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Epoxidation of Pyrrolizidine Alkaloids. (1). Chemical Conversion of Seneciphylline and Jacozine to Senecicannabine¹⁾

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A new pyrrolizidine alkaloid, senecicannabine (**4**) which was isolated from *Senecio cannabinifolius* was derived from seneciphylline (**1**) by oxidation with performic acid. The transformation of jacozine (**6**) to **4** was also carried out with performic acid, and the configuration of the epoxide ring of **6** was chemically determined to be 15*S* and 20*S*.

Keywords—pyrrolizidine alkaloid; senecicannabine; seneciphylline; jacozine; epoxidation

In a preliminary communication,²⁾ we reported the isolation of a new macrocyclic pyrrolizidine alkaloid, named senecicannabine (**4**), together with two known alkaloids, seneciphylline (**1**) and jacozine (**6**), from *Senecio cannabinifolius* (Japanese name: Hangan-so). The structure of senecicannabine (**4**) was previously proposed by us on the basis of hydrolysis results and X-ray analysis.²⁾ It was pointed out that senecicannabine (**4**) was highly oxidized in the necic acid moiety and its structure corresponded to a diepoxide of seneciphylline (**1**). This paper deals with the chemical conversion of seneciphylline (**1**) and jacozine (**6**) to senecicannabine (**4**) and the configuration of the epoxide ring in jacozine (**6**).

Seneciphylline (**1**) was oxidized with performic acid for 45 h at room temperature to give two monoepoxides (**2** and **3**) and two diepoxides (**4** and **5**) (Chart 1).

