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CONSTITUTION OF ZUCCAGIN : A SYNTHETIC STUDY

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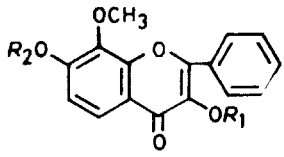
Constitution of a new trioxygenated flavone, zuccagin isolated from *Zuccagnia punctata* has now been confirmed by its synthesis as 3,7-dihydroxy-8-methoxyflavone (I) using 2′-hydroxy-3′-methoxy-4′-benzyloxychalkone (II) as an essential intermediate. AFO oxidation[2,3] of II gave 3-hydroxy-7-benzyloxy-8-methoxyflavone (III) which on catalytic debenzylation furnished I.

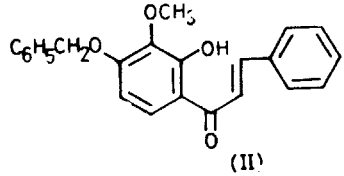
Key Words : Synthesis; Zuccagin; 3,7-Dihydroxy-8-methoxyflavone

ZUCCAGIN, a new pigment isolated from *Zuccagnia punctata* of family Leguminosae was chemically examined by Pederiva *et al.*[1] and assigned its structure as 3,7-dihydroxy-8-methoxyflavone (I) on the basis of spectral data. However, this proposed constitution of zuccagin had not been confirmed by any synthetic evidence. This paper describes the synthesis of 3,7-dihydroxy-8-methoxyflavone (I) thereby confirming the proposed constitution of zuccagin as I.

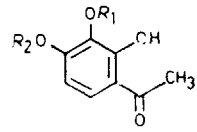
Synthesis of zuccagin has been achieved using 2′-hydroxy-3′-methoxy-4′-benzyloxychalkone (II) as and essential intermediate. This chalkone (II) in turn was obtained by the condensation of 2-hydroxy-3-methoxy-4-benzyloxycetophenone with benzaldehyde in the presence of an aqueous ethanolic alkali. 2-Hydroxy-3-methoxy-4-benzyloxyacetophenone (VIII) itself was obtained by selective benzylation of gallacetophenone in a mixture of dry acetone : ethanol (9 : 1) and potassium bicarbonate followed by its methylation. The above chalkone (II) was subjected to AFO oxidation[2,3] using alkaline hydrogen peroxide to give 3-hydroxy-7-benzyloxy-8-methoxyflavone (III). Catalytic debenzylation (Pd/C) of III gave I which on selective methylation gave a mixture of two compounds as 3-hydroxy-7,8-dimethoxyflavone (IV) and 3,7,8-trimethoxyflavone (V). The physical and spectral



I, $R_1 = R_2 = H$
III, $R_1 = H$, $R_2 = -CH_2C_6H_5$
IV, $R_1 = H$, $R_2 = CH_3$
V, $R_1 = R_2 = CH_3$



(II)



VI, $R_1 = R_2 = -CH_2C_6H_5$
VII, $R_1 = H$, $R_2 = -CH_2C_6H_5$
III, $R_1 = CH_3$, $R_2 = -CH_2C_6H_5$

properties of synthetic I, IV and V now observed agreed with those reported for natural metabolite, zuccagin, its mono and dimethyl ethers respectively thereby supporting the proposed constitution of zuccagin as I.

Experimental

Selective Benzylation of Gallacetophenone

To a solution of gallacetophenone (10g) in dry acetone : ethanol (9 : 1; 150ml), benzyl chloride (6.5ml) and potassium bicarbonate (15g) were then added and refluxed for 3–4hrs. Usual work up of the reaction gave a mixture of three products namely compounds —A, —B and —C. These three compounds were separated by column chromatography and characterised as 2-hydroxy-3,4-dibenzyloxyacetophenone (VI) 2,3-dihydroxy-4-benzyloxyacetophenone (VII) and starting material gallacetophenone respectively.

2-Hydroxy-3,4-dibenzyloxyacetophenone (Compound-A) (VI)

It crystallised from benzene-pet. ether as colourless needles (2.5g), m.p. 113–15°. It developed green colouration with ethanolic ferric chloride.

NMR Spectrum $CDCl_3$, TMS as an Internal Standard) δ 2.57 (3H, *s*, $-COCH_3$), 5.20 (2H, *s*, $-OCH_2C_6H_5$), 5.26 (2H, *s*, $-OCH_2C_6H_5$), 6.53 (1H, *d*, J = 9Hz, C-5-H), 7.26–7.43 (10H, *m*, 2X-$OCH_2C_6H_5$), 7.54 (1H, d, J = 9Hz, C-6-H), 12.78 (1H, *s*, C-2-OH).

