Tetrahedron Letters No. 41, pp 3657 - 3660, 1974. Pergamon Press. Printed in Great Britain.

SYNEILESINE, A NEW PYRROLIZIDINE ALKALOID FROM SYNEILESIS PALMATA[1]

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(Received in Japan 18 July 1974; received in UK for publication 3 September 1974)

In the course of our continuing chemical study on pyrrolizidine alkaloids in crude drugs[2], we have isolated a new pyrrolizidine alkaloid, together with two unknown alkaloids, from the fresh and dried roots of Syneilesis palmata Maxim. (Japanese name: Yaburegasa, Compositae) which was collected near the Sagami-ko, Kanagawa-ken, Japan in 1973.

The present paper deals with the structure determination of a new secopyrrolizidine alkaloid, named syneilesine(I) which has highly cytotoxic activity[3].

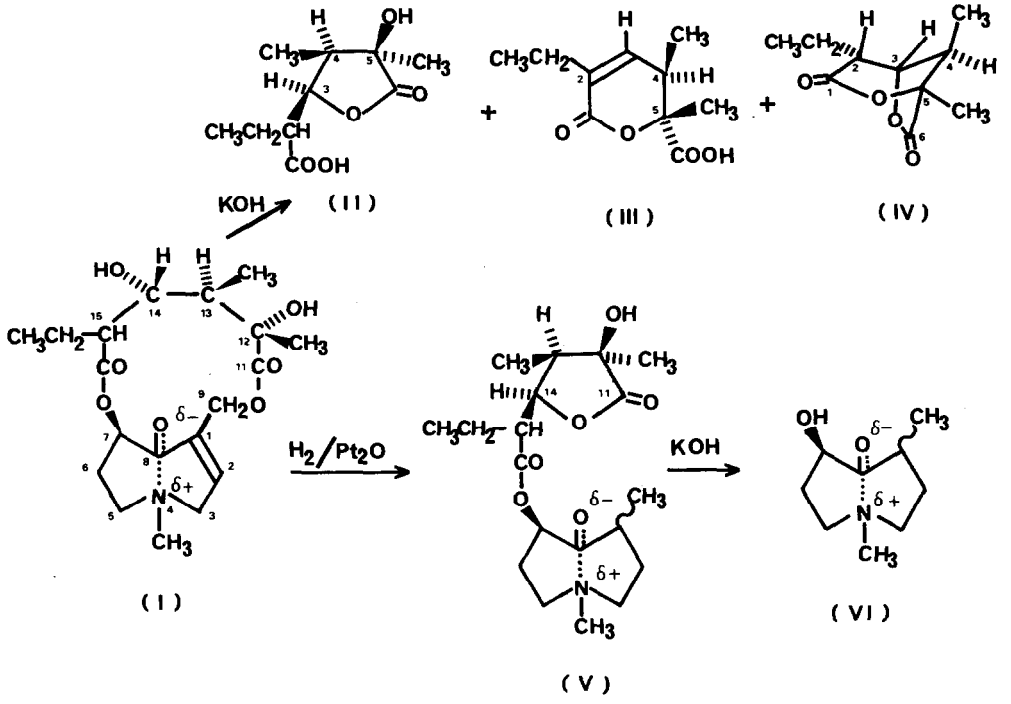
The crude alkaloid extracted from the MeOH ext. of the dried roots (5.08 kg) was chromatographed on silica gel column and eluted with $CHCl_3$-MeOH-NH_4OH solvent system to yield syneilesine(I), colorless needles(from petroleum b.p.60-80°), 0.762 g(0.015%), m.p.195°, CD $[\theta]^{25°}_{max}$ (MeOH); +30500(232nm), +43500(275), $C_{19}H_{29}O_7N$, IR ν^{KBr}_{max}; 3500cm^{-1}, 3450, 1735, 1720. ^{13}C-NMR spectrum shows 19 detectable signals of carbon, of which signals at δ ; 134.2ppm, 136.0, 171.4, 176.7 and 189.4 were easily assigned[4]. The signals at 171.4ppm and 176.7 indicate the presence of two ester carbonyl carbons[5] which were also ascertained by IR spectral absorption at 1720cm^{-1} and 1735. The signals at 134.2ppm, 136.0 and 189.4 are responsible for α,β-unsaturated carbonyl group. A little high field shift of the signal of carbonyl carbon at 189.4ppm, relative to the ordinary α,β-unsaturated carbonyl carbons[6], should be caused from the influences of transannular interactions of the nitrogen atom in the pyrrolizidine nucleus[7]. Proton NMR spectral pattern of the alkaloid also shows a typical macrocyclic secopyrrolizidine alkaloid; a singlet at δ 2.07ppm corresponds to CH_3-N< at N-4, two broad singlets at 6.05ppm and 5.02 to the olefinic proton at C-2 and >CH-OCO- at C-7, respectively. The complicated peaks at 2.00ppm to 3.70 are due to the methylene protons at C-3, C-5 and C-6 in secopyrrolizidine nucleus. The signals of the geminal protons at C-9 are represented as a pair of doublets at 5.50ppm and 4.80(J=11.5Hz each other).

