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Synthetic Studies of the Flavone Derivatives. XX.[1] The Synthesis of Sorbifolin

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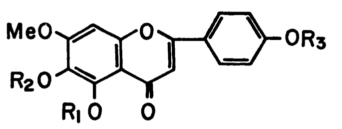
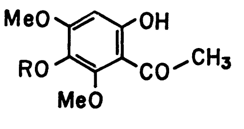
Recently, sorbifolin[2] was isolated, along with sorbarin (scutellarein-7-monorhamnoside), from the fresh leaves of *Sorbaria stellipila* SCHNEID. Its structure was identified as 7-methoxy-5,6,4′-trihydroxyflavone (I) on the basis of chemical and spectral evidence.[2]

The present paper will describe the synthesis of I from 3,6-dihydroxy-2,4-dimethoxyacetophenone (II).[3] The monobenzyl ether (III)[4] of II was esterified with *p*-benzyloxybenzoyl chloride in the presence of anhydrous pyridine, and then the resulting ester was converted into 3-benzyloxy-2,4-dimethoxy-6-hydroxy-ω-(4-benzyloxybenzoyl)acetophenone (IV) by Baker-Venkataraman transformation. The cyclodehydration of IV with anhydrous sodium acetate in acetic acid afforded 6,4′-dibenzyloxy-5,7-dimethoxyflavone (V). The debenzylation of V by hydrogenolysis gave the 6,4′-dihydroxyflavone derivative (VI). Then, the partial demethylation of VI with anhydrous aluminum chloride in acetonitrile gave the desired flavone I, which was easily converted into the acetate (VII).

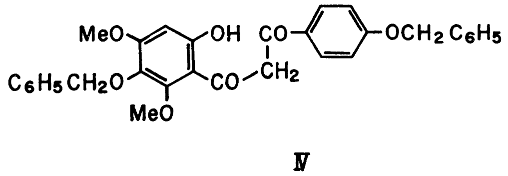
I and VII were shown to be identical with the natural pigment and its acetate respectively by a mixed-melting-point determination and by NMR, IR, and UV spectral comparisons.



I $R_1 = R_2 = R_3 = H$
V $R_1 = Me$, $R_2 = R_3 = C_6H_5CH_2$
VI $R_1 = Me$, $R_2 = R_3 = H$
VII $R_1 = R_2 = R_3 = Ac$



II $R = H$
III $R = C_6H_5CH_2$



IV

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[1] XIX of this series: M. Nakayama, K. Fukui, T. Horie, and M. Masumura, *Nippon Kagaku Zasshi*, **91**, 739 (1970).

[2] M. Arisawa, T. Takakuwa, and T. Nakaoki, *Chem. Parm. Bull.* (Tokyo), **18**, 916 (1970).

[3] V. D. Nageswara Sastri and T. R. Seshadri, *Proc. Indian Acad, Sci. Sect. A*, **23**, 262 (1946).

[4] K. Fukui, M. Nakayama, M. Matsui, M. Masumura, and T. Horie, *Nippon Kagaku Zasshi*, **90**, 1270 (1969).

Experimental[5]

3-Benzyloxy-2,4-dimethoxy-6-hydroxy-ω-(4-benzyloxybenzoyl)-acetophenone (IV). A mixture of the crude III[4] (2 g) and *p*-benzyloxybenzoyl chloride (2.5 g) in anhydrous pyridine (10 m*l*) was heated at 120°C for 2 hr. The cooled reaction mixture was poured into dilute hydrochloric acid and then extracted with ether. The removal of the solvent gave a semisolid (a crude ester).

A mixture of the above ester, freshly-powdered potassium hydroxide (2.0 g), and pyridine (15m*l*) was heated at 60°C for 4 hr with stirring. The reaction mixture was acidified with dilute hydrochloric acid, and then extracted with ether. The ether layer was washed with a sodium carbonate solution and water, and then evaporated. The resulting residue was treated with methanol-ether (1:1). The separated crystals were recrystallized from methanol-ethyl acetate to give IV as yellow prisms; mp 111—112.5°C; yield, 1.0 g (30% from III).

Found: C, 72.58; H, 5.52%. Calcd for $C_{31}H_{28}O_7$: C, 72.64; H, 5.51%.