2,3-Dihydroxy-4-benzyloxyacetophenone (Compound-B) (VII)

It crystallised from ethyl acetate-pet. either as colourless needles (2g), m.p. 132°. It gave green colouration with ethanolic ferric chloride and found to be insoluble in aqueous sodium carbonate (10 per cent).

NMR Spectrum ($CDCl_3$, TMS as an Internal Standard) δ 2.52 (3H, *s*, $-COCH_3$), 5.21 (2H, *s*, $-OCH_2C_6H_5$), 6.53 (1H, *d*, J = 9Hz, C-5-H), 7.26 (1H, *d*, J = 9Hz, C-6-H), 7.40 (5H, *s* $-OCH_2C_6H_5$) 12.38 (1H, *s*, C-2-OH).

2-Hydroxy-3-methoxy-4-benzyloxyacetophenone (VIII)

To a solution of 2,3-dihydroxy-4-benzyloxyacetophenone (1.8g) in dry acetone (75ml), freshly distilled dimethyl sulphate (1ml) and anhydrous potassium carbonate (5g) were added. The resulting reaction mixture was refluxed for 6hrs. Usual

work up of the reaction gave VIII, crystallised from ethyl acetate-pet ether as colourless needles (1.5g), m.p. 142°. It developed brownish-green colouration with ethanolic ferric chloride.

NMR Spectrum (*$CDCl_3$, TMS as an Internal Standard*) δ 2.57 (3H, *s*, $-COCH_3$), 3.97 (3H, *s*, $-OCH_3$), 5.26 (2H, *s*, $-OCH_2C_6H_5$), 6.53 (1H, *d*, J = 9Hz, C-5-H), 7.28–7.5 (6H, *m*, C-6-H and $-OCH_2C_6H_5$), 12.76 (1H, *s*, C-2-OH).

2'-Hydroxy-3'm-ethoxy-4'-benzyloxychalkone (*II*)

A solution of 2-hydroxy-3-methoxy-4-benzyloxyacetophenone (VIII) (1.5g) and benzaldehyde (1.6g) in ethanol (20ml) was treated with an aqueous solution of potassium hydroxide (10 per cent, 10ml) and stirred well for 2–3 hrs. It was left at room temperature for 72hrs. The reaction mixture was then diluted with water and the excess of benzaldehyde was removed by extraction with ether. The clear alkaline solution was acidified to congo-red using concentrated hydrochloric acid. The chalkone (II) thus obtained as a yellow solid was filtered, washed with water and then with aqueous sodium bicarbonate solution (10 per cent) finally with water and then dried. It crystallised from ethanol as yellow needles (2*g*), m.p. 145°, $C_{23}H_{20}O_4$ and developed brown colouration with ethanolic ferric chloride.

UV Spectrum (λ_{max})— MeOH : 220 (sh), 336nm.

IR Spectrum (ν_{max}, *KBr*)—2890, 1692, 1632, 1568, 1492, 1448, 1372, 1344, 1288, 1128, 1064, 1008, 976, 868, 776, 756, 704cm^{-1}.

NMR Spectrum (*$CDCl_3$, TMS as an Internal Standard*)—δ 3.91 (3H, *s*, $-OCH_3$), 5.21 (2H, *s*, $-OCH_2C_6H_5$), 6.5 (1H, *d*, J = 8.5Hz, C-5'—H), 7.22–7.59 (12H, *m*, $-OCH_2C_6H_5$, $-C_6H_5$, C-α-H and C-6'—H), 7.78 (1H, *d*, J = 17Hz, C-β-H), 13.38 (1H, *s*, C-2'-OH).

3-Hydroxy-7-benzyloxy-8-methoxyflavone (*III*)

A solution of the above chalkone (II) (3.4g) in a mixture of pyridine (10ml) and aqueous potassium hydroxide (30ml, 10 per cent) was heated on a water-bath at 60–70°. To the resulting hot solution, hydrogen peroxide (13ml, 10 per cent) was added dropwise with shaking during a period of half-an-hour. It was then cooled and extracted with solvent ether to remove the insoluble portion (aurone) that separated out during the reaction. The aqueous portion was then acidified with concentrated hydrochloric acid in cold and the solid thus obtained was filtered, washed with water and dried. It crystallised from chloroform-petroleum ether to give III as colourless needles (0.350g), m.p. 170–72°, $C_{23}H_{18}O_5$. It developed an olive green colouration with ethanolic ferric chloride.

