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Epoxidation of Pyrrolizidine Alkaloids. (1). Chemical Conversion of Seneciphylline and Jacozine to Senecicannabine[1)]

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A new pyrrolizidine alkaloid, senecicannabine (**4**) which was isolated from *Senecio cannabifolius* 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 cannabifolius* (Japanese name: Hangon-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).

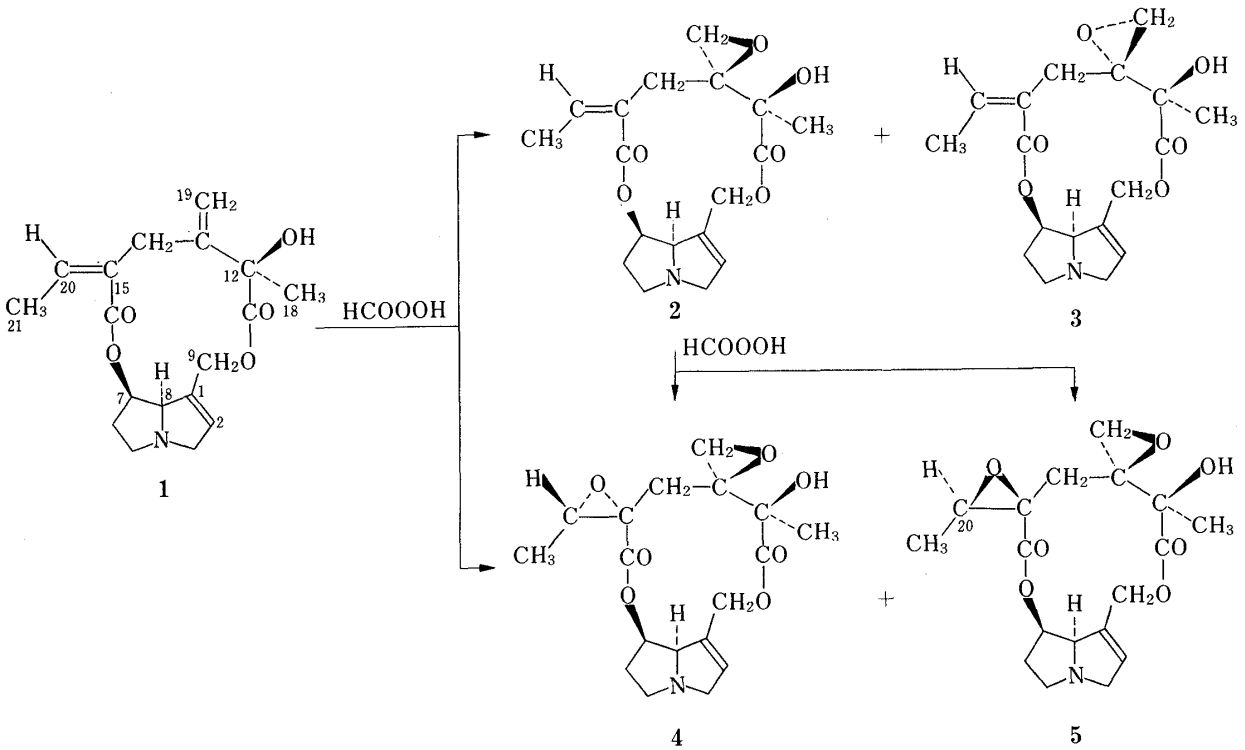

Chart 1

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 seneciphylline (**1**), in the MS spectrum. In the ^{1}H-nuclear magnetic resonance (^{1}H-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 ^{1}H-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 seneciphylline (**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 ^{1}H-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 seneciphylline (**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 jacozine (**6**) into **4** was also attempted to determine the configuration of the epoxide ring in **6**. Jacozine (**6**) was proposed to be the 15,20-epoxide of seneciphylline (**1**) on the basis of the chemical conversion of jacozine (**6**) to **1** on treatment

