

SYNTHETIC STUDIES OF BIFLAVONOIDS. PART I

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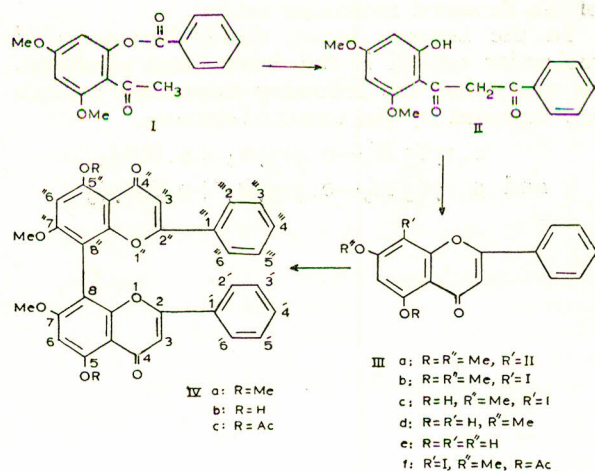
5,5'-Dihydroxy-7,7'-dimethoxybiflavone, a dimer of the naturally occurring flavone (tecto-chrysin) has been prepared by Ullman coupling of 5,7-dimethoxy-8-iodoflavone. The synthesis of the biflavone and related compounds is described.

It is believed that the biflavones are formed in Nature by means of oxidative coupling of simpler flavones. This lead us to the synthesis of a biflavone (IVb) which may be found in Nature on biogenetic grounds.¹

Thus 5,7-dimethoxyflavone (IIIa) was prepared as follows: Benzoylation of 2-hydroxy 4,6-dimethoxyacetophenone gave ester I. It gave negative ferric test. Baker-Venkataraman transformation of I gave diketone II. It gave positive ferric reaction. Compound II was smoothly cyclised to flavone IIIa. The flavone, m.p. 148-50°C (lit.³ 143-45°), had the expected NMR spectrum (discussed later).

Iodination⁴ of flavone IIIa with iodine monochloride in acetic acid gave the iodo derivative IIIb. Demethylation of IIIb with boron trichloride⁵ gave 5-hydroxy-7-methoxy-8-iodoflavone (IIIc) which gave negative Gibb's test, indicating substitution of iodine at position 8. This was confirmed by the comparison of NMR spectrum of IIIa with IIIb. The former showed two doublets τ 3.61 (H, J 2 c/s) τ 3.42 (H, J 2 c/s) assigned to the protons at 6 and 8 position, respectively, whereas in the latter a singlet appeared at τ 3.57 assigned to the proton at 6th position.^{6,7}

5,7-Dimethoxy-8-iodoflavone (IIIb) on Ullman^{2,8} coupling gave a dark brown solid which failed to crystallise. On methylation, this solid gave colourless prisms, m.p. 318-19° of the biflavone (IVa). This structure was supported by microanalysis and mass spectrum (M^+ ; 562). The NMR showed a singlet at τ 3.37 (2H) due to the two identical protons² at positions 6 and 6". Two singlets at τ 5.9 (6H) and τ 6.1 (6H) were assigned to methoxyl protons at 5,5"-and 7,7"- positions, respectively.⁹ Demethylation of IVa with boron trichloride⁵ gave 5,5'-dihydroxy-7,7'-dimethoxybiflavone (IVb), a dimer of the natural flavone tecto-chrysin (IIIId).³ It gave positive ferric test. The proposed structure was supported by the mass spectrum (M^+ ; 534), analysis and the NMR spectrum of the compound (see Experimental). Treatment of IVb with acetic anhydride and pyridine gave the diacetate IVc, m.p. 297-300°, the mass spectrum of which showed (M^+ ; 618).



Demethylation of 5,7-dimethoxyflavone with boron trichloride⁵ gave tecto-chrysin³ IIIId while demethylation with HI gave chrysin³ IIIe. This also constitutes a synthesis of chrysin and tecto-chrysin which to our knowledge have not been synthesised by this method.

Experimental

All m.ps are uncorrected. The IR spectra were recorded as nujol mulls on Beckman IR 4. The NMR spectra were determined on deuterio-chloroform solutions using TMS as internal standard in a Varian A-100 spectrometer.

4,6-Dimethoxy-2-benzoyloxyacetophenone (I).— 2-Hydroxy-4,6-dimethoxyacetophenone (17 g) and benzoyl chloride (30 ml) were added to pyridine (30 ml) and the solution was heated on water bath for $\frac{1}{2}$ hr and was left overnight at room temperature. Ice-cold water was added to the solution which was extracted with ether. The ethereal layer was successively washed with 20% HCl, 10% NaHCO₃ and water. The ethereal layer was dried and evaporated to give a thick oil which was crystallised from methanol as colourless prisms of 4,6-dimethoxy-2-benzoyloxyacetophenone (13.4 g), m.p. 86-87°. ν_{\max} 1742, 1680 and 1620

cm^{-1} . τ 7.56 (3H)_s; 6.16 (3H)_s; 6.12 (3H)_s; 3.61 (1H)_d J 1.5 c/s; 3.57 (1H)_d, J 1.5 c/s; 2.35–2.5 (3H)_m; 1.78–1.88 (2H)_m. Found: C, 67.75; H, 5.45; OMe, 21.02%. $\text{C}_{17}\text{H}_{16}\text{O}_5$ requires: C, 67.99; H, 5.37; OMe, 20.66%.

