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NEOCARYACHINE, A NEW PAVINE ALKALOID FROM *CRYPTOCARYA CHINENSIS*, AND NMR SPECTRAL PROPERTIES OF RELATED ALKALOIDS

SHOEI-SHENG LEE,* YI-CHU LIU, and CHUNG-HSIUNG CHEN*

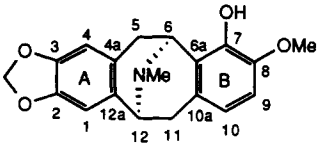
School of Pharmacy, National Taiwan University, 1 Jen-Ai Road, Section 1, Taipei, Taiwan, Republic of China

ABSTRACT.—A new pavine alkaloid, neocaryachine [**1**], was isolated from the bark of *Cryptocarya chinensis*. Its structure was established by spectral analysis including nOe and 2D nmr techniques. ^{13}C-nmr assignments of the related pavine alkaloids (−)-caryachine [**2**], (−)-eschscholtzine [**3**], (+)-eschscholtzidine [**4**], and their corresponding *N*-metho iodides **6** and **7** were also made by using **1** and (−)-caryachine *N*-metho perchlorate [**5**] as model compounds.

Cryptocarya chinensis Hemsl. (Lauraceae) is a perennial plant widely distributed in forests on lowlands of altitude 500–1000 m in Taiwan and in southeastern China (1). Past studies on the alkaloidal constituents of this species have revealed that it is a good source for pavine alkaloids (2–4). So far, three tertiary pavine alkaloids, namely (−)-caryachine [**2**], (−)-eschscholtzine [**3**], and (+)-eschscholtzidine [**4**], and a quaternary pavine, (−)-caryachine *N*-metho perchlorate [**5**], have been isolated from this species. Here we report the isolation and characterization of an additional new pavine alkaloid, neocaryachine [**1**], from the stem bark of this plant.

The phenolic fraction was obtained by general procedures as described in the Experimental section. Tlc analysis of this fraction indicated an additional spot besides caryachine [**2**]. Separation of both compounds was achieved on a Si gel column, which afforded neocaryachine [**1**] in a yield of 0.02%.

Neocaryachine, an amorphous solid, $[\alpha]^{25}D$ −197° (c = 0.36, MeOH), showed in its ms a molecular ion at m/z 325.1310, corresponding to a formula of $C_{19}H_{19}NO_4$ (calcd 325.1314), which is identical to caryachine. The ir absorption at 3468 cm^{-1} and a small bathochromic shift of the uv band at 286.5 nm under alkaline conditions indicated the presence of a phenolic function. Its ^{1}H-nmr spectrum showed four aromatic proton signals, appearing as an AB quartet (δ 6.64 and 6.45, J_{AB} = 8.2 Hz), and two singlets (δ 6.55 and 6.39). In the aliphatic region it displayed signals of methylenedioxy (δ 5.79, dd, J = 1.5 Hz), methoxy (δ 3.78), and *N*-methyl (δ 2.50) groups. In addition, two sets of AMX spin systems were observed, one appearing at δ 4.33 (d, J = 5.6 Hz), 3.30 (dd, J = 16.1, 5.6 Hz), and 2.67 (d, J = 16.1 Hz), and the



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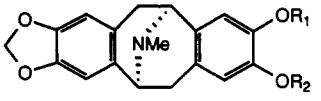
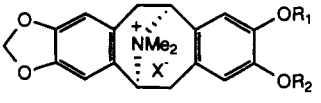




