Synthetic Studies of the Flavone Derivatives. IV. The Synthesis of Cirsimaritin*

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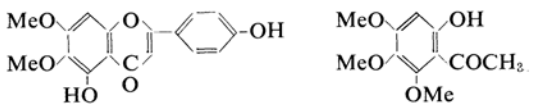
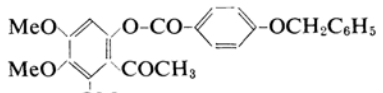
Cirsimarin, an almost colorless glycoside, has been isolated from *Cirsium martimum* MAKINO (Compositae) by Morita and Shimizu.[1] Their hydrolysis of this glycoside with hydrochloric acid has afforded cirsimaritin, a slightly yellow aglycone. They established the latter constitution as 4', 5-dihydroxy-6, 7-dimethoxyflavone (I) on the basis of analytical, spectroscopic and degradative studies. The substitution pattern belongs to the 5, 6, 7-hydroxy or methoxy type as found in scutellarein[2] and pectolinarigenin.[3] However, the new flavone has a unique structure in that it contains two methoxyl groups in the 6, 7-positions. The present report will describe the synthesis of the flavone I.

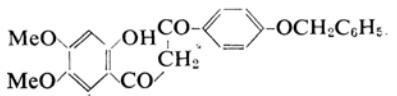
The esterification of 6-hydroxy-2, 3, 4-trimethoxyacetophenone (II)[4] with *p*-benzyloxybenzoyl chloride in the presence of dry pyridine gave the benzoate III. III was subjected to the Baker-Venkataraman rearrangement with pyridine-potassium hydroxide. The resulting diketone IV was converted into 4'-benzyloxy-5, 6, 7-trimethoxyflavone (V) by heating it with acetic acid and sodium acetate. The debenzylation of V with hydrogen afforded 4'-hydroxy-5, 6, 7-trimethoxyflavone (VI), which was demethylated with aluminum chloride in the 5-position to the flavone I. The synthetic product was identical with the natural cirsimaritin in melting point, color reactions and spectral characteristics (Figs. 1 and 2). I was partially methylated with diazomethane in the 4'-position to 5-hydroxy-4', 6, 7-trimethoxyflavone (scutellarein 4', 6, 7-trimethyl ether) (VII). The permethylation of VI or VII gave the same 4', 5, 6, 7-tetramethoxyflavone (scutellarein tetramethyl ether) (VIII).



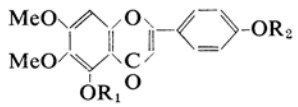
I II



III



IV



V R_1=Me R_2=$CH_2C_6H_5$
VI R_1=Me R_2=H
VII R_1=H R_2=Me
VIII R_1=R_2=Me

* Part III: K. Fukui, T. Matsumoto and S. Matsuzaki, This Bulletin, **37**, 265 (1964).

1) N. Morita and M. Shimizu, *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*), **83**, 615 (1963).

2) G. Goldschmiedt et al,, *Monatsh*, **22**, 679 (1901); **31**, 439 (1910).

3) K. W. Merz and Y. H. Wu, *Arch. Pharm.*, **274**, 126 (1936); *Chem. Abstr.*, **30**, 4166 (1936).

4) V. D. N. Sastri and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **23A**, 262 (1946).

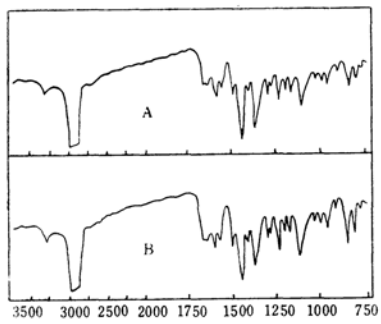


Fig. 1. Infrared absorption spectra of synthetic (A) and natural cirsimaritin (B) in Nujol.

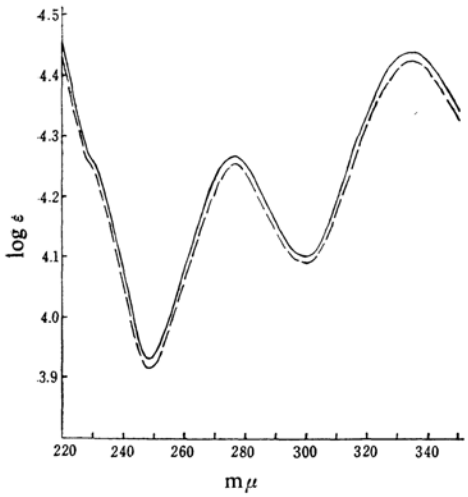


Fig. 2. Ultraviolet absorption spectra of natural (----) and synthetic cirsimaritin (——) in ethanol.

Experimental*

6-(*p*-Benzyloxy)benzoyloxy-2, 3, 4-trimethoxyacetophenone (III).—A mixture of *p*-benzyloxybenzoic acid (1.0 g.) and thionyl chloride (10 ml.) was gently refluxed for 30 min. The acid chloride, obtained by the removal of the excess thionyl chloride under reduced pressure, was added to the solution of 6-hydroxy-2, 3, 4-trimethoxyacetophenone[4] (II, 1.0 g) in dry pyridine (10 ml.). The mixture was refluxed in an oil bath for 30 min. After it had cooled, the reaction mixture was poured into ice-cold dilute hydrochloric acid. The precipitate was collected, washed with water and recrystallized from methanol to give III as colorless needles (m. p. 113~115°C; yield 0.8 g.).

