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SENECICANNABINE, A NEW PYRROLIZIDINE ALKALOID FROM SENECIO CANNABIFOLIUS[1]

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Abstract: The structure of senecicannabine(1), a new macrocyclic pyrrolizidine alkaloid isolated from Senecio cannabifolius, has been established by chemical study and X-ray analysis.

In the course of the studies on carcinogenic pyrrolizidine alkaloids in Compositae plants, a new macrocyclic pyrrolizidine alkaloid, named senecicannabine(1) was isolated from the roots and aerial parts of Senecio cannabifolius (Japanese name : Hangon-so) together with known pyrrolizidine alkaloids, seneciphylline(2) and jacozine(3).

The present paper deals with the structural determination of senecicannabine(1) by discussing the results of chemical study and X-ray analysis.

The crude alkaloids obtained from the MeOH exts. of the roots and aerial parts were chromatographed on silica gel column using C_6H_6:AcOEt:$HN(Et)_2$ solvent system to give senecicannabine(1)(0.036% dried roots, 0.0014% dried aerial parts), seneciphylline(2)(0.47%, 0.0043%)[2,3] and jacozine(3)(0.026%, 0.00023%).[4,5]

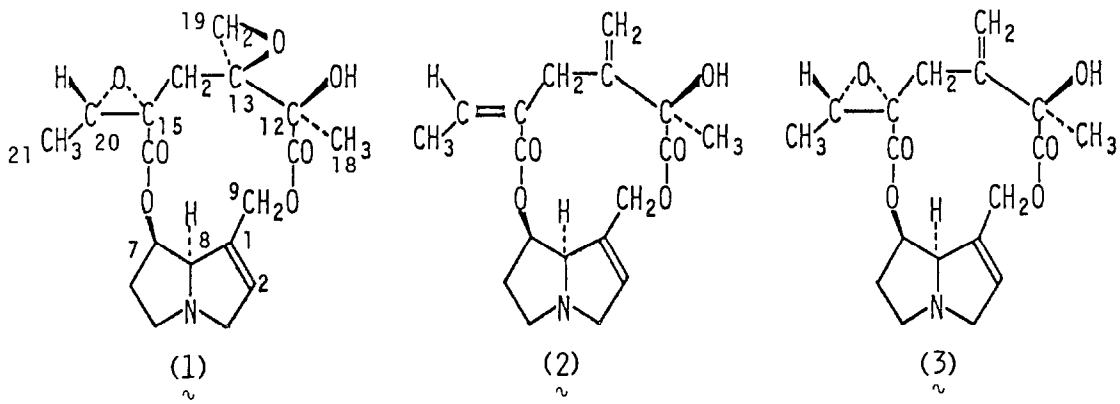
Senecicannabine(1), colorless prisms, m.p. 198° and $[\alpha]_D^{25}$ -8.9°($CHCl_3$), shows a molecular formula $C_{18}H_{23}O_7N$ and 18 carbon signals in the carbon thirteen nuclear magnetic resonance(CMR) spectrum.[6] Signals at (ppm) 175.0 and 168.6 are showing the presence of two ester carbonyl carbons. This fact is also ascertained by IR spectral absorptions at ν_{max}^{KBr} 1740 and 1730 cm^{-1}. Signals at 136.8 and 131.0 are responsible for two olefinic carbons in the necine moiety and signals at 60.5, 60.1, 58.8 and 49.4 are showing the presence of two pairs of epoxide carbons in the necic acid moiety. The proton magnetic resonance (PMR) spectrum of (1) shows a typical pattern of twelve-membered macrocyclic pyrrolizidine alkaloid.[7] Three broad singlets at (ppm) 6.24, 5.28 and 4.33 correspond to the olefinic proton at C-2 and two methine protons at C-7 and C-8,

respectively. Signals of the geminal methylene protons at C-9 appear as a pair of doublets at 5.50 and 4.12(J=12Hz). From the appreciable difference of the shifts (ΔH=1.38 ppm) and the coupling constant(J=12Hz) between the geminal protons at C-9, (1) is classified as a twelve-membered macrocyclic pyrrolizidine alkaloid. Other assignable signals in the necic acid moiety are as follows : 1.82(1H,d, J=16Hz) and 2.64(1H,d,J=16Hz) for methylene protons at C-14, 1.28(3H,s) for methyl protons at C-18, 2.82(1H,d,J=4Hz) and 3.07(1H,d,J=4Hz) for methylene protons at C-19, 2.95(1H,q,J=6Hz) for methine proton at C-20 and 1.23(3H,d, J=6Hz) for methyl protons at C-21, respectively.

