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Chemistry

CONSTITUTIONS OF PROSOGERIN-A & B : SYNTHETIC STUDIES

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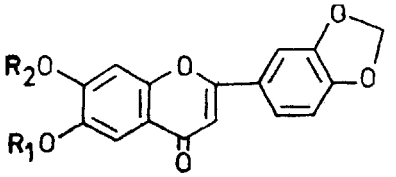
Constitutions assigned to prosogerin-A and B isolated from *Prosopis spicigera* as 6-methoxy-7-hydroxy-3′,4′-methylenedioxyflavone (I) and 2′,4′-dihydroxy-5′-methoxy-3,4-methylenedioxychalkone (II) respectively, have been now confirmed by synthesis.

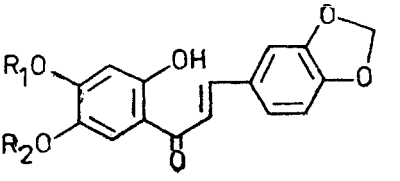
INTRODUCTION

PROSOGERIN-A and B, two phenolic components isolated (Bhardwaj *et al.*, 1978*a*) from *Prosopis spicigera* were proposed their constitutions as 6-methoxy-7-hydroxy-3′,4′-methylenedioxyflavone (I) and 2′,4′-dihydroxy-5′-methoxy-3,4-methylenedioxy-chalkone (II) respectively on the basis of their colour reactions, spectral data and degradative studies. The N.M.R. spectrum of prosogerin-A acetate showed (Bhardwaj *et al.*, 1978*a*) it to be a 6, 7, 3′, 4′-tetraoxygenated flavone having methoxyl at C_6, hydroxyl (acetoxyl) at C_7 and methylenedioxy function at $C_{3'}$ and $C_{4'}$ positions. On the contrary, the U.V. spectrum of prosogerin-A when recorded in the presence of sodium acetate, did not show the essential spectral shifts characteristic (Geissman, 1962; Mabry *et al.*, 1970; Harborne *et al.*, 1975) of a free hydroxyl at C_7 position of the flavonoids thereby suggesting the probability of the placements of the methoxyl at C_7 and the hydroxyl at C_6 position of the molecule. In order to settle this discrepancy, prosogerin-A and B were characterised as ethyl ethers. For this purpose, 6-ethoxy-7-methoxy-3′,4′-methylenedioxyflavone (III), 6-methoxy-7-ethoxy-3′,4′-methylenedioxyflavone (IV), 2′-hydroxy-4′-methoxy-5′- ethoxy-3,4-methylenedioxychalkone (V) and 2′-hydroxy-4′-ethoxy-5′-methoxy-3, 4-methylenedioxychalkone (VI) were synthesised as described in this paper.

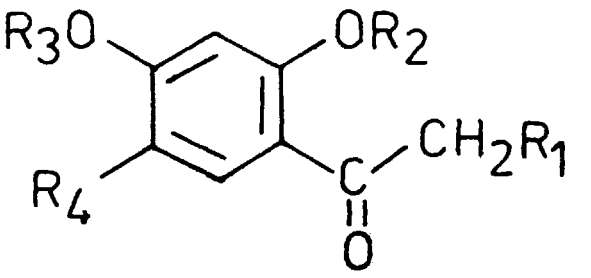
The flavone (III) was made using 2-hydroxy-4-methoxy-5-ethoxy acetophenone (VIII) obtained by the ethylation of 2, 5-dihydroxy-4-methoxyacetophenone (VII) (Bargellini & Aureli, 1911). Esterification of the ketone (VIII) with piperonyl chloride followed by Baker-Venkataraman migration (Baker, 1933; Doyle *et al.*, 1948; Dunne *et al.*, 1950; Mahal & Venkataraman, 1933) of the resulting ester (IX) yielded the β-diketone (X) which on cyclodehydration (Bhardwaj *et al.*, 1965, 1968; Bhardwaj *et al.*, 1978*b*) gave 6-ethoxy-7-methoxy-3′,4′-methylenedioxyflavone (III). For the synthesis of the second flavone (IV) 2-hydroxy-4-ethoxyacetophenone (XI) when subjected to nuclear hydroxylation as done in the similar cases (Bargellini & Aureli, 1911; Bhardwaj *et al.*, 1968, 1978*c*; Laumas *et al.*, 1933), yielded 2, 5-dihydroxy-4-ethoxy acetophenone (XII) which was methylated to obtain the required 2-hydroxy-4-ethoxy-5-methoxy acetophenone (XIII). Esterification of the ketone (XIII) with piperonyl chloride followed by the Baker-Venkataraman migration of the resulting ester (XIV) gave the β-diketone (XV) which on cyclo-dehydration yielded the required 6-methoxy-7-ethoxy-3′,4′-methylenedioxyflavone(IV). Identity of



