[Chem. Pharm. Bull. 21(12)2757—2759(1973)]

UDC 547.814.5.057 : 581.192

Synthetic Studies of the Flavone Derivatives. I.[1] Syntheses of Cirsiliol and Cirsilineol

SHIN MATSUURA, TOSHINOBU KUNII, and AKIRA MATSUURA

Gifu College of Pharmacy[2]

(Received June 23, 1973)

5,3′,4′-Trihydroxy-6,7-dimethoxyflavone and 5,4′-dihydroxy-6,7,3′-trimethoxyflavone were synthesized and identified with cirsiliol and cirsilineol obtained from *Cirsium lineare* SCH. BIP.

Recently the glucosides of cirsiliol (5,3′,4′-trihydroxy-6,7-dimethoxyflavone) and cirsilineol (5,4′-dihydroxy-6,7,3′-trimethoxyflavone) has been isolated from *Cirsium lineare* SCH. BIP. (Yanagiazami) by Morita, *et al.*[3] This paper reports the syntheses of cirsiliol and cirsilineol for the confirmation of their structures.

2-Hydroxy-4,5,6-trimethoxyacetophenone (I) was condensed with 4-benzyloxy-3-substituted benzaldehyde (II) in the presence of 50% potassium hydroxide in ethanol, and 4-benzyloxy-3-substituted-2′-hydroxy-4′,5′,6′-trimethoxychalcones (III, III′) were obtained. These chalcones were cyclodehydrogenated into 4′-benzyloxy-3′-substituted-5,6,7-trimethoxyflavones (IV, IV′) with selenium dioxide in isoamylalcohol. These two flavones gave 3′,4′-dihydroxy-5,6,7-trimethoxy- (V) and 4′-hydroxy-5,6,7,3′-tetramethoxy-flavone (V′) by catalytic hydrogenolysis using palladium charcoal as catalyst. They were treated with anhydrous aluminum chloride in dry nitrobenzene for 5 hr at room temperature and partially demethylated flavones were obtained as yellow plates, mp 279°, which is 5,3′,4′-trihydroxy-6,7-dimethoxyflavone (VI) and yellow needles, mp 203°, which is 5,4′-dihydroxy-6,7,3′-trimethoxyflavone (VI′).

The mass spectrum of VI showed a molecular ion peak at m/e 330, supporting the molecular formula of $C_{17}H_{14}O_7$ (mol. wt., 330.28); the nuclear magnetic resonance (NMR) spectrum in dimethyl sulfoxide-d_6 showed the presence of two methoxyl groups at δ 3.79 and 3.96 (each 3H, singlet), five aromatic protons at 6.69 (C_3–H, singlet), 6.83 (C_8–H, singlet) 6.93 ($C_{5'}$–H,

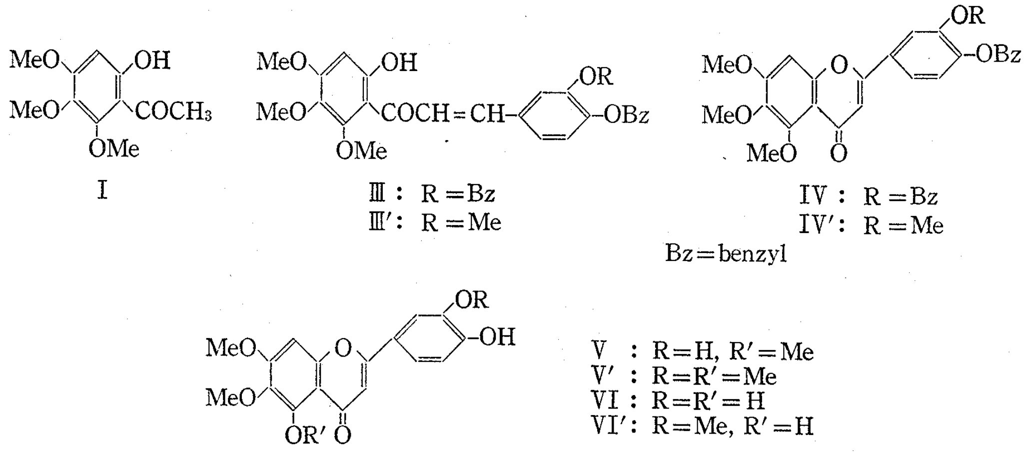

Chart 1

---

[1] Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Kanazawa, June 1973.

