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STEREOCHEMISTRY OF PETASITENINE, THE CARCINOGENIC ALKALOID FROM PETASITES JAPONICUS MAXIM. AND TRANSFORMATION OF PETASITENINE TO SENKIRKINE

Kiyoyuki YAMADA,*§ Hiroshi TATEMATSU,* Yoshimasa HIRATA,* Masanobu HAGA,** and Iwao HIRONO†

* Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya 464

** Department of Pharmaceutical Sciences, Higashi Nippon Gakuen University, Ishikari, Hokkaido

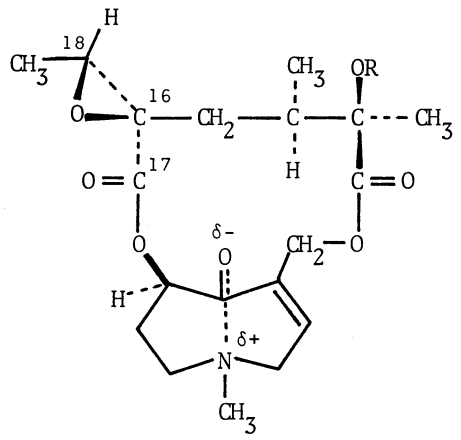
† Department of Pathology, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu 500

Stereochemistry at C-18 of petasitenine, the carcinogenic alkaloid isolated from Petasites japonicus Maxim. was established by chemical and spectral means: the structure of petasitenine was thus determined completely, which is represented by (1). Transformation of petasitenine (1) into senkirkine (3) was achieved by low valent tungusten complexes.

The carcinogenic activity of Petasites japonicus Maxim. ("Fukinotoh" in Japanese) was reported by one of the authors (I.H.) in 1973.[1] In search of the carcinogen(s) of Petasites japonicus Maxim., extensive studies on the chemical constituents of this plant had been performed in our laboratories, and two new pyrrolizidine alkaloids, petasitenine (1) and neopetasitenine (O-acetyl petasitenine) were isolated, the structures of which were elucidated except for the stereochemistry at C-18.[2] Petasitenine has recently been found to be the carcinogen of this plant.[3]

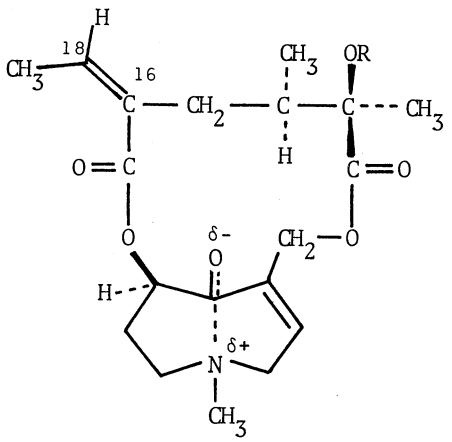
Herein we wish to describe the experimental evidence which proves the stereochemistry regarding C-18 as depicted in (1). Hydrolysis of petasitenine (1) under acidic conditions (e.g., 6N H_2SO_4, reflux, 1 hr) was unsuited for the purpose of preparing the necic acid with the epoxide ring intact, since the epoxide group in (1) was labile under these conditions, and there was obtained, after methylation (ethereal CH_2N_2), a triol diester (6)[4,5,6b] (amorphous). Since the epoxide ring of petasitenine (1) undergoes readily cleavage due to the intramolecular displacement by the tertiary hydroxyl group during the alkaline hydrolysis of (1) to give petasitenecic acid (10),[2] protection of the tertiary hydroxyl group in (1) was attempted, in order to obtain some derivatives of the necic acid possessing the intact epoxide group (7). Petasitenine (1) was converted (Ac_2O - DMSO, room temp.)[7] to the methylthiomethyl ether derivative

