

ALKALOIDS FROM *CYNANCHUM HANCOCKIANUM* (MAXIM.) AL. ILJINSKI.
(ASCLEPIADACEAE)

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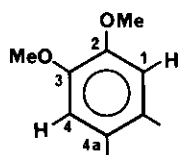
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Abstract — Two alkaloids have been isolated from *Cynanchum hancockianum* (Maxim.) Al. Iljinski. (Asclepiadaceae) grown in the Inner Mongolia. These alkaloids are identified to be antofine and de-6-O-methylantofine by a combination of high-resolution (^1H , 400 MHz; ^{13}C , 100.6 MHz) nmr and chiroptical (ord and cd) spectroscopy.

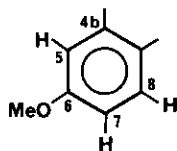
In the course of our studies on natural products containing antitumor activity, alkaloids A and B were isolated from *Cynanchum hancockianum* (Maxim.) Al. Iljinski. (Asclepiadaceae) grown in the Inner Mongolia. The physico-chemical and spectral properties of these alkaloids were similar to those of phenanthro-indolizidine alkaloids, antofine (1) and de-6-O-methylantofine (2), isolated from *C. vincetoxicum* L. (Asclepiadaceae)¹ and *Ficus septica* (Moreceae).² However, it was found that there are enormous discrepancies in the specific rotations and ord spectra (*vide infra*). Because of the shortage of authentic samples, the structure elucidation of these alkaloids based on the direct comparison could not be achieved. We now attempt to identify their structures to be 1 and 2 by a combination of high-resolution (^1H , 400 MHz; ^{13}C , 100.6 MHz) nmr and chiroptical (ord and cd) spectroscopy.

Nmr Spectroscopy

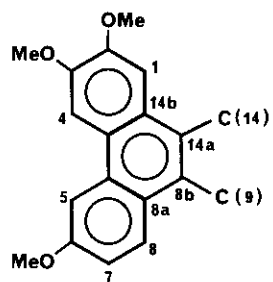
The 1D nmr spectra of alkaloids A and B showed the number of hydrogens and carbons corresponding to their molecular formulas. The number of hydrogens attached to each individual carbon was determined by DEPT experiments. Each proton and carbon belonging to protonated carbons were straightly associated



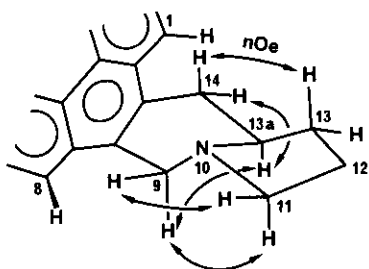
I



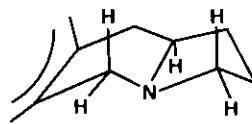
II



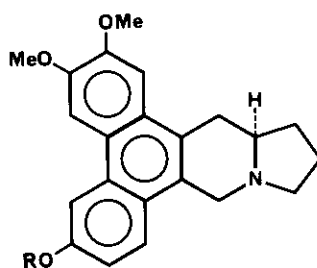
III



1a



1b



1: R = Me

2: R = H

Scheme 1

with each other by the $^1\text{H}-^{13}\text{C}$ (one-bond) COSY spectra. The assignments of protons and carbons were unambiguously made by the $^1\text{H}-^1\text{H}$ and $^1\text{H}-^{13}\text{C}$ (long-range) COSY spectra. The gross structures were determined by 2D nmr spectroscopy, and the relative stereochemistry was established by $^1\text{H}-^1\text{H}$ nOe difference spectroscopy.

Alkaloid A

Alkaloid A, $\text{C}_{23}\text{H}_{25}\text{NO}_3$, was obtained as colorless crystals of mp 210–212°C (mp 212–214°C for 1),^{1,2} $[\alpha]_{\text{D}} -86.0^\circ$ (CHCl_3) ($[\alpha]_{\text{D}} -165\pm 3^\circ$ (CHCl_3),¹ $[\alpha]_{\text{D}} -32.0^\circ$ (CHCl_3)² for 1). DEPT experiments and the examinations of the proton and carbon resonances provided three aromatic (vinylic) O-methyls, five methylenes, one aliphatic and five aromatic (vinylic) methines, nine aromatic (vinylic) quaternary carbons and no hydrogen attached to hetero atoms (no proton exchangeable with D_2O). The assignments of protons and carbons and the spectral parameters are shown in Table 1. The nOe data are given in Table 2.