[2] Location: *Mitahora Gifu.*

[3] N. Morita, M. Shimizu, and M. Arisawa, *Phytochemistry*, 12, 421 (1973).

doublet, J=9 cps), 7.45 ($C_{6'}$-H, double doublet, J=2.5 cps, 9 cps) and 7.47 ($C_{2'}$-H, doublet, J=2.5 cps), and three hydroxy groups at 9.6 and 13.04 (2H, broad, 1H singlet).

The mass spectrum of VI′ showed a molecular ion peak at *m/e* 344, supporting the molecular formula of $C_{18}H_{16}O_7$ (mol. wt., 344.31); the NMR spectrum in dimethyl sulfoxide-d_6 showed the presence of three methoxyl groups at δ 3.77 and 3.94 (3H, singlet, 6H, singlet), five aromatic protons at 6.87 (C_3-H, singlet), 6.89 (C_8-H, singlet), 6.94 ($C_{5'}$-H, doublet, J=9 cps), 7.57 ($C_{2'}$-H, doublet, J=2.5 cps) and 7.58 ($C_{6'}$-H, double doublet, J=2.5 cps, 9 cps), and two hydroxyl groups at 9.96 and 13.01 (each 1H, broad).

The demethylated flavones (VI and VI′) were further methylated to 5,6,7,3′,4′-pentamethoxyflavone (sinensetin), which were identified with an authentic sample.[4]

The synthetic flavones (VI and VI′), compared with natural products by mixed melting point determination, thin-layer chromatography (TLC), paper partition chromatography (PPC) and infrared spectrum (IR), were identified to cirsiliol and cirsilineol.

Experimental[5]

3,4-Dibenzyloxy-2′-hydroxy-4′,5′,6′-trimethoxychalcone (III)——A mixture of 2-hydroxy-4,5,6-trimethoxyacetophenone (I) (2.3 g, 0.01 mole), 3,4-dibenzyloxybenzaldehyde (3.2 g, 0.01 mole), aqueous potassium hydroxide (50%, 22.4 g, 0.1 mole), dimethylformamide (10 ml), and ethanol (20 ml) was kept under agitation for two days at room temperature. The reaction mixture was acidified with acetic acid, and the crude product was recrystallized from ethanol to give III as yellow needles, mp 108.5°. Alc. $FeCl_3$ reaction gave a brown color. Yield 3.7 g (70.3%). *Anal.* Calcd. for $C_{32}H_{30}O_7$: C, 72.99; H, 5.74. Found: C, 72.88; H, 5.71.

3′,4′-Dibenzyloxy-5,6,7-trimethoxyflavone (IV)——A mixture of III (2.64 g, 0.005 mole), selenium dioxide (3.33 g, 0.03 mole), and freshly distilled isoamylalcohol (50 ml) was gently refluxed for 6 hr. After the metal selenium had been filtered off, most of the solvent was evaporated *in vacuum*, and the residue was kept overnight. The precipitate was collected and washed with methanol. The pale brown precipitate was recrystallized from ethanol to give IV as colorless needles, mp 122°. Alc. $FeCl_3$ reaction: colorless; Mg-HCl reaction: red. Yield 2.24 g (85.4%). *Anal.* Calcd. for $C_{32}H_{28}O_7$: C, 73.27; H, 5.38. Found: C, 73.32; H, 5.43. IR ν_{max}^{KBr} cm^{-1} 1625 (C=O).

3′,4′-Dihydroxy-5,6,7-trimethoxyflavone (V)——A solution of IV (1.05 g, 0.002 mole) in ethyl acetate (200 ml) was submitted to catalytic hydrogenolysis at room temperature in the presence of Pd-C (5%, 1.5 g). After catalyst had been filtered off, the filtrate was evaporated, and then the residue was recrystallized from methanol to give V as colorless needles, mp 251°. Alc. $FeCl_3$ reaction: yellowish green; Mg-HCl reaction: deep red. Yield 0.58 g (84.2%). *Anal.* Calcd. for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68. Found: C, 62.55; H, 4.63. UV λ_{max}^{MeOH} 264, 333. IR ν_{max}^{KBr} cm^{-1}: 1630 (C=O).

