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CONSTITUTION OF PREMTORIN : SYNTHETIC STUDIES

D K BHARDWAJ, A K GUPTA, A JAIN, V K SHRAWAT *and* A SHARMA

Department of Chemistry, University of Delhi, Delhi-110 007, India

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Premtorin, (6,7,3′,4′-monohydroxytrimethoxyflavone) isolated from *Abrus precatorius* (*Yrm. Leguminosae*) gave an ethyl ether which was found to be identical with 6,7,4′-trimethoxy-3′-ethoxyflavone (II) but not with three other isomers; 6,3′,4′-trimethoxy-7-ethoxyflavone (III), 7,3′,4′-trimethoxy-6-ethoxyflavone (IV) and 6,7,3′-trimethoxy-4′-ethoxyflavone (V). Based on these facts, the constitution of premtorin was shown to be 6,7,4′-trimethoxy-3′-hydroxyflavone (I). All the isomeric monoethoxytrimethoxyflavones (II, III, IV & V) were synthesised for comparison.

Key Words : Premtorin; 6,7,4′-Trimethoxy-3′-Hydroxyflavone (I)

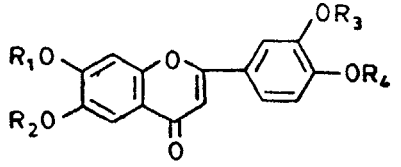
THE structure of premtorin, isolated[1] from *Abrus precatorius* was proposed as 6,7,4′-trimethoxy-3′-hydroxyflavone (I) on the basis of colour reactions and spectral analysis but no synthetic or any chemical evidence had been provided. Based on similar considerations, premtorin ethyl ether among the four possible isomers, 6,7,4′-trimethoxy-3′-ethoxyflavone (II), 6,3′,4′-trimethoxy-7-ethoxyflavone (III), 7,3′,4′-trimethoxy-6-ethoxyflavone (IV) and 6,7,3′-trimethoxy-4′-ethoxyflavone (V), was assumed to be subsequently confirmed by synthesis I. This paper describes the syntheses of four isomeric trimethoxymonoethoxyflavones (II, III, IV and V) in order confirm the constitution to premtorin ethyl ether from which follows the constitution (I) for premtorin.

The syntheses of 6,3′,4′-trimethoxy-7-ethoxyflavone (III) and 7,3′,4′-trimethoxy-6-ethoxyflavone (IV) were effected by the condensation of 2-hydroxy-4-ethoxy-5-methoxyacetophenone[2] and 2-hydroxy-5-ethoxy-4-methoxyacetophenone[2] respectively with veratraldehyde in the presence of aqueous ethanolic alkali followed by the cyclodehydrogenation[3–6] of the resulting chalkones (VII and VIII) using selenium dioxide in iso-amyl alcohol to afford the resulting (flavones) III and IV. Similarly, the condensation of 2-hydroxy-4,5-dimethoxyacetophenone with O-ethyl vanillin and O-ethyl iso-vanillin gave the corresponding chalkones (IX and VI). Similar cyclodehydrogenation of IX and VI yielded the corresponding (flavones) V and II respectively. On direct comparison, premtorin ethyl ether was found to be identical with II but not with other three isomers (III, IV and V) thereby confirming the proposed constitution of this ethyl ether and premtorin as 6,7,4′-trimethoxy-3′-ethoxyflavone (II) and 6,7,4′-trimethoxy-3′-hydroxyflavone (I) respectively.

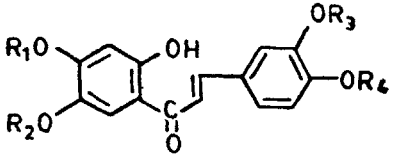
EXPERIMENTAL

2′-Hydroxy-3,4,5′-trimethoxy-4′-ethoxychalkone (VII)

A solution of 2-hydroxy-4-ethoxy-5-methoxyacetophenone (1.0g) and veratraldehyde (1.5g) in ethanol (15ml) was treated with aq. potassium hydroxide



I, $R_1 = R_2 = R_4 = CH_3$; $R_3 = H$
II, $R_1 = R_2 = R_4 = CH_3$; $R_3 = C_2H_5$
III, $R_2 = R_3 = R_4 = CH_3$; $R_1 = C_2H_5$
IV, $R_1 = R_3 = R_4 = CH_3$; $R_2 = C_2H_5$
V, $R_1 = R_2 = R_3 = CH_3$; $R_4 = C_2H_5$



VI, $R_1 = R_2 = R_4 = CH_3$; $R_3 = C_2H_5$
VII, $R_2 = R_3 = R_4 = CH_3$; $R_1 = C_2H_5$
VIII, $R_1 = R_3 = R_4 = CH_3$; $R_2 = C_2H_5$
IX, $R_1 = R_2 = R_3 = CH_3$; $R_4 = C_2H_5$

