

SYNTHESES OF *Inula cappa* FLAVONOIDS

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Constitution assigned to two new *Inula cappa* flavonoids as 3,5,2'-trihydroxy-7,5'-dimethoxyflavone (I) and 5,7,2',5'-tetrahydroxyflavanone (II) have now been confirmed by their syntheses.

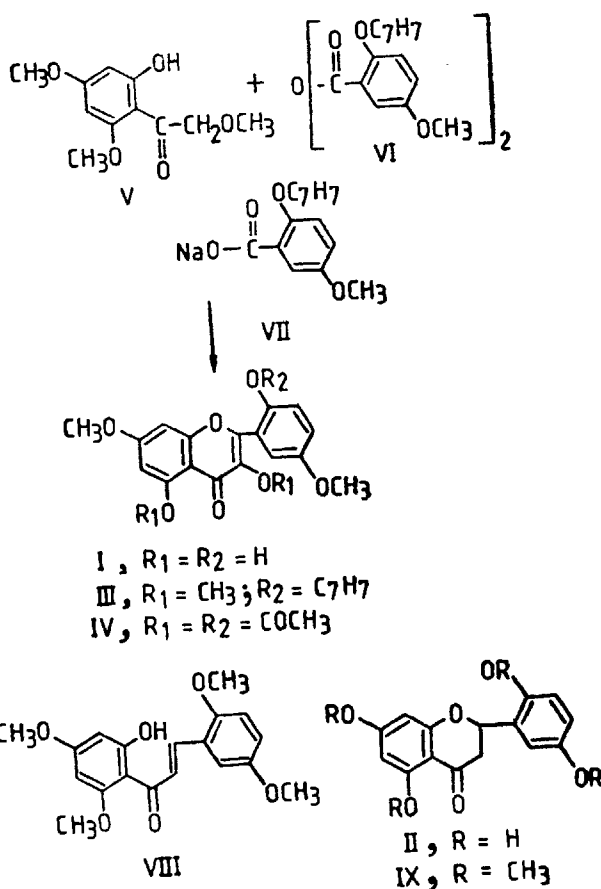
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INTRODUCTION

AMONG the naturally occurring flavonoids those having 2',5-dioxygenation pattern constitute an interesting group. Recently, two new flavonoids having a rare 2',5'-dioxygenation functions, were isolated from *Inula cappa* (Baruah *et al.*, 1979) and were proposed their constitutions as 3,5,2'-trihydroxy-7,5'-dimethoxyflavone (I) and 5,7,2',5'-tetrahydroxyflavanone (II) respectively, on the basis of spectral data only. This communication now confirms the proposed structures of *Inula cappa* flavonoids (I & II) by their syntheses.

Allan-Robinson condensation (Allan & Robinson, 1926) of 2-hydroxy- ω , 4,6-trimethoxyacetophenone (V) (Row & Seshadri, 1946) with 2-benzyloxy-5-methoxybenzoic anhydride (VI) in the presence of sodium salt (VII) of 2-benzyloxy-5-methoxybenzoic acid gave 3,5,7,5'-tetramethoxy-2'-benzyloxyflavone (III). The anhydride (VI) was made from 2-benzyloxy-5-methoxybenzoic acid by treating it with thionyl chloride and pyridine. Selective demethylation as well as debenzylation of flavone (III) with hydrobromic acid in acetic acid (Bhardwaj *et al.*, 1966; and Shah *et al.*, 1942) yielded the required 3,5,2'-trihydroxy-7,5'-dimethoxyflavone (I). 'I' on acetylation with acetic anhydride and pyridine gave its triacetate (IV).

The tetrahydroxyflavanone (II) has been prepared by the aldol condensation of 2-hydroxy-4, 6-dimethoxyacetophenone (Sastri & Seshadri, 1946) and 2,5-dimethoxybenzaldehyde. 2'-Hydroxy-2,5,4',6'-tetramethoxychalkone (VIII) thus obtained was subjected to cyclisation with methanolic sulphuric acid (Zamplan & Dognas, 1942) to give 5,7,2',5'-tetramethoxyflavanone (IX). Demethylation of IX with pyridinium hydrobromide (Mabry & Geraldin, 1970) yielded the corresponding 5,7,2',5'-tetrahydroxyflavanone (II). The natural samples of *Inula cappa* flavonoids could not be obtained for their direct comparisons. However, the properties now observed for the synthetic flavonoids (I & II) are in agreement with those reported for natural samples of *Inula cappa* flavonoids thereby unequivocally confirming their proposed constitutions.



