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Synthetic Studies of the Flavone Derivatives. XXIII.[1] The Synthesis of Eupatilin

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Eupatilin, isolated from *Eupatorium semiserratum* D C., has been identified as 5,7-dihydroxy-6,3′,4′-trimethoxyflavone (I) on the bases of its spectral data and degradative studies.[2] The present paper will describe the synthesis of I from 2,4-dibenzyloxy-6-hydroxy-3-methoxyacetophenone (II).

The esterification of II with 3,4-dimethoxybenzoyl chloride (III) yielded 2,4-dibenzyloxy-3-methoxy-6-(3,4-dimethoxybenzoyloxy)acetophenone (IV). The IV ester was converted into 2,4-dibenzyloxy-6-hydroxy-3-methoxy-ω-(3,4-dimethoxybenzoyl)acetophenone (V) by the Baker-Venkataraman transformation. The cy-

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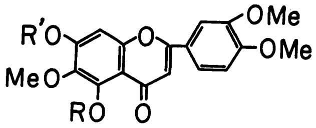
[1] XXII of this series: T. Matsumoto, S. Imai, and K. Fukui, This Bulletin, **44**, 1698 (1971).

[2] S. M. Kupchan, C. W. Sigel, R. J. Hemingway, J. R. Knox, and M. S. Udayamurty, *Tetrahedron*, **25**, 1603 (1969).



I R=R′=H
VI R=H, R′=C_7H_7
VII R=R′=Ac
VIII R=R′=Et
IX R=H, R′=Et

clodehydration of V with sodium acetate afforded 7-benzyloxy-5-hydroxy-6,3′,4′-trimethoxyflavone (VI). The catalytic hydrogenolysis of VI gave the desired flavone I, which was then easily converted into the diacetate (VII), the diethyl ether (VIII), and the monoethyl ether (IX). The flavone I was shown to be identical with the natural pigment[3] by a mixed-melting-point determination and by IR and UV spectral comparisons.

Experimental[4]

2,4-Dibenzyloxy-3-methoxy-6-(3,4-dimethoxybenzoyloxy)acetophenone (IV). A mixture of the crude II[5] (2.3 g) and III (2.3 g) in anhydrous pyridine (10 m*l*) was heated at 120°C for 2 hr. The cooled reaction mixture was poured into diluted hydrochloric acid, and then extracted with ether. The ether layer was allowed to stand overnight in a refrigerator. The separated crystals were recrystallized from ethyl acetate to give IV; mp 155—157°C (colorless prisms); yield, 800 mg (24%).

Found: C, 70.83; H, 5.53%. Calcd for $C_{32}H_{30}O_8$: C, 70.83; H, 5.57%.

2,4-Dibenzyloxy-6-hydroxy-3-methoxy-ω-(3,4-dimethoxybenzoyl)-acetophenone (V). A mixture of IV (0.9 g), powdered potassium hydroxide (1 g), and anhydrous pyridine (15 m*l*) was heated at 60°C for 4 hr with stirring. The reaction mixture was acidified with diluted hydrochloric acid, and then extracted with ether. The ether layer was allowed to stand overnight in a refrigerator. The separated crystals were recrystallized from ethyl acetate to give V; mp 131—132°C (yellow needles); yield, 450 mg (50%).

Found: C, 70.85; H, 5.33%. Calcd for $C_{32}H_{30}O_8$: C, 70.83; H, 5.57%.

7-Benzyloxy-5-hydroxy-6,3′,4′-trimethoxyflavone (VI). A mixture of V (370 mg), sodium acetate (1 g), and acetic acid (10 m*l*) was heated at 140°C for 4 hr. The reaction mixture was diluted with water, and then extracted with ether. The product was recrystallized from ethyl acetate to give VI; mp 175—177°C (pale yellow plates); yield, 210 mg (71%). UV: $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε); 244(4.26), 251.5(4.23), 278 (4.25), 344 (4.39). NMR:[6] ($CDCl_3$) 12.82_s (5-OH).

Found: C, 69.18; H, 5.19%. Calcd for $C_{25}H_{22}O_7$: C, 69.11; H, 5.10%.

5,7-Dihydroxy-6,3′,4′-trimethoxyflavone (Eupatilin) (I). A mixture of VI (150 mg) and palladium charcoal (Pd: 10%; 75 mg) in a mixed solvent of ethyl acetate and methanol (1:1; 80 m*l*) was shaken in an atmosphere of hydrogen for 3 hr. The product was recrystallized from ethyl acetate to give I; mp 241—242°C (yellow prisms); yield, 92 mg (77%). UV: $\lambda_{\max}$ mμ (log ε); (EtOH) 242(4.30), 277(4.29), 345 (4.38); (EtOH–AcONa) 278(4.45), 316(4.20), 376(4.26); (EtOH–$AlCl_3$) 254(4.18), 290(4.24), 352(4.39). NMR: (DMSO) 3.76_s, 3.84_s, 3.87_s (3×MeO); 6.60_s, 6.90_s, 7.09_d (J=9), 7.53_d(J=2), 7.65_q(J=9, 2) (5×Arom.H); 10.5_b, 13.07_s (2×OH) (Natural Pigment:[7] mp 240—241.5°C).

Found: C, 62.51; H, 4.47%. Calcd for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68%.

Diacetate (VII): mp 154—155°C (colorless needles from methanol). UV: $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε); 249(4.35), 265_{sh}(4.16),[8] 338(4.40). NMR: ($CDCl_3$) 2.37_s, 2.47_s (2×MeCO); 3.83_s, 3.92_s (6H) (3×MeO); 6.56_s, 6.96_d(J=9), 7.29_s, 7.30_d(J=2.5), 7.49_q(J=9, 2.5) (5×Arom.H).

Found: C, 61.68; H, 4.63%. Calcd for $C_{22}H_{20}O_9$: C, 61.68; H, 4.71%.

Diethyl Ether (VIII): mp 165.5—166.5°C (colorless needles from ethanol). UV: $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε); 240(4.34), 266 (4.15), 327(4.42). NMR: ($CDCl_3$) 1.46_t, 1.50_t, 4.14_q (J=7) (2×EtO); 3.87_s, 3.91_s(6H) (3×MeO); 6.51_s, 6.73_s, 6.91_d (J=9), 7.27_d(J=2.5), 7.46_q(J=9, 2.5) (5×Arom. H) (lit,[2] mp 164—166°C).

Found: C, 66.24; H, 6.26%. Calcd for $C_{22}H_{24}O_7$: C, 65.99; H, 6.04%.

Monoethyl Ether (IX): mp 176—177°C (pale yellow needles from ethanol). UV: $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε); 244(4.29), 253_{sh} (4.25), 278.5(4.27), 344(4.45). NMR: ($CDCl_3$) 12.80_s(5-OH).

Found: C, 64.80; H, 5.40%. Calcd for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41%.

Acetate of IX: mp 176—177°C (colorless needles from methanol). UV: $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε); 240(4.30), 260_i(4.06),[9] 330(4.35).

Found: C, 63.94; H, 5.21%. Calcd for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35%.

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[3] The natural pigment was kindly supplied by Professor S. M. Kupchan, University of Virginia.

[4] All the melting points are uncorrected.

[5] K. Fukui, M. Nakayama, and T. Horie, This Bulletin, **42**, 2327 (1969).

[6] The NMR spectra were measured with a Hitachi R-20 spectrometer (60 MHz), using tetramethylsilane as the internal standard (δ, ppm): s, singlet; d, doublet; q, quartet; b, broad.

[7] The natural pigment was measured in this laboratory.

[8] sh=shoulder.

[9] i=inflection.