(2)[4,5,6a] (amorphous), which was hydrolyzed [10% $Ba(OH)_2$, reflux, 2 hr] and subsequently methylated (ethereal CH_2N_2), affording the dimethyl ester (8)[4,5,6b] (amorphous). Stereospecific deoxygenation of the dimethyl ester (8) could be effected by potassium selenocyanate[8] (KSeCN - aqueous EtOH, 50°, 20 hr) to yield an α,β-unsaturated ester (9)[4,6b,9] (amorphous). Senkirkine (3),[10] an alkaloid with the whole stereochemistry secured was converted to the methylthiomethyl ether derivative (4),[4,5] mp 130 - 131° by the same procedure as described above, which on hydrolysis [10% $Ba(OH)_2$, reflux, 2 hr] followed by methylation (ethereal CH_2N_2) gave the α,β-unsaturated ester (9)[4,6b,9] (amorphous) identical with the one obtained from petasitenine (1) by spectral (ir, nmr, and mass) comparison. From these findings, stereochemistry at C-18 was determined as shown in (1).[11] Petasitenine (1) is therefore a stereoisomer of otosenine (5)[12] regarding the epoxide group.



1 : R = H (petasitenine)

2 : R = CH_2SCH_3



3 : R = H (senkirkine)

4 : R = CH_2SCH_3

Deoxygenation of the epoxide group in the alkaloid (1) itself was extensively studied. Among the various methods examined, the procedure developed by Sharpless[13] was found to be effective: petasitenine (1) was transformed [WCl_6 (1 molar equiv.) - n-BuLi (2 molar equiv.), THF, room temp., 1 hr] into a mixture of senkirkine (3) and its stereoisomer regarding the C_{16}—C_{18} double bond (ratio, 4:1), which was separated[6a] to give pure senkirkine (3), mp 193 - 194° (ca. 60%).[14]

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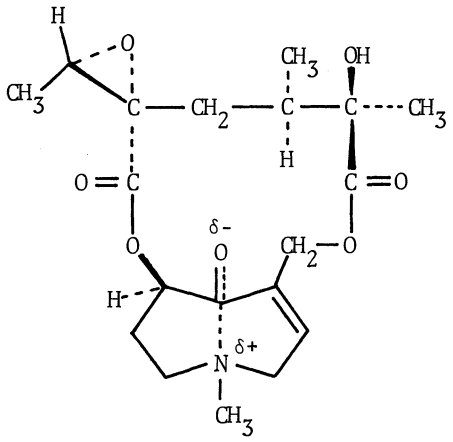
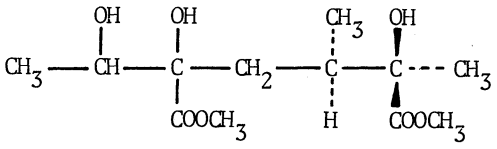


5 (otosenine)



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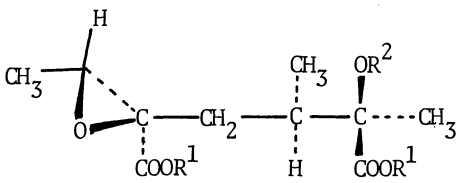
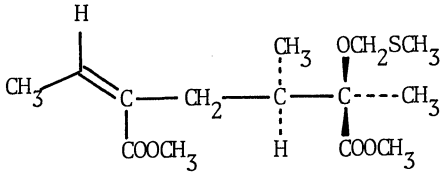


7 : $R^1 = R^2 = H$

8 : $R^1 = CH_3$, $R^2 = CH_2SCH_3$



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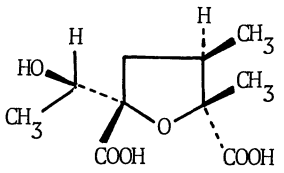

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4. Satisfactory microanalyses or high resolution mass spectral data were obtained.
5. The ir, nmr, and mass spectral data for this new compound were in accord with the structure assigned.
6. Purification was carried out by preparative layer chromatography on: a) aluminum oxide or b) silica gel.

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§ Author to whom correspondence should be addressed.

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