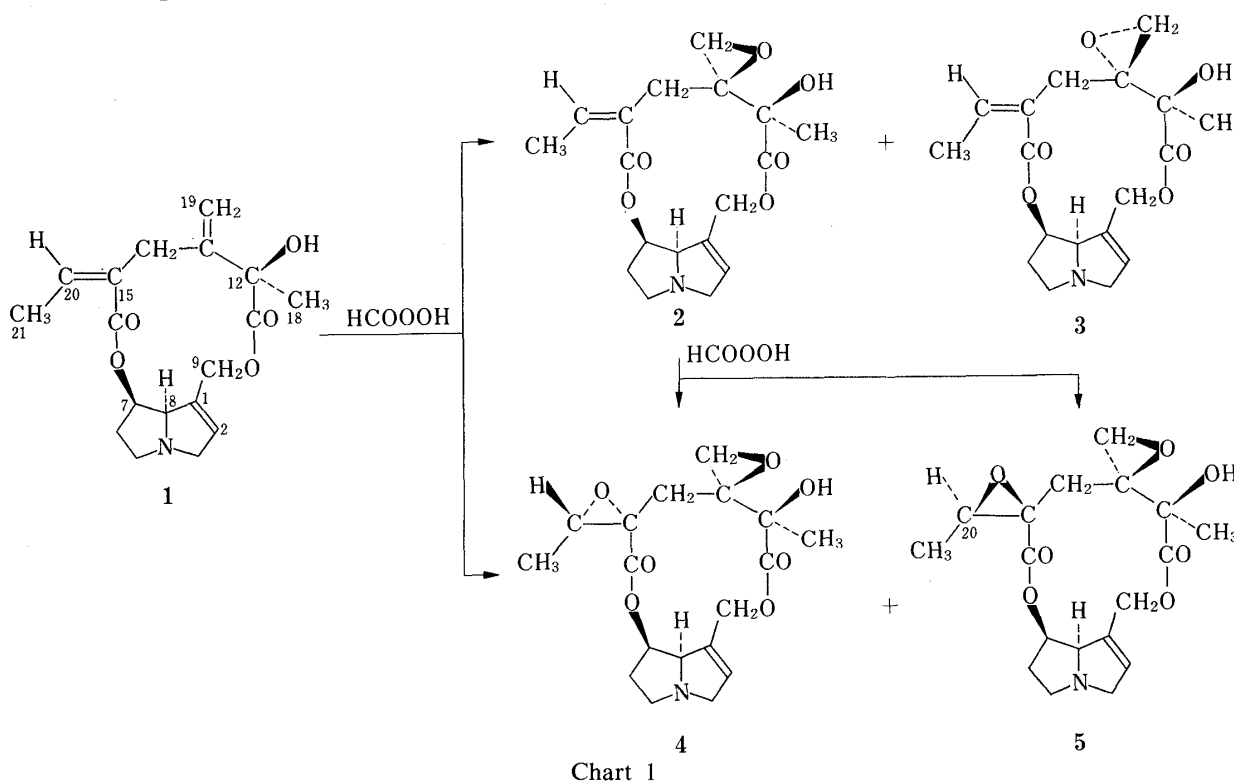


TABLE I. ^{13}C -NMR Chemical Shifts and Assignments^{a)}

Carbon	2	3	4	5
1	132.0	132.0	131.0	132.0
2	137.1	137.3	136.8	136.6
3	62.9	63.0	62.8	63.0
5	53.9	53.1	53.3	54.2
6	34.5	34.9 ^{b)}	35.1 ^{b)}	33.7
7	74.8	75.5	75.7	75.7
8	77.7	78.0	77.6	76.9
9	61.7	61.2	60.5	62.7
11	176.4	176.8	175.0	175.1
12	76.3	76.3	76.4	75.8
13	60.3	58.5	60.5 ^{c)}	59.0 ^{b)}
14	36.2	34.7 ^{b)}	34.1 ^{b)}	36.9
15	127.9	128.4	60.1 ^{c)}	60.2 ^{b)}
16	167.5	167.1	168.6	168.6
18	21.9	20.7	20.6	22.4
19	49.8	43.0	49.4	51.1
20	140.3	138.2	58.8	59.4
21	15.8	15.1	13.0	13.7

a) Chemical shifts in ppm downfield from TMS; solvent CDCl_3 .

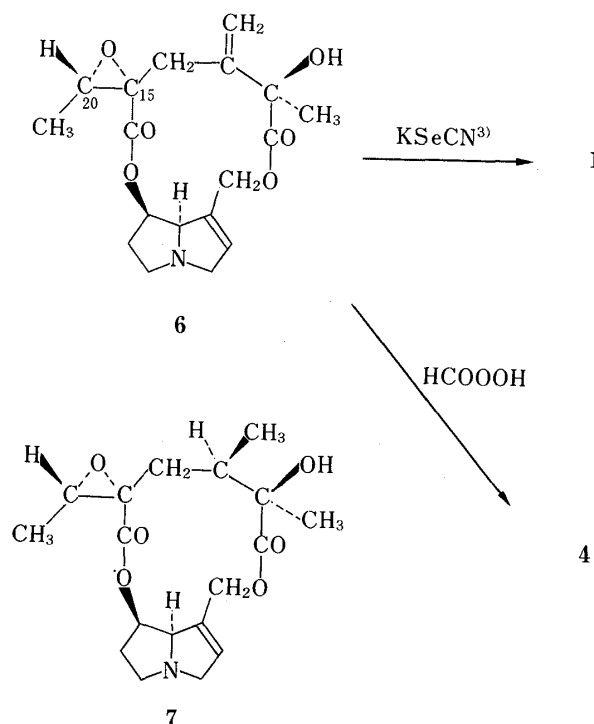
b, c) Assignments in each column may be interchanged.

