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YAMATAIMINE, A NEW PYRROLIZIDINE ALKALOID FROM CACALIA YATABEI[1]

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In the course of the studies on carcinogenic activity of pyrrolizidine alkaloids in Compositae plants, a new pyrrolizidine alkaloid, named yamataimine(1) was isolated from the roots of Cacalia yatabei Maxim. (Japanese name : yama-taimingasa)

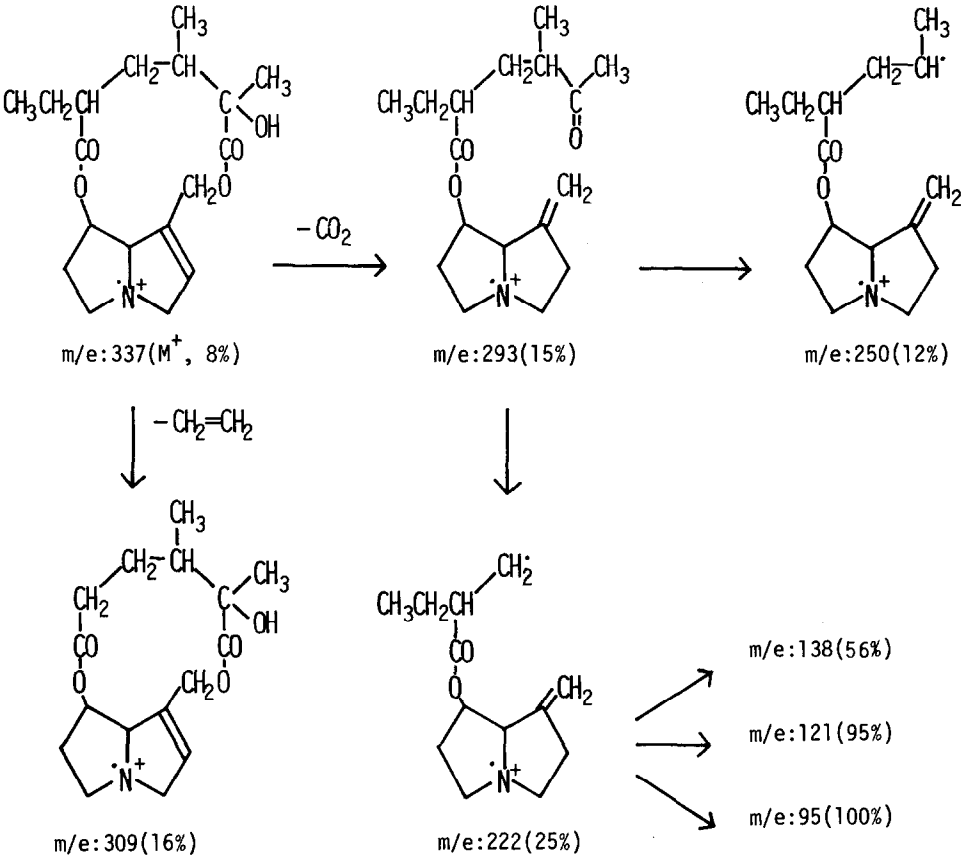
The present paper deals with the structural determination of yamataimine by discussing the results of chemical study and X-ray crystallographic analysis.

The crude alkaloid extracted from MeOH ext. of the roots(2.2kg) was chromatographed on silica gel column and eluted with $CHCl_3$-MeOH-NH_4OH solvent system to yield 1, colorless needles, m.p. 181-182°(petroleum-acetone), $C_{18}H_{27}O_5N$(M^+ 337.189), $[\alpha]_D^{18}$+63.6°(EtOH).

The ^{13}C-NMR(CMR) spectrum of 1 shows 18 detectable signals of carbons[2], of which signals at 174.4 and 173.9ppm are showing the presence of two ester carbonyl carbons, which are also ascertained by IR spectral absorption at ν_{max}^{KBr} 1720 and 1735cm^{-1}. The signals at 135.7 and 131.4 are responsible for two olefinic carbons in the necine moiety. The proton magnetic resonance(PMR) spectrum of 1 shows a typical pattern of twelve membered macrocyclic pyrrolizidine alkaloid.[3] The three broad singlets at δ6.10, 4.98 and 3.85ppm correspond the olefinic proton(>C=C<u>H</u>-) at C-2, and two methine protons (>C<u>H</u>-OCO- and >C<u>H</u>-N<) at C-7 and C-8, respectively. The signals of the geminal methylene protons at C-9 appear as a pair of doublet at δ5.52 and 4.30(J=11.5Hz). From the appreciable differences of the shift (H=1.22ppm) and the coupling constant (J=11.5Hz), 1 is classified as a twelve membered macrocyclic pyrrolizidine alkaloid. Other assignable signals are at 0.82ppm (3H, t, J=7.5Hz) for C<u>H</u>$_3$-CH$_2$-C-15, 0.98ppm (3H, d, J=8.0Hz) for C<u>H</u>$_3$-CH- and 1.18ppm (3H, s) for C<u>H</u>$_3$-C-12, respectively. The complicated peaks at 1.25 to 3.50ppm are due to the methylene protons at C-3, C-5 and C-6 and methine protons at C-13 and C-15.

