Chem. Pharm. Bull. 39(5) 1340—1342 (1991) Vol. 39, No. 5

AILANTHOIDINE, A NOVEL BENZO[C]PHENANTHRIDINE ALKALOID WITH A CYANOPYRIDINE PENDANT, FROM A XANTHOXYLUM SPECIES

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The structure of ailanthoidine isolated from the bark of *Xanthoxylum ailanthoides* Sieb. et Zucc. has been deduced as **1** on the basis of its spectral data including 2-D NMR spectroscopy and an X-ray analysis of **7B**.

KEYWORDS *Xanthoxylum ailanthoides*; benzo[c]phenanthridine; alkaloid; 2-D NMR; COLOC; X-ray analysis

In a previous paper,1) we reported the isolation of a new alkaloid, ailanthoidine, along with many known components from the bark of *Xanthoxylum ailanthoides* Sieb. et Zucc.. Here we describe the structure elucidation of the new alkaloid (**1**).

Ailanthoidine (**1**), mp 260-263°C, $[\alpha]_D$ =0, shows a blue fluorescence on TLC and turns yellow on prolonged exposure to air or light, indicating that it is a dihydrobenzo[c]phenanthridine alkaloid.2) Its IR spectrum shows a cyano group at 2235 cm^{-1}. Its ^{1}H-NMR spectrum shows signals2-4) characteristic of dihydrobenzo[c]phenanthridine with a substituent at C_6 (Table I), although C_4-H is shifted upfield by 1.11 ppm in comparison with dihydrochelerythrine (**2**) because of shielding by the C_6-substituent (*vide infra*).

An NOE analysis (Fig.1) confirmed the assignment. The EIMS of **1** showed a small molecular ion peak at *m/z* 479 corresponding to $C_{29}H_{25}N_3O_4$ and showed a diagnostic ion peak fragment at *m/z* 348 (M^+-131) due to the loss of the C_6-substituent ($C_8H_7N_2$, *m/z* 131) from the molecular ion. The ^{1}H-NMR spectrum also showed five additional signals due to the C_6-substituent group (Table I). Decoupling experiments showed that the signal at δ 2.68 was coupled with C_6-H (δ 4.75) and a methyl group (δ 1.22), suggesting that the substituent group on C_6 has a secondary methyl moiety. Moreover, the coupling pattern (ABX system) of three aromatic protons indicates the presence of a 2,4-disubstituted pyridine ring containing a cyano group in the C_6-substituent. NOE enhancement occurred between C_α-H and $C_{3'}$-H (12.8%) but not between C_α-H and $C_{5'}$-H. This shows that a plane structure of ailanthoidine can be represented by formula **1**, as an NOE would exist between C_α-H and both $C_{3'}$-H and $C_{5'}$-H if ailanthoidine (**1**) had a 2-cyanopyridine moiety. To obtain additional support for the structure (**1**) of ailanthoidine, the ^{13}C-NMR spectra of **1**, **2**, 4-cyano-2-ethylpyridine (**3**),5) and 2-cyano-4-ethylpyridine (**4**)7) were measured. The ^{13}C-NMR spectrum data are given in Tables II and III. Methyl, methylene, and methine carbons of **1** and **2** were assigned using ^{1}H-^{13}C COSY, and quarternary carbons were assigned by COLOC except the 2' and 4' carbons (δ 119.4 and 166.7) in the pyridine ring.(Fig 2). Table III shows that the chemical shifts of the carbons in the C_6-substituent of **1** are very similar to those of **3** (not **4**). This allowed us to assign these two unidentified carbons, as shown in Table III and indicates that the plane structure of ailanthoidine can be represented by formula **1** having a 4-cyanopyridine moiety. To determine the stereochemistry, we subjected **1** to X-ray analysis, but it did not provide crystals suitable for the structural determination.

In a synthesis study on ailanthoidine (**1**), treatment of chelerythrine chloride (**6**) with carbanion prepared from 4-ethylpyridine and LDA9) in HMPA-THF afforded two diastereomeric adducts, A (**7A**), mp 217-219°C, and B (**7B**), mp 178-180°C, in 19 and 11% yields, respectively.10) As shown in Table I, the signals due to C_4-H (δ 6.95) in **7A** and to C_7-OCH_3 (δ 3.50) in **7B** are shifted upfield by 0.72 and 0.38 ppm, respectively, in comparison with the corresponding signals in **2**. These observations could be reasonably explained by anisotropy due to a newly introduced pyridine ring.

