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Senepodine A, a novel $C_{22}N_2$ alkaloid from *Lycopodium chinense*

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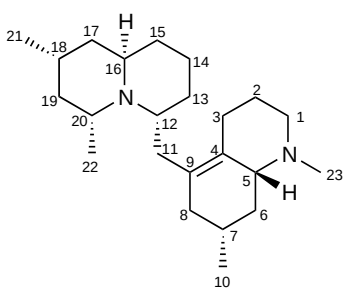
Abstract—A new class of $C_{22}N_2$ *Lycopodium* alkaloid consisting of an octahydroquinoline and a quinolizidine ring, senepodine A (**1**), has been isolated from the club moss *Lycopodium chinense*, and the structure including relative stereochemistry was elucidated on the basis of spectroscopic data.

A wide variety of *Lycopodium* alkaloids from many kinds of club moss have been reported so far.[1] These alkaloids with unique heterocyclic frameworks are classified into three groups, $C_{16}N$ (lycopodane skeleton), $C_{16}N_2$ (flabellidane, phlegmarane, and cernuane skeletons), and $C_{27}N_3$ (lucidine B) alkaloids,[1] and they have attracted great interest from synthetic,[2] biogenetic,[1,3] and biological[4] points of view. In our search for biogenetically interesting alkaloids from club moss, we previously isolated serratezomine A[5] with a *seco*-serratinine-type skeleton from *Lycopodium serratum* var. *serratum*, and complanadine A[6] with a lycodine dimeric skeleton from *L. complanatum*. Our recent investigation on extracts of *Lycopodium chinense* resulted in the isolation of a new class of $C_{22}N_2$ alkaloid, senepodine A (**1**). This paper describes the isolation and structure elucidation of **1**.

The club moss *L. chinense* collected in Hokkaido was extracted with MeOH, and the MeOH extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, after being adjusted at pH 10 with sat. Na_2CO_3, were partitioned with $CHCl_3$. $CHCl_3$-soluble materials were subjected to an amino silica gel column (Hex/EtOAc, 1:0→0:1), in which fractions eluted with Hex/EtOAc (3:2) were purified by a silica gel column ($CHCl_3$/MeOH, 4:1) to afford senepodine A (**1**, 0.003% yield) together with a known $C_{16}N_2$ alkaloid, cernuine (0.004%).[7]



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Senepodine A (**1**), colorless solid, $[\alpha]_D$ −33° (*c* 0.6, MeOH), was shown to have the molecular formula of $C_{23}H_{41}N_2$ by HRFABMS [*m*/*z* 345.3283, $(M+H)^+$, Δ +1.3 mmu]. The ^1H NMR spectrum of **1** in $CDCl_3$ showed broad signals, while the ^1H and ^{13}C NMR (Table 1) spectra in CD_3OD showed relatively well resolved signals and disclosed the existence of a tetra-substituted olefin, eleven sp^3 methylenes, six sp^3 methines, and four methyls. Among them, the signals due to four methines (δ_C 66.02; δ_H 2.63, δ_C 53.88; δ_H 3.48, δ_C 52.93; δ_H 3.46, δ_C 50.14; δ_H 3.44), one methylene (δ_C 58.22; δ_H 2.31 and 2.92), and one methyl (δ_C 43.29; δ_H 2.30) were ascribed to those bearing a nitrogen. Since one out of five unsaturations was accounted for, **1** was inferred to possess four rings. Interpretation of the 2D NMR data including the ^1H–^1H COSY, HOHAHA, HMQC, and HMBC spectra in CD_3OD (Fig. 1) revealed the presence of an octahydroquinoline moiety constructed by units **a** and **b**, a tetra-substituted olefin, and an N-CH_3, and a quinolizidine moiety consisting of unit **c** and a nitrogen atom.