5,3′,4′-Trihydroxy-6,7-dimethoxyflavone (VI)——To a cold solution of anhydrous aluminum chloride (8 g, 0.06 mole) and dry nitrobenzene (70 ml) was added a solution of the flavone (V) (0.69 g, 0.002 mole) in dry nitrobenzene (10 ml). After standing for 5 hr at room temperature, the reaction mixture was poured into a mixture of ice (50 g) and hydrochloric acid (50 g), removed nitrobenzene by steam distillation, and the residual precipitate was collected and washed with water, and then methanol. The crude product was recrystallized from methanol to give VI as pale yellow plates, mp 279°. Acl. $FeCl_3$ reaction: brownish violet; Mg-HCl reaction: deep red. Yield 0.62 g (95.5%). *Anal.* Calcd. for $C_{17}H_{14}O_7$: C, 61.82; H, 4.27. Found: C, 61.80; H, 4.25. Mass Spectrum *m/e*: 330 (M^+), 315 (M^+-CH_3), 287 (M^+-CH_3-CO), 181, 153, 134. UV λ_{max}^{MeOH} mμ: 271, 335. IR ν_{max}^{KBr} cm^{-1}: 1636 (C=O). NMR (in DMSO-d_6) δ: 3.79, (OCH_3, s), 3.96, (OCH_3, s), 6.69 (C_3-H, s), 6.83 (C_8-H, s), 6.93 ($C_{5'}$-H, d, J *ortho*=9 cps), 7.45 ($C_{6'}$-H, dd, J *ortho*=9 cps, J *meta*=2.5cps), 7.47 ($C_{2'}$-H, d, J *meta*=2.5 cps), 9.6 ($C_{3'}$- and $C_{4'}$-OH, b) and 13.04 (C_5-OH, s).

The melting point was undepressed on admixture with natural cirsiliol (mp 279°, lit[3] 280°). TLC: *Rf* 0.58, Cirsiliol 0.58 ($CHCl_3$: AcOH=3: 1), PPC: *Rf* 0.57, Cirsiliol 0.57 (60% AcOH).

4-Benzyloxy-2′-hydroxy-3,4′,5′,6′-tetramethoxychalcone (III′)——A mixture of I (2.3 g, 0.01 mole), 4-benzyloxy-3-methoxybenzaldehyde (3.0 g, 0.0125 mole), aqueous potassium hydroxide (50%, 22.4 g, 0.1

---

[4] S. Matsuura, T. Kunii, and M. Iinuma, *Yakugaku Zasshi*, **93**, 1517 (1973).

[5] All melting points were not corrected. IR spectra were taken with a Japan Spectroscopic Co. Model IRA-I spectrometer and ultraviolet (UV) spectra were taken on a Shimazu Model MPS-50L spectrometer. Mass spectra were measured with Japan Electron Co. Model JMS-01SG spectrometer and NMR spectra were taken with a Hitachi Model R-20B and Japan Electron Co. Model JNM-PS100 spectrometer with tetramethylsilan as an internal standard. For analytical TLC Silica gel G and PPC Toyo Roshi No. 51 were used as adsorbent.

mole) and ethanol (25 ml) was kept for two days at room temperature. The reaction mixture was acidified with acetic acid, and the crude product was recrystallized from acetic acid to give III′ as orange needles, mp 157.5°. Alc. $FeCl_3$: brown. Yield 4.13 g (91.8%). *Anal.* Calcd. for $C_{26}H_{26}O_7$: C, 69.32; H, 5.82. Found: C, 69.24; H, 5.78.