(3g in 30ml) and kept at room temperature for 48 hrs. The reaction mixture when worked up as usual, gave the chalkone (VII) which crystallised from ethanol as yellowish-orange needles (0.9g), m.p. 110–11° (*Found* : C, 66.61; H, 6.09. $C_{20}H_{22}O_6$ requires C, 67.04; H, 6.15 per cent). It gave brown colouration with ethanolic ferric chloride. *PMR Spectrum* (δ, *$CDCl_3$, TMS as an internal standard*) : 1.38–1.54 (3H,*t*,–OCH_2CH_3), 3.84–3.90 (9H, m, 3 X-OCH_3), 4.0–4.20 (2H, q, —OCH_2CH_3), 6.43 (1H, s, $C_{3'}$ — H), 6.86 (1H, d, J = 9 Hz, C_5 — H), 7.10–7.38 (4H, m, C_2 — H, C_6 — H, $C_{6'}$ — H and C_α — H), 7.82 (1H, d, J = 17 Hz, C_3 — H), 13.48 (1H, s, — OH).

6,3',4'–Trimethoxy-7-ethoxyflavone (*III*)

The above chalkone (VII) 0.8g), selenium dioxide (0.4g) and iso-amyl alcohol (20ml) were refluxed in an oil-bath for 72hrs. The reaction mixture was then filtered to remove selenium metal and its dioxide. Removal of the solvent from the filtrate gave III which crystallised from chloroform-pet. ether as colourless needles (0.4g), m.p. 210° (*Found* : C, 67.01; H, 5.64. $C_{20}H_{20}O_6$ requires C, 67.40; H, 5.62 per cent). *PMR Spectrum* (δ, *$CDCl_3$, TMS as an internal standard*) : 1.45–1.60 (3H, *t*, — OCH_2CH_3), 3.93–4.00 (9H, m, 3 X — OCH_3), 4.05–4.28 (2H, q,–OCH_2CH_3), 6.63 (1H, s, C_3 — H), 6.80–6.92 (2H, m, C_8 — H and $C_{5'}$ — H), 7.24–7.32 (2H, m, $C_{2'}$ — H and $C_{6'}$ — H), 7.48 (1H, s, C_5 — H).

2'–Hydroxy-3,4,4'-trimethoxy-5'-ethoxychalkone (*VIII*)

2-Hydroxy-4-methoxy-5-ethoxyacetophenone (1.0g) and veratraldehyde (1.5g) in ethanol (20ml) were treated with aq. potassium hydroxide (3g in 20ml) and kept

at room temperature for 48hrs. The reaction product was then worked up as usual. The chalkone (VIII) thus obtained, crystallised from ethyl acetate-pet. ether as yellowish-orange needles (0.8g), m.p. 94° (*Found* : C, 66.93, H, 6.12. $C_{20}H_{22}O_6$ requires C, 67.04; H, 6.15 per cent). It gave brown colouration with ethanolic ferric chloride. *PMR Spectrum* (δ, *CDCl₃, TMS as an internal standard*) : 1.38-1.54 (3H, *t*, — OCH_2CH_3), 3.88 (9H, s, 3 X — OCH_3), 4.0-4.23 (2H, q, — OCH_2CH_3), 6.45 (1H, s, $C_{3'}$ — H), 6.85 (1H, d, J = 9 Hz, C_5 — H), 7.13-7.40 (4H, m, C_2 — H, C_6 — H, $C_{6'}$ — H and C_α — H), 7.83 1H, d, J = 17 Hz, C_β — H), 13.56 (1H, s, — OH).

7,3',4'-Trimethoxy-6-ethoxyflavone (IV)

The above chalkone (VIII) (0.7g) and selenium dioxide (0.3g) in iso-amyl alcohol (20ml) were refluxed for 72hrs and the reaction product was worked up. When the flavone (IV) was obtained, it crystallised from chloroform-pet. ether as colourless microprisms (0.4g), m.p. 211-12° (*Found* : C, 67.42; H, 5.61. $C_{20}H_{20}O_6$ requires C, 67.40; H, 5.62 per cent). *PMR Spectrum* (δ, *CDCl₃, TMS as an internal standard*) : 1.42-1.54 (3H, *t*, — OCH_2CH_3), 3.89 — 4.00 (9H,m 3X — OCH_3), 4.1-'4.26 (2H, q, — OCH_2CH_3), 6.62 (1H, s, C_3 — H), 6.80-6.88 (2H, m, C_8 — H and $C_{5'}$ — H), 7.23-7.34 (2H, m, $C_{2'}$ — H and $C_{6'}$ — H), 7.50 (1H, s, C_5 — H).