The mass spectrum of senecicannabine(1) exhibits a molecular ion peak at m/e 365. Other prominent peaks appear at m/e 321(M^+-CO_2), 288, 138, 120(base peak), 119 and 95.

Comparison of the IR, PMR and mass spectra of senecicannabine(1) with those[8] of various pyrrolizidine alkaloids suggests that (1) is a macrocyclic diester of retronecine type amino alcohol.

From the data mentioned above, the planar structure of senecicannabine(1) is shown to be 13,19-15,20-diepoxy-15,20-dihydro-12-hydroxy-senecionan-11,16-dione.



(1) (2) (3)

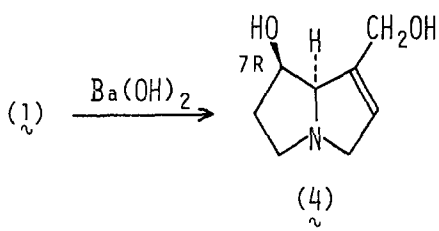
Figure 1

Hydrolysis of senecicannabine(1) with $Ba(OH)_2$ gave (7R)-retronecine(4),[9] m.p. 115.0-116.0°(acetone-n-hexane), $[\alpha]_D^{27}$+50.8°(EtOH), which was identical with the authentic sample on the basis of mixed m.p. and comparison of $[\alpha]_D$ and IR spectrum.

The relative configuration of asymmetric carbons of senecicannabine(1) was decided by X-ray analysis, as shown in Figure 2.

Crystal data : Senecicannabine($\underset{\sim}{1}$) crystallized in monoclinic with a=11.714(1), b=8.774(1), C=9.372(1)Å and β=111.70(1)°. Systematic extinctions indicated space group $P2_1$ and density considerations suggested one molecule of $C_{18}H_{23}O_7N$ per an asymmetric unit. All unique diffraction maxima with $2\theta \leq 140°$ were recorded on a Rigaku diffractometer using graphite monochromated Cu-Kα (1.54178Å) radiation. Of the 1778 reflections surveyed, 1687(95%) were used after correction for Lorentz and polarization. The structure was solved by use of the program MULTAN[10] and refined by the block-diagonal least-squares method to R value of 0.034.[11]

From the result of the hydrolysis and X-ray analysis, the absolute molecular structure of senecicannabine($\underset{\sim}{1}$) was determined to be (12R,13S,15S,20S)-13,19-15,20-diepoxy-15,20-dihydro-12-hydroxy-senecionan-11,16-dione, as shown in Figure 1.



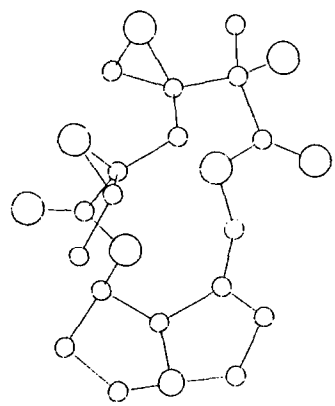


Figure 2. A computer-generated perspective drawing of ($\underset{\sim}{1}$)

The structural feature of senecicannabine($\underset{\sim}{1}$) is highly oxidized in the necic acid moiety, i.e. its structure corresponds to a diepoxide of senecicphylline($\underset{\sim}{2}$). The presence of ($\underset{\sim}{1}$) is a first example of pyrrolizidine alkaloid possessing two epoxide rings. ($\underset{\sim}{1}$),($\underset{\sim}{2}$) and ($\underset{\sim}{3}$) isolated from Senecio cannabifolius differ from each other in the oxidative stage and may be biosynthesized in order of ($\underset{\sim}{2}$)⟶($\underset{\sim}{3}$)⟶($\underset{\sim}{1}$).

The tribe Senecioneae plants are widely used as foods and crude drugs in Japan[12] and the young leaves of Senecio cannabifolius are used for foods in various districts. Therefore senecicannabine($\underset{\sim}{1}$) becomes just urgent to test the carcinogenic activity like as fukinotoxin[13] and clivorine.[14]

The tests of mutagenicity[15], carcinogenicity and other biological activities are now in progress.

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