Found: C, 68.67; H, 5.67. Calcd. for $C_{25}H_{24}O_7$: C, 68.80; H, 5.54%.

α-(*p*-Benzyloxy)benzoyl-6-hydroxy-2, 3, 4-trimethoxyacetophenone (IV).—A mixture of the benzoate III (13.2 g.), powdered potassium hydroxide (2.6 g.) and dry pyridine (40 ml.) was heated at 45~50°C for 1 hr. while being stirred; then it was poured into ice-cold dilute hydrochloric acid, and the precipitate was collected, washed with water and crystallized from ethanol to give IV as yellow needles (m. p. 113~114°C), which gave a green ferric reaction in ethanol; yield 8.0 g.

Found: C, 69.07; H, 5.59. Calcd. for $C_{25}H_{24}O_7$: C, 68.80; H, 5.54%.

4'-Benzyloxy-5, 6, 7-trimethoxyflavone (V).—The above diketone IV (0.8 g.) was refluxed with acetic acid (10 ml.) and fused sodium acetate (2.0 g.) for 4 hr., and then the solvent was removed under reduced pressure. The residue was washed with water and recrystallized from methanol to give V as colorless plates (m. p. 156~157°C), which gave a yellow solution with concentrated sulfuric acid; yield 0.6 g. UV λ_{max}^{EtOH} mμ (log ε); 268 (4.27) 322 (4.54).

Found: C, 71.67; H, 5.17. Calcd. for $C_{25}H_{22}O_6$: C, 71.76; H, 5.30%.

4'-Hydroxy-5, 6, 7-trimethoxyflavone (VI).—A solution of the above benzyloxyflavone V (1.0 g.) in ethanol (130 ml.) was shaken with hydrogen in the presence of palladized charcoal (10%; 1.5 g.) until the absorption of hydrogen ceased. The filtered solution was evaporated under reduced pressure, leaving an almost colorless residue. The residue was recrystallized from aqueous methanol to give VI as colorless needles (m. p. 230~231°C (reported m. p. 228°C[1]); yield 0.7 g.). This substance gave a yellow solution with concentrated sulfuric acid. UV λ_{max}^{EtOH} mμ (log ε); 266 (4.17) 325 (4.45).

Found: C, 65.52; H, 4.93. Calcd. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91%.

It formed an acetate (by the use of acetic anhydride-pyridine), which was crystallized as colorless needles (from aqueous methanol) (m. p. 139~140°C). UV λ_{max}^{EtOH} mμ (log ε); 266.5 (4.38) 309 (4.39).

Found: C, 64.64; H, 4.83. Calcd. for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90%.

Cirsimaritin (4', 5-Dihydroxy-6, 7-dimethoxyflavone) (I).—A mixture of the hydroxyflavone VI (1.0 g) and anhydrous aluminum chloride (10.0 g.) in dry ether (150 ml.) was refluxed for 10 hr. After it had cooled, the reaction mixture was poured into ice-water. The yellow precipitate was collected, then refluxed with a mixture of concentrated hydrochloric acid (40 ml.) and acetic acid (60 ml.) for 30 min., and the reaction mixture was diluted with water. The yellow precipitate was collected, washed with water and recrystallized from methanol to give I as yellow needles (m. p. 257~258°C (reported m. p. 257°C[1])), alone or mixed with natural cirsimaritin; yield 385 mg. It shows all the color reactions of the natural cirsimaritin. IR 3273 (OH), 1665 (C=O), 1029 cm^{-1} (=C-O-C) (Nujol). UV λ_{max}^{EtOH} mμ (log ε); 277 (4.27) 336 (4.44).

Found: C, 64.70; H, 4.34. Calcd. for $C_{17}H_{14}O_6$: C, 64.96; H, 4.49%.

5-Hydroxy-4', 6, 7-trimethoxyflavone (VII).—The flavone I was partially methylated with diazomethane according to the method of Morita and Shimizu.[1] Recrystallization from ethanol gave VII as yellow needles (m. p. 187~188°C (reported m. p.

* All melting points are uncorrected.

183,[1] 188,[3] 189~190°C[5])). UV λ_{max}^{EtOH} mμ (log ε); 278.5 (4.31) 331 (4.45).

Found: C, 65.83; H, 4.62. Calcd. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91%.

4', 5, 6, 7-Tetramethoxyflavone (VIII).—*From VI.*—The treatment of VI (200 mg.) in acetone (50 ml.) with an ethereal solution of diazomethane for a day at room temperature gave VIII as colorless plates (from methanol) (m. p. 161~162°C (reported m. p. 158~159,[1] 161°C[6])), which in turn gave a yellow solution with concentrated sulfuric acid; yield 130 mg. UV λ_{max}^{EtOH} mμ (log ε); 267.5 (4.23) 321 (4.49).

Found: C, 66.54; H, 5.08. Calcd. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30%.

From VII.—To a solution of VII (90 mg.) and dimethyl sulfate (0.1 ml.) in acetone (50 ml.), potassium carbonate (2.0 g) was added; the mixture was then refluxed for 48 hr. The product was recrystallized from methanol to give VIII (m. p. and mixed m. p, 161~162°C); yield, 40 mg.

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6) R. Robinson and G. Schwarzenbach, *J. Chem. Soc.*, **1930**, 829.

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