2 R_1=Me, R_2=H
3 R_1+R_2=CH_2
4 R_1=R_2=Me, (6*R*,12*R*)

5 R_1=Me, R_2=H, X=ClO_4
6 R_1+R_2=CH_2, X=I
7 R_1=R_2=Me, (6*R*,12*R*), X=I

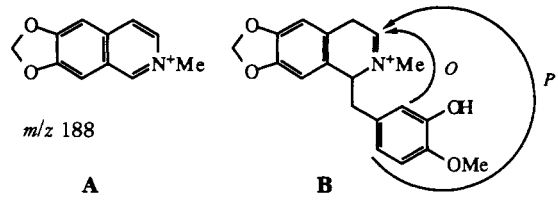
other at δ 3.95 (d, J = 5.1 Hz), 3.37 (dd, J = 16.1, 5.1 Hz), and 2.55 (d, J = 16.1 Hz) (Table 1), both of which were identified by a COSY-45 spectrum. The appearance of two aliphatic AMX spin systems is a characteristic of pavinane alkaloids (5). The ^{13}C-nmr spectrum also supported this point by displaying signals of methine carbons (δ 56.8 and 51.5) and methylene carbons (δ 32.5 and 31.4) (6,7). The large chemical shift difference between these methine carbons (Δδ 5.3) and protons (Δδ 0.38) reflects an unsymmetrically substituted pavinane skeleton. In the nOe difference study, part of the aromatic AB quartet (δ 6.64) was enhanced by irradiation of the methoxyl singlet at δ 3.78, indicating their adjacent relationship. This would require that the methylenedioxy group be placed in the other aromatic ring. The presence of two isolated aromatic proton singlets and the major fragment ion **A** at *m/z* 188 in its eims suggest a 2,3-methylenedioxy substituted A ring similar to **2**. Thus, all this evidence could be accommodated in one of the following three substitution patterns, C-2–C-3–C-7–C-8, C-2–C-3–C-7–C-10, or C-2–C-3–C-9–C-10. The relative downfield shift of the methine proton at δ 4.33 suggested that C-7 is oxygenated (8), which is also reflected in the upfield shift of the methine carbon C-6 (δ 51.5) relative to C-12 (δ 56.8) (9). On the other hand, the closeness of methylene carbon signals (δ 32.5 vs. 31.4) suggests that C-10 is not oxygenated. Thus, the remaining two oxygenated substituents are located at C-7 and C-8 positions on the B ring. This conclusion, along with the above nOe result and the left-handed optical property, established the structure of neocaryachine as **1**.

The proposed structure **1** is confirmed further by a carbon-proton shift correlation via long-range coupling (COLOC) experiment, the analysis of which is based on the assignment of proton signals from nOe difference studies. The enhancements of the methine proton at δ 3.95 (d) and a methylene proton at δ 2.55 (d) (part of an AMX system) upon irradiating the singlet at δ 6.55 allow unambiguous assignment of the H-12, H-11β, and H-1 signals. In the COLOC spectrum, C-10 (δ 119.5, d) is three-bond coupled to H-11β (δ 2.55, d), which is only possible for structure **1**. Because this is the first natural occurrence of this base, it is named neocaryachine because of its structural similarity with caryachine [**2**].

As proposed by Stermitz and Sieber (10) regarding the biosynthesis of pavine al-

TABLE 1. ^{1}H-nmr (300 MHz) Spectral Data of Pavines **1** and **5** (δ in ppm, J in Hz)

Proton	Compound		
	1 ($CDCl_3$)	**5** (C_5D_5N)	**5** (DMSO-d_6)
H-1	6.55 s	6.88 s	6.92 s
H-4	6.39 s	6.53 s	6.69 s
H-5α	3.30 dd (16.3, 5.6)	3.80 dd (18.0, 5.5)	3.62 dd (18.0, 5.5)
H-5β	2.67 d (16.3)	3.27 d (18.0)	3.00 d (18.0)
H-6	4.33 d (5.6)	5.22 d (5.5)	4.80 d (5.5)
H-7	—	7.02 s	6.86 s
8-OMe	3.78 s	3.74 s	3.76 s
H-9	6.64 d (8.3)	—	—
H-10	6.45 d (8.3)	6.90 s	6.49 s
H-11α	3.37 dd (16.1, 5.6)	3.76 dd (18.0, 5.5)	3.60 dd (18.0, 5.5)
H-11β	2.55 d (16.1)	3.16 d (18.0)	2.92 d (18.0)
H-12	3.95 d (5.6)	5.15 d (5.5)	4.82 d (5.5)
OCH_2O	5.82 d (1.6)	6.00 d (1.1)	5.98 d (1.0)
	5.77 d (1.6)	5.95 (1.1)	5.94 d (1.0)
NMe	2.50 s	—	—
$^+NMe_2$	—	3.50 s	3.17 s