Since C_4-H of ailanthoidine (**1**) also was shifted upfield, the findings definitely indicate that **7A** has the same stereochemical relationship as **1** with respect to C_6 and C_α, although the position of the substituent group(s) on the pyridine ring was different. Unfortunately, a natural type of **7A** did not provide crystals suitable for X-ray analysis, so an artificial type of **7B** was analyzed by X-ray.[11] The molecular structure of **7B** is shown in Fig. 3, so the stereostructure of adduct A can be represented by formula **7A**. Consequently, we propose formula **1** as the stereostructure of ailanthoidine.[13]

Table I. ^{1}H-NMR Data for Ailanthoidine (**1**), Dihydrochelerythrine (**2**), Adduct A (**7A**), and Adduct B (**7B**)$^{a)}$

	1$^{b)}$	**2**	**7A**$^{b)}$	**7B**$^{b)}$
NMe	2.39 s	2.60 s	2.45 s	2.62 s
C_7-OMe	3.99 s	3.88 s	3.99 s	3.50 s
C_8-OMe	3.97 s	3.93 s	3.96 s	3.80 s
OCH_2O	6.05, 6.06 d (1.4)	6.04 s	5.99, 6.04 d (1.3)	6.06, 6.08 d (1.3)
1-H	7.11 s	7.11 s	7.08 s	7.13 s
4-H	6.56 s	7.67 s	6.95 s	7.68 s
6-H	4.75 d (10.5)	4.29 s	4.52 d (10.7)	4.43 d (8.2)
9-H	7.02 d (8.5)	6.94 d (8.5)	7.00 d (8.4)	6.91 d (8.6)
10-H	7.57 d (8.5)	7.51 d (8.5)	7.54 d (8.4)	7.50 d (8.6)
11-H	7.74 d (8.5)	7.70 d (8.5)	7.68 d (8.6)	7.74 d (8.6)
12-H	7.49 d (8.5)	7.47 d (8.5)	7.45 d (8.6)	7.48 d (8.4)
CMe	1.22 d (6.9)	---	1.12 d (7.2)	1.21 d (7.1)
C_α-H	2.68 dq (10.5, 6.9)	---	2.56 dq (10.7, 7.2)	2.71 dq (8.2, 7.1)
3'-H	6.41 br s	---	---	---
5'-H	7.31 dd (5.0, 1.4)	---	6.82 d (5.9)$^{c)}$	6.89 d (5.9)$^{c)}$
6'-H	8.79 dd (5.0, 0.6)	---	8.36 d (5.9)$^{d)}$	8.35 d (5.9)$^{d)}$

a) Chemical shifts are given in δ (ppm) and the values in parentheses are coupling constants in Hz.
b) Assignments were made with the aid of NOE analysis. c) Including 3'-H. d) Including 2'-H.

Table II. ^{13}C-NMR Data for the Skeletal Carbons in **1** and **2**

	1	**2**
NMe	41.8	41.3
OMe	55.8, 61.0	55.8, 61.1
OCH_2O	101.1	101.0
1	104.4	104.3
2	148.0	148.1
3	147.6	147.5
4	100.2	100.7
4a	130.9	130.8
4b	139.3	142.7
6	62.6	48.7
6a	124.0	124.2
7	147.0	146.1
8	152.1	152.3
9	111.5	111.0
10	119.3	118.7
10a	127.3	126.4
10b	124.9	126.3
11	119.8	120.1
12	123.8	123.8
12a	126.7	126.3