The $^1\text{H}-^{13}\text{C}$ (long-range) COSY spectrum associated 2-OMe and 3-OMe with C-2(s) and C-3(s), respectively, which were correlated to 4-H(s) and 1-H(s), respectively, as shown in Figure 1. (The numbering refers to that of 1 in order to avoid confusion). NOe experiments revealed the interactions between 1-H and 2-OMe and between 3-OMe and 4-H. These observations suggest the presence of the fragment I in the molecule as shown in Scheme 1. The correlations of C-6(s) to 6-OMe and 8-H(s) ($^1\text{H}-^{13}\text{C}$) and the observations of nOes at 5-H(d) and 7-H(dd) on irradiation of 6-OMe lead to the fragment II. Since C-4a(s) and C-4b(s) were related to 5-H (1-H) and 4-H (8-H) ($^1\text{H}-^{13}\text{C}$), respectively, I and II are bonded between C (4a) and C(4b). The following correlations were observed in the $^1\text{H}-^{13}\text{C}$ (long-range) COSY spectrum: C-8a(s)—9-H(δ 4.668) (5-H, 7-H); C-8b(s)—14-H₂, 8-H; C-14a(s)—9-H₂, 1-H; C-14b(s)—14-H(δ 3.310) (4-H). These findings lead to the fragment III which is supported by nOes observed between 1-H and 14-H₂ and between 8-H and 9-H. The $^1\text{H}-^1\text{H}$ COSY spectrum and examinations of the proton splitting patterns indicated *ortho*-interbenzylic couplings³ between 9-H₂ and 14-H₂, vicinal couplings between 13a-H(m) and 14-H and no vicinal coupling for 9-H₂ (i.e. neighboring atom, N). The $^1\text{H}-^{13}\text{C}$ (long-range) COSY spectrum correlated C-9(t) and C-13a(d) to 13a-H and 9-H(δ 4.668), respectively. These facts lead to a piperidine moiety. Bridging between N(10) and C(13a) with the remaining three methylenes constructs the gross structure, 2,3,6-trimethoxy-9,11,12,13,13a,14-hexahydrodibenzo[*f,h*]pyrrolo[1,2-*b*]isoquinoline, for alkaloid A.

Table 1. Nmr data for alkaloid A^a.

No	Carbon		Correlated proton ^b		¹ H- ¹ H ^c
	δ_c		One-bond ^d	Long-range	
1	103.895	t	1-H 7.287 s		
2	149.302	s		1-H, 4-H, 2-OMe	
3	148.248	s		1-H, 4-H, 3-OMe	
4	103.720	d	4-H 7.892 s		
4a	123.448	s		1-H, 4-H, 5-H	
4b	130.094	s		4-H, 5-H, 8-H	
5	104.582	d	5-H 7.882 d (2.3)	7-H	7-H, 8-H
6	157.391	s		8-H, 6-OMe	
7	114.798	d	7-H 7.192 dd (9.0, 2.3)	5-H	5-H, 8-H
8	124.217	d	8-H 7.797 d (9.0)	7-H	5-H, 7-H
8a	124.064	s		5-H, 7-H, 8-H, 9 β -H	
8b	126.603	s		8-H, 9 α, β -H ₂ , 14 α, β -H ₂	
9	53.803	t	9 α -H 3.662 dt (14.5, 1.5) 9 β -H 4.668 d (14.5)	13 α -H	9 β -H, 11 α -H, 13 α -H, 14 α, β -H ₂ 9 α -H, 14 β -H
11	55.040	t	11 α -H 2.429 q (9.0) 11 β -H 3.450 dt (2.0, 9.0)	9 α -H, 12-H _B , 13 α -H	9 α -H, 11 β -H, 12-H _{A, B} 11 α -H, 12-H _{A, B}
12	21.550	t	12-H _A 1.920 m 12-H _B 2.016 m	13 β -H	11 α, β -H ₂ , 12-H _B 13 α, β -H ₂ 11 α, β -H ₂ , 12-H _A 13 α, β -H ₂
13	31.244	t	13 α -H 2.223 m 13 β -H 1.758 m	11 β -H, 14 β -H	12-H _{A, B} , 13 β -H, 13 α -H 12-H _{A, B} , 13 α -H, 13 α -H
13a	60.160	d	13 α -H 2.458 m	9 β -H, 11 β -H	9 α -H, 13 α, β -H ₂ , 14 α, β -H ₂