From the appreciable difference of the shift (δ H=0.70ppm) between the geminal protons and the coupling constant(J=11.5Hz), syneilesine is classified as a characteristic 12-membered macrocyclic secopyrrolizidine alkaloid[8]. Other assignable signals are at 0.91ppm(3H, t, J=7.5Hz) for $\underline{CH}_3$-CH_2- and 1.50(3H, d, J=7.5Hz) for $\underline{CH}_3$-CH<, respectively.

High resolution mass spectrometric studies on this alkaloid showed that the fragment ions at m/e; 168($C_9H_{14}O_2N$), 152($C_9H_{14}ON$) and 151($C_9H_{13}ON$) arose from the secopyrrolizidine moiety[9]. The significant fragment ions at m/e; 339($C_{18}H_{29}O_5N$) and 266($C_{14}H_{20}O_4N$) indicate that the two hydroxyl groups are located at C-12 and C-14 in the necic acid moiety.

Hydrolysis of syneilesine with 10% KOH in EtOH gave three new lactones, such as syneilesinolide-A(γ-lactone), m.p.134°, CD$[\theta]^{15°}_{max}$(MeOH); +3700(215nm), $C_{10}H_{16}O_5$, IRν^{KBr}_{max}; 3400cm^{-1}, 1790, 1700, PMR($CDCl_3$)δ; 1.04ppm(3H, t, J=7.5Hz), 1.00(3H, d, J=6.2), 1.52(3H, s), 4.58(1H, d-d, J=10.0 and 5.2), syneilesinolide-B(α,β-unsaturatedδ-lactone), m.p.121°, CD$[\theta]^{15°}_{max}$(MeOH); -82500(203nm), -61000(223), -6600(257), $C_{10}H_{14}O_4$, IRν^{KBr}_{max}; 3300cm^{-1}, 1740, 1690, PMR($CDCl_3$)δ; 0.98ppm(3H, d, J=7.5Hz), 1.09(3H, t, J=8.0), 1.58(3H, s), 2.30(2H, broad q, J=8.0), 2.88(1H, d-q, J=7.5), 6.58(1H, broad d, J=7.5) and syneilesinolide-C(γ,δ-dilactone), m.p.86°, CD$[\theta]^{15°}_{max}$(MeOH); +9800(210nm), $C_{10}H_{14}O_4$, IRν^{KBr}_{max}; 1790cm^{-1}, 1745, PMR($CDCl_3$)δ; 0.92ppm(3H, t, J=7.5Hz), 0.98(3H, d, J=8.0), 1.50(3H, s), 4.75(1H, d-d, J=5.4 and 3.0), 1.60-2.60(3H, complicated peaks). Hydrogenation of syneilesinolide-B gave dihydrosyneilesinolide-B, m.p.85°, $C_{10}H_{16}O_4$, CD$[\theta]^{20°}_{max}$(MeOH); -2400(238nm), whose negative Cotton effect at 238nm indicates that the configuration at C-5 in dihydrosyneilesinolide-B is the same with that at C-2 in (2R)-dihydrosenecic acid[10]. From IR, NMR, Mass and CD spectroscopic studies, syneilesinolide-A, syneilesinolide-B and syneilesinolide-C were assumed to be (3R),(4R),(5R)-2-ethyl-5-hydroxy-4,5-dimethylhexanoic acid-6,3-olide(II), (4R),(5R)-5-carbohydroxy-2-ethyl-4,5-dimethyl-2-pentene-5-olide(III) and (2R),(3R),(4R),(5R)-2-ethyl-4,5-dimethylhexane-1,5:6,3-diolide(IV), respectively.

On the other hand, hydrogenolysis of syneilesine was carried out with Adam's catalyst in dil.HCl solution to give dihydrodesoxysyneilesine-11,14-olide(V), m.p.109.5°, CD$[\theta]^{16°}_{max}$(MeOH); -17500(230nm), $C_{19}H_{31}O_6N$, IRν^{KBr}_{max}; 3450cm^{-1}, 1770, 1740, 1620, which was hydrolyzed to give the necic acid, syneilesinolide-A, syneilesinolide-B and a small amount of syneilesinolide-C and the necine, dihydrodesoxyotonecine(VI)[7], whose hydrochloride was identical with the authentic sample by mixed m.p., $[\alpha]_D$ and IR spectrum.



The structure of the basic moiety and the acidic moiety and the formation of dihydrodesoxysyneilesine-11,14-olide leads to the conclusion that the structure of syneilesine is (12R), (13R),(14R)-15-ethyl-12,14-dihydroxy-4,12,13-trimethyl-8-oxo-4,8-seco-senec-1-enine(I).

The structural studies and cytotoxic bioassay of other alkaloids are now in progress.

Acknowledgements — The authors wish to thank Professor F. Šantavý, Chemical Institute, Medical Faculty, Palacky University, for a gift of the authentic sample of dihydrodesoxyotonecine hydrochloride and this work was supported in part by the Grant-in-Aid for Scientific Research from the Ministry of Education of Japan.

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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 in good agreement with the calculated values.

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