In the octahydroquinoline moiety, the connectivity of units **a** (C-1 ~ C-3) and **b** (C-5 ~ C-8 and C-10) revealed by the ^1H–^1H COSY and HOHAHA spectra were analyzed by the HMBC spectrum. HMBC correlations from H_3-23 to C-1 (δ_C 58.22) and C-5 (δ_C 66.02), and H_a-1 to C-5 established the connection among C-1, C-5, and C-23 through a nitrogen. HMBC cross peaks of H_2-3 and H-5 to C-4 (δ_C 131.74), and H_2-8 to C-9 (δ_C

Keywords: *Lycopodium chinense*; $C_{22}N_2$ alkaloid; Lycopodiaceae.

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Table 1. ^{1}H and ^{13}C NMR data of senepodine A (**1**) in CD_3OD at 300 K

	δ_H	δ_C	HMBC (^{1}H)
1a	2.92 (1H, brd, 11.8)	58.22	2a, 3a, 23
1b	2.31 (1H, m)		
2a	1.54 (1H, m)	26.53	1a, 1b, 3a
2b	1.73 (1H, m)		
3a	2.86 (1H, brd, 13.6)	29.17	1a, 1b, 2b
3b	1.75 (1H, m)		
4		131.74	2b, 3a, 3b, 5, 6b, 11a, 11b
5	2.63 (1H, brt, 8.0)	66.02	1a, 3a, 6a, 6b, 23
6a	1.04 (1H, dt, 10.3, 12.5)	38.95	8b, 10
6b	2.09 (1H, m)		
7	1.58 (1H, brd, 14.0)	29.02	6a, 8b, 10
8a	1.79 (1H, m)	40.45	6a, 6b, 10, 11a, 11b
8b	1.92 (1H, brd, 16.1)		
9		130.91	3b, 8a, 8b, 11a, 11b
10	0.99 (3H, d, 6.6)	22.44	
11a	2.13 (1H, brd, 12.8)	35.37	12, 13b
11b	3.03 (1H, t, 12.2)		
12	3.48 (1H, m)	53.88	11a, 11b, 14b
13a	1.34 (1H, brd, 12.6)	19.24	11a, 11b, 14a, 15a
13b	1.70 (1H, m)		
14a	1.77 (1H, m)	20.07	12, 13b, 15a
14b	1.68 (1H, m)		
15a	1.28 (1H, brd, 17.9)	24.54	13a, 17a
15b	2.04 (1H, ddd, 4.1, 13.1, 13.1)		
16	3.46 (1H, m)	52.93	12, 14b, 15b, 17a
17a	1.47 (1H, dt, 4.9, 13.1)	39.88	19b, 21
17b	1.59 (1H, brd, 12.4)		
18	1.82 (1H, m)	26.10	17a, 17b, 19a, 19b, 21
19a	1.13 (1H, ddd, 12.5, 12.5, 12.5)	44.11	17b, 18, 21, 22
19b	1.72 (1H, m)		
20	3.44 (1H, m)	50.14	16, 19a, 22
21	0.90 (3H, d, 6.5)	22.44	19a
22	1.18 (3H, d, 6.1)	20.28	19a
23	2.30 (3H, s)	43.29	1a, 1b, 5

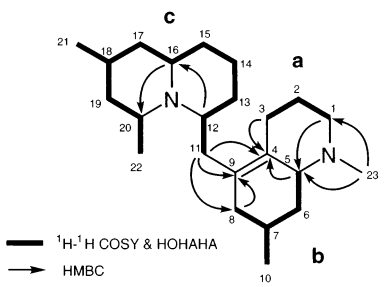


Figure 1. Selected 2D NMR correlations for senepodine A (**1**).