EXPERIMENTAL

2-Benzyloxy-5-methoxybenzoic anhydride (VI)

A suspension of 2-benzyloxy-5-methoxybenzoic acid (10g) in anhydrous ether (40ml) and dry pyridine (4ml), was treated dropwise with a solution of thionyl chloride (1.6ml) in dry ether (10ml). The solution was stirred for 2 hours and then left at 0° C for 24 hours. The reaction mixture was treated with crushed ice and the solid thus obtained was filtered, washed with dil. hydrochloric acid then with aqueous sodium bicarbonate (10 per cent) and finally with water. The anhydride (VI) crystallised from ethyl acetate-petroleum ether as colourless needles (7.5g), m.p. 95–96° (*Found*: C, 72.0; H, 5.5. $C_{20}H_{24}O_7$ requires C, 72.28; H, 5.26 per cent).

3,5,7,5'-Tetramethoxy-2'-benzyloxyflavone (III)

A mixture of 2-hydroxy- ω , 4,6-trimethoxyacetophenone (V) (0.5g), 2-benzyloxy-5-methoxybenzoic anhydride (VI) (6g) and sodium salt of 2-benzyloxy-5-methoxybenzoic acid (1.5g) was heated at 175–180 °C for 4 hours, and then refluxed with

aqueous sodium hydroxide (30ml, 10 per cent) for 15 min. The reaction product thus obtained, was worked up as usual to give 3,5,7,5'-tetramethoxy-2'-benzyloxyflavone (III). It crystallised from ethyl acetate-petroleum ether as colourless plates (0.4g), m.p. 85–86 °C (*Found*: C, 69.2; H, 5.8. $C_{26}H_{24}O_7$ requires C, 69.63; H, 5.39 per cent). It gave pinkish-red colouration on reduction with magnesium and hydrochloric acid.

NMR (δ , $CDCl_3$, TMS as Internal Standard)

3.78 (9H, s, 3 X—OCH₃), 3.94 (3H, s, —OCH₃), 5.07 (2H, s, —OCH₂C₆H₅), 6.35 (2H, bs, C₆-H & C₈-H), 6.98–7.03 (2H, m, C₃'-H & C₄'-H), 7.20–7.35 (6H, m, —OCH₂C₆H₅ & C₆'-H).

3,5,2'-Trihydroxy-7,5'-dimethoxyflavone (I)

3,5,7,5'-Tetramethoxy-2'-benzyloxyflavone (III) (0.35g) was treated with hydrobromic acid in acetic acid (20ml) and the resulting reaction mixture was then heated on a water-bath at 100 °C for 3–4 hours. It was cooled and treated with crushed ice with constant stirring. The reaction mixture was extracted with ethyl acetate, washed with aqueous sodium bicarbonate (10 per cent) and finally with water. Ethyl acetate solution was dried over anhydrous sodium sulphate. Removal of the solvent from ethyl acetate layer gave I as a yellow residue which crystallised from methanol as yellow needles (0.1g), m.p. 203–204 °C (*Found*: C, 61.5; H, 4.6. $C_{17}H_{14}O_7$ requires C, 61.82; H, 4.27 per cent). It gave green colouration with ethanolic ferric chloride. *UV* (λ_{max} , MeOH): 260, 370nm; +NaOAc: 262, 384nm; +NaOAc + H₃BO₃: 262, 380nm; + AlCl₃: 245, 300, 355, 445nm; + AlCl₃ + HCl: 245, 300, 355, 440nm.

3,5,2'-Triacetoxy-7,5'-dimethoxyflavone (IV)

The trihydroxydimethoxyflavone (I) (0.05g) was treated with acetic anhydride (0.5ml) and pyridine (0.4ml), warmed on a water-bath to obtain a clear solution and then left overnight. It was then treated with ice and the acetate (IV) thus obtained was filtered, washed with water and dried. It was crystallised from chloroform-petroleum ether as colourless needles (0.03g), m.p. 87–88 °C (*Found*: C, 60.1; H, 4.9. $C_{23}H_{20}O_{10}$ requires C, 60.52; H, 4.42 per cent).