The high resolution mass spectrometric studies on this alkaloid show also a typical macrocyclic pyrrolizidine derivatives of retronecine[4]. The fragment ions at m/e 138($C_8H_{12}ON$),

121($C_8H_{11}N$) and 95 (C_6H_9N 100%) arose from the necine moiety. The significant fragment ions at m/e 309($C_{16}H_{23}O_5N$), 293($C_{17}H_{27}O_3N$) and 222($C_{13}H_{20}O_2N$) indicate that the ethyl group attached at C-15 and one hydroxy group is located at C-12 in the necic acid moiety.

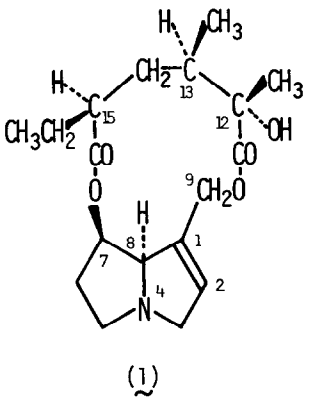


The chemical hydrolysis of 1 with 10% KOH in EtOH gave (7R)-retronecine[5], m.p.115.0-116.0° (acetone), $[\alpha]_D$+45.5°, which was identical with the authentic sample by direct comparison with mixed m.p., $[\alpha]_D$ and IR spectrum, and the mixture of necic acids.

From the data mentioned above, the structure of 1 was estimated to be 15-ethyl-12-hydroxy-12,13-dimethylsenec-1-enine.

The absolute configurations of asymmetric carbons in the necic acid moiety were revealed by X-ray crystallographic analysis. The crystals of yamataimine·HBr for X-ray analysis were prepared from EtOH-HBr solution of 1. Recrystallization from EtOH gave colorless needles, m.p.249°, d=1.158.

Crystal data : Colorless needles, orthorhombic space group $P2_12_12_1$ with four molecules of $C_{18}H_{27}O_5N \cdot HBr$ in a unit cell of the dimensions a=14.888, b=17.092 and c=7.607Å. 1213 Hkl reflections were observed on a Rigaku four-circle X-ray diffractometer ($2\theta \leq 140°$) by using monochromated Cu-Kα radiation(λ=1.5418Å). The structure was solved by the heavy atom method and was refined by the block-diagonal matrix least-squares method to a final R value of 0.094, when the anomalous dispersion effect of the bromine atom for Cu-Kα radiation was taken into account. This value was increased to 0.11 if the reversed absolute configuration was assumed. From the experimental results which accord with the chemical result, the absolute molecular structure of 1 was determined to be (12S,13R,15S)-15-ethyl-12-hydroxy-12,13-dimethylsenec-1-enine, as shown in Fig. 1.



(1)

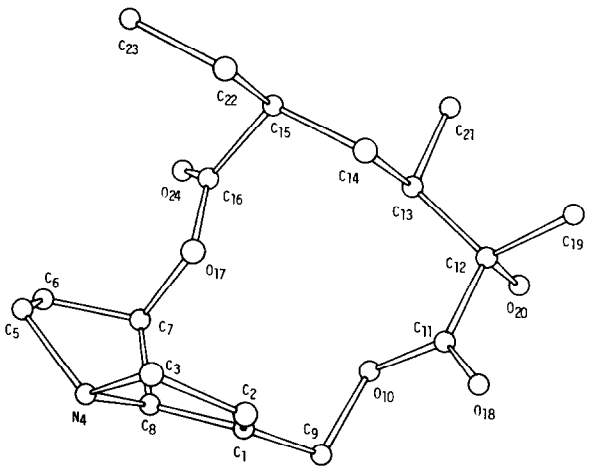


Fig. 1

The new necic acid moiety in yamataimine(1) shows the characteristic structure in the presence of ethyl group at C-15 and (S)-configuration at C-12, being different from the macrocyclic pyrrolizidine alkaloids[6] from Cacalia floridana[7] and C. hastata[8]. Moreover, it became just interesting to test the carcinogenic activity like as fukinotoxin[9] because of the genus Cacalia widely used as food in the country of Japan. The tests of cytotoxicity and other biological activity are now in progress.

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* All melting points are uncorrected and the molecular formulae were measured by high resolution mass spectrometer and the analytical values were good agreement with the calculated values.

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