The monoepoxide (**2**), the main product, showed a molecular ion peak at m/z 349, which was larger by 16 mass (MS) units than that of seneciophylline (**1**), in the MS spectrum. In the ^1H -nuclear magnetic resonance (^1H -NMR) spectrum of **2**, the signals of *exo*-methylene protons at C-19 of **1** had disappeared and the signals of epoxide methylene protons at C-19 appeared at δ 2.73 (2H, s). The other monoepoxide (**3**) showed the same molecular ion peak at m/z 349 and its MS fragmentation pattern was similar to that of **2**. In the ^1H -NMR spectrum of **3**, the signals of epoxide methylene protons at C-19 appeared at δ 2.43, and 2.78 (2H, AB q, $J=4$ Hz). Therefore, **2** and **3** were considered to be 13,19-epoxide of seneciophylline (**1**). The configuration of the epoxide ring at C-13,19 was deduced from a spectral comparison with senecicannabine (**4**) having β -epoxide at C-13,19. In the ^{13}C -NMR spectrum, the C-19 epoxide carbon signal was observed at δ 49.4 in senecicannabine (**4**) and at δ 49.8 and 43.0 in **2** and **3**, respectively. Therefore, **2** was concluded to be the β -epoxide and **3** to be the α -epoxide (Table I).

The diepoxide (**4**) was identical with naturally occurring senecicannabine on the basis of mixed fusion, $[\alpha]_D$, the infrared (IR) spectrum, and other spectral data. The other diepoxide (**5**) showed the same molecular ion peak at m/z 365 and its MS fragmentation pattern resembled that of **4**. In the ^1H -NMR spectrum of **5**, the signals of *exo*-methylene protons at C-19 and the olefinic proton at C-20 in **1** had disappeared, and the signals of epoxide methylene protons at C-19 and an epoxide methine proton at C-20 appeared at δ 2.86, 2.95 (2H, AB q, $J=4.5$ Hz) and δ 3.03 (1H, q, $J=5.5$ Hz), respectively. Therefore, **5** was concluded to be the 13,19; 15,20-diepoxide of seneciophylline (**1**). In order to determine the configuration of the epoxide ring in the diepoxide **5**, the monoepoxide **2** was further oxidized with performic acid to give **4** and **5**. Since compound **5** was isomeric to **4** as regards the stereochemistry of the epoxide ring at C-15,20, it was clarified that the configuration of the epoxide ring at C-15,20 in **5** is β .

Next, the conversion of jacozone (**6**) into **4** was also attempted to determine the configuration of the epoxide ring in **6**. Jacozone (**6**) was proposed to be the 15,20-epoxide of seneciophylline (**1**) on the basis of the chemical conversion of jacozone (**6**) to **1** on treatment

with potassium selenocyanate, the similarity of the ^1H -NMR spectrum to that of jacobine (7) and moreover the similarity to 7 as regards reactivity on deepoxidation using KSeCN (Chart 2).³⁾



Jacozine (6) was oxidized with performic acid for 6 d at room temperature to afford senecicannabine (4), which was identical with naturally occurring senecicannabine on the basis of mixed fusion, $[\alpha]_D$, and other spectral data. Thus, the epoxide structure of jacozine (6) was chemically proved to be α -epoxide (15*S*,20*S*).

It appears that the epoxidation of the double bond at C_{13} – C_{19} in seneciphylline (1) and jacozine (6) mainly progresses from the β -side, which is the less hindered side of the double bond. We have already reported that the β -epoxide was mainly obtained on oxidizing the double bond at C_{15} – C_{20} in acetylsenkirkine and neoligularidine because of the steric hindrance due to the methyl group at C-19.¹⁾ On the other hand, the mixture of α - and β -epoxides (4 and 5) may be obtained on oxidizing 2 because of the change of the conformation in the macrocyclic ring.

Since a macrocyclic pyrrolizidine alkaloid, fukinotoxin, having an epoxide group in the necic acid part is carcinogenic,⁴⁾ tests for carcinogenicity, mutagenicity and other biological activities of the epoxides of seneciphylline (1) are in progress.

Experimental

Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO IRA-1 spectrometer. ^1H -NMR and ^{13}C -NMR spectra were taken on a JEOL PS 100 Fourier-transform spectrometer and chemical shifts are given on the δ (ppm) scale with tetramethylsilane as an internal standard. MS spectra were obtained with JEOL JMS-D100 and DX-300 MS spectrometers.