I, $R_1 = CH_3$; $R_2 = H$
III, $R_1 = C_2H_5$; $R_2 = CH_3$
IV, $R_1 = CH_3$; $R_2 = C_2H_5$



II, $R_1 = H$; $R_2 = CH_3$
V, $R_1 = CH_3$; $R_2 = C_2H_5$
VI, $R_1 = C_2H_5$; $R_2 = CH_3$



VII, $R_1 = R_2 = H$; $R_3 = CH_3$; $R_4 = OH$
VIII, $R_1 = R_2 = H$; $R_3 = CH_3$; $R_4 = OC_2H_5$
XI, $R_1 = H$; $R_2 =$ piperonyl; $R_3 = CH_3$, $R_4 = OC_2H_5$
X, $R_1 =$ piperonyl; $R_2 = H$; $R_3 = CH_3$; $R_4 = OC_2H_5$
XI, $R_1 = R_2 = R_4 = H$; $R_3 = C_2H_5$
XII, $R_1 = R_2 = H$; $R_3 = C_2H_5$; $R_4 = OH$
XIII, $R_1 = R_2 = H$; $R_3 = C_2H_5$; $R_4 = OCH_3$
XIV, $R_1 = H$; $R_2 =$ piperonyl; $R_3 = C_2H_5$; $R_4 = OCH_3$
XV, $R_1 =$ piperonyl; $R_2 = H$; $R_3 = C_2H_5$; $R_4 = OCH_3$

prosogerin-A ethyl ether with ethyl ether (IV) but not with the other isomer (III) supports the placement of the ethoxyl at C_7 and thereby confirms the proposed constitution of prosogerin-A as 6-methoxy-7-hydroxy-3',4'-methylenedioxyflavone (III).

Prosogerin-B ethyl ether was also characterised by its comparisons with the synthetic isomeric 2'-hydroxy-4'-methoxy-5'-ethoxy-3, 4-methylenedioxychalkone (V) and 2'-hydroxy-4'-ethoxy-5'-methoxy-3,4-methylenedioxychalkone (VI) which were made by the condensations of piperonal with the two isomeric acetophenones VIII and XIII respectively. Identity of prosogerin-B ethyl ether with the chalkone (VI) but not with the other isomer (V), fully supports the proposed constitution for prosogerin-B.

Experimental

2-Hydroxy-4-Methoxy-5-Ethoxy Acetophenone(VIII): A mixture of 2,5-dihydroxy-4-methoxy acetophenone (VII) (Bargellini & Aureli, 1911) (5.0 g), diethyl sulphate (3.75 ml) and anhydrous potassium carbonate (15 g) in dry acetone (100 ml) was heated under reflux for 8 hrs. and then filtered. The inorganic salts were washed with acetone. On distilling off the solvent from the combined filtrate and washings,

a solid residue was obtained which was treated with ice, filtered and dried. 2-Hydroxy-4-methoxy-5-ethoxy acetophenone (VIII) thus obtained crystallised from ethanol as colourless needles (4.1 g), m.p. 101–2° (Found : C, 62.5; H, 6.5. $C_{11}H_{14}O_4$ requires C, 62.84; H, 6.71 per cent).

