

SYNTHETIC STUDIES OF BIFLAVONOIDS

Part II

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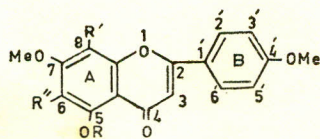
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Abstract. 8-Iodo-5,7,4'-trimethoxyflavone and 6-iodo-5,7,4'-trimethoxyflavone have been synthesised by direct iodination of the flavone molecule and their structures have also been established by NMR spectra and analysis. The 8-iodo isomer is an important intermediate in the synthesis of natural biflavones^{1,2} which has been obtained by a convenient method and in better yield.

Several syntheses of 8-iodo-5,7,4'-trimethoxyflavone (II) have been described. Nakazawa¹ synthesised this compound by benzylation of 5,7,4'-trihydroxyflavone followed by iodination, debenylation and methylation. Chen³ obtained the same compound by starting with 3-iodo-2-hydroxy-4,6-dimethoxyacetophenone followed by a standard method of flavone synthesis.

We treated 5,7,4'-trimethoxyflavone (I) with iodine monochloride in acetic acid to give pale yellow needles of 8-iodo-5,7,4'-trimethoxyflavone (II). The structure of this compound was proved by NMR spectroscopy. The presence of ortho split protons of ring B at τ 2.0 and τ 3.0 (*J* 9 c/s) and the olefinic proton at τ 3.39 clearly indicated that iodination had not taken place either in ring B or at position 3. That iodination indeed had taken place at position 8 was shown by the presence of a proton at position 6 which resonated at τ 3.60. The proton at position 8 resonates lower downfield.^{4,5} This structure was further confirmed by direct comparison of this compound with authentic II prepared by the known method.³ Both the compounds were identical (TLC analysis, NMR) in all respects.



I, R=Me, R'=R''=H; II, R=Me, R'=I, R''=H; III, R=R'=R''=H; IV, R=R'=H, R''=I; V, R=R''=H, R'=I; VI, R=Me, R'=H, R''=I.

Treatment of 5-hydroxy-7,4'-dimethoxyflavon (III) with iodic acid and iodine gave the 6-iodo isomer (IV) as the major product and the 8-iodo compound V as the minor one. The former on methylation gave 6-iodo-5,7,4'-trimethoxyflavone (VI). Its NMR spectrum showed a singlet at τ 3.23 due to the proton at position 8 which as expected is lower downfield than the proton at 6 position (τ 3.60) of 8-iodo isomer (II). The rest of the spectrum of the compound VI was similar to II.

Demethylation of 8-iodo compound II with borontrichloride at 0°C gave compound V. It gave a positive ferric test. Comparison of the NMR spec-

trum of the demethylated flavones IV and V again showed that the proton at 8 position in the former resonates lower downfield at τ 3.47 than the proton at 6 position in the latter which gave the signal at τ 3.60. All compounds gave satisfactory analyses.

Experimental

All m.ps. are uncorrected. The NMR spectra were determined on deuterochloroform using TMS as internal standard in a varian A-100 spectrophotometer.

8-Iodo-5,7,4'-trimethoxyflavone (II). Iodine monochloride (0.57 g) was added to the solution of 5,7,4'-trimethoxyflavone (1 g) in glacial acetic acid (50 ml), heated at 120°C for 5 min to dissolve the compound and then the temperature was maintained at 100°C for 1 hr. It was then poured into ice-cold water and the reaction mixture extracted with chloroform. Organic layer was successively washed with 5% sodium sulphite, 5% sodium hydroxide and water. Chloroform was evaporated to give a yellow solid which on crystallization from chloroform-methanol mixture afforded yellow micro needles of the product (II) weighing 0.91 g, m.p. 233–35°C (lit. 236–37°C). It gave positive Beilstein test. NMR τ 6.13 (3*H*)_s; 6.0 (3*H*)_s; (1*H*)_s; 3.39 (1*H*)_s; 3.0 (1*H*)_d (*J* 9 c/s); 2.0 (1*H*)_d (*J* 9 c/s). (Found: C, 49.54; H, 3.48; I, 28.5). Calc. for C₁₈H₁₅O₅I: C, 49.34; H, 3.46; I, 28.96%.

8-Iodo-5-hydroxy-7,4'-dimethoxyflavone (V). A solution containing excess of borontrichloride in methylene chloride was added to a solution of the compound II (0.6 g) in methylene chloride at 0°C. After 15 min the solution was 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 crystallization from chloroform-methanol mixture gave yellow needles (0.4 g), m.p. 240–43°C. The compound gave positive ferric test. NMR τ 6.10 (3*H*)_s; 6.03 (3*H*)_s; 3.57 (1*H*)_s; 3.40 (1*H*)_s; 2.97 (1*H*)_d (*J* 9 c/s); 1.98 (1*H*)_d (*J* 9 c/s). (Found C, 48.38; H, 3.03; I, 30.0; C₁₇H₁₃O₅I requires: C, 48.12; H, 3.08; I, 29.91%.

6-Iodo-5-hydroxy-7,4'-dimethoxyflavone (IV). The compound III (200 mg) was dissolved in 5 ml ethanol and added to solutions of iodic acid (21 mg) in 2 ml

water and iodine in 25 ml alcohol. After heating the solution on water-bath for $\frac{1}{2}$ hr, it was left overnight at room temperature. Yellow precipitate was filtered and crystallized from chloroform-methanol mixture to give yellow needles (11 mg) of the compound IV, m.p. 205–7°C. NMR τ 6.07 (3H)_s; 5.97 (3H)_s; 3.47 (1H)_s; 3.37 (1H)_s; 3.0 (1H)_d (J 9 c/s); 2.06 (1H)_d (J 9 c/s). (Found C, 48.40; H, 3.10; I, 28.1, C₁₇H₁₃O₅I requires: C, 48.12; H, 3.08, I, 29.91 %).

Concentration of mother liquors from the above gave 45 mg 8-iodo-5-hydroxy-7,4'-dimethoxyflavone identical with the compound V, (m.p. and mixed m.p.).

6-Iodo-5,7,4'-trimethoxyflavone (VI). Methylation of 100 mg of the compound by standard method with acetone, potassium carbonate and dimethyl sulphate gave 88 mg colourless needles of the compound VI from methanol, m.p. 191–94°C, NMR τ 6.13 (3H)_s; 6.03(3H)_s; 5.98 (3H)_s; 3.41 (1H)_s; 3.23 (1H)_s; 3.0 (1H)_d (J 9 c/s), 2.21 (1H)_d (J 9 c/s). (Found

C, 49.85; H, 3.48; I, 28.7, C₁₈H₁₅O₅I requires: C, 49.34 H, 3.48; I, 28.5 %.)

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