NMR (δ , $CDCl_3$, TMS as Internal Standard)

2.32 (6H, s, 2X —OCOCH₃), 2.44 (3H, s, —OCOCH₃), 3.85 (3H, s, —OCH₃), 3.92 (3H, s, —OCH₃), 6.7 (2H, bs, C₆-H & C₈-H), 7.2 (1H, *d*, *J* = 9Hz, C₄'-H), 7.72–7.80 (2H, m, C₃'-H & C₆'-H).

2'-Hydroxy-2,5,4', 6'-tetramethoxychalkone (VIII)

A solution of 2-hydroxy-4,6-dimethoxyacetophenone (0.5g) and 2,5-dimethoxybenzaldehyde (0.8g) in ethanol (20ml) was treated with an aqueous solution of potassium hydroxide (5ml, 20 per cent), left at room temperature for 48 hours and then acidified with hydrochloric acid. The chalkone (VIII) thus obtained was filtered out, washed with water and dried. It was crystallised from ethanol as yellow

needles (0.4g), m.p. 170–171 °C (*Found*: C, 66.1; H, 6.1. $C_{19}H_{20}O_6$ requires C, 66.27; H, 5.85 per cent). It gave brown colouration with ethanolic ferric chloride.

NMR spectrum (δ , $CDCl_3$, TMS as Internal Standard)

3.82 (6H, s, 2X $-OCH_3$), 3.85 (3H, s, $-OCH_3$), 3.98 (3H, s, $-OCH_3$), 5.95 (1H, *d*, $J = 2$ Hz, C_3' -H), 6.08 (1H, *d*, $J = 2$ Hz, C_5' -H), 6.85 (2H, s, C_3 -H & C_4 -H), 7.09 (1H, *d*, $J = 2$ Hz, C_6 -H), 7.95 (2H, C_α -H & C_β -H), 14.34 (1H, s, $-OH$).

5,7,2',5'-Tetramethoxyflavanone (IX)

The chalcone (VIII) (0.35g) was refluxed with methanolic sulphuric acid (50ml, 2 per cent) for 30 hours. The solvent was removed and the reaction product was treated with crushed ice. 5,7,2',5'-Tetramethoxyflavanone (IX) thus obtained was filtered, washed with water and dried. It crystallised from ethyl acetate-petroleum ether as colourless needles (0.2g), m.p. 125–126 °C. (*Found*: C, 66.0; H, 5.9. $C_{19}H_{20}O_6$ requires C, 66.27; H, 5.85 per cent). It did not give any colouration with ethanolic ferric chloride.

NMR spectrum (δ , $CDCl_3$, TMS as Internal Standard)

2.77–2.97 (2H, m, C_3 -protons), 3.77 (9H, s, 3X $-OCH_3$), 3.85 (3H, s, $-OCH_3$), 5.62–5.81 (1H, *dd*, $J = 11$ Hz & 5Hz, C_2 -H), 6.07 (1H, *d*, $J = 2$ Hz, C_6 -H), 6.12 (1H, *d*, $J = 2$ Hz, C_8 -H), 6.85 (2H, bs, C_3' -H & C_4' -H), 7.13 (1H, bs, C_6' -H).

5,7,2',5'-Tetrahydroxyflavanone (II)

A mixture of 5,7,2',5'-tetramethoxyflavanone (IX) (0.17g) and pyridinium hydrobromide (1.5g) was heated till it melted. The reaction mixture was cooled and then treated with crushed ice. The solid thus obtained was filtered, washed with water and dried. It crystallised from methanol as colourless needles (0.02g), m.p. 188–189 °C (*Found*: C, 62.3; H, 4.5. $C_{15}H_{12}O_6$ requires C, 62.50; H, 4.20 per cent). It gave greenish-brown colouration with ethanolic ferric chloride.

UV (λ_{max} , MeOH): 290, 365(sh)nm; + $AlCl_3$: 310nm; + NaOAc: 290, 325(sh)nm.

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