2-(3′,4′-*Methylenedioxybenzoyloxy*)-4-*Methoxy*-5-*Ethoxy Acetophenone* (*IX*) : A solution of the above acetophenone (VIII) (2g) in dry pyridine (15 ml) was treated with piperonyl chloride (2.5 g). The reaction mixture was heated on a boiling water-bath for 30 minutes and the resulting ester (IX) was worked out as usual. It crystallised from acetone as colourless tiny needles (2.7 g), m.p. 146–47°. (Found : C, 63.4; H, 5.2. $C_{19}H_{18}O_7$ requires C, 63.68; H, 5.06 per cent). It did not give any colouration with alcoholic ferric chloride.

2-*Hydroxy*-4-*Methoxy*-5-*Ethoxy*-3′,4′-*Methylenedioxydibenzoylmethane* (*X*) : A solution of the above ester (IX) (2.5 g) in dry pyridine (15 ml) was treated with powdered potassium hydroxide (2 g). The reaction mixture was thoroughly shaken and its temperature was maintained at 40° by occasional warming on a water-bath. In about 45 minutes, the mixture became viscous due to the separation of the yellow potassium salt of β-diketone (*X*). It was cooled and acidified with hydrochloric acid. The β-diketone (*X*) obtained as a yellow crystalline solid was filtered, washed with water and dried. It crystallised from ethyl acetate-petroleum ether mixture as golden yellow needles (1.5 g), m.p. 178–79° (Found : C, 63.3; H, 4.9. $C_{19}H_{18}O_7$ requires C, 63.68; H, 5.06 per cent). It dissolved in aqueous sodium hydroxide and gave a brown colouration with alcoholic ferric chloride.

6-*Ethoxy*-7-*Methoxy*-3′,4′-*Methylenedioxyflavone* (*III*) : A mixture of the above β-diketone (X) (1 g), glacial acetic acid (20 ml) and fused sodium acetate (1 g) was gently refluxed in an oil-bath at 120° for 3 hrs. The reaction mixture was cooled, treated with crushed ice and the flavone (III) then obtained as a colourless crystalline solid was filtered, washed with water and dried. It crystallised from ethyl acetate-petroleum ether mixture as small colourles needless (0.8 g) m.p. 230-31° (Found : C, 67.1; H, 4.8. $C_{19}H_{16}O_6$ requires C, 67.05, H, 4.75 per cent). It was insoluble in aqueous sodium hydroxide and did not give any colouration with alcoholic ferric chloride. The synthetic flavone (III) on comparison was found to be different from prosogerin-A ethyl ether (m.p., m.m.p. Co-TLC).

2,5-*Dihydroxy*-4-*Ethoxy Acetophenone* (*XII*) : To a solution of resacetophenone 4-ethyl ether (XI) (5 g) in aqueous sodium hydroxide (7 g in 50 ml), aqueous potassium persulphate (5 g in 120 ml) was added dropwise with stirring during a period of 8 hrs at 15–20°. After keeping at room temperature for 24 hrs., the solution was cooled and then acidified to congo-red with hydrochloric acid. The unchanged ketone (XI) (0.5 g) was removed by extraction with ether, and the clear filtrate treated with sodium sulphite (10 g) and hydrochloric acid (20 ml). The solution when heated on water-bath at 80–90° for 30 mts., gave 2,5-dihydroxy-4-ethoxyacetophenone (XII) (1.3 g) as yellow needles, m.p. 129–30°. (Found : C, 61.1; H, 6.3. $C_{18}H_{16}O_7$ requires C, 61.22; H, 6.12 per cent). It dissolved in aqueous sodium carbonate (10 per cent) and gave a greenish-brown colouration with alcoholic ferric chloride.

