

Synthetic Studies of the Flavone Derivatives. VI.*¹ The Synthesis of 3',6-Dimethoxy-4',5,7-triethoxyflavone

Tokunaru HORIE and Mitsuo MASUMURA

Department Applied of Chemistry, Faculty of Engineering, University of Tokushima, Tokushima

and Kenji FUKUI and Mitsuru NAKAYAMA

Department of Chemistry, Faculty of Science, Hiroshima University, Higashi Sendamachi, Hiroshima

(Received November 27, 1967)

In 1963, a flavonoid pigment was isolated from *Digitalis lanata* L. by Whalley *et al.*^{1,2} They established that the pigment was 3',6-dimethoxy-4',5,7-trihydroxyflavone (I) on the basis of degradative studies of its trimethyl ether (II) and triethyl ether (III). In this paper, we wish to report the synthesis of 3,6'-dimethoxy-4',5,7-triethoxyflavone (III), which confirms the proposed structure (I) of the pigment by an unambiguous method.

The esterification of 4,6-diethoxy-2-hydroxy-5-methoxyacetophenone (IV)^{2,3} with 4-ethoxy-5-methoxybenzoyl chloride in the presence of anhydrous pyridine yielded 4,6-diethoxy-2-(4'-ethoxy-3'-methoxybenzoyloxy)-5-methoxyacetophenone (V) (mp 102–103°C). According to the Baker-Venkataraman rearrangement,³ the subsequent reaction of the acetophenone (V) with sodium amide gave 3',5-dimethoxy-2-hydroxy-4,4',6-triethoxy-dibenzoylmethane (VI) (mp 124.5–

125.5°C). The cyclization of the dibenzoylmethane (VI) with concentrated sulfuric acid afforded the desired flavone (III) (mp 172–173°C) (lit.^{1,2} mp 165–168°C). The structure of this compound was confirmed by a study of its infrared, ultraviolet, and NMR spectra.

Experimental*³

4,6-Diethoxy-2-hydroxy-5-methoxyacetophenone (IV). This acetophenone was prepared from 3,5-diethoxy-4-methoxyphenol⁴ in the manner described by Farkas *et al.*²; bp 135–137°C/1.5 mmHg (62%). Found: C, 61.69; H, 7.17%. Calcd for C₁₃H₁₈O₅: C, 61.40; H, 7.14%.

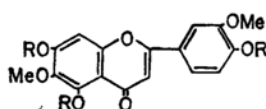
4,6-Diethoxy-2-(4'-ethoxy-3'-methoxybenzoyloxy)-5-methoxyacetophenone (V). A mixture of IV (2.5 g), 4-ethoxy-3-methoxybenzoyl chloride (2.5 g), and anhydrous pyridine (4.0 ml) was heated in an oil bath at 120°C for 1.5 hr. After having then been cooled, the reaction mixture was poured into ice-cold dilute hydrochloric acid and extracted with ether. The ether solution was washed with dilute hydrochloric acid, with an aqueous sodium carbonate solution, and finally with water. The resulting solution being dried over sodium sulfate and evaporated, the residual product was recrystallized from methanol to give V in the form of colorless needles, mp 102–103°C; yield 2.2 g (52%).

Found: C, 64.18; H, 6.57%. Calcd for C₂₅H₂₈O₈: C, 63.88; H, 6.53%.

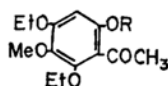
3',5-Dimethoxy-2-hydroxy-4,4',6-triethoxy-dibenzoylmethane (VI). The acetophenone (V) (1.9 g) was heated with finely powdered sodium amide (1.9 g) in anhydrous xylene (15 ml) at 110°C for 1 hr. After the excess sodium amide had been completely decomposed with ice water, the resulting solution was saturated with carbon dioxide. The precipitate was collected, washed with water, and recrystallized from ethanol to give VI in the form of golden yellow prisms, mp 124.5–125.5°C; yield 760 mg (40%). This substance gave a green ferric reaction in ethanol.

Found: C, 63.86; H, 6.50%. Calcd for C₂₅H₂₈O₈: C, 63.88; H, 6.53%.

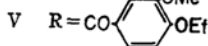
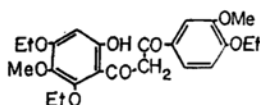
3',6-Dimethoxy-4',5,7-triethoxyflavone (III). To a solution of VI (360 mg) in glacial acetic acid (8.0 ml), concentrated sulfuric acid (1 ml) was added; the mixture



- I R=H
II R=Me
III R=Et



IV R=H



VI

*¹ Part V: K. Fukui and T. Matsumoto, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **86**, 1079 (1965).

*² Presented in part at the Okayama Meeting of the Chemical Society of Japan, Okayama, October, 1967.

1) J. W. ApSimon, N. B. Haynes, K. Y. Sim and W. B. Whalley, *J. Chem. Soc.*, **1963**, 3780.

2) L. Farkas, L. Hörhammer, H. Wagner, H. Rösler and R. Gurniak, *Chem. Ber.*, **97**, 610 (1964).

3) W. Baker, *J. Chem. Soc.*, **1933**, 1381; H. S. Mahal and K. Venkataraman, *ibid.*, **1934**, 1767.

*³ All melting points are uncorrected.

4) M. Krishnamuri and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **39A**, 144 (1954).

was heated at 70°C for 5 min. Then, it was cooled and treated with water. The resulting mixture was boiled until a crystalline solid separated. The precipitate was collected, washed with water, and recrystallized from ethanol to give III in the form of colorless prisms, mp 172–173°C (lit.¹³) mp 165–168°C; yield 310 mg

*⁴ The NMR spectrum was measured with Hitachi Model R-20 NMR Spectrometer (60 Mc) for CDCl₃ solution containing tetramethylsilane as internal reference.

(90%). This substance gave a yellow solution when treated with concentrated sulfuric acid. IR: ν_{max}^{Nujol} cm⁻¹; 1635 (γ -pyrone). UV: λ_{max}^{EtOH} m μ (log ϵ); 215.5 (4.67), 240.5 (4.36), 266 (4.17), 328 (4.45). NMR*⁴ ppm; 6.59_s (H-3), 6.81_s (H-8), 7.36_d ($J=2.5$ Hz) (H-2'), 6.99_d ($J=9$ Hz) (H-5'), 7.53_q ($J=9, 2.5$ Hz) (H-6').

Found: C, 66.89; H, 6.26%. Calcd for C₂₃H₂₆O₇: C, 66.65; H, 6.32%.
