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Structures of Ikemagenin and Isoikemagenin

The isolation of penupogenin,[1] cynanchogenin,[1] caudatin,[2] gagaminin,[3] and four other aglycones[4] from the rhizome of *Cynanchum caudatum* MAX. (Asclepiadaceae) and their structure have been reported previously. In this communication, we wish to describe the structure of two new aglycones, ikemagenin (I) and isoikemagenin (II). The aglycone mixture, obtained after a mild acid hydrolysis of the crude glycoside, was separated by repeated silica gel column and preparative thin-layer chromatography. I has the following physical constants: mp 210—215°, $[\alpha]_D^{18}$ −5.5° (c=0.965, $CHCl_3$). *Anal.* Calcd. for $C_{30}H_{38}O_6$: C, 72.85; H, 7.74. Found: C, 72.87; H, 7.96. The infrared (IR) absorption ($\nu_{max}^{CHCl_3}$ cm^{-1}: 1705, 1640, 1580, 1500) demonstrates the presence of an aromatic group and $\alpha\beta$-unsaturated ester in I. From the ultraviolet (UV) absorption, λ_{max}^{EtOH} nm (ε): 217 (19.600), 223 (16.600), 276 (24.000), the presence of a cinnamoyl group was anticipated. The nuclear magnetic resonance (NMR) and mass spectral data of I are listed in Tables I and II.

TABLE I. NMR Spectral Data of I and II

	C-19	C-18	C-20	C-3α-H	C-12α-H	C-6-H	-CH=CH-	
I	1.14	1.59	2.17	3.56	2.76	5.33	6.28	7.62
II	1.21	1.27	2.22	3.58	4.82	5.39	6.48	7.75

NMR spectra were taken in $CDCl_3$ and the signals were designated in δ value using tetramethylsilane as an internal standard.

TABLE II. Mass Spectral Data of I and II

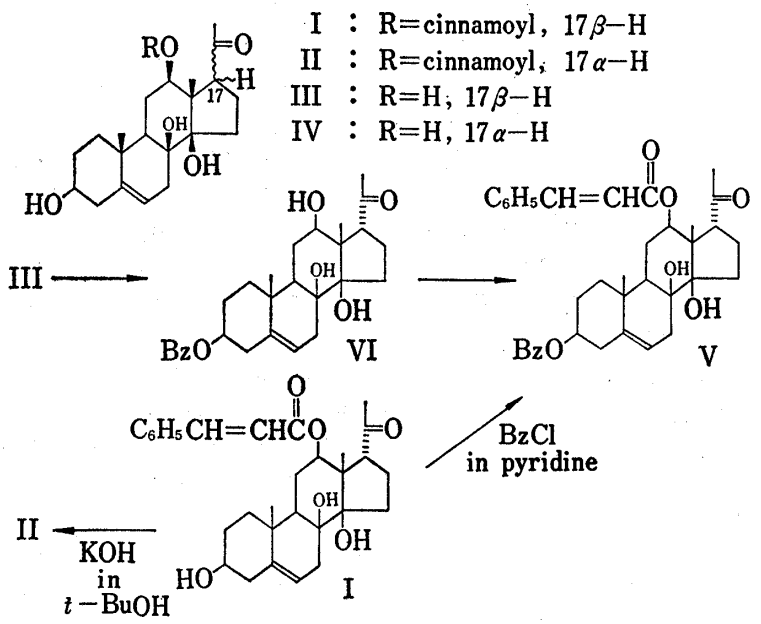
m/e	494[a]	346	208	180	153	138	131	123	120
I	no peak	39[b]	17	36	27	6	100	60	45
II	0.8	7	84	7	10	21	100	17	53

a) molecular peak *b*) percentage to base peak (*m/e* 131)

Treatment of I with benzoyl chloride in pyridine afforded a monobenzoate (V), mp 232—236°. *Anal.* Calcd. for $C_{37}H_{42}O_7$: C, 74.22; H, 7.07. Found: C, 74.14; H, 7.25. Mass Spectrum *m/e*: 476 (M^+-benzoic acid), 450 (M^+-cinnamic acid). Hydrolysis of I with 5% methanolic potassium hydroxide gave an acidic substance which was identified with cinnamic acid. The neutral fraction was a mixture of two substances, lineolon (III) and isolineolon (IV), which were identified with the samples isolated from the same plant. Therefore, ikemagenin (I) is a cinnamoyl ester of lineolon or isolineolon. The location of the ester linkage was assumed as C-12 by the splitting pattern of the hydrogen adjacent to the esterified hydroxyl group (double-doublet, J=6.5 and 8.0 Hz).[5]

1) H. Mitsuhashi and Y. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **7**, 647 (1959); *idem*, *ibid.*, **7**, 949 (1959); *idem*, *ibid.*, **8**, 565 (1960); *idem*, *ibid.*, **8**, 738 (1960); *idem*, *ibid.*, **10**, 719 (1962); *idem*, *ibid.*, **10**, 725 (1962).
2) T. Yamagishi and H. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 625 (1972).
3) T. Yamagishi, K. Hayashi, and H. Mitsuhashi, Abstr. Papers, 92nd Annu. Meet. Pharm. Soc. Japan, II, 174 (1972); T. Yamagishi, K. Hayashi, and H. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), accepted.
4) H. Mitsuhashi and Y. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **10**, 433 (1962); H. Mitsuhashi, Y. Shimizu, T. Nomura, T. Yamada, and E. Yamada, *ibid.*, **11**, 1198 (1963).
5) N.S. Bhacca and D.H. Williams, "Applications of NMR spectroscopy in Organic Chemistry," Holden-Day, San Francisco, 1964, p. 80.

The remaining problem of the stereochemistry at C-17 was established from the following evidences. The treatment of III (17β-H) with one molar equivalent of benzoyl chloride in pyridine gave 3-O-benzoyllineolon (VI), mp 221—227°. *Anal.* Calcd. for $C_{28}H_{36}O_6$: C, 71.77; H, 7.74. Found: C, 71.87; H, 7.79. The signal at δ 4.88 as a multiplet in its NMR spectrum indicates the location of the ester linkage (3α-H). Treatment of the monobenzoate with cinnamoyl chloride in pyridine afforded 3-O-benzoyl-12-O-cinnamoyllineolon, mp 233—237°. *Anal.* Calcd. for $C_{37}H_{42}O_7$: C, 74.22; H, 7.07. Found: C, 74.32; H, 7.17. Mass Spectral *m/e*: 476 (M^+ -benzoic acid), 450 (M^+ -cinnamic acid). These physical constants were in good agreement with those of monobenzoylikemagenin (V). The identity was also established by the IR spectrum and the mixed melting point. Thus, it is concluded that I and lineolon have the same configuration at C-17.



Isoikemagenin (II), mp 198—202°, has a formula $C_{30}H_{38}O_6$ (M^+ at *m/e* 496). The mass, UV, and NMR spectral data of I and II are very similar except for the chemical shift of the C-18-methyl and the relative intensity of the corresponding fragments (Tables I and II). Hydrolysis of II with 5% methanolic potassium hydroxide gave an acidic substance which was identified with cinnamic acid. The neutral fraction was a mixture of two substances, III and IV. By treatment with potassium hydroxide in *tert*-BuOH, I isomerized to II.[6] The C-18-methyl protons of II appeared in a higher field than those of I (Table I). This striking shift should be attributed to the C-17 $COCH_3$ group, which is very near the C-18-methyl group. These results suggest that the structure of isoikemagenin is 12-O-cinnamoylisolineolon.

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