UV Spectrum (λ_{max})

MeOH..... : 252, 308 (sh), 348nm

MeOH + $AlCl_3$..... : 266, 322 (sh), 408nm

MeOH + $AlCl_3$ + HCl..... : 266, 322 (sh), 408nm

IR Spectrum (ν_{max}, *Nujol*)—3270, 1630, 1560, 1504, 1450, 1410, 1380, 1280, 1220, 1195, 1135, 1065, 1022, 992, 920, 764, 740cm^{-1}.

NMR Spectrum (*$CDDl_3$, TMS as an Internal Standard*)—δ 4.03 (3H, *s*, —OCH_3), 5.24 (2H, *s* —$OCH_2C_6H_5$), 7.45 (1H, *d*, J = 9Hz, C-6-H), 7.19–7.53 (8H, *m*, C-3′-H, C-4′-H, C-5′-H and —$OCH_2C_6H_5$), 7.89 (2H, *m*, C-2′-H and C-6′-H), 8.22 (1H. *d*, J = 9Hz, C-5-H), 9.5 (1H, *s*, C-3-OH).

3,7-Dihydroxy-8-methoxyflavone (*I*)

3-Hydroxy-7-benzyloxy-8-methoxyflavone (III) (0.300g) was dissolved in ethyl acetate (50ml). Palladium-charcoal (0.1 g, 10 per cent) was added to it and the resulting solution was stirred in an atmosphere of hydrogen till the adsorption of hydrogen completed. The catalyst was removed by filtration and removal of the solvent from the filtrate gave reduction product (I). It crystallised from methanol as light yellow needles (0.12g), m.p. > 200° (*d*), $C_{16}H_{12}O_5$.

UV Spectrum (λ_{max})

MeOH ..... : 256, 312, 350nm.

MeOH + NaOAc..... : 273, 346 (sh), 404nm.

MeOH + $AlCl_3$ ..... : 266, 322, 408nm.

MeOH + $AlCl_3$ + HCl..... : 266, 322, 408nm.

IR Spectrum (ν_{max}, *nujol*)—1638, 1562, 1505, 1450, 1412, 1380, 1284, 1224, 1200, 1140, 1068, 998, 920, 765 cm^{-1}.

NMR Spectrum (*$DMSO$-d_6, TMS as an Internal Standard*)—δ 3.9 (3H, *s*, -OCH_3), 7.22 (1H, *d*, J = 9Hz, C-6-H), 7.51 (3H, *m*, C-3′-H, C-4′-H and C-5′-H), 7.62 (1H, *d*, J = 9Hz, C-5-H), 8.21 (2H, *m* C-2′-H and C-6′-H), 9.52 (2H, *m*, C-3-OH and C-7-OH).

Methylation of 3,7-dihydroxy-8-methoxyflavone (*I*)

To a solution of I (100mg) in dry acetone (75ml), anhydrous potassium carbonate (300mg) and dimethyl sulphate (0.04ml) were added. Usual work up of the reaction gave a mixture of two compounds (IV and V).

3-Hydroxy-7,8-dimethoxyflavone (*IV*)

IV crystallised from methanol as light yellow needles (30mg), m.p. 204–5°.

NMR Spectrum (*$CDCl_3$, TMS as an Internal Standard*) δ 3.92 (6H, *s*, 2*X*-OCH_3), 7.22 (1H, *d*, J = 9Hz, C-6-H), 7.52 (3H, *bs*, C-3′-H, C-4′-H and C-5′-H), 7.83 (1H, *d*, J = 9Hz, C-5-H), 8.22 (2H, *m*, C-2′-H and C-6′-H), 9.52 (1H, s, C-3-OH).

3,7,8-Trimethoxyflavone (*V*)

V Crystallised from methanol as colourless needles (30mg), m.p. 153–54°. It did not give any colouration with ethanolic ferric chloride.

NMR Spectrum (*$CDCl_3$, TMS as an Internal Standard*)—δ 3.92 (3H, *s*, $-OCH_3$), 3.95 (6H, *s*, $2X-OCH_3$), 7.22 (1H, *d*, J = 9Hz, C-6-H), 7.55 (5H, *m*, $-C_6H_5$), 7.85 (1H, *d*, J = 9Hz, C-5-H).

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REFERENCES

1. R Pederiva and O S Giordano *Phytochem* **23**(6) (1984) 1340
2. J Algar and J P Flynn *Proc Roz Irish Acad* **42B** (1934) 1
3. T Oyamada *J chem Soc Japan* **55** (1934) 1256