2-*Hydroxy*-4-*Ethoxy*-5-*Methoxy Acetophenone* (*XIII*) : A mixture of 2,5-dihy-

droxy-4-ethoxyacetophenone (XII) (4.0 g), dimethyl sulphate (3.0 ml) and anhydrous potassium carbonate (12 g) in acetone (100 ml) was heated under reflux for 8 hrs. and worked up as described earlier. The methylation product (XIII) crystallised from ethanol as colourless needles (3.5 g), m.p. 94–95° (Found : C, 62.5; H, 6.4. $C_{11}H_{14}O_4$ requires C, 62.84; H, 6.7 per cent). It did not dissolve in aqueous sodium carbonate (10 per cent) and gave brown colouration with alcoholic ferric chloride.

2-(3',4'-*Methylenedioxybenzoyloxy*)-4-*Ethoxy*-5-*Methoxyacetophenone* (*XIV*) : A solution of the above acetophenone (XIII) (2g) in dry pyridine (15ml) was treated with piperonyl chloride (2.5 heated on a boiling water-bath for 30 mts. and the resulting ester (XIV) was worked out as usual. It crystallised from acetone as colourless needles (2.7 g), m.p. 150–51°. (Found : C, 63.4; H, 4.9. $C_{19}H_{18}O_7$ requires C, 63.68; H, 5.06 per cent). It did not give any colouration with alcoholic ferric chloride and was insoluble in aqueous sodium hydroxide.

2-*Hydroxy*-4-*Ethoxy*-5-*Methoxy*-3',4'-*Methylenedioxydibenzoylmethane* (*XV*) : A solution of the above ester (XIV) (2.5 g) in dry pyridine (15 ml) was treated with powdered potassium hydroxide (2 g). The reaction mixture was thoroughly shaken and its temperature was maintained at 40° by occasional warming on a water-bath. In about 45 minutes, the reaction mixture became viscous due to the separation of the yellow potassium salt of β-diketone (XV). It was cooled and acidified with hydrochloric acid. The β-diketone (XV) obtained as a yellow crystalline solid was filtered, washed with water and dried. It crystallised from ethyl acetate-petroleum ether mixture as golden yellow needles (1.3 g), m.p. 230–31° (Found : C, 63.5; H, 4.8. $C_{19}H_{18}O_7$ requires C, 63.68 & H, 5.06 per cent). It dissolved in aqueous sodium hydroxide and gave a brown colouration with alcoholic ferric chloride.

6-*Methoxy*-7-*Ethoxy*-3',4'-*Methylenedioxyflavone* (*IV*) : A mixture of the β-diketone (XV) (1g), glacial acetic acid (20 ml) and fused sodium acetate (1 g) was refluxed gently in an oil-bath for 4 hrs. It was cooled treated with crushed ice and the resulting flavone (IV) was worked out as usual. It crystallised from ethyl acetate-petroleum ether mixture as colourless amorphous powder (0.8g), m.p. 227–28° (Found : C, 66.7; H, 5.0 $C_{19}H_{16}O_6$ requires C, 67.05; H, 4.75 per cent). It was insoluble in aqueous sodium hydroxide and did not give any colouration with identical alcoholic ferric chloride. The synthetic flavone (IV) on comparison was found to be with prosogerin-A ethyl ether (m.p., m.m.p. and Co-TLC).

2'-*Hydroxy*-4'-*Methoxy*-5'-*Ethoxy*-3,4-*Methylenedioxychalkone* (*V*) : A solution of the ketone (VIII) (0.8 g) and piperonal (1.2 g) in ethanol (25 ml) was treated with aqueous potassium hydroxide (5 g, 10 ml) and then left at room temp. for 48 hrs. The reaction product was worked up as usual. The chalkone (V) crystallised from ethanol as yellow tiny prisms (1.0 g), m.p. 152–53° (Found : C, 66.2; H, 5.5. $C_{19}H_{18}O_6$ requires C, 66.66; H, 5.3 per cent). It gave brown colouration with alcoholic ferric chloride and on comparison was found to be different from prosogerin-B ethyl ether.