General Procedure for Epoxidation of Seneciphylline (1), 2, and Jacozine (6)—Seneciphylline (501 mg, 1.5 mmol) was dissolved in 99% formic acid (1 ml). Thirty percent hydrogen peroxide (3 ml) was gently added to the above solution and the mixture was allowed to stand for 45 h at room temperature. Aqueous sulfuric acid (2 N, 40 ml) was added to the reaction mixture in an ice-bath and the solution was reduced with zinc dust (8 g). The solution was

filtered, made alkaline with 5% aqueous NH_4OH and extracted with CHCl_3 to give a mixture of epoxides (518 mg). The mixture was separated by high performance liquid chromatography (HPLC) on a Senshu pack N505 column (solvent, C_6H_6 : AcOEt : Et_2NH = 77.7 : 20 : 2.3; flow rate, 6 ml/min) to afford **2** (200 mg), **3** (23 mg), **4** (14 mg) and **5** (15 mg) after recrystallization from acetone. **2**: Colorless needles, mp 150–151 °C (acetone), $[\alpha]_D^{26} - 4.1^\circ$ ($c=0.26$, CHCl_3). Anal. Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 61.64; H, 6.61; N, 3.84. IR $\nu_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 3400, 1740, 1710, 1655. MS m/z (%): 349 (M^+ , 16), 305 ($\text{M}^+ - \text{CO}_2$, 4), 260 (6), 138 (42), 136 (46), 121 (44), 120 (81), 119 (100), 95 (54), 94 (26). $^1\text{H-NMR}$ (CDCl_3) δ : 1.21 (3H, s, $\text{C}_{18}\text{-H}$), 1.85 (3H, d, $J=7.5$ Hz, $\text{C}_{21}\text{-H}$), 2.45, 2.85 (2H, AB q, $J=15$ Hz, $\text{C}_{14}\text{-H}$), 2.73 (2H, s, $\text{C}_{19}\text{-H}$), 4.09 (1H, br d, $J=12$ Hz, $\text{C}_9\text{-Ha}$), 4.31 (1H, br s, $\text{C}_8\text{-H}$), 5.20 (1H, m, $\text{C}_7\text{-H}$), 5.35 (1H, d, $J=12$ Hz, $\text{C}_9\text{-Hb}$), 5.97 (1H, q, $J=7.5$ Hz, $\text{C}_{20}\text{-H}$), 6.22 (1H, br s, $\text{C}_2\text{-H}$). **3**: Colorless prisms, mp 221–222 °C (acetone), $[\alpha]_D^{26} - 120^\circ$ ($c=0.16$, CHCl_3). Anal. Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 62.09; H, 6.60; N, 3.93. IR $\nu_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 3400, 1738, 1720, 1655. MS m/z (%): 349 (M^+ , 18), 305 ($\text{M}^+ - \text{CO}_2$, 3), 260 (6), 138 (32), 136 (39), 121 (38), 120 (72), 119 (100), 96 (62), 95 (50). $^1\text{H-NMR}$ (CDCl_3) δ : 1.20 (3H, s, $\text{C}_{18}\text{-H}$), 1.90 (3H, d, $J=7.5$ Hz, $\text{C}_{21}\text{-H}$), 2.43, 2.78 (2H, AB q, $J=4$ Hz, $\text{C}_{19}\text{-H}$), 4.15 (1H, br d, $J=11$ Hz, $\text{C}_9\text{-Ha}$), 4.30 (1H, br s, $\text{C}_8\text{-H}$), 5.03 (1H, t, $J=3.5$ Hz, $\text{C}_7\text{-H}$), 5.53 (1H, d, $J=11$ Hz, $\text{C}_9\text{-Hb}$), 5.74 (1H, q, $J=7.5$ Hz, $\text{C}_{20}\text{-H}$), 6.23 (1H, br s, $\text{C}_2\text{-H}$). **4**: Colorless prisms, mp 197.5–198 °C (acetone), $[\alpha]_D^{27} - 19.4^\circ$ ($c=0.15$, CHCl_3). Anal. Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_7$: C, 59.18; H, 6.33; N, 3.83. Found: C, 59.08; H, 6.41; N, 3.81. IR $\nu_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 3400, 1740, 1730, MS m/z (%): 365 (M^+ , 17), 321 ($\text{M}^+ - \text{CO}_2$, 3), 304 (4), 234 (5), 222 (4), 138 (17), 136 (22), 121 (32), 120 (100), 119 (46), 95 (51). $^1\text{H-NMR}$ (CDCl_3) δ : 1.23 (3H, d, $J=6$ Hz, $\text{C}_{21}\text{-H}$), 1.28 (3H, s, $\text{C}_{18}\text{-H}$), 1.82, 2.64 (2H, AB q, $J=16$ Hz, $\text{C}_{14}\text{-H}$), 2.82, 3.07 (2H, AB q, $J=4$ Hz, $\text{C}_{19}\text{-H}$), 2.95 (1H, q, $J=6$ Hz, $\text{C}_{20}\text{-H}$), 4.12 (1H, br d, $J=12$ Hz, $\text{C}_9\text{-Ha}$), 4.33 (1H, m, $\text{C}_8\text{-H}$), 5.28 (1H, m, $\text{C}_7\text{-H}$), 5.50 (1H, d, $J=12$ Hz, $\text{C}_9\text{-Hb}$), 6.24 (1H, br s, $\text{C}_2\text{-H}$). **4** was identical with naturally occurring senecicannabine on the basis of mixed fusion, $[\alpha]_D$ and other spectral data. **5**: Colorless needles, mp 185–186 °C (acetone), $[\alpha]_D^{28} + 18.1^\circ$ ($c=0.17$, CHCl_3). Anal. Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_7$: C, 59.18; H, 6.33; N, 3.83. Found: C, 59.09; H, 6.23; N, 3.73. IR $\nu_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 3200, 1740, 1720. MS m/z (%): 365 (M^+ , 19), 321 ($\text{M}^+ - \text{CO}_2$, 6), 288 (6), 260 (9), 149 (35), 138 (25), 136 (21), 121 (68), 120 (100), 119 (71), 95 (69), 94 (24), 93 (29). $^1\text{H-NMR}$ (CDCl_3) δ : 1.19 (3H, s, $\text{C}_{18}\text{-H}$), 1.27 (3H, d, $J=5.5$ Hz, $\text{C}_{21}\text{-H}$), 2.16, 2.32 (2H, AB q, $J=15$ Hz, $\text{C}_{14}\text{-H}$), 2.86, 2.95 (2H, AB q, $J=4.5$ Hz, $\text{C}_{19}\text{-H}$), 3.03 (1H, q, $J=5.5$ Hz, $\text{C}_{20}\text{-H}$), 4.23 (1H, br d, $J=12$ Hz, $\text{C}_9\text{-Ha}$), 4.28 (1H, br s, $\text{C}_8\text{-H}$), 5.22 (1H, d, $J=12$ Hz, $\text{C}_9\text{-Hb}$), 5.23 (1H, m, $\text{C}_7\text{-H}$), 6.22 (1H, br s, $\text{C}_2\text{-H}$).

Epoxidation of 2—According to the general procedure, **4** (7.1 mg) and **5** (6.1 mg) were obtained from **2** (41 mg). **4** and **5** were identical with the products obtained from the epoxidation of seneciphylline (**1**) on the basis of mixed fusion, $[\alpha]_D$ and IR spectra.

Conversion of Jacozine (6) into Senecicannabine (4)—According to the general procedure, **6** (17.5 mg) was oxidized to afford **4** (9.3 mg). This product was identical with a naturally occurring specimen on the basis of mixed fusion, $[\alpha]_D$, and other spectral data.

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