Table 1. (Continued)

No	Carbon		Correlated proton ^b		¹ H- ¹ H ^c
	δ_c		One-bond ^d	Long-range	
14	33.662	t	14 α -H 3.310 ddd (15.1, 3.5, 1.5) 14 β -H 2.878 ddt (15.1, 10.5, 1.5)		9 α -H, 13a-H, 14 β -H 9 α, β -H ₂ , 13a-H, 14 α -H
14a	125.494	s		1-H, 9 α, β -H ₂ , 14 α, β -H ₂	
14b	127.018	s		4-H, 14 α -H	
2-OMe	55.823	q	2-OMe 4.054 s		
3-OMe	55.948	q	3-OMe 4.100 s		
6-OMe	55.467	q	6-OMe 4.008 s		

a) The spectra were taken on a Varian XL-400 (¹H, 400 MHz; ¹³C, 100.6 MHz) in CDCl₃; ppm. b) These data were obtained by ¹H-¹³C COSY experiments. c) These data were obtained by ¹H-¹H COSY experiments. d) Figures in parentheses are coupling constants (Hz): $J_{5,7} = 2.3$, $J_{7,8} = 9.0$, $J_{9\alpha, \beta} = 14.5$, $J_{9\alpha, 14\alpha} = 1.5$, $J_{9\alpha, 14\beta} = 1.5$, $J_{11\alpha, \beta} = 9.0$, $J_{11\alpha, 12} = 9.0$, $J_{11\beta, 12} = 9.0$, $J_{13a, 14\alpha} = 3.5$, $J_{13a, 14\beta} = 10.5$, $J_{14\alpha, \beta} = 15.1$.

Table 2. NOe data for alkaloid A (CDCl₃).

Irradiated Proton	Observed Proton (nOe %)
1-H	14 α -H(7.4), 14 β -H(2.2), 2-OMe(2.8)
4-H	3-OMe(1.8)
5-H	6-OMe(1.8)
7-H	8-H(6.1), 6-OMe(1.8)
8-H	7-H(9.5), 9 α -H(1.7), 9 β -H(6.9)
9 α -H	8-H(2.6), 9 β -H(14.0), 11 α -H, 13a-H(3.0)
9 β -H	8-H(8.8), 9 α -H(11.0), 11 β -H(2.2)
14 α -H	1-H(7.1), 13a-H(2.7), 14 β -H(12.0)
14 β -H	1-H(2.4), 13 β -H(2.8), 14 α -H(10.3)
2-OMe	1-H(9.5)
3-OMe	4-H(4.2)
6-OMe	5-H(1.7), 7-H(3.1)

Table 3. Nmr data for alkaloid B^a.

No	Carbon		Correlated proton ^b		¹ H- ¹ H ^c
	δ_c		One-bond ^d	Long-range	
1	104.218	d	1-H 7.308 s		
2	149.185	s		1-H, 4-H, 2-OMe	
3	148.193	s		1-H, 4-H, 3-OMe	
4	104.074	d	4-H 7.922 s		
4a	122.803	s		1-H, 4-H, 5-H	
4b	130.082	s		4-H, 5-H, 8-H	
5	106.551	d	5-H 7.947 d (2.5)		7-H, 8-H
6	155.429	s		8-H	
7	116.405	d	7-H 7.087 dd (8.7, 2.5)		5-H, 8-H
8	124.218	d	8-H 7.732 d (8.7)		5-H, 7-H
8a	122.460	s		5-H, 7-H	
8b	126.585	s		9 α , β -H ₂	
9	53.444	t	9 α -H 3.508 d (15.0) 9 β -H 4.553 d (15.0)		9 β -H, 14 α -H 9 α -H, 11 β -H, 14 α -H
11	54.575	t	11 α -H 2.310 q (8.5) 11 β -H 3.300 m		11 β -H, 12-H ₂ 9 β -H, 11 α -H, 12-H ₂
12	21.286	t	12-H ₂ 1.838 m		11 α , β -H ₂ , 13 α , β -H ₂
13	31.017	t	13 α -H 2.152 m 13 β -H 1.646 m		12-H ₂ , 13 β -H, 13 α -H 12-H ₂ , 13 α -H
13a	60.015	d	13a-H 2.367 m		13 α -H, 14 α , β -H ₂

Table 3. (Continued)