2-Hydroxy-4,6-dimethoxy-dibenzoylmethane (II).—Powdered anhydrous KOH (16 g) was added to a solution of 4,6-dimethoxy-2-benzoyloxyacetophenone (16 g) in dry pyridine (130 ml). The flask was allowed to shake overnight. The yellow solution was acidified with 10% HCl, and extracted with ether. The ethereal layer was washed with water, dried and evaporated to give an oil which on crystallisation from chloroform-methanol mixture gave pale yellow rhomboids of 2-hydroxy-4,6-dimethoxydibenzoylmethane (5 g), m.p. 134–135°. ν_{max} 1688, 1580–1640 cm^{-1} (broad band) τ 6.54 (3H)_s; 6.19 (3H)_s; 5.44 (2H)_s; 4.16 (1H)_d. J 2 c/s, 3.9 (1H)_d, J 2 c/s, 2.35–2.5 (3H)_m; 1.95–2.05 (2H)_m; Found: C, 68.30; H, 5.49%. $\text{C}_{17}\text{H}_{16}\text{O}_5$ requires: C 67.99; H, 5.37%.

5,7-Dimethoxyflavone (IIIa).—The solution of 2-hydroxy-4,6-dimethoxydibenzoylmethane (4.94 g) in glacial acetic acid (75 ml) containing a few drops of concd H_2SO_4 was refluxed for $\frac{1}{2}$ hr. The solution was poured in ice-cold water. The precipitated compound was filtered, dried and crystallised from methanol-ether mixture to give colourless prisms of 5,7-dimethoxyflavone (4.58 g), m.p. 148–50° (lit.³; 143–45°. ν_{max} 1655 and 1601 cm^{-1} . τ 6.08 (3H)_s; 6.03 (3H)_s; 3.61 (1H)_d. J 2 c/s 3.42 (1H)_d, J 2 c/s, 3.32 (1H)_s; 2.05–2.52 (5H)_m. Found: C, 72.83; H, 5.09; OMe, 21.82%. Calc. for $\text{C}_{17}\text{H}_{14}\text{O}_4$. C, 72.33; H, 4.99; OMe, 21.99%.

5,7-Dimethoxy-8-iodoflavone (IIIb).—Iodine monochloride (2.52 g) was added to the solution of 5,7-dimethoxyflavone (4 g) in glacial acetic acid (80 ml). The solution was heated (80°C) with stirring for 1 hr. The solution was poured in ice-cold water which was extracted with chloroform. The chloroform layer was successively washed with 5% sodium sulphite, 5% NaOH and water and dried (Na_2SO_4). The organic layer on evaporation gave a solid which on crystallisation from chloroform-methanol mixture gave colourless needles of 5,7-dimethoxy-8-iodoflavone (3.99 g), m.p. 246–247°. It gave positive Beilstein test. ν_{max} 1654, 1590 and 1542 cm^{-1} ; τ 5.97 (6H)_s; 3.57 (1H)_s; 3.27 (1H)_s; 2.50–2.87 (5H)_m. Found: C, 50.0; H, 3.39; I, 31.85; OMe, 15.53%. $\text{C}_{17}\text{H}_{13}\text{O}_4\text{I}$ requires: C, 50.02; H, 3.21; I, 31.09; OMe, 15.25%.

5-Hydroxy-7-methoxy-8-iodoflavone (IIIc).—A solution of boron trichloride in methylene chloride was added to a solution of 5,7-dimethoxy-8-iodoflavone (2 g) in methylene chloride at 0°C. The solution was kept at 0°C for 15 min and then

poured into aqueous sodium acetate and finally extracted with chloroform. The organic layer was washed, dried and evaporated to leave behind a yellow solid which on crystallisation from chloroform-methanol mixture afforded lemon yellow needles of 5-hydroxy-7-methoxy-8-iodoflavone (1.6 g), m.p. 231°. ν_{max} 1650, 1590 cm^{-1} . τ 6.03 (3H)_s; 3.57 (1H)_s; 3.27 (1H)_s; 1.88–2.18 (5H)_m. Found: C, 48.50; H, 3.07; I, 32.67; OMe, 7.82%. $\text{C}_{16}\text{H}_{11}\text{O}_4\text{I}$ requires: C, 48.75; H, 2.81; I, 32.2; OMe, 7.81%. This on treatment with acetic anhydride and pyridine in the usual manner gave 5-acetoxy-7-methoxy-8-iodoflavone (III_f) as colourless needles from methanol, m.p. 240–41°. ν_{max} 1771, 1638 and 1600 cm^{-1} . τ 7.56 (3H)_s; 5.98 (3H)_s; 3.33 (1H)_s; 3.36 (1H)_s; 1.88–2.55 (5H)_m. Found: C, 49.80; H, 3.34; I, 30.12; OMe, 6.80%. $\text{C}_{18}\text{H}_{13}\text{O}_5\text{I}$ requires: C, 49.56; H, 3.0; I, 29.09; OMe, 7.12%.

