NOTES

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Synthetic Studies of the Flavone Derivatives. XXII.[1] The Synthesis of Eupatoretin and Eupatin

Kenji FUKUI, Takashi MATSUMOTO, and Sachihiko IMAI

Department of Chemistry, Faculty of Science, Hiroshima University, Higashi-sendamachi, Hiroshima

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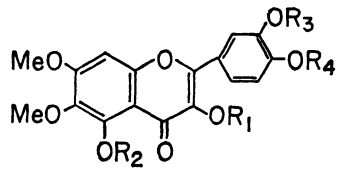
Recently, Kupchan *et al.*[2] reported the isolation of two new cytotoxic flavonols, eupatoretin and eupatin, from *Eupatorium semiserratum*. On the bases of chemical and spectral studies, they proposed that the structures of these flavonols were 3,3′-dihydroxy-4′,5,6,7-tetramethoxyflavone (I) for eupatoretin and 3,3′,5-trihydroxy-4′,6,7-trimethoxyflavone (II) for eupatin. In a previous paper,[3] we reported the synthesis of 3,4′,5-trihydroxy-3′,6,7-trimethoxyflavone (III), an isomer of eupatin, the structure of which had earlier been assigned to chrysosplenetin.[4]

For the structural confirmation of these natural pigments, we have now studied the syntheses of flavonols, I and II. By the method of Hörhammer *et al.*,[5] 3-benzyloxy-2′-hydroxy-4,4′,5′,6′-tetramethoxychalcone (IV) was converted into 3′-benzyloxy-3-hydroxy-4′,5,6,7-tetramethoxyflavone (V) in an 18% yield under improved reaction conditions without chromatographic purification (lit.[5]:10% yield after chromatography). The catalytic debenzylation of V in ethanol in the presence of Pd-C (10%) gave I, mp 150—151°C, which was shown to be identical with natural eupatoretin by a mixed-melting-point determination and by a spectral comparison. The synthetic I was further characterized by the preparation of its diacetate (VI), mp 151—152°C. Subsequently, the selective demethylation[3] of the C_5-methoxyl group in I with anhydrous aluminum chloride in dry nitrobenzene was carried out; the demethylated flavonol II was thus obtained as golden yellow needles, mp 244.5—245.5°C, which then gave triacetate (VII), mp 218—220°C. The synthetic II was also found to be identical with natural eupatin by a direct comparison.

The structures of eupatoretin and eupatin are thus confirmed to be I and II respectively.



I $R_1=R_3=H$, $R_2=R_4=Me$

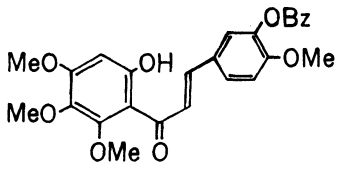
II $R_1=R_2=R_3=H$, $R_4=Me$

III $R_1=R_2=R_4=H$, $R_3=Me$

V $R_1=H$, $R_2=R_4=Me$, $R_3=Bz$

VI $R_1=R_3=Ac$, $R_2=R_4=Me$

VII $R_1=R_2=R_3=Ac$, $R_4=Me$



IV

Experimental[6]

3′-Benzyloxy-3-hydroxy-4′,5,6,7-tetramethoxyflavone (V). To a hot solution of IV (830 mg) in methanol (83 ml), we added hydrogen peroxide (30%: 3.5 ml) and an aqueous potassium hydroxide solution (20%: 13 ml). The mixture was refluxed for 1 min, poured into a mixture of ice and water (300 ml), and then immediately acidified with dilute hydrochloric acid. The yellow precipitates were collected, washed with water, and then recrystallized from ethanol to give V as yellow needles, mp 146—148°C, which gave a brown ferric chloride reaction in ethanol; yield, 150 mg (18%) (lit.[5] mp 142—143°C, yield 10%). UV λ_{max}^{EtOH} mμ (log ε); 235[7] (4.35), 254.5 (4.37), 360 (4.36).

