

Synthesis of 3-(*p*-Hydroxycinnamoyl)-5-methylfilicinic Acid and Dehydro-3,3'-diacetyl-5,5'-methylenedifilicinic Acid¹⁾

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Synopsis. In connection with studies on the structure of carthamin (**1**), two analogous compounds of **1**, 3-(*p*-hydroxycinnamoyl)-5-methylfilicinic acid and dehydro-3,3'-diacetyl-5,5'-methylenedifilicinic acid have been synthesized.

The structure for carthamin **1**, the red coloring matter of the flowers of Safflower (*Carthamus tinctorius* L.) has recently been proposed on the basis of spectroscopic evidence and hydrolytic behavior.¹⁾ In this paper, the synthesis of two compounds, 3-(*p*-hydroxycinnamoyl)-5-methylfilicinic acid (**3**) and dehydro-3,3'-diacetyl-5,5'-methylenedifilicinic acid (**6**), will be reported. These compounds have been offered as the analogs of **1** in a previous communication.¹⁾

3-(*p*-Hydroxycinnamoyl)-5-methylfilicinic acid (**3**) was synthesized by the condensation of 3-acetyl-5-methylfilicinic acid (**2**),²⁾ obtained by the methylation of phloracetophenone, with *p*-hydroxybenzaldehyde in the presence of piperidine³⁾ by reference to the synthesis of ceroptene. Dehydro-3,3'-diacetyl-5,5'-methylenedifilicinic acid (**6**) was prepared by the condensation of 3-acetyl-5-formylfilicinic acid (**4**), obtained by the methylation of formylphloracetophenone,⁴⁾ with acetylfilicinic acid (**5**)²⁾ and 1% aqueous potassium hydroxide solution at -10—-15 °C. The structures of **3** and **6** were confirmed by IR, PMR, and mass spectra, and elemental analysis.

Compounds **3** and **6** both showed a characteristic enol proton signal at very low field (19.30 and 18.38

ppm) in the PMR spectra, which have been observed in other enolized 1,3,5-triketone structure.⁵⁾ Hydrogenation of **6** gave 3,3'-diacetyl-5,5'-methylenedifilicinic acid (**7**), which was identical to the specimen obtained by the condensation of **5** with formaldehyde.

Compound **6**, light yellow crystals, exhibited an absorption maximum at 350 nm in chloroform solution, but shifted to the long-wavelength region, 490 nm, in ethanol solution. The unusual red shift has been ascribed to the formation of the stable enol anion of **6** in ethanol.

Experimental

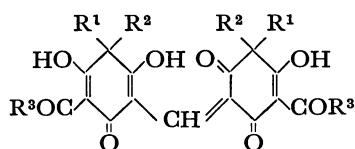
All melting points are uncorrected. The UV and IR spectra were recorded on a Hitachi 135 and a Hitachi EPI-S2 spectrophotometer, respectively. The PMR spectra were measured with a Hitachi R-22 spectrometer (90 MHz), using tetramethylsilane as an internal standard. The mass spectra were obtained on a Hitachi RMU-6M mass spectrometer.

3-(*p*-Hydroxycinnamoyl)-5-methylfilicinic Acid (3**).** A mixture of 3-acetyl-5-methylfilicinic acid (**2**) (2.0 g), *p*-hydroxybenzaldehyde (6.0 g), and piperidine (2 ml) was heated on a water bath for 1 h. The reaction mixture was poured into dilute hydrochloric acid and extracted with ethyl acetate. The ethyl acetate solution was washed with water, dried over anhydrous Na₂SO₄, and evaporated *in vacuo*. The residue was chromatographed on a silica-gel column with benzene-ethyl acetate (4:1) to give crude crystals, which were further chromatographed with a benzene-ethyl acetate-acetic acid mixture (80:20:1). Recrystallization from methanol gave **3** (380 mg, 13%) as yellow needles, mp 215—216 °C. UV_{max} (EtOH) 350 and 415 nm; IR (KBr) 1600, 1624, and 1663 cm⁻¹; PMR (acetone-*d*₆) δ 1.39 (6H, s, C₃-Me×2), 1.87 (3H, s, C₅-Me), 6.90 (2H, d, *J*=8.5 Hz, C_{3,5}-H), 7.58 (2H, d, *J*=8.5 Hz, C_{2,6}-H), 7.80 (1H, d, *J*=16 Hz, C_α-H), 8.22 (1H, d, *J*=16 Hz, C_β-H), 19.30 (s, OH). Found: C, 68.55; H, 5.80%; M⁺, 314. Calcd for C₁₈H₁₈O₅: C, 68.78; H, 5.77%; M, 314.