6,4′-Dibenzyloxy-5,7-dimethoxyflavone (V). A mixture of IV (720 mg) and anhydrous sodium acetate (1.6 g) in acetic acid (8 m*l*) was heated at 140°C for 1 hr. The reaction mixture was then diluted with water and ether. The separated crystals were recrystallized from ethyl acetate to give V as colorless prisms; mp 154.5—155.5°C; yield, 600 mg (86%). UV: $\lambda_{\max}^{\mathrm{EtOH}}$ mμ(log ε); 271(4.26), 330(4.50). NMR: ($CDCl_3$) 6.53(s, H-3), 6.72(s, H-8), 7.02(d, *J*=9.0 Hz, H-3′, -5′), 7.80(d, *J*=9.0 Hz, H-2′, -6′).

Found: C, 75.07; H, 5.24%. Calcd for $C_{31}H_{26}O_6$: C, 75.29; H, 5.30%.

6,4′-Dihydroxy-5,7-dimethoxyflavone (VI). A mixture of V (890 mg) and Pd-C (10%; 90 mg) in ethyl acetate-methanol (2:1: 150 m*l*) was shaken in an atmosphere of hydrogen for 5 hr. After the catalyst had been filtered off, the filtrate was evaporated. The residue was recrystallized from ethanol to give VI as colorless needles; mp 286—288°C; yield, 500 mg (88%). UV: $\lambda_{\max}$ mμ (log ε); (EtOH) 280(4.30), 334(4.50); (EtOH-AcONa) 285_{sh}(4.21),[6] 332 (4.32), 380(4.15). NMR: (DMSO) 6.56(s, H-3), 6.89(d, *J*=8.3 Hz, H-3′, -5′), 7.08(s, H-8), 7.88(d, *J*=8.3 Hz, H-2′, -6′).

Found: C, 64.87; H, 4.24%. Calcd for $C_{17}H_{14}O_6$: C, 64.96; H, 4.49%.

Diacetate: mp 213—214°C (colorless prisms from ethyl acetate). UV: $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε); 264(4.35), 312(4.41). NMR: ($CDCl_3$) 6.58(s, H-3), 6.80(s, H-8), 7.21(d, *J*=9.0 Hz, H-3′, -5′), 7.88(d, *J*=9.0 Hz, H-2′, -6′).

Found: C, 63.03; H, 4.63%. Calcd for $C_{21}H_{18}O_8$: C, 63.31; H, 4.55%.

Sorbifolin (7-Methoxy-5,6,4′-trihydroxyflavone) (I). A mixture of VI (300 mg) and anhydrous aluminum chloride (2.0 g) in anhydrous acetonitrile (20 g) was heated at 65°C for 12 hr. The reaction mixture was then diluted with 1% hydrochloric acid (100 m*l*). After the solvent had been removed as much as possible under a vacuum, the separated solid was recrystallized from methanol to give I as yellow needles; mp 290—292°C; yield, 140 mg (49%). UV: $\lambda_{\max}$ mμ (log ε); (EtOH) 290(4.31), 343(4.41); (EtOH-$AlCl_3$) 306 (4.38), 366(4.47); (EtOH-AcONa) 380(4.25) (natural pigment:[7] (EtOH) 290(4.29), 343(4.39); (EtOH-$AlCl_3$) 306 (4.36), 366(4.44); (EtOH-AcONa) 380(4.17)). NMR: (DMSO) 3.89(s, OCH_3), 6.75(s, C-3 or -8), 6.80(s, H-8 or -3), 6.90(d, *J*=8.3 Hz, H-3′, -5′), 7.93(d, *J*=8.3 Hz, H-2′, -6′), 8.63(bs, OH-6), 10.3(bs, OH-4′), 12.65(s, OH-5).

Found: C, 64.06; H, 3.93%. Calcd for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03%.

Triacetate (VII): mp 228—229°C (colorless needles from methanol). UV: $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε); 261.5(4.28), 310(4.43).

Found: C, 61.70; H, 4.22%. Calcd for $C_{22}H_{18}O_9$:C, 61.97; H, 4.26%.

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[5] All the melting points are uncorrected. The NMR spectra were measured with a Hitachi R-20 spectrometer (60 MHz), using tetramethylsilane as the internal standard (δ, ppm); s, singlet; bs, broad singlet; d, doublet.

[6] sh=shoulder

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