130.91) indicated the connection among units **a** and **b**, and the tetra-substituted olefinic carbons assigned to C-4 and C-9, constructing the octahydroquinoline ring (C-1∼C-9 and N) with a methyl group (C-10) at C-7. On the other hand, HMBC correlations from H-12 to C-16 (δ_C 52.93) and H-16 to C-20 (δ_C 50.14) in the unit **c** established the connection among C-12, C-16, and C-20 through a nitrogen atom, constructing the quinolizidine ring with two methyl groups (C-21 and C-22) at C-18 and C-20, respectively. The final carbon–carbon connectivity of the two heterocyclic rings through C-11 was elucidated by HMBC correlations of H_2-11 to C-4, C-8 (δ_C 40.45), and C-9. Thus, the gross structure of senepodine A was assigned as **1**.

The relative stereochemistry in **1** was deduced from NOESY data and proton–proton couplings. The H-5, H-7, H-12, H-18, and H-20 were assigned as all β-orientation and H-16 as α-orientation by NOESY cross-peaks as shown in Fig. 2. On the other hand, the

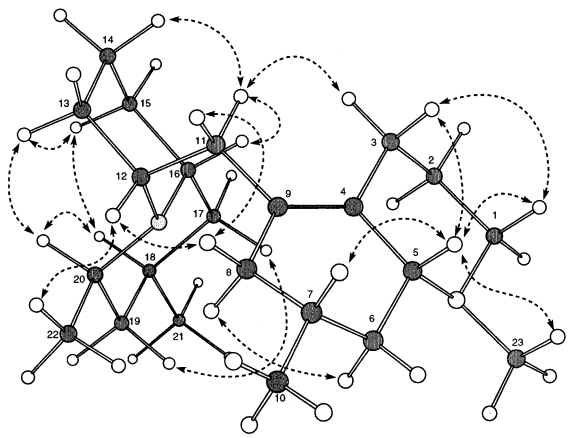
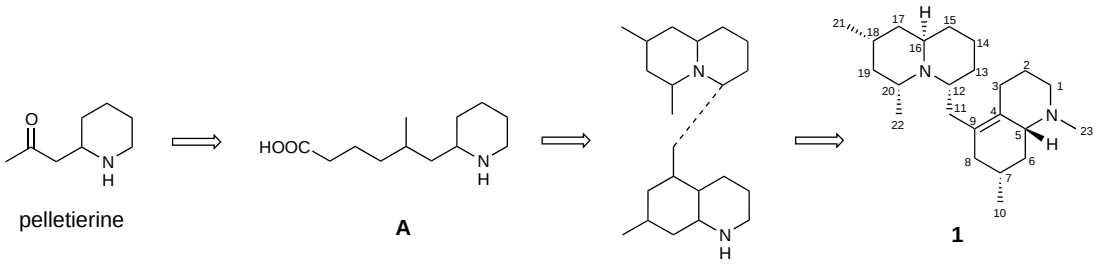


Figure 2. Selected NOESY correlations (dotted arrows) and relative configurations for senepodine A (**1**).



Scheme 1.

junction of the two piperidine rings with chair-forms in the quinolizidine ring was elucidated to be *cis* by NOESY correlations of H_b-13/H-20, H_b-13/H_b-15, H-18/H-20, and H_b-15/H-18. The large vicinal coupling constant (12.2 Hz) between H-12 and H_b-11, and NOESY correlations of H_b-11/H_a-3, H_a-11/H_b-8, and H_b-8/H-12 indicated that the two heterocyclic rings did not rotate around the C-9–C-11 and C-11–C-12 bonds. Thus the relative stereochemistry of **1** was assigned as shown in Fig. 2.

Senepodine A (**1**) is a new class of $C_{22}N_2$ *Lycopodium* alkaloid, consisting of an octahydroquinoline and a quinolizidine ring. A plausible biogenetic path for senepodine A (**1**) is proposed as shown in Scheme 1. Biogenetically, the octahydroquinoline and quinolizidine units in **1** may be both derived from an intermediate **A** with loss of a carbon.[1c,3] Senepodine A (**1**) exhibited cytotoxicity against murine lymphoma L1210 cells (IC_{50} 0.1 μg/mL), while it did not show such activity against human epidermoid carcinoma KB cells (IC_{50} >10 μg/mL) in vitro.

Acknowledgements

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