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The Synthesis of Desmethylencecalin

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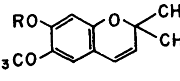
Recently, desmethylencecalin[1] (eupatoriochromene)[2] was isolated along with several acetophenone derivatives from the roots of *Helianthella uniflora* and some *Eupatorium* species. Its structure was identified as 6-acetyl-7-hydroxy-2,2-dimethyl-2H-chromene (I) on the basis of the spectral evidence.[1,2] Encecalin (methyl ether of I) (II) was also isolated from *Encelia californica*.[3]

The present paper will describe the synthesis of I from 7-hydroxy-2,2-dimethylchroman (III) *via* the corresponding acetophenone (IV).

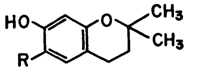
The Hoesch reaction of III[4] with acetonitrile afforded a hydroxy-acetophenone derivative, which was then easily converted into an acetate and may be expected to have one of two structures (IV or V). The NMR spectrum of the acetophenone shows two proton signals, at δ 7.50 and 6.35 ppm (each 1H, singlet) (para positions at C-5 and C-8 on the aromatic ring). Therefore, it can be formulated as 6-acetyl-7-hydroxy-2,2-dimethylchroman (IV). The dehydrogenation of IV with 2,3-dichloro-5,6-dicyano-*p*-quinone in anhydrous benzene gave the desired chromen I. Then, the I was easily converted into acetate (VI) and methyl ether (II) by the usual methods.



I R = H

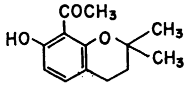
II R = CH_3

VI R = CH_3CO



III R = H

IV R = $COCH_3$



V

The properties of the synthetic I and II were superimposable upon those recorded for natural desmethylencecalin and encecalin.[1-3]

Experimental[*1]

6-Acetyl-7-hydroxy-2,2-dimethylchroman (IV). A mixture of III[4] (2.0 g), acetonitrile (0.7 g), and anhydrous zinc chloride in anhydrous ether (50 m*l*) was saturated with dried hydrogen chloride in an ice bath and then allowed to stand for 24 hr. After the ether layer had been decanted, the ketimine hydrochloride was washed with anhydrous ether and then hydrolyzed with water (100 m*l*) on a steam bath for 1 hr. The precipitates were then collected and recrystallized from methanol to give IV as colorless plates; mp 119.5—120°C; yield, 0.6 g (24%). IR: 1649 (C=O) cm^{-1}. UV: λ_{max} mμ (log ε); 236 (3.98), 242_{sh} (3.93),[*2] 283 (4.18), 327 (3.85). NMR: 1.36_s (6H) ($(CH_3)_2C<$); 1.82_t, 2.76_t (each 2H, J=7.0 Hz) ($-CH_2-CH_2-$); 2.54_s (3H) (CH_3-COC); 6.35_s (C_8-H); 7.50_s (C_5-H); 12.38_s (OH).

Found: C, 70.80; H, 7.43%. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32%.

Acetate. Mp 141.5—142°C (colorless needles from ethanol). IR: 1768, 1671 (C=O) cm^{-1}. UV: λ_{max} mμ (log ε); 230 (4.17), 275 (4.16). NMR: 1.36_s (6H) ($(CH_3)_2C<$); 1.83_t, 2.80_t (each 2H, J=7.0 Hz) ($-CH_2-CH_2-$); 2.34_s (3H) (CH_3COO); 2.49_s (3H) (CH_3COC); 6.52_s (C_8-H); 7.67_s (C_5-H).

Found: C, 68.76; H, 6.83%. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92%.

Desmethylencecalin (6-Acetyl-7-hydroxy-2,2-dimethyl-2H-chromene) (I). A mixture of IV (0.1 g) and DDQ (0.1 g) in anhydrous benzene (30 m*l*) was refluxed for 1.5 hr. After the solution had then been cooled, the precipitated hydroquinone derivative was filtered off and the solvent was removed as far as possible. The chromatography of the resulting viscous oil on silica gel (8 g) with benzene gave a pale yellow solid, a soild which crystallized from ethanol as pale yellow needles,

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[1] F. Bohlmann and M. Grenz, *Chem. Ber.*, **103**, 90 (1970).

[2] T. Anthonsen, *Acta Chem. Scand.*, **24**, (1970), in press.

[3] L. F. Bjeldanes and T. A. Geissman, *Phytochem.*, **8**, 1293 (1970).

[4] W. Bridge, A. J. Crocker, T. Cubin and A. Robertson, *J. Chem. Soc.*, **1937**, 1530.

[*1] The melting points are uncorrected. The infrared spectra were measured in Nujol, while the ultraviolet spectra were measured in an ethanol solution. The NMR spectra were measured with a Hitachi R-20 spectrometer (60 MHz), using tetramethylsilane as the internal standard (δ-value in $CDCl_3$): s, singlet; d, doublet; t, triplet. The mass spectra were measured with a Hiatchi RMS-4 mass spectrometer.

[*2] sh=shoulder.

I; mp 80.5—81°C (lit, mp 77°C,1) mp 76°C2)); yield, 54 mg (54%). IR: 1650 (C=O) cm^{-1}. UV: λ_{max} mμ (log ε); 234.5 (3.95), 257.5 (4.23). NMR: 1.44$_s$ (6H) ($(CH_3)_2C<$); 2.54$_s$ (3H) (CH_3COC); 5.59$_d$, 6.32$_d$ (J=10 Hz) (–CH=CH–); 6.37$_s$ (C_8–H); 7.38$_s$ (C_5–H); 12.78$_s$ (OH). MS: M$^+$ *m/e* 218.

Found: C, 71.57; H, 6.44%. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47%.

Acetate (VI). Mp 80—81.5°C (colorless needles from ethanol). IR: 1768, 1685 (C=O) cm^{-1}. UV: λ_{max} mμ (log ε); 251.5 (4.55), 300 (4.12). NMR: 1.46$_s$ (6H) ($(CH_3)_2C<$); 2.34$_s$ (3H) (CH_3COO); 2.50$_s$ (3H) (CH_3–COC); 5.64$_d$, 6.36$_d$ (J=10 Hz) (–CH=CH–); 6.51$_s$ (C_8–H); 7.53$_s$ (C_5–H).

Found: C, 68.95; H, 6.23%. Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20%.

Methyl Ether (II). Viscous oil. IR: 1675 (C=O) cm^{-1}. UV: λ_{max} mμ (log ε); 255 (4.43), 335 (3.77). NMR: 1.44$_s$ (6H) ($(CH_3)_2C<$); 2.56$_s$ (3H) (CH_3COC); 3.87$_s$ (3H) (CH_3O); 5.52$_d$, 6.34$_d$ (J=10 Hz) (–CH=CH–); 6.41$_s$ (C_8–H); 7.57$_s$ (C_5–H). MS: M$^+$ *m/e* 232. Oxime; mp 137—138°C (lit,3) mp 140°C).