3,3′-Dihydroxy-4′,5,6,7-tetramethoxyflavone (I). A solution of V (145 mg) in ethanol (50 ml) was submitted to catalytic hydrogenolysis at *ca.* 30°C in the presence of Pd-C (10%: 75 mg). After the catalyst had been filtered off, the filtrate was evaporated and the residue was recrystallized from benzene to give I as bright yellow plates, mp 150—151°C, which gave a brown ferric chloride reaction in ethanol; yield, 75 mg (62%). The mixed melting point with natural eupatoretin (mp 150—152°C[8]) was 150—152°C. UV: λ_{max}^{EtOH} mμ (log ε); 256 (4.34), 361 (4.29).

Found: C, 60.96; H, 4.72%. Calcd for $C_{19}H_{18}O_8$: C, 60.96; H, 4.85%.

3,3′-Diacetoxy-4′,5,6,7-tetramethoxyflavone (VI). A mixture of I (30 mg), acetic anhydride (0.4 ml), and dry pyridine (0.6 ml) was refluxed for 1 hr. The crude product was

1) Part XXI: M. Nakayama, K. Fukui, T. Horie, Y. Shimizu, and M. Masumura, *Nippon Kagaku Zasshi*, **91**, 1174 (1970).

2) S. M. Kupchan, C. W. Sigel, J. R. Knox, and M. S. Udayamurthy, *J. Org. Chem.*, **34**, 1460 (1969).

3) K. Fukui, T. Matsumoto, and S. Tanaka, This Bulletin, **42**, 1398 (1969).

4) M. Shimizu and N. Morita, *Chem. Pharm. Bull.* (Tokyo), **16**, 2310 (1968).

5) L. Hörhammer, H. Wagner, H. Rösler, E. Graf, and L. Farkas, *Chem. Ber.*, **97**, 2857 (1964).

6) All melting points were uncorrected.

7) Schoulder.

8) Observed in this laboratory.

recrystallized from benzene containing *n*-hexane to give the diacetate (VI) as colorless needles, mp 151—152°C, which gave a negative ferric chloride reaction in ethanol; yield, 27 mg (73%). UV: λ_{max}^{EtOH} mμ (log ε); 232[7](4.33), 264.5 (4.25), 319(4.42). Lit.[2] mp 145—147°C, UV: λ_{max}^{EtOH} mμ (ε); 235(28300), 263(25000), 316(31000).

3,3′,5-Trihydroxy-4′,6,7-trimethoxyflavone (II). The flavonol I (50 mg) was added to a mixture of anhydrous aluminum chloride (0.5 g) and dry nitrobenzene (5.0 m*l*). The mixture was allowed to stand at room temperature for 5 hr and then poured into a mixture of ice (10 g) and concentrated hydrochloric acid (3.0 m*l*) with stirring and cooling. After the removal of the nitrobenzene by steam distillation, the residual precipitates were collected, washed with water, and then recrystallized from methanol to give II as yellow needles, mp 244.5—245.5°C, which gave a dark green ferric chloride reaction in ethanol; yield, 18 mg (37%). The mixed melting point with natural eupatin (mp 244.5—245.5°C[8]) was 244.5—245.5°C. UV: λ_{max}^{EtOH} mμ (log ε); 259(4.34), 272[7](4.19), 294[7](3.83), 368(4.33).

Found: C, 60.04; H, 4.41%. Calcd for $C_{18}H_{16}O_8$: C, 60.00; H, 4.48%.

3,3′,5-Triacetoxy-4′,6,7-trimethoxyflavone (VII). A mixture of II (12.5 mg), acetic anhydride (0.2 m*l*), and dry pyridine (0.3 m*l*) was refluxed for 2 hr. The crude product was then recrystallized from benzene containing *n*-hexane to give the triacetate (VII) as colorless needles, mp 218—220°C, which gave a negative ferric chloride reaction; yield, 10 mg (60%). UV: λ_{max}^{EtOH} mμ (log ε); 260(4.19), 319(4.44).

Found: C, 59.22; H, 4.47%. Calcd for $C_{21}H_{22}O_{11}$: C, 59.26; H, 4.56%.

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