4′-Benzyloxy-5,6,7,3′-tetramethoxyflavone (IV′)——A mixture of III (2.25 g, 0.005 mole), selenium dioxide (3.33 g, 0.03 mole) and freshly distilled isoamylalcohol (50 ml) was gently refluxed for 7 hr. The reaction mixture was treated with a method similar to that of IV. The residue was recrystallized from chloroform and ethanol to give IV′ as colorless prisms, mp 178°. Alc. $FeCl_3$ reaction gave no color; Mg-HCl reaction: pale red. Yield 1.85 g (82.6%). *Anal.* Calcd. for $C_{26}H_{24}O_7$: C, 69.63; H, 5.39. Found: C, 69.71; H, 5.37. IR ν_{max}^{KBr} cm^{-1}: 1635 (C=O).

4′-Hydroxy-5,6,7,3′-tetramethoxyflavone (V′)——A solution of IV′ (1.8 g, 0.004 mole) in ethyl acetate was submitted to catalytic hydrogenolysis at room temperature in the presence of Pd-C (5%, 1.8 g). The reaction mixture was treated by a method similar to that of V. The residue was recrystallized from ethanol to give V′ as colorless needles, mp 206.5°. Alc. $FeCl_3$ reaction: pale yellowish green; Mg-HCl reaction: red. Yield 1.13 g (79.0%). *Anal.* Calcd. for $C_{19}H_{18}O_7$: C, 63.68; H, 5.06. Found: C, 63.79; H, 5.08. UV λ_{max}^{MeOH} mμ: 264, 333. IR ν_{max}^{KBr} cm^{-1}: 1635 (C=O).

4′,5-Dihydroxy-6,7,3′-trimethoxyflavone (VI′)——To a cold solution of anhydrous aluminum chloride (8 g, 0.06 mole) and dry nitrobenzene (70 ml) was added a solution of the flavone (V′) (0.72 g, 0.002 mole) in dry nitrobenzene (10 ml). The mixture was treated as VI. After washing with water the crude product was recrystallized from ethanol to give VI′ as pale yellow needles, mp 203°. Alc. $FeCl_3$: brownish violet; Mg-HCl reaction: red. Yield 0.61 g (88.7%). *Anal.* Calcd. for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68. Found: C, 62.72; H, 4.71. Mass Spectrum *m/e*: 344 (M^+), 329 (M^+-CH_3), 301 (M^+-CH_3-CO), 181, 148, 153. IR ν_{max}^{KBr} cm^{-1}: 1640 (C=O). UV λ_{max}^{MeOH} mμ: 276, 344. NMR (in DMSO-d_6) δ: 3.77 (OCH_3, s), 3.96 ($2\times OCH_3$, s), 6.87 (C_3-H, s), 6.89 (C_8-H, s), 6.94 ($C_{5'}$-H, d, *J ortho*=9 cps), 7.57 ($C_{2'}$-H, d, *J meta*=2.5 cps), 7.58 ($C_{6'}$-H, dd, *J ortho*=9 cps, *J meta*=2.5 cps), 9.96 ($C_{4'}$-OH, b), and 13.01 (C_5-OH, b).

The melting point was undepressed on admixture with natural cirsilineol (mp 203°, lit.3) 208—210°). TLC: *Rf* 0.68, Cirsilineol 0.68 ($CHCl_3$: MeOH=95: 5). PPC *Rf* 0.80, Cirsilineol 0.80 (60% AcOH).

Methylation of VI and VI′——A mixture of VI or VI′ (50 mg), dimethylsulfate (0.5 g), potassium carbonate (0.6 g) and methyl ethyl ketone was refluxed for 5 hr. The reaction mixture was treated with the usual method. The crude product was recrystallized from acetone to give 5,6,7,3′,4′-pentamethoxyflavone (sinensetin), mp 175°, which gave no color ferric chloride reaction in ethanol. The melting point was undepressed on admixture with an authentic sample (mp 175°4)). TLC: *Rf* 0.81, sinensetin4) 0.81 ($CHCl_3$: MeOH=95: 5).

Acknowledgement The authors are grateful to Prof. N. Morita, University of Toyama, for his gifts of natural cirsiliol and cirsilineol. Thanks are also due to the members of Eizai Co., Ltd. for mass spectrum and NMR spectral measurement and Miss. S. Sumi of Analytical Laboratory of Gifu College of Pharmacy.