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

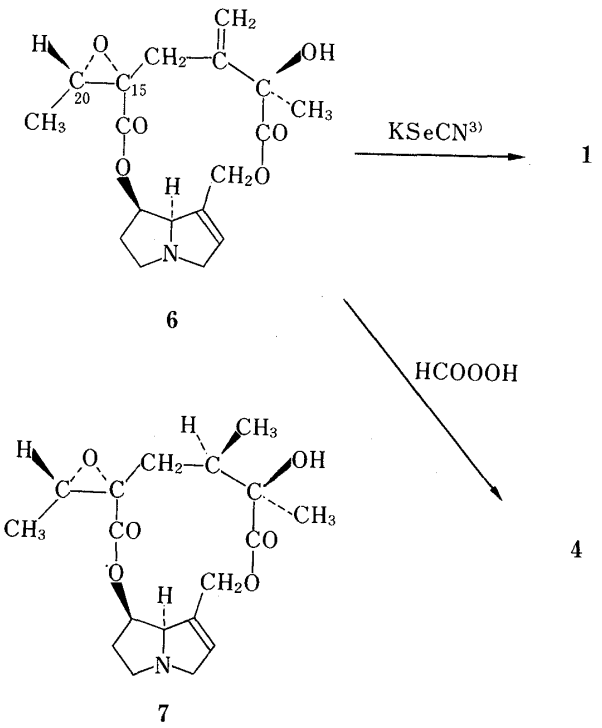

Chart 2

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. ^{1}H-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° (c = 0.26, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 61.64; H, 6.61; N, 3.84. IR ν_{max}^{KBr} cm^{-1}: 3400, 1740, 1710, 1655. MS m/z (%): 349 (M^+, 16), 305 ($M^+ - CO_2$, 4), 260 (6), 138 (42), 136 (46), 121 (44), 120 (81), 119 (100), 95 (54), 94 (26). ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, s, C_{18}–H), 1.85 (3H, d, J = 7.5 Hz, C_{21}–H), 2.45, 2.85 (2H, AB q, J = 15 Hz, C_{14}–H), 2.73 (2H, s, C_{19}–H), 4.09 (1H, br d, J = 12 Hz, C_9–Ha), 4.31 (1H, br s, C_8–H), 5.20 (1H, m, C_7–H), 5.35 (1H, d, J = 12 Hz, C_9–Hb), 5.97 (1H, q, J = 7.5 Hz, C_{20}–H), 6.22 (1H, br s, C_2–H). **3**: Colorless prisms, mp 221—222 °C (acetone), $[\alpha]_D^{26}$ −120° (c = 0.16, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{23}NO_6$; C, 61.88; H, 6.64; N, 4.01. Found: C, 62.09; H, 6.60; N, 3.93. IR ν_{max}^{KBr} cm^{-1}: 3400, 1738, 1720, 1655. MS m/z (%): 349 (M^+, 18), 305 ($M^+ - CO_2$, 3), 260 (6), 138 (32), 136 (39), 121 (38), 120 (72), 119 (100), 96 (62), 95 (50). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, s, C_{18}–H), 1.90 (3H, d, J = 7.5 Hz, C_{21}–H), 2.43, 2.78 (2H, AB q, J = 4 Hz, C_{19}–H), 4.15 (1H, br d, J = 11 Hz, C_9–Ha), 4.30 (1H, br s, C_8–H), 5.03 (1H, t, J = 3.5 Hz, C_7–H), 5.53 (1H, d, J = 11 Hz, C_9–Hb), 5.74 (1H, q, J = 7.5 Hz, C_{20}–H), 6.23 (1H, br s, C_2–H). **4**: Colorless prisms, mp 197.5—198 °C (acetone), $[\alpha]_D^{27}$ −19.4° (c = 0.15, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{23}NO_7$: C, 59.18; H, 6.33; N, 3.83. Found: C, 59.08; H, 6.41; N, 3.81. IR ν_{max}^{KBr} cm^{-1}: 3400, 1740, 1730, MS m/z (%): 365 (M^+, 17), 321 ($M^+ - CO_2$, 3), 304 (4), 234 (5), 222 (4), 138 (17), 136 (22), 121 (32), 120 (100), 119 (46), 95 (51). ^{1}H-NMR ($CDCl_3$)δ: 1.23 (3H, d, J = 6 Hz, C_{21}–H), 1.28 (3H, s, C_{18}–H), 1.82, 2.64 (2H, AB q, J = 16 Hz, C_{14}–H), 2.82, 3.07 (2H, AB q, J = 4 Hz, C_{19}–H), 2.95 (1H, q, J = 6 Hz, C_{20}–H), 4.12 (1H, br d, J = 12 Hz, C_9–Ha), 4.33 (1H, m, C_8–H), 5.28 (1H, m, C_7–H), 5.50 (1H, d, J = 12 Hz, C_9–Hb), 6.24 (1H, br s, C_2–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° (c = 0.17, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{23}NO_7$: C, 59.18; H, 6.33; N, 3.83. Found: C, 59.09; H, 6.23; N, 3.73. IR ν_{max}^{KBr} cm^{-1}: 3200, 1740, 1720. MS m/z (%): 365 (M^+, 19), 321 ($M^+ - CO_2$, 6), 288 (6), 260 (9), 149 (35), 138 (25), 136 (21), 121 (68), 120 (100), 119 (71), 95 (69), 94 (24), 93 (29). ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, s, C_{18}–H), 1.27 (3H, d, J = 5.5 Hz, C_{21}–H), 2.16, 2.32 (2H, AB q, J = 15 Hz, C_{14}–H), 2.86, 2.95 (2H, AB q, J = 4.5 Hz, C_{19}–H), 3.03 (1H, q, J = 5.5 Hz, C_{20}–H), 4.23 (1H, br d, J = 12 Hz, C_9–Ha), 4.28 (1H, br s, C_8–H), 5.22 (1H, d, J = 12 Hz, C_9–Hb), 5.23 (1H, m, C_7–H), 6.22 (1H, br s, C_2–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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