kaloids, neocaryachine and caryachine could be derived from the same iminium intermediate **B**. The intramolecular cyclization at positions either ortho or para to the phenolic group would lead to **1** and **2**, respectively.

The complete ^{13}C-nmr assignment of neocaryachine was made by a direct heteronuclear correlation (hetero-COSY) in combination with a COLOC study. Among these, the quaternary oxygenated carbons, C-2 (δ 145.8), C-3 (δ 146.1), C-7 (δ 142.0), and C-8 (δ 144.3), are distinguished by their three-bond couplings to adjacent protons, H-4 (C-2), H-1 (C-3), H-9 (C-7), and H-10, 8-OMe (C-8), respectively. The quaternary nonoxygenated carbons, C-4a (δ 126.8), C-6a (δ 124.5), C-10a (δ 125.3), and C-12a (δ 130.9), were also identified by their long-range couplings to the vicinal protons. For example, the signal at δ 125.3, showing a three-bond coupling to H-9 (δ 6.64, d), was assigned to C-10a, whereas the signal at δ 126.2 was assigned to C-4a by its coupling to H-1 and H-5β. Thus, the carbon chemical shifts of **1** are established as shown in Table 2.

Besides the structural elucidation of neocaryachine, we also examined the spectral properties of caryachine *N*-metho perchlorate [**5**], a quaternary base previously isolated from *C. chinensis* (4). Its ^{1}H chemical shifts (Table 1) were assigned by nOe studies and double resonance experiments. For instance, in an nOe study (in C_5D_5N) the irradiation of the H-7 singlet enhanced the signals of 8-OMe, H-6, and H-5β, and the latter signal was also enhanced by irradiation of the H-4 singlet. In another study, the irradiation of the H-1 singlet enhanced the signals of H-12 and H-11β, and the latter signal was in turn enhanced by irradiation of the H-10 singlet. An additional double resonance experiment was performed in which the double doublet signals of H-5α (δ 3.76) were collapsed to a doublet upon irradiation of the H-6 doublet (δ 5.22). These results taken together distinguished the chemical shifts of the two AMX systems and consequently allowed the total assignments of its ^{1}H nmr (Table 1). It is worth noting that in C_5D_5N the signal of H-10 appears downfield from that of H-1, while a reversal of chemical shifts was observed for both signals taken in DMSO-d_6.

Based on the above proton assignments, the carbon chemical shifts of **5** were established by a hetero long range COSY experiment as illustrated in Figure 1. The resulting carbon chemical shift assignments are listed in Table 2. This assignment indicates that C-4a (δ 120.9) resonates at lower field compared to C-10a (δ 119.6). By applying this

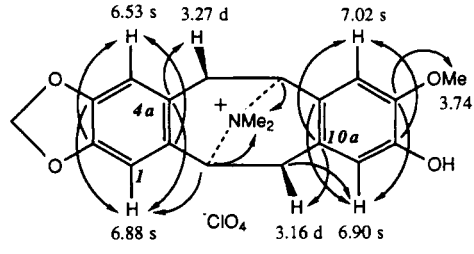


FIGURE 1. Results of hetero long-range COSY of **5** in C_5D_5N.

TABLE 2. ^{13}C-nmr (20.14 MHz) Spectral Data of Pavines **1–7** (δ in ppm, m).

