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SHORT COMMUNICATION

# SESQUITERPENE LACTONES. CONSTITUENTS OF *AMBROSIA ARTEMISIIFOLIA* L. (COMPOSITAE)

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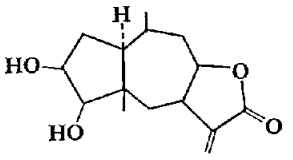
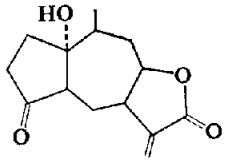
**Abstract**—New collections of *Ambrosia artemisiifolia* were found to contain the pseudoguaianolides cumanin, peruvin and dihydrocumanin. This is the first report of the natural occurrence of dihydrocumanin.

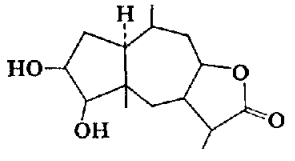
IN CONNEXION with our general biochemical systematic investigation of sesquiterpene lactones in *Ambrosia* species,[1] we recently examined *A. artemisiifolia* plant material collected in August 1967 and 1968 near Chippawa Falls, Wisconsin. A $CHCl_3$ extract of dried leaves and stems yielded a syrup which afforded three crystalline substances, two of which were shown to be identical with the known sesquiterpene lactones cumanin (I)[1,2] and peruvin (II).[3] We report here evidence which establishes that the new compound is dihydrocumanin (III), a compound previously reported only as a reduction product of cumanin.[2] Previously, the sesquiterpene lactones coronopilin,[4] psilostachyin A,[5] artemisiifolin[6] and isabelin were reported from different collections of *A. artemisiifolia.*




(I) Cumanin




(II) Peruvin




(III) Dihydrocumanin

The new sesquiterpene lactone to which we assign structure III, $C_{15}H_{24}O_4$, m.p. 179–181°, $[\alpha]_D^{25°}+77°$ (*c* 0·55, MeOH), showed i.r. bands (in nujol) at 3450 (hydroxyls) and 1745 ($\gamma$-lactone) $cm^{-1}$. The NMR spectrum[7] of the compound (in $CHCl_3$) exhibited signals for two secondary methyl groups (1·01, *d*, *J* about 7; 1·14, *d*, *J* about 7), one tertiary methyl group (0·98), and for two protons on carbon atoms bearing hydroxyl groups (3·30, *d*, $J=7$; 4·12, m).

[1] See, for example, H. E. MILLER, T. J. MABRY, B. L. TURNER and W. W. PAYNE, *Am. J. Botany* **55**, 316 (1968).
[2] J. ROMO, P. JOSEPH-NATHAN and G. SIADE, *Tetrahedron* **22**, 1499 (1966).
[3] P. JOSEPH-NATHAN and J. ROMO, *Tetrahedron* **22**, 1723 (1966).
[4] W. HERZ and G. HÖGENAUER, *J. Org. Chem.* **26**, 5011 (1961).
[5] E. BIANCHI, C. C. J. CULVENOR and J. W. LODER, *Australian J. Chem.* **21**, 1109 (1968).
[6] T. H. PORTER, T. J. MABRY, H. YOSHIOKA and N. H. FISCHER, in preparation.
[7] Chemical shifts are reported in ppm (δ-scale), coupling constants, *J*-values, in c/s, and signals are denoted as follows: *d*=doublet and *m*=multiplet.

A multiplet for a lactonic proton appeared at 4·57 ppm. Oxidation of the diol with Jones reagent afforded light-yellow crystals which exhibited a weak absorption (shoulder) at 452 nm typical for an α-diketo system in a five-membered carbocyclic ring, thus indicating that the hydroxyl groups were on adjacent carbon atoms in a five-membered ring in the natural product. Hydrogenation of cumanin with Pd-C as catalyst yielded dihydrocumanin (III),[2] identical in all respects (m.p., m.m.p., and NMR) with the new sesquiterpene lactone. The diacetyl derivative of the new natural product melted at 105–106° in agreement with the reported value for diacetyldihydrocumanin.[2]

## EXPERIMENTAL

The NMR spectra were recorded in $CDCl_3$ with a Varian A-60 spectrometer using tetramethylsilane as an internal standard. M.p.s are uncorrected.

*Isolation of the Sesquiterpene Lactones*

Collections of *Ambrosia artemisiifolia* L. were made near Chippawa Falls, Wisconsin (voucher numbers[8] 563211 and 333333), in August 1967 and again in 1968. Examination (by NMR) of the extract from each collection indicated that they were similar in their sesquiterpene lactone content. The plant material was extracted with $CHCl_3$ by standard procedures;[9] 500 g of dried stems and leaves of the plant material yielded 15 g of a thick yellow-green syrup which contained about ten substances by TLC analysis (silica gel G, ether). Three compounds were obtained crystalline by column chromatography of the syrup over silica gel using ether as eluant. Some of the early fractions yielded about 300 mg of a compound ($C_{15}H_{20}O_4$, m.p. 160°, $[\alpha]_D^{25}+158°$) subsequently shown to be identical with an authentic sample of peruvin (II). Work-up of later fractions yielded 250 mg of cumanin (I), m.p. 76–83° (recrystallization from acetone–hexane), identical by NMR, i.r. and m.p. with an authentic sample of cumanin, and approximately 190 mg of a new sesquiterpene lactone, $C_{15}H_{24}O_4$, m.p. 178–181° after recrystallization from acetone–hexane. The material yielded a diacetate, m.p. 105–106°.

*Oxidation of Dihydrocumanin (III)*

A 40 mg sample of the new natural product, dihydrocumanin (III), dissolved in acetone, was cooled in an ice bath and oxidized by adding a few drops of Jones reagent[10] until an excess of reagent was present. The solution was then allowed to warm to room temperature. The reaction mixture yielded, after addition of water and extraction with ethyl acetate, 11 mg of bright yellow crystals, m.p. 212–215°, with decomposition from 200°. The product had the following spectral properties: $\lambda_{max}$ at 205 nm (ε 1100) and a low intensity shoulder at 452 nm; i.r. bands (nujol): 1760 and 1770 $cm^{-1}$; and NMR signals at 4·91 (m), 2·0–3·0 (m), 1·48–1·9 (m), and 0·87–1·47 (m) ppm.

*Hydrogenation of Cumanin (I)*

The catalyst (250 mg of 5% Pd-C) was mixed with 10 ml of methanol and pre-hydrogenated for 2 hr. A solution of 100 mg of cumanin in 30 ml of methanol was added dropwise during a 4 hr period to the $H_2$/Pd-C hydrogenating system.[11] The solution was filtered, and the filtrate afforded a syrup which crystallized from acetone–hexane. Recrystallization from the same solvent afforded 30 mg of needles, m.p. 178–180°, identical by m.p., m.m.p. and NMR spectrum with the new natural product from *A. artemisiifolia*.

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[8] The voucher specimens are deposited in the University of Texas Herbarium, Austin.
[9] T. J. MABRY, H. E. MILLER, H. B. KAGAN and W. RENOLD, *Tetrahedron* **22**, 1139 (1966).
[10] C. DJERASSI, R. R. ENGLE and A. BOWERS, *J. Org. Chem.* **21**, 1547 (1956).
[11] This hydrogenation procedure minimized the conversion of cumanin into isocumanin in which the double bond has migrated into the lactone ring.