No	Carbon		Correlated proton ^b		¹ H- ¹ H ^c
	δ_c		One-bond ^d	Long-range	
14	33.107	t	14 α -H 3.320 m 14 β -H 2.736 dd (15.0, 11.0)		9 β -H, 13a-H, 14 β -H 9 α -H, 13a-H, 14 α -H
14a	124.590	s		1-H, 9 β -H, 14 α , β -H ₂	
14b	126.344	s		4-H	
2-OMe	55.473	q	2-OMe 3.935 s		
3-OMe	55.594	q	3-OMe 3.993 s 6-OH 9.680 s		

a) The spectra were taken on a Varian XL-400 (¹H, 400 MHz; ¹³C, 100.6 MHz) in DMSO-*d*₆; ppm. b) These data were obtained by ¹H-¹³C COSY experiments. c) These data were obtained by ¹H-¹H COSY experiments. d) Figures in parentheses are coupling constants (Hz): $J_{5,7}=2.5$, $J_{7,8}=8.7$, $J_{9\alpha,\beta}=15.0$, $J_{11\alpha,\beta}=8.5$, $J_{11\alpha,12}=8.5$, $J_{13a,14\beta}=11.0$, $J_{14\alpha,\beta}=15.0$.

Table 4. NOe data for alkaloid B (DMSO-*d*₆).

Irradiated Proton	Observed Proton (nOe %)
9 α -H	8-H(2.4), 9 β -H(8.7), 11 α -H, 13a-H(1.7)
9 β -H	8-H(4.8), 9 α -H(7.7), 11 β -H(3.3)
11 β -H	11 α -H(13.6), 12-H ₂ (1.6)
14 α -H	1-H(4.2), 13a-H(2.2), 14 β -H(8.4)
14 β -H	1-H(2.2), 13 β -H(2.2), 14 α -H(7.3)
2-OMe	1-H(2.7)
3-OMe	4-H(4.0)

The ir spectrum showed Bohlmann bands in the 2800-2700 cm^{-1} region. The appearances of the bands for nitrogen bridgehead compounds are due to two axial C-H bonds α to the nitrogen lone pair.⁴ The possible configurations and ring conformations are given in the Dreiding model drawings 1a and 1b depicted on the basis of 13a α -H. NOes observed between 9-H(δ 3.662) and 13a α -H and between 9-H(δ 3.662) and 11-H(δ 2.429) suggest that the indolizidine moiety exists in 1a and three hydrogens in question are α (axial) with respect to related rings, and that 1b is ruled out. Thus, alkaloid A contains the *trans*-indolizidine moiety, in which the piperidine moiety adopts a half-chair form and the pyrrolidine moiety a puckered form with N(10) out of the ring.

The examinations of 1a indicated that 9 β (eq)-H and 14 α (eq)-H are in the vicinity of 8-H and 1-H, respectively, and that NOes to be observed on them are larger than that on each geminal counterpart. Thus, the orientations of 9-H₂ and 14-H₂ were confirmed by the observed NOes. NOe experiments determined the orientations of the remaining ring hydrogens on the basis of those of 9-H₂, 13a-H and 14-H₂. The interacting patterns observed are in accord with 1a (Scheme 1).

Alkaloid B

Alkaloid B, C₂₂H₂₃NO₃, was obtained as colorless crystals of mp 225-227°C (mp 226-228°C for 2),¹ $[\alpha]_D -51.5^\circ$ (pyridine) ($[\alpha]_D -125\pm 6^\circ$ (pyridine) for 2).¹ The 2D nmr and NOe data observed for alkaloid B are given in Tables 3 and 4, respectively. The comparisons of the nmr data and molecular formulas observed for alkaloids A and B provided the lack of one methyl in alkaloid B. Actually, the treatment of alkaloid B with CH₂N₂ gave alkaloid A. The assignments of 2-OMe, 3-OMe and 6-OH were made in the same manner as employed for alkaloid A. The gross structure and relative stereochemistry of alkaloid B were determined to be the same as those of alkaloid A by nmr spectroscopy.