2'-Hydroxy-3,4',5'-trimethoxy-4-ethoxychalkone (IX)

A solution of 2-hydroxy-4,5-dimethoxyacetophenone (1.0g) and O-ethyl vanillin (1.5g) in ethanol (20ml) was treated with aq. potassium hydroxide (3g in 30ml) and kept at room temperature for 48hrs. The reaction product was then worked up as usual and the chalkone (IX) thus obtained crystallised from ethyl acetate pet. ether as yellowish-orange needles (0.80g), m.p. 162° (*Found* : C, 67.12; H, 6.10. $C_{20}H_{22}O_6$ requires C, 67.04; H, 6.15 per cent). It gave brown colouration with ethanolic ferric chloride. *PMR Spectrum* (δ, *CDCl₃, TMS as internal standard*) : 1.39-1.55 (3H, *t*, — OCH_2CH_3), 3.85-3.91 (9H, m, 3 X — OCH_3), 4.02-4.25 (2H, *q*, — OCH_2CH_3), 6.47 (1H, *s*, $C_{3'}$ — H), 6.87 (1H, d, J = 9Hz, C_5 — H), 7.15-7.40 (4H, *m*, C_2 — H, C_6 — H, $C_{6'}$ — H and C_α — H), 7.83 (1H, d, J = 17 Hz, C_β — H), 13.60 (1H, *s*, — OH).

6,7,3'-Trimethoxy-4'-ethoxyflavone (V)

The above chalkone (IX) (0.7g) on cyclo-dehydrogenation with selenium dioxide as described for the flavones III and IV afforded V which crystallised from chloroform-pet. ether as colourless needles (0.3g), m.p. 227-28° (*Found* : C, 67.39, H, 5.65. $C_{20}H_{20}O_6$ requires C, 67.40; H, 5.62 per cent). *PMR Spectrum* (δ, *CDCl₃, TMS as internal standard*) : 1.40-1.55 (3H, *t*, — OCH_2CH_3), 3.90-4.00 (9H, *m*, 3 X — OCH_3), 4.0-4.24 (2H, *q*, — OCH_2CH_3), 6.60 (1H, *s*, C_3 — H), 6.82-6.89 (2H, *m*, C_8 — H and C_5 — H), 7.25-7.32 (2H, *m*, $C_{2'}$ — H & $C_{6'}$ — H), 7.45 (1H, *s*, C_5 — H).

2'-Hydroxy-4'4',5'-trimethoxy-3-ethoxychalkone (VI)

Condensation of 2-hydroxy-4,5-dimethoxyacetophenone (1.0g) with O-ethyl iso-vanillin (1.5g) in the presence of aq. ethanolic potassium hydroxide (3g in 30ml) at room temperature afforded the chalkone (VI) which crystallised from chloroform pet. ether as yellowish-orange plates (0.8g), m.p. 128° (*Found* : C, 67.15, H, 6.15. $C_{20}H_{22}O_6$ requires C, 67.04; H, 6.15 per cent). It gave brown colouration with ethanolic ferric chloride. *PMR Spectrum* (δ, *CDCl₃*, *TMS as internal standard*) : 1.39–1.54 (3H, *t*, — OCH_2CH_3), 3.87–3.92 (9H, *m*, 3 X — OCH_3), 4.0–4.24 (2H, *q*, — OCH_2CH_3), 6.42 (1H, *s*, $C_{3'}$ — H), 6.85 (1H, d, J = 9 Hz, C_5 — H), 7.12-7.37 (4H, *m*, C_2 — H, C_6 — H, $C_{6'}$ — H and C_α — H), 7.78 (1H, d, J = 17 Hz, C_β — H), 13.60 (1H, *s*, — OH).

6,7,4'-Trimethoxy-3'-ethoxyflavone (II)

The above chalkone (VI) (0.6g), selenium dioxide (0.2g) and iso-amyl alcohol (15ml) were refluxed for 72 hrs. and then the reaction product was worked up as usual. The flavone (II) thus obtained crystallised from ethanol as colourless microneedles (0.25g), m.p. 179–80° (*Found* : C, 67.29; H, 6.63. $C_{20}H_{20}O_6$ requires C, 67.40; H, 5.62 per cent). *PMR Spectrum* (δ, *CDCl₃*, *TMS as an internal standard*) : 1.38–1.54 (3H, *t*, — OCH_2CH_3), 3.90–4.00 (9H, *m*, 3 X — OCH_3), 4.0–4.23 (2H, *q*, — OCH_2CH_3), 6.57 (1H, *s* C_3 — H), 6.78–6.87 (2H, *m*, C_8 — H and $C_{5'}$ — H), 7.22–7.30 (2H, *m* $C_{2'}$ — H and $C_{6'}$ — H), 7.41 (1H, *s*, C_5–H).

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