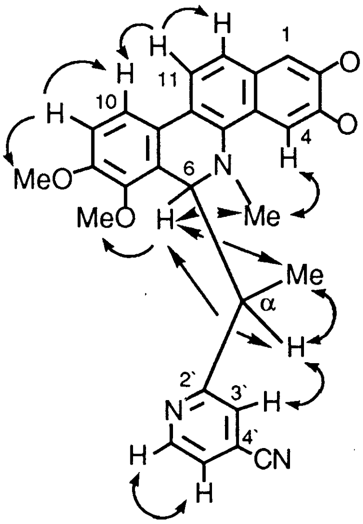


Fig. 1. NOEs Observed in **1**

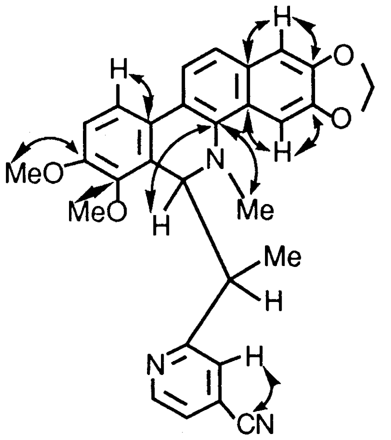
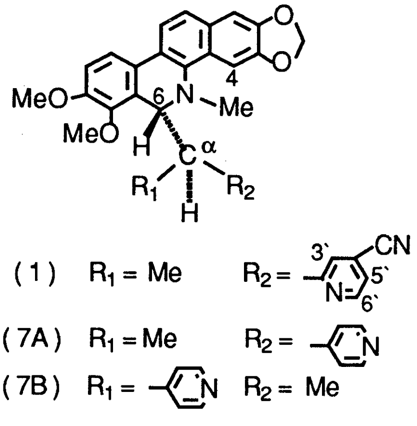
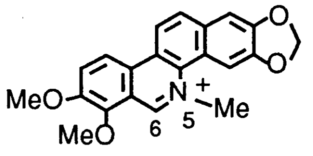


Fig. 2. Long - Range Coupling Observed in COLOC Experiment of **1**

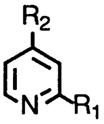
Table III. ^{13}C-NMR Data for the C_6 Side Chain of **1**, **3**, and **4**

	1	**3**	**4**
CMe	16.9	13.4	14.0
C_α or CH_2	44.9	31.3	28.0
CN	116.8	116.8	117.5
2'	166.7	165.1	133.8
3'	126.0	123.8	128.3
4'	119.4	120.6	154.7
5'	122.1	122.4	126.7
6'	149.9	150.2	150.9





(2) 5,6-dihydro
(6)



(3) R_1=Et R_2=CN
(4) R_1=CN R_2=Et

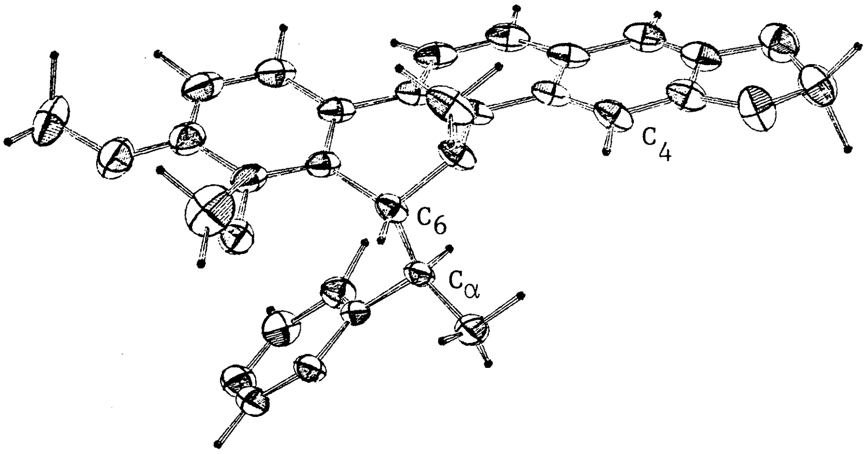


Fig. 3. Molecular Structure of Adduct B (**7B**)

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5) 4-Cyano-2-ethylpyridine (**3**) was prepared by dehydration of ethionamide with bis(tri-n-butyl)tin oxide$^{6)}$ in 80.3% yield.
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10) Treating **6** with 2-ethylpyridine, **3** or **4** did not give isolable products under similar reaction conditions.
11) Crystal data for **7B**: $C_{28}H_{26}N_2O_4$, M=454.5, triclinic, space group P_1 with unit cell dimensions a=14.441(7), b=18.523(3), c=9.041(6) Å, α=93.07(4)°, β=102.47(5)°, γ=86.63(2)°, U=2355.2 Å^3, Z=4, and D_c=1.282 g/cm^3. The reflection data were collected on a Rigaku AFC-5 diffractometer for 3°< 2θ< 120° using CuK_α radiation (λ=1.54 Å) and the ω<30°<ω−2θ scan method at a 2θ scan speed of 4°/min. The structure was solved by the direct method using MULTAN (UNICS-III system$^{12)}$ program and refined by full-matrix least-squares. The final R value was 0.0623 for 5948 independent reflections $[F_o>3\sigma(F_o)]$.
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13) To our knowledge, this is the first alkaloid having a cyanopyridine pendant.

(Received March 11, 1991)