Ord and Cd Spectroscopy

It has been rationalized that the ord and cd spectra of phenanthroindolizidine alkaloids with no other chiral center show the characteristic Cotton effects in the 240-260 nm region (positive for 13aR and negative for 13aS).⁵ Positive Cotton effects were observed in the ord ($[\phi]_{251.5} +6852$) and cd ($[\theta]_{242} +4283$) spectra of alkaloid A as shown in Figures 2 and 3, respectively, leading to the 13aR-configuration for alkaloid A. The 13aR-configuration of 1 had been previ-

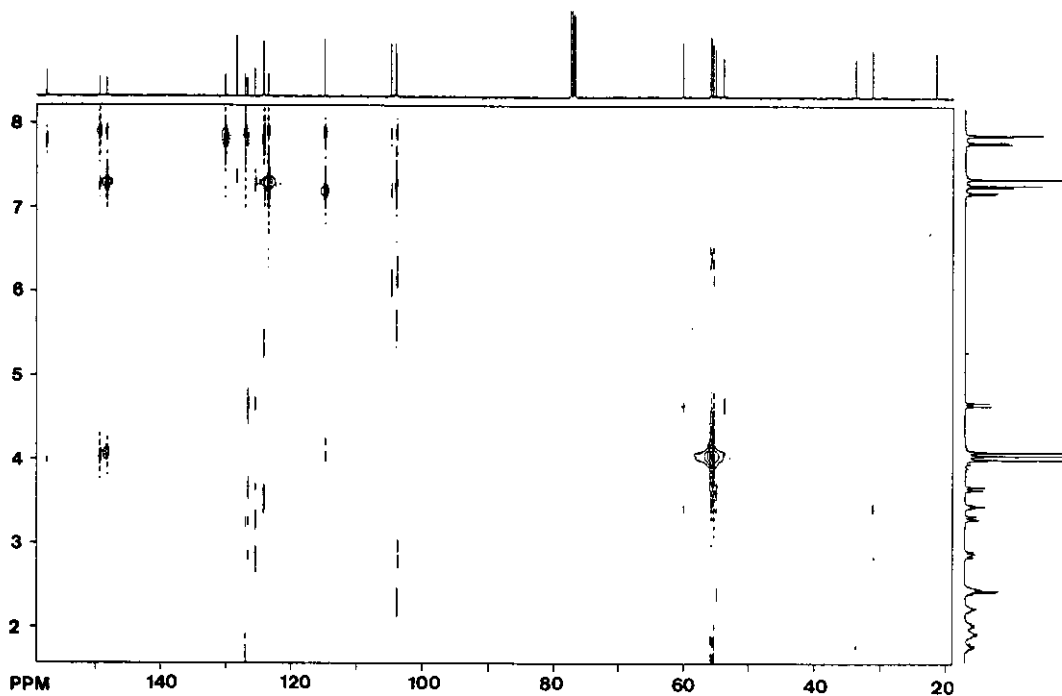


Figure 1. $^1\text{H} - ^{13}\text{C}$ (long-range) COSY spectrum of alkaloid A.

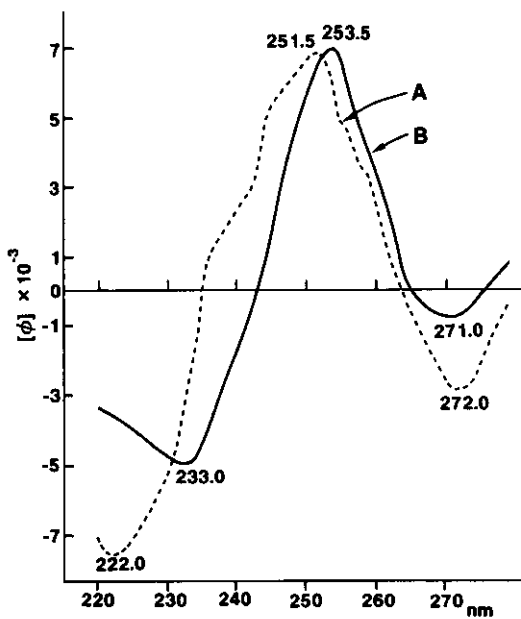


Figure 2. Ord spectra of alkaloids A and B (0.01N HCl).

