

Structure Confirmation for an Unusual Flavanone from *Encelia stenophylla*

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5,7,3'-Trihydroxy Flavanone, Unusual Substitution,
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A flavanone with 3'-OH as the sole B-ring substituent has been reported recently as a leaf and stem exudate constituent of *Encelia stenophylla*. The correctness of this unusual substitution is confirmed by synthesis of this flavanone.

Introduction

Theoretically, an immense number of flavonoid aglycones can be suggested which are based on the well-known C₁₅-skeleton and differ simply by number and position of attached OH- and OMe-groups. However, comparatively few of the conceivable structures are realized in nature. Certain substitution patterns are obviously prevailing, due to the biosynthesis from malonate units condensing with a phenylalanine-derived C₆–C₃ precursor as well as to specific and sequential enzyme activities for additional substitution. No natural flavonoid was known, for instance, with 3'-OH or 3'-OMe as the sole substituent at the B-ring, no natural flavonoid is known so far with 3',5'-di-O-substitution. On the other hand, the improvement of isolation techniques and advances in spectroscopic analysis have recently allowed the detection of flavonoids with unexpected oxygenation patterns such as the previously reported *Primula* flavones (for a survey see [1]). Lately the first natural flavonoid with a 3'-O-substituted B-ring has been

reported, namely 5,7,3'-trihydroxy flavanone, isolated from the leaf and stem exudate of *Encelia stenophylla* as a minor constituent [2]. We deemed it very important to confirm the identity of this unusual product by synthesis and this will be reported in the following.

Materials and Methods

¹H NMR spectra were recorded at 270 MHz, MS were recorded at 70 eV by direct inlet.

Synthesis of 2'-hydroxy-3,4',6'-triisopropoxychalcone

2-Hydroxy-4,6-diisopropoxyacetophenone (2.5 g, 10 mmol) and 3-isopropoxybenzaldehyde (1.7 g, 10 mmol) were added to ethanolic potassium hydroxide (4 g KOH in 50 ml 80% ethanol). The reaction mixture was stirred at room temperature overnight. By the usual procedure [3], 2'-hydroxy-3,4',6'-triisopropoxychalcone (1.5 g) was obtained as a reddish-orange oil. MS *m/z* (rel. int.): 398 (M⁺, 66), 355 (25), 313 (20), 281 (37), 263 (60), 221 (64), 179 (100). ¹H NMR (CDCl₃) δ: 1.32, 1.34, 1.45 (6H, each d, *J* = 7 Hz; CH₃), 4.55 (3H, m; 3 × CH<), 5.96, 6.05 (1H, each d, *J* = 2 Hz; H-3' and H-5'), 6.90–7.29 (4H, m; H-2, 4, 5, and 6), 7.70, 7.98 (1H, each d, *J* = 16 Hz; Ha and Hβ), 14.24 (1H, s; C-2-OH).

Synthesis of 5,7,3'-triisopropoxyflavanone

The above chalcone (500 mg, 1.3 mmol) and phosphoric acid (8 g) in 2-methoxyethanol (100 ml) were refluxed for 200 h. By column chromatography of the reaction mixture on silica gel (eluent: hexane/acetone 5:1) 5,7,3'-triisopropoxyflavanone (110 mg) was obtained as a pale yellow oil along with starting material (300 mg). MS *m/z* (rel. int.): 398 (M⁺, 16), 383 (93), 356 (24), 341 (17), 314 (22), 281 (36), 221 (71), 194 (47), 179 (100), 152 (93), 120 (68). ¹H NMR (acetone-d₆) δ: 1.30–1.35 (18H, m; 6 × CH₃), 2.65 (1H, dd, *J* = 16 and 3 Hz; H-3), 2.91 (1H, dd, *J* = 16 and 12 Hz; H-3), 4.55–4.69 (3H, m; 3 × CH<), 5.45 (1H, dd, *J* = 12 and 3 Hz; H-2), 6.15 (1H, d, *J* = 2 Hz; H-6), 6.16 (1H, d, *J* = 2 Hz; H-8), 6.92 (1H, br dd, *J* = 8 and 2 Hz; H-4'), 7.03–7.12 (2H, m; H-2' and H-6'), 7.33 (1H, br t, *J* = 8 Hz; H-5').

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Synthesis of 5,7,3'-trihydroxyflavanone

The above flavanone (100 mg) was dissolved in dichloromethane (20 ml), the solution was cooled to -60°C and BCl_3 (0.5 ml) was added. The reaction mixture was kept at room temperature for 2 h and then poured into water. By the usual procedure 5,7,3'-trihydroxyflavanone was isolated. After purification by column chromatography on silica gel (eluent: hexane/acetone 2:1), the flavanone was obtained as colourless rectangles, m.p. $234\text{--}235^{\circ}\text{C}$. MS m/z (rel. int.): 272 (M^+ , 100), 254 (6), 229 (4), 201 (5), 180 (14), 179 (98), 153 (66), 152 (43), 124 (27), 120 (23). ^1H NMR (DMSO-d_6) δ : 2.70 (1H, dd, $J = 17.2, 2.9$ Hz; H-3 *trans*), 3.17 (1H, dd, $J = 17.2$ and 12.5 Hz; H-3 *cis*), 5.49 (1H, dd, $J = 12.3$ and 2.9 Hz; H-2), 5.88 (1H, d, $J = 2.2$ Hz; H-6), 5.91 (1H, d, $J = 2.2$ Hz; H-8), 6.75 (1H, ddd, $J = 8.1, 1.4, 1.4$ Hz; H-6'), 6.88–6.91 (2H, m; H-2' and H-4'), 7.20 (1H, t, $J = 8.1$ Hz; H-5'), 9.53, 10.81 (1H, each s; OH), 12.11 (1H, s; C-5–OH). UV $\lambda_{\text{MeOH}}^{\text{max}}$ nm (log ϵ): 231 sh (3.85), 288 (3.91), 321 sh (3.50); +NaOMe: 241, 324; + AlCl_3 : 222, 240 sh, 310, 370; + AlCl_3 + HCl: 222, 240 sh, 309, 367; +NaOAc: 240 sh, 288, 324; +NaOAc + H_3BO_3 : 240 sh, 287, 325 sh.

Results and Discussion

An unambiguous synthesis of 5,7,3'-trihydroxyflavanone was performed, starting by condensation of 2-hydroxy-4,6-diisopropoxyacetophenone with 3-isopropoxybenzaldehyde in alkaline solution. This reaction yielded 2'-hydroxy-3,4,6'-triisopropoxychalcone which was isomerized, by reaction with phosphoric acid in 2-methoxyethanol, to 5,7,3'-triisopropoxyflavanone. This product was deisopropylated with boron trichloride at -60°C to give the desired 5,7,3'-trihydroxyflavanone in good yield.

Unfortunately all the original 5,7,3'-trihydroxyflavanone, isolated previously from leaf and stem exudate of *Encelia stenophylla* (compound **10** in [2]), was used up during structural analysis. Direct comparison of the synthetic with the natural product is hence impossible at present. However, all spectral data of the synthetic product are in accordance with those of the natural flavanone and we take it as granted, therefore, that both are identical. We thus confirmed that 5,7,3'-trihydroxyflavanone from *Encelia* is, in fact, the first flavonoid with a 3'-O-substituted B-ring found in nature.

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