2'-*Hydroxy*-4'-*Ethoxy*-5'-*Methoxy*-3,4-*Methylenedioxychalkone* (*VI*) : A solution of the ketone (XIII) (0.6 g) and piperonal (1.0 g) in ethanol (20 ml) was treated with aqueous potassium hydroxide (4 g, 8 ml) and left at room temperature for 48 hrs. The reaction product was worked up as usual. The chalkone (VI) thus

obtained crystallised from ethanol as yellow prisms (0.6 g), m.p. 219–20° (Found : C, 66.3; H, 5.5. $C_{19}H_{18}O_6$ requires C, 66.66; H, 5.30 per cent). It gave brown coloura tion with alcoholic ferric chloride and on comparison was found to be identical with prosogerin-B ethyl ether (m.p., m.m.p. and Co-TLC).

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REFERENCES

Baker, W. (1933) Molecular rearrangement of some 0-acyloxyacetophenones and the mechanism of the production of 3-acylchromones. *J. chem. Soc.*, 1381.

Bhardwaj, D. K., Bisht, M. S., Mehta, C. K., and Sharma, G. C. (1978*a*) Phenolic components of *Prosopis spicigera* flowers. *Phytochemistry*, **17** (*Under publication*).

Bhardwaj, D. K., Jain, R. K., Mehta, C. K., and Sharma, G. C. (1978*b*). Prosogerin-C A new flavone from *Prosopis spicigera*. *Indian J. Chem.*, **16B**, (*Under publication*).

Bhardwaj, D. K., Jain, S. C., and Singh, R. (1978*c*), A convenient synthesis of athyriol. *Indian J. Chem.*, **16B**, 150.

Bhardwaj, D. K., Neelakantan, S., and Seshadri, T. R. (1965) A convenient synthesis of Oroxylin A and Pectolinarigenin. *Indian J. Chem.*, **3**, 559.

———(1968). Isomeric triethylmonomethyl ethers of scutellarien. *Indian J. Chem.*, **6**, 229.

Bargellini, G., and Aurelik, S. (1911) Hydroxyquinone derivatives. *Atti Accad. Lincei*, **20**, 118 (*Chem. Abstr.*, 1911, **5**, 3683).

Doyle, B. G., Gogan, F., Gowan, J. E., Keane, J., and Wheeler, T. S. (1948) Transformation reactions I. The mechanism of the transformations of 0-aroylacetarones into 0-hydroxydiaroylmethanes and the synthesis of flavones. *Sci. Proc. R. Dublin Soc.*, **24**, 291.

Dunne, A. T. M., Gowan, J. R., Keane, J., Keeley, B. M. O., Sullivan, D. O., Roche, M. M., Ryan, P. M., and Wheeler, T. S. (1950) Thermal cyclisation of 0-aroyacetarones : a new synthesis of flavones. *J. chem. Soc.*, 1252.

Geissman, T. A. (1962) *The Chemistry of Flavonoid Compounds*. Pergamon Press, London, p. 107.

Harborne, J. B., Mabry, T. S., and Mabry, H. (1975) *The Flavonoids*. Chapman and Hall, London, p. 45.

Laumas, K. R., Neelakantan, S., and Seshadri, T. R. (1933). A synthesis of stillopsidin and its methyl ethers. *Proc. Indian Acad. Sci.*, **46A**, 343.

Mabry, J. J., Markham, K. R., and Thomas, M. B. (1970). *The Systematic Identification of Flavonoids*. Springer & Verlag, New York, p. 41.

Mahal, H. S., and Venkataraman, K. (1933) 4-Styrylcoumarins. *Curr. Sci.*, **4**, 214.