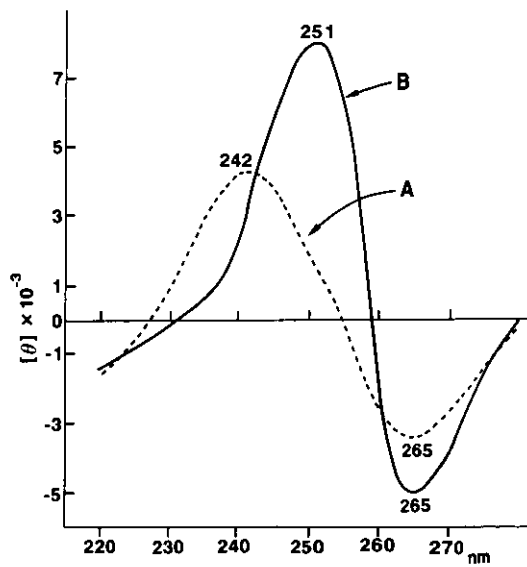


Figure 3. Cd spectra of alkaloids A and B (0.01N HCl).

ously elucidated on the basis of the ozonolysis to yield D-proline.⁶ Thus, alkaloid A has been identified to be antofine (1).

It is additionally remarked that a published ord spectrum of 1 showed a positive Cotton effect shifted upper by ca. 15 nm than that observed for alkaloid A and no Cotton effect in the 240-260 nm region, despite the same solvent was employed.⁷

The ord and cd spectra of alkaloid B also showed positive Cotton effects in the 240-260 nm region ($[\phi]_{253.5} +6980$ and $[\theta]_{251} +7977$), suggesting alkaloid B to be *de-6-O-methylantofine* (2) with the 13*aR*-configuration.

EXPERIMENTAL

Melting points (uncorrected) were determined on a micro hot-stage apparatus. Specific rotations were taken on a JASCO DPI-181 polarimeter. Spectra were recorded on the following spectrometers: uv, Hitachi EPS-2U; cd, JASCO J-20; ord, JASCO J-20C; ir, Hitachi 260-30; ¹H nmr, XL-400 at 400 MHz; ¹³C nmr, Varian XL-400 at 100.6 MHz; ms, JEOL JMS DX-300; elemental analysis, Perkin-Elmer 240B. All nmr spectra were taken at a probe temperature, 18°, using a 5 mm tube.

The 2D nmr spectra of alkaloids A and B were run under the following conditions. The conditions for alkaloid B are given in parentheses.

¹H-¹H COSY: ¹H single probe; relaxation delay 1 sec; 90° (¹H)=14.3 μ s; 90° mixing pulse; F₁=F₂=2587 (2741) Hz; data matrix 1024×128; 16 scans during 128 time increments (zero filling in F₁); 2 dummy scans; spectra were symmetrized about diagonal axis using FOLDT command after 2D transformation.

¹H-¹³C COSY: ¹³C, 30~105 MHz probe; relaxation delay 1 sec; 1 dummy scan; 90° ¹H and ¹³C pulses were calibrated at 14.3 and 9.6 μ s, respectively. One-bond correlation: F₁=2658 (3358) Hz, F₂=14534 (17421) Hz; data matrix: 2048×256; 32 (128) scans during 48 time increments; aquisition time, 0.070 (0.059) sec; ¹J_{CH} (average), 140 Hz; size of final data points, 2K. Long-range correlation: F₁=2658 (3358) Hz, F₂=14534 (17421) Hz; data matrix: 2048×256; 640 (2048) scans during 64 time increments (zero filling in F₁); aquisition time, 0.070 (0.059) sec; ^{LR}J_{CH} (average) 7.0 Hz; size of final points 2K.

The nOe spectra were recorded by means of nOe difference spectroscopy. The preirradiation time of each resonance was 2 sec. The interpulse delay was zero sec. The irradiation data sets were interleaved to cancel drift and changing magnet homogeneity. These spectra were transformed by the difference

between two free induction decays.

The DEPT spectra were taken with $\theta = 90^\circ$ and 142° .

