

A Synthetic Route to (±)-Humulone

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Synopsis. The synthesis of (±)-humulone was achieved by the prenylation of 2,3,4,6-tetrahydroxyisovalerophenone with 1-bromo-3-methyl-2-butene.

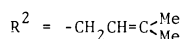
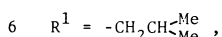
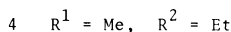
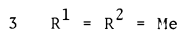
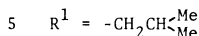
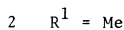
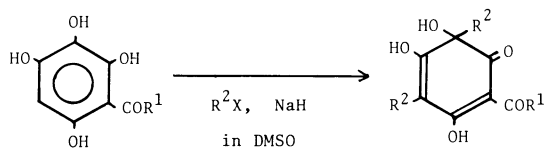
Humulone, an antibiotic and bitter constituent of hop (*Humulus lupulus* L.), was first isolated by Lintner and Schnell¹⁾ in 1904; the structure was determined to be 3,5,6-trihydroxy-4,6-bis(3-methyl-2-butenyl)-2-(3-methyl-1-oxobutyl)-2,4-cyclohexadien-1-one (**6**) by the synthesis of its racemate²⁾ and on the basis of its spectral data.³⁾

However, the method for synthesizing (±)-humulone is not applicable to the preparative purpose because of the tedious procedure and poor yield.²⁾ In this paper we wish to report a new synthetic route to (±)-humulone.

We first succeeded in the synthesis of model compounds of **6**, 3,5,6-trihydroxy-2-acetyl-4,6-dimethyl- and 3,5,6-trihydroxy-2-acetyl-4,6-diethyl-2,4-cyclohexadien-1-one (**3** and **4**), by the di-*C*-alkylation of 2,3,4,6-tetrahydroxyacetophenone (**2**)⁴⁾ with methyl or ethyl iodide in the presence of sodium hydride in dimethyl sulfoxide. This method was applied to the convenient synthesis of (±)-**6**.

(±)-Humulone was synthesized by the prenylation of 2,3,4,6-tetrahydroxyisovalerophenone (**5**) obtained by the acylation of 1,2,3,5-benzenetetrol (**1**)⁵⁾ with isovaleryl chloride by Friedel-Crafts reaction. The acylation of **1** with isovaleronitrile by the Hoesch reaction did not succeed. The IR and ¹H NMR spectra of this synthetic humulone and its *o*-phenylenediamine complex were identical with those of natural specimens.

It is assumed that this synthetic method is applicable to the preparation of such other hop constituents as cohumulone⁶⁾ or adhumulone.⁷⁾



Experimental

The UV and IR spectra were recorded with Hitachi 100-50 spectrophotometer and Hitachi 215 spectrophotometers, respectively. The mass spectra were recorded with a Hitachi

RMU-6M mass spectrometer. ¹H and ¹³C NMR spectra were recorded with Hitachi R-600 spectrometer and Hitachi R-90H spectrometers using tetramethylsilane as an internal standard, respectively.

3,5,6-Trihydroxy-2-acetyl-4,6-dimethyl-2,4-cyclohexadien-1-one (3). To a mixture of **2** (3.68 g) and sodium hydride (1.6 g) in dry dimethyl sulfoxide (150 ml) was added methyl iodide (9.0 g) under cooling with cold water; the mixture was then stirred for 3 h at room temperature. The reaction mixture was poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The extract was chromatographed on a column of silica gel with carbon tetrachloride-ethyl acetate-acetic acid (60:30:1) to afford **3** (2.36 g, 57%). Mp 153–154 °C (lit.⁸⁾ 150.5–151.5 °C. MS m/z 212 (M^+). ES λ_{max} (EtOH) 229, 321, and 358 nm ($\log \epsilon=4.18, 4.09$, and 4.01). IR (KBr) ν 3400, 3250, and 1660 cm^{-1} . ¹H NMR (CDCl_3) $\delta=1.58$ and 1.84 (each 3H, s), 2.57 (3H, s), and 18.42 (1H, s). Found: C, 56.56, H, 5.74%. Calcd for $\text{C}_{10}\text{H}_{12}\text{O}_5$: C, 56.60, H, 5.70%.

3,5,6-Trihydroxy-2-acetyl-4,6-diethyl-2,4-cyclohexadien-1-one (4). Compound **4** (0.2 g, 17%) was obtained from **2** (0.92 g), sodium hydride (0.4 g), and ethyl iodide (2.34 g) by way of **3** as described above. Mp 106–107 °C. MS m/z 240 (M^+). ES λ_{max} (EtOH) 229, 322, and 358 nm ($\log \epsilon=4.19, 4.08$, and 3.97). IR (KBr) ν 3350, 3250, and 1660 cm^{-1} . ¹H NMR (CDCl_3) $\delta=0.97$ (6H, m), 1.86 and 2.35 (each 2H, m), 2.52 (3H, s), 18.59 (1H, s). Found: C, 59.93, H, 6.89%. Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_5$: C, 59.97, H, 6.71%.

