction;  $\delta$  3.65 (12H, s), 3.8 (6H, s) 4.9 (4H, s), 6.3 (2H, s), 6.8 (2H, d,  $J$  16Hz), 6.75 (4H, d,  $J$  9Hz), and 7.1-7.4 (16H, m).

**Dibenzyl bischalcone epoxide (10):** Dibenzyl bischalcone (9; 500 mg) was dissolved in dry acetone (10.0 ml) and an aqueous solution of 8% NaOH (0.8 ml) was added to it. The solution was sufficiently cooled in an ice-salt bath and then  $H_2O_2$  (1.0 ml, 100 vol) was added under cold condition. The reaction mixture was then shaken

for 1 h with cooling at intervals of 15 min.  $\text{H}_2\text{O}_2$  (1.0 ml) was added again at the end of the reaction and the contents allowed to stand at room temperature for 8 h when a precipitate separated out and was filtered. The filtrate was diluted with an equal volume of water, the precipitated solid was filtered. The two precipitates were combined together and crystallised from methanol to give cream coloured fine needles (300 mg), m.p.  $110^\circ$ ;  $\nu_{\text{max}}$   $1670\text{ cm}^{-1}$ ;  $\delta$  3.4 (4H, unresolved m), 3.7 (12H, s), 3.86 (6H, s), 5.0 (4H, s), 6.4 (2H, s), 6.8 (4H, d,  $J$  9Hz), 7.1 (4H, d,  $J$  9Hz) and 7.35 (10H, m).

**Bisisoflavone (11):** The epoxide (500 mg) was dissolved in dry benzene (10.0 ml) and reacted with  $\text{BF}_3$ -etherate (0.5 ml). The reaction mixture was shaken at room temperature for 45 min. It was then diluted with ether (100 ml). The ethereal solution was washed with water and dried over  $\text{Na}_2\text{SO}_4$ . It was then filtered and the solvent was distilled off. The residue was taken up in glacial acetic acid (10.0 ml) and concentrated  $\text{HCl}$  (5.0 ml) was added to it. The contents were heated on a boiling water bath for about 2 h, cooled to the room temperature, diluted with water and extracted with ether. The ethereal layer was washed with  $\text{NaHCO}_3$  solution (5%) and then with water. Recovery of the solvent left a semi-solid mass which on crystallisation from methanol gave the bisisoflavone, 11, as colourless needles (250 mg), m.p.  $175-76^\circ$ ; gave a positive ferric reaction;  $\delta$  3.9 (6H, s), 4.0 (6H, s), 6.52 (2H, s), 6.95 (4H, d,  $J$  9Hz), 7.5 (4H, d,  $J$  9Hz); 7.9 (2H, s).

**Bisdihydroflavonol (12) and bisaurone (13):** The bischalcone (3; 500 mg) was dissolved in 1N  $\text{NaOH}$  (50 ml). The solution was cooled in an ice-salt bath and when sufficiently cold  $\text{H}_2\text{O}_2$  (1.0 ml, 100 vol) was added to it and the contents left in an ice chest for 72 h. Another 1 ml of  $\text{H}_2\text{O}_2$  was added into the reaction mixture and

kept in an ice chest for another 24 h. Then glacial acetic acid was added dropwise to neutralise the alkali, while keeping the temperature below  $0^\circ$ .

The precipitated solid was filtered, washed with water, dried and fractionally crystallised from methanol to give the bisdihydroflavonol, 12, m.p.  $200^\circ$  which gave a positive test with  $\text{Mg/HCl}$  for flavonoids and a negative  $\text{FeCl}_3$  test; and a bisaurone, 13, m.p.  $185^\circ$ , gave a negative  $\text{FeCl}_3$  test and a negative  $\text{Mg/HCl}$  test. A few crystals on treatment with one drop of concentrated  $\text{H}_2\text{SO}_4$  gave a red colour characteristic of the 4'-methoxyaurones. Bisdihydroflavonol 12,  $\delta$  7.7 (4H, d,  $J$  9Hz), 7.1 (4H, d,  $J$  9Hz), 6.3 (2H, s), 5.2 (2H, d,  $J$  12Hz), 4.4 (2H, d,  $J$  12Hz), 4.1 (12H, s), 3.9 (6H, s). Bisaurone 13,  $\lambda_{\text{max}}$  (EtOH)<sup>s</sup> 380 (inf) and 400 nm.

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