Synthesis of 3-(*p*-Hydroxycinnamoyl)-5-methylfilicinic Acid and Dehydro-3,3′-diacetyl-5,5′-methylenedifilicinic Acid[1)]

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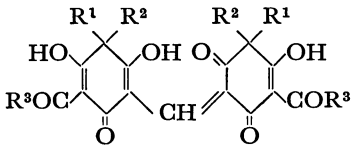
Synopsis. In connection with studies on the structure of carthamin (**1**), two analogous compounds of **1**, 3-(*p*-hydroxycinnamoyl)-5-methylfilicinic acid and dehydro-3,3′-diacetyl-5,5′-methylenedifilicinic acid have been synthesized.

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 phloroacetophenone, with *p*-hydroxybenzaldehyde in the presence of piperidine[3)] 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 formylphloroacetophenone,[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.

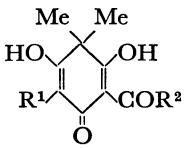
Compounds **3** and **6** both showed a characteristic enol proton signal at very low field (19.30 and 18.38 ppm) in the PMR spectra, which have been observed in other enolized 1,3,5-triketone structure.[5)] Hydrogenation of **6** gave 3,3′-diacetyl-5,5′-methylenedifilicinic acid (**7**), which was identical 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.



1 R^1=Gl, R^2=OH, R^3=-CH=CH-⟨○⟩-OH

6 R^1=R^2=R^3=Me

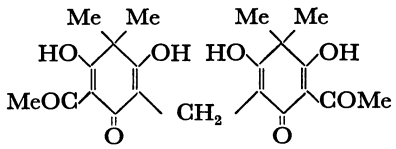


2 R^1=R^2=Me

3 R^1=Me, R^2=-CH=CH-⟨○⟩-OH

4 R^1=CHO, R^2=Me

5 R^1=H, R^2=Me



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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 Na_2SO_4, 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, $C_{3'}$-Me×2), 1.87 (3H, s, $C_{5'}$-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 $C_{18}H_{18}O_5$: 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 $C_{22}H_{22}O_7$: C, 66.32; H, 5.57%; M, 398.

3-Acetyl-5-formylfilicinic Acid (4). To a solution of formylphloroacetophenone (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 Na_2SO_4 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 $C_{11}H_{12}O_5$: C, 58.92; H, 5.40%; M, 224.

Dehydro-3,3′-diacetyl-5,5′-methylenedifilicinic Acid (6). A

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 ε=4.33), UV_{max} (EtOH) 300 and 490 nm (log ε= 4.17 and 4.85); IR (KBr) 1670, 1648, and 1628 cm^{-1}; PMR (DMSO-d_6) δ 1.28 (12H, s, $-CH_3\times4$), 2.57 (6H, s, $-COCH_3\times2$), 7.95 (1H, s, -CH=), 18.38 (2H, br s, $-OH\times2$). Found: C, 62.73; H, 5.59%; M^+, 402. Calcd for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51%; M, 402.

*3,3'-Diacetyl-5,5'-methylenedifilicinic Acid (**7**).* To a solution of 3-acetylfilicinic acid[2] (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} (C=O); PMR (pyridine-d_5) δ 1.53 (12H, s, $-CH_3\times4$), 2.72 (6H, s, $-COCH_3\times2$), 3.96 (2H, s, $-CH_2-$), 18.47 (2H, s, $-OH\times2$). Found: C, 62.16; H, 6.13%; M^+, 404. Calcd for $C_{21}H_{24}O_8$: 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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References

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