2,3,4,6-Tetrahydroxyisovalerophenone (5). To a mixture of **1**⁹⁾ (9.0 g) and anhydrous aluminium chloride (10.0 g) in nitrobenzene (100 ml) was added isovaleryl chloride (6.6 g) at 0 °C; the mixture was then stirred for 3 days at room temperature. The reaction mixture was poured into cold 10% hydrochloric acid and extracted with ether. The ether was distilled away and the remaining nitrobenzene was taken off by steam distillation. The residue was chromatographed on a column of silica gel with benzene-ethyl acetate (3:1) to give **5** (4.44 g, 38%). Mp 167–168 °C. MS m/z 226 (M^+). ES λ_{max} (EtOH) 237 and 298 nm ($\log \epsilon=3.94$ and 4.28). ¹H NMR ($\text{DMSO}-d_6$) $\delta=0.92$ (6H, d, $J=7.0$ Hz), 2.18 (1H, m), 2.90 (2H, d, $J=7.0$ Hz), 5.89 (1H, s), 11.12 and 12.19 (each 1H, s). Found: C, 58.55, H, 6.40%. Calcd for $\text{C}_{11}\text{H}_{14}\text{O}_5$: C, 58.40, H, 6.24%.

(±)-Humulone. To a mixture of **5** (2.0 g) and sodium hydride (0.64 g) in dry dimethyl sulfoxide (60 ml) was added 1-bromo-3-methyl-2-butene (2.8 g) under cooling with cold water; the mixture was then stirred for 2 h at room temperature. The reaction mixture was poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The extract was chromatographed on silica gel with benzene-methyl acetate-acetic acid (300:20:1) to give (±)-**6** (1.06 g, 33%) as viscous pale brown oil. MS m/z 362 (M^+). ES λ_{max} (EtOH) 228, 327, and 356 nm ($\log \epsilon=4.15, 4.03$, and 3.95). IR (CCl_4) ν 3370, 2970, 2870, 1660, 1530, 1460, 1355, 1340, 1290, 1240, 1215, 1170, and 1100 cm^{-1} . ¹H NMR (CDCl_3) $\delta=0.98$ and 1.02 (each 3H, d, $J=7.0$ Hz), 1.54 and 1.69 (12H, s), 2.17 (1H, m), 2.50, 2.70, and 3.09 (each 2H, d, $J=7.0$ Hz), 5.08 (2H, m), 18.89 (1H, s). ¹³C NMR (CDCl_3) $\delta=17.7$ and 17.8 (each q), 21.1 (d), 22.5, 22.8, 25.7, and 25.9 (each q), 26.4, 42.6, and 46.3 (each t), 78.8, 105.9, and 109.3 (each s), 115.7 and 121.0 (each d), 132.0, 137.9, 167.6, 190.6,

195.0, and 200.0 (each s). The IR and ^1H NMR spectra of this compound were completely identical with those of natural (–)-humulone.

(–)-**Humulone**. Natural humulone-*o*-phenylenediamine complex (0.5 g, mp 103–104 °C) was chromatographed on a column of silica gel with benzene–methyl acetate–acetic acid (300:20:1) as an eluent to give (–)-**humulone** (0.2 g), $[\alpha]_D^{25} = -136.0^\circ$ (c 1.39, chloroform), as a pale brown viscous solid.

***o*-Phenylenediamine Complex of (±)-6**. A mixed solution of (±)-**6** (167 mg) and *o*-phenylenediamine (50 mg) in benzene (7 ml) was allowed to stand overnight in a refrigerator. The resulting precipitate was recrystallized from benzene to afford the complex (42 mg, 20%) as light-yellow needles. Mp 104–105 °C (lit.² mp 105–106 °C). The IR and ^1H NMR spectra of this complex were completely identical with those of the natural specimen.

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References

- 1) C. J. Lintner and J. Schnell, *Z. Ges. Brauw.*, **1904**, 668.
- 2) W. Riedle, *Chem. Ber.*, **85**, 692 (1952).
- 3) D. De Keukelele and M. Verzele, *Tetrahedron*, **26**, 385 (1970).
- 4) H. Obara, J. Onodera, Y. Kurihara, and F. Yamamoto, *Bull. Chem. Soc. Jpn.*, **51**, 3627 (1978).
- 5) J. Onodera and H. Obara, *Nippon Kagaku Kaishi*, **1973**, 1808.
- 6) F. L. Rigby and J. L. Bethune, *J. Chem. Soc.*, **1954**, 3400; M. Verzele, *Bull. Soc. Chim. Belg.*, **64**, 70 (1955).
- 7) F. L. Rigby and J. L. Bethune, *J. Am. Chem. Soc.*, **77**, 2828 (1955).
- 8) T. W. Campbell and G. M. Coppinger, *J. Am. Chem. Soc.*, **73**, 1849 (1951).