Diacetate, mp 152—153 °C; IR (KBr) 1673, 1662, 1650, and 1600 cm⁻¹. Found: C, 66.32; H, 5.63%; M⁺, 398. Calcd for C₂₂H₂₂O₇: C, 66.32; H, 5.57%; M, 398.

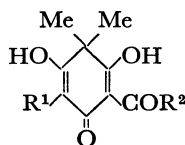
3-Acetyl-5-formylfilicinic Acid (4**).** To a solution of formylphloracetophenone (4.9 g)⁴⁾ in dried methanol (25 ml) was added a sodium methylate solution, which was prepared from sodium (1.8 g), methanol (40 ml), and methyl iodide (21 g). The reaction mixture was allowed to stand for 3 days in the dark at room temperature. Removal of the solvent *in vacuo* gave a residue. The residue, after the addition of 1 M hydrochloric acid, was extracted with ethyl acetate. The ethyl acetate solution was washed with water, dried over anhydrous Na₂SO₄ and evaporated *in vacuo* to yield a viscous oil, which on crystallization from ligroin, gave compound **4** (1.85 g, 33%), mp 56—58 °C; IR (KBr) 1675 and 1625 cm⁻¹. Found: C, 58.94; H, 5.45%; M⁺, 224. Calcd for C₁₁H₁₂O₅: C, 58.92; H, 5.40%; M, 224.

Dehydro-3,3'-diacetyl-5,5'-methylenedifilicinic Acid (6**).**



1 R¹=G1, R²=OH, R³=-CH=CH-C₆H₄-OH

6 R¹=R²=R³=Me

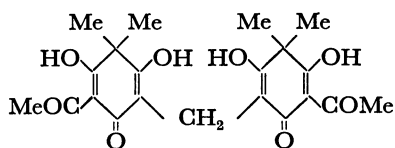


2 R¹=R²=Me

3 R¹=Me, R²=-CH=CH-C₆H₄-OH

4 R¹=CHO, R²=Me

5 R¹=H, R²=Me



7

mixed solution of 3-acetylfilicinic acid (**5**)²⁾ (600 mg) and **4** (860 mg) in 1% aqueous potassium hydroxide solution (17 ml) was allowed to stand for 12 h at -10 — -15°C . The reaction mixture was acidified with 2 M hydrochloric acid and extracted with ether. Removal of the solvent from the ether solution gave a residue, which was extracted with ethyl acetate. The ethyl acetate, on removal of the solvent *in vacuo*, gave a residue. The residue gave **6** (550 mg, 44%) as yellow needles, which on recrystallization from benzene showed a mp 173 — 174.5°C . UV_{max} (CHCl_3) 350 nm ($\log \epsilon=4.33$), UV_{max} (EtOH) 300 and 490 nm ($\log \epsilon=4.17$ and 4.85); IR (KBr) 1670, 1648, and 1628 cm^{-1} ; PMR ($\text{DMSO}-d_6$) δ 1.28 (12H, s, $-\text{CH}_3 \times 4$), 2.57 (6H, s, $-\text{COCH}_3 \times 2$), 7.95 (1H, s, $-\text{CH}=\text{}$), 18.38 (2H, br s, $-\text{OH} \times 2$). Found: C, 62.73; H, 5.59%; M^+ , 402. Calcd for $\text{C}_{21}\text{H}_{24}\text{O}_8$: C, 62.68; H, 5.51%; M , 402.

3,3'-Diacetyl-5,5'-methylenedifilicinic Acid (7). To a solution of 3-acetylfilicinic acid²⁾ (100 mg) in 1% aqueous potassium hydroxide solution (0.4 ml) was added paraformaldehyde (25 mg) under cooling with ice-water and the mixture allowed to stand for 30 min. The reaction mixture was acidified with 2 M hydrochloric acid and extracted with ether. The ether solution was evaporated and the residue was recrystallized from methanol to give **7** (40 mg, 19%), mp 170 — 172°C . IR (KBr) 1640 cm^{-1} ($\text{C}=\text{O}$); PMR (pyridine- d_5) δ 1.53 (12H, s, $-\text{CH}_3 \times 4$), 2.72 (6H, s, $-\text{COCH}_3 \times 2$), 3.96 (2H, s, $-\text{CH}_2-$), 18.47 (2H, s, $-\text{OH} \times 2$). Found: C, 62.16;

H, 6.13%; M^+ , 404. Calcd for $\text{C}_{21}\text{H}_{24}\text{O}_8$: C, 62.37; H, 5.98%; M , 404.

Reduction of 6. Compound **6** (80 mg) was hydrogenated in methanol (8 ml) with 4% aqueous palladium chloride solution (1.5 ml) for 5 h. The reaction mixture was filtered and the filtrate cooled to give a small amount of colorless prisms, mp 170 — 172°C . The IR spectrum of this reduction product was identical with that of a synthetic sample of **7**.

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