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SYNTHESIS OF 2-(*p*-HYDROXYCINNAMOYL)-4-HYDROXY-4,6-DIMETHYL-CYCLOHEXANE-1,3,5-TRIONE, AN ANALOG OF SAFFLOMIN A

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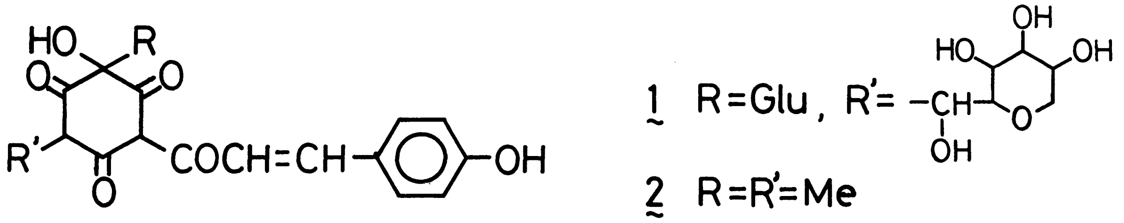
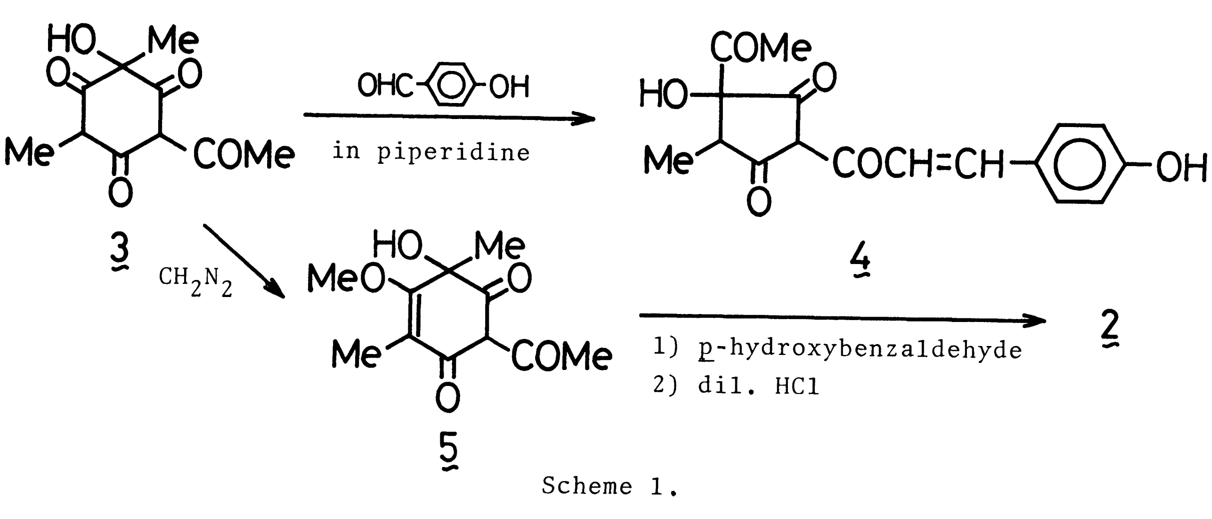
The synthesis of 2-(*p*-hydroxycinnamoyl)-4-hydroxy-4,6-dimethylcyclohexane-1,3,5-trione, an analog of safflomin A, was investigated.

In 1981, we have first proposed the structure **1** for safflomin A, a yellow pigment of the flowers of Safflower (*Carthamus tinctorius* L.).1) However, the synthetic studies of **1** have not been reported yet. In this communication, we wish to report the synthesis of an analog of **1**, 2-(*p*-hydroxycinnamoyl)-4-hydroxy-4,6-dimethylcyclohexane-1,3,5-trione (**2**), as shown in scheme 1, and the comparison of its behaviours with those of **1**.



A mixed solution of **3**2) (0.4 g) and *p*-hydroxybenzaldehyde (0.46 g) in piperidine (2 ml) was stirring at 50 °C for 8 h. The reaction mixture was neutralized with dilute hydrochloric acid and extracted with ethyl acetate. The resulting product was chromatographed on silica gel (Wakogel C-200) using CCl_4-AcOEt-AcOH (60:30:1) to give only **4**3) as orange crystals in a 22% yield.



Scheme 1.

The structure of 4 was identified from its ^{1}H-NMR spectrum.[3] It is assumed that the formation of 4 occurred during condensation in piperidine in the same manner as humulone, a bitter constituent of hop, which is easily rearranged to isohumulone with dilute alkali.[4] Consequently, the protection of 3 against alkali was necessitated. Fortunately, we found that the monomethyl ether (5)[5] of the enolic form of 3, which was obtained by methylation of 3 with diazomethane, could be used as a protected compound in this condensation. A mixed solution of 5 (0.4 g) and p-hydroxybenzaldehyde (1.08 g) in piperidine (6 ml) was stirred at 50 °C for 7 h. The resulting crude crystals were recrystallized from ethyl acetate to afford the monomethyl ether (6)[6] of 2 in a 40% yield. Deprotection of 6 in methanol containing 10% hydrochloric acid gave 2 quantitatively, and the structure of this target was identified from its spectral data.[7] Interestingly, silk could be dyed yellow, though cotton could not be colored, with 2 in a similar manner as safflomin A. The electronic spectrum of 2 was also very analogous to that of the natural one (Fig. 1).