5,5',7,7'-Tetramethoxy biflavone (IVa).—A mixture of 5,7-dimethoxy-8-iodoflavone (2.2 g) and activated copper bronze (1.8 g) was heated at 255–260°C for $\frac{1}{2}$ hr. The solid cake was cooled, powdered, exhaustively extracted with chloroform and the solvent removed to leave behind red brown residue.

The crude reaction product was methylated by refluxing with dimethyl sulphate (10 ml), dry acetone (150 ml) and 20 g anhydrous K_2CO_3 for 22 hr). K_2CO_3 was filtered off and water (30 ml) was added to the filtrate which was left overnight. Most of the acetone was distilled off under reduced pressure. The aqueous solution was extracted with chloroform. The organic layer was washed with water, dried and evaporated to give a solid which crystallised from chloroform-methanol mixture as colourless prisms of 5,5',7,7'-tetramethoxybiflavone (0.52 g), m.p. 318–319°. ν_{max} 1655 and 1595 cm^{-1} . τ 6.12 (6H)_s; 5.86 (6H)_s; 3.37 (2H)_s; 3.31 (2H)_s; 2.55–2.69 (10H)_m. Found: C, 72.50; H, 4.90; OMe, 21.82%; mass spectrum (M^+ ; 562). $\text{C}_{34}\text{H}_{26}\text{O}_8$ requires: C, 72.59; H, 4.55; OMe, 22.06%; (M^+ ; 562).

5,5'-Dihydroxy-7,7'-dimethoxybiflavone (IVb).—100 mg of IVa was treated with boron trichloride as in the previous demethylation to give a yellow solid. Crystallisation from chloroform-methanol mixture gave yellow prisms of 5,5'-dihydroxy-7,7'-dimethoxybiflavone (65 mg), m.p. 292–293°C. ν_{max} 1660 and 1590 cm^{-1} . τ 6.17 (6H)_s; 3.38 (2H)_s; 3.29 (2H)_s; 2.45–2.61 (10 H)_m. Found: C, 71.80; H, 4.30; OMe 11.42%; mass spectrum (M^+ ; 534). $\text{C}_{32}\text{H}_{22}\text{O}_8$ requires: C, 71.90; H, 4.14; OMe, 11.61%; (M^+ ; 534).

5,5'-Diacetoxy-7,7'-dimethoxybiflavone (IVc).—Acetylation of 75 mg of IVb with acetic anhydride and pyridine gave colourless crystals of 5,5'-diacetoxy-7,7'-dimethoxybiflavone (72 mg), m.p.

297–300°. ν_{\max} 1776, 1640 and 1600 cm^{-1} . τ 7.47 (6H)_s; 6.13 (6H)_s; 3.38 (2H)_s; 3.14 (2H)_s; 2.67 (10H)_s. Found: C, 69.80; H, 4.35; OMe, 10.20%; mass spectrum (M^+ ; 618). $\text{C}_{36}\text{H}_{26}\text{O}_{10}$ requires: C, 69.89; H, 4.25; OMe, 10.03%; (M^+ ; 618).

5-Hydroxy-7-methoxyflavone (III_d).—Treatment of 1.23 g of III_a with boron trichloride as described previously gave yellow prisms of tectochrysin (III_d), (0.893 g) m.p. 162–63° (lit.³ 165–66°). ν_{\max} 1675 and 1602 cm^{-1} ; τ 6.11 (3H)_s; 3.63 (1H)_d; J 2 c/s, 3.49 (1H)_d J 2 c/s, 3.34 (1H)_s; 2.04–2.50 (5H)_m. Found: C, 71.8; H, 4.66; mass spectrum (M^+ ; 268). Calc. for $\text{C}_{16}\text{H}_{12}\text{O}_4$: C, 71.63; H, 4.50%; (M^+ ; 268). This compound on treatment with HI in the usual manner gave chrysin (III_e) as yellow needles from ethanol, m.p. 288–89° (lit.³ 289–90). ν_{\max} 1670 and 1600 cm^{-1} . Found: C, 70.51; H, 3.82%. Calc. for $\text{C}_{15}\text{H}_{10}\text{O}_4$: C, 70.72; H, 3.95.

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