Extraction and Isolation

The aerial parts of *Cynanchum hancockianum* (Maxim.) Al. Iljinski. (Asclepiadaceae) were collected in the Inner Mongolia. The air-dried plant material (12 kg) was percolated with 1% HCl (90 l) at 30°C for 12 h. The percolate was adjusted with conc. NH_4OH to pH 9-10, and extracted with CHCl_3 to yield a dark brown oil (40 g) which was chromatographed over silica gel (600 g) eluting successively with CHCl_3 , $\text{CHCl}_3/\text{Et}_2\text{O}$ (1:1), $\text{CHCl}_3/\text{Me}_2\text{CO}$ (25:1 \rightarrow 10:1) and $\text{CHCl}_3/\text{MeOH}$ (25:1 \rightarrow 10:1). Elution with $\text{CHCl}_3/\text{MeOH}$ (25:1) afforded a pale solid which was rechromatographed over neutral Al_2O_3 (400 g). Elution with CH_2Cl_2 gave alkaloid A (400 mg) as colorless needles of mp $210\text{--}212^\circ\text{C}$ (decomp) (from $\text{CH}_2\text{Cl}_2/\text{MeOH}$), $[\alpha]_{\text{D}}^{26} -86.0^\circ$ ($c=1.47$, CHCl_3), R_f 0.72 (silica gel; $\text{CHCl}_3/\text{MeOH}$, 9:1). Elution with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (25:1) afforded alkaloid B (20 mg) as colorless needles of mp $225\text{--}227^\circ\text{C}$ (decomp) (from $\text{C}_6\text{H}_6/\text{CHCl}_3$), $[\alpha]_{\text{D}}^{26} -51.5^\circ$ ($c=0.47$, pyridine), R_f 0.46 (silica gel; $\text{CHCl}_3/\text{MeOH}$, 9:1).

Spectral Properties of Alkaloid A

Uv λ_{max} (0.01N HCl) ($\log \epsilon$): 310 (3.57), 283 (4.17), 258 (4.42), 240 (4.19), 225 (4.05). Cd ($c=2.12 \times 10^{-5}$, 0.01N HCl) $[\theta]^{25}$ (nm): 0 (330), -1542 (295) (negative maximum), 0 (283) (positive maximum), -3427 (265) (negative maximum), 0 (254), +4283 (240) (positive maximum), 0 (228). Ord (2.12×10^{-5} , 0.01N HCl) $[\phi]^{25}$ (nm): 0 (286), +343 (284) (peak), 0 (281), -2912 (272) (trough), 0 (264), +6852 (252) (peak), 0 (235), -7537 (222) (trough), -5139 (212) (peak). Ir ν_{max} (KBr) cm^{-1} : 2825, 2780, 2730 (Bohmann bands). Ms m/z : $[\text{M}]^+$, 363.1833 (363.1834 for $\text{C}_{23}\text{H}_{25}\text{NO}_3$). Anal. calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_3$: C, 76.01; H, 6.93; N, 3.85. Found: C, 76.29; H, 7.05; N, 3.49. For ^1H and ^{13}C nmr, see Table 1.

Spectral Properties of Alkaloid B

Uv λ_{max} (0.01N HCl) ($\log \epsilon$): 310 (3.28), 283 (3.80), 257 (4.11), 240 (3.89), 225 (3.77). Cd ($c=3.50 \times 10^{-5}$, 0.01N HCl) $[\theta]^{25}$ (nm): 0 (340), -2792 (297) (negative maximum), 0 (282) (positive maximum), -4985 (265) (negative maximum), 0 (259), +7977 (251) (positive maximum), 0 (231). Ord ($c=3.50 \times 10^{-5}$, 0.01N HCl) $[\phi]^{25}$ (nm) 0 (292), +1396 (282) (peak), 0 (276), -798 (271) (trough), 0 (265), +6980

(254) (peak), 0 (243), -4985 (233) (trough), -3589 (218) (peak). Ir ν_{\max} (KBr) cm^{-1} : 3425 (OH), 2800, 2705 (Bohlmann bands). Ms m/z : $[M]^+$, 349.1657 (349.1677 for $\text{C}_{22}\text{H}_{23}\text{NO}_3$). For ^1H and ^{13}C nmr, see Table 3.

Methylation of Alkaloid B to Alkaloid A

A solution of alkaloid B (2.7 mg) in MeOH (1 ml) was treated with a saturated solution of CH_2N_2 in Et_2O (0.5 ml) at room temperature for 15 min. Work-up of the reaction mixture, followed by preparative tlc (silica gel; $\text{CHCl}_3/\text{MeOH}$, 5:1) of the product, furnished alkaloid A (1.7 mg) as colorless needles of mp 208-210°C (decomp) (from EtOH), $[\alpha]_{\text{D}}^{26} -82.9^\circ$ ($c=0.07$, CHCl_3), R_f 0.72 (silica gel; $\text{CHCl}_3/\text{MeOH}$, 9:1). Ir ν_{\max} (KBr) cm^{-1} : 2825, 2780, 2730 (Bohlmann bands). Ms m/z : $[M]^+$, 363.1818 (363.1833 for $\text{C}_{23}\text{H}_{25}\text{NO}_3$).

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