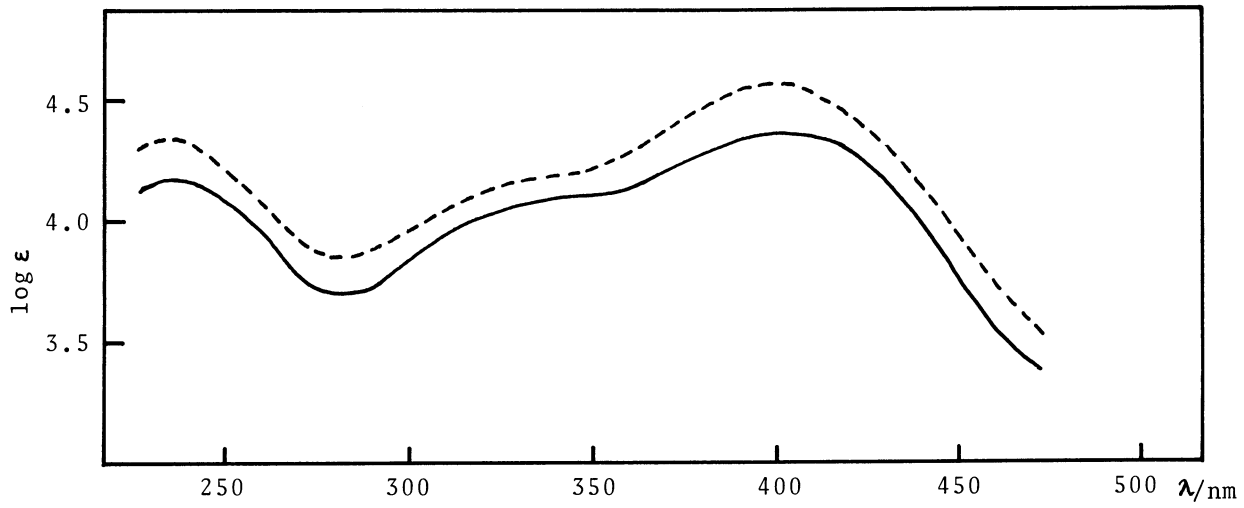


Fig.1. The electronic spectra of safflomin A (——) and 2 (---) in ethanol.

References

1) J. Onodera, H. Obara, M. Osone, Y. Maruyama, and S. Sato, Chem. Lett., 1981, 433.
2) T. W. Cambell and G. M. Coppinger, J. Am. Chem. Soc., 73, 1849 (1951).
3) Compound 4; mp 185-186 °C, MS m/z 316 (M^+), UVλ_{max} (EtOH) 244, 352, and 422 nm (ε =15300, 20100, and 13800), ^{1}H-NMR (DMSO-d_6) δ 1.08 (3H, d, J=8 Hz, COCHC$\underline{H}_3$), 2.29 (3H, s, $COCH_3$), 3.12 (1H, q, J=8 Hz, CO$\underline{C}$HCH$_3$), 6.90 and 7.66 (each 2H, J= 8 Hz, aromatic protons), 7.50 and 8.04 (each 1H, d, J=16 Hz, -COC$\underline{H}$=C$\underline{H}$-).
4) W. Windish, P. Kolbach, and R. Schleicher, Wochschr. Brau., 44, 453 (1927); G. A. Howard, J. Inst. Brewing, 65, 417 (1959).
5) Compound 5; mp 55-56 °C, MS m/z 226 (M^+), ^{1}H-NMR ($CDCl_3$) δ 1.57 and 1.85 (each 3H, s, CH_3×2), 2.57 (3H, s, $COCH_3$), 4.23 (3H, s, OCH_3), 18.71 (1H, s, chelated OH). The yield of this compound from 3 was 61%.
6) Compound 6; mp 205-206 °C, MS m/z 330 (M^+), UVλ_{max} (EtOH) 237 and 403 nm (ε = 12800 and 37400), ^{1}H-NMR (DMSO-d_6) δ 1.51 and 1.82 (each 3H, s, CH_3×2), 4.14 (3H, s, OCH_3), 6.90 and 7.57 (each 2H, d, J=8 Hz, aromatic protons), 6.80 and 8.02 (each 1H, d, J=16 Hz, -COC$\underline{H}$=C$\underline{H}$-). ^{13}C-NMR (DMSO-d_6) δ 8.1, 26.8, and 60.4 (each q), 74.9, 104.3, and 111.7 (each s), 111.8, 114.7, and 116.0 (each d), 125.6 (s), 150.6 (d), 160.4, 171.0, 183.9, 190.8, and 195.7 (each s).
7) Compound 2; mp 207-208 °C, MS m/z 316 (M^+), ^{1}H-NMR (DMSO-d_6) δ 1.45 and 1.76 (each 3H, s, CH_3x2), 6.87 and 7.57 (each 2H, d, J=8 Hz, aromatic protons), 6.81 and 8.02 (each 1H, d, J=16 Hz, -COC$\underline{H}$=C$\underline{H}$-), 19.15 (1H, s, chelated OH). ^{13}C-NMR (DMSO-d_6) δ 15.1 and 35.7 (each q), 82.4, 111.4, and 112.8 (each s), 123.8 and 126.4 (each d), 133.7 (s), 138.2 and 151.3 (each d), 168.0, 180.9, 191.4, 198.5 and 203.8 (each s).

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