Carbon	Compound						
	1 $CDCl_3$	**2** $CDCl_3$	**3** $CDCl_3$	**4** $CDCl_3$	**5** C_5D_5N	**6** CD_3OD	**7** CD_3OD
C-1	107.0 d	106.8 d	106.7 d	106.6 d	107.2 d	107.9 d	107.9 d
C-2	145.8 s	145.8 s	145.8 s	145.7 s	147.8 s	149.2 s	149.0 s
C-3	146.1 s	146.1 s	146.1 s	146.0 s	148.5 s	150.0 s	149.8 s
C-4	108.7 d	108.4 d	108.3 d	108.3 d	108.4 d	109.2 d	109.2 d
C-4a	126.8 s	124.9 s	124.6 s	124.7 s	120.9 s	121.8 s	122.0 s
C-5	31.4 t	34.2 t	33.8 t	33.8 t	34.4 t	35.1 t	35.1 t
C-6	51.5 d	56.2 d	56.4 d	56.0 d	65.7 d	66.8 d	66.3 d
C-6a	124.5 s	129.0 s	130.7 s	129.6 s	122.8 s	126.1 s	125.3 s
C-7	142.0 s	109.6 d	106.7 d	110.1 d	111.1 d	107.9 d	111.8 d
C-8	144.3 s	145.6 s	145.8 s	147.4 s	148.7 s	149.2 s	150.5 s
C-9	109.3 d	144.7 s	146.1 s	147.8 s	148.7 s	150.0 s	151.2 s
C-10	119.5 d	114.8 d	108.3 d	111.5 d	115.9 d	109.2 d	112.9 d
C-10a	125.3 s	124.4 s	124.6 s	123.6 s	119.6 s	121.8 s	120.6 s
C-11	32.5 t	33.0 t	33.8 t	33.2 t	33.7 t	35.1 t	34.8 t
C-12	56.8 d	56.7 d	56.4 d	56.5 d	65.9 d	66.8 d	66.9 d
C-12a	130.9 s	131.0 s	130.7 s	130.7 s	125.3 s	126.1 s	126.2 s
OCH_2O	100.4 t	100.3 t	100.3 t	100.2 t	101.9 t	103.0 t	102.9 t
NMe	40.7 q	40.5 q	40.4 q	40.4 q	—	—	—
$^+NMe_2$	—	—	—	—	50.5 q	51.1 q	51.2 q
8-OMe	56.0 q	55.8 q	—	55.7 q[a]	56.2 q	—	57.0 q[a]
9-OMe	—	—	—	55.4 q[a]	—	—	56.7 q[a]

[a]These chemical shifts are tentatively assigned and may be interchanged for values in the same column with the same superscript.

result and also cross comparison with the assignment of **1**, the carbon chemical shifts of compounds **2–4** were assigned as shown in Table 2. Similar correlations made possible the assignments of the carbon chemical shifts (Table 2) of (−)-eschscholtzine *N*-metho iodide [**6**] and (+)-eschscholtzidine *N*-metho iodide [**7**], which were prepared by reacting the corresponding bases with MeI (4). Provision of these data will serve as a useful aid for the structural elucidation of related pavine alkaloids.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Optical rotation was measured on a JASCO DIP-181 digital polarimeter. Ir spectra were recorded on a Perkin-Elmer 1760-X Infrared FT spectrometer. The uv spectra were recorded on a Hitachi 150-20 spectrophotometer. Eims was recorded on a Finnigan Mat 4500 series GC/MS and JEOL JMS-HX 110 mass spectrometer. The ^{1}H-nmr and ^{13}C-nmr spectra were recorded on Bruker AC-80 and AM-300 spectrometers. They were measured in appropriate solvents using each solvent peak as internal standard. The 2D nmr spectra were recorded by using Bruker's standard pulse programs. In the hetero-COSY, hetero long-range COSY, and COLOC experiments, a 1-sec delay was allowed between each scan, and the coupling constant was optimized for J = 125 Hz, 8 Hz, and 8 Hz, respectively. The homo-COSY correlation maps consisted of 512 × 1 K data points per spectrum, each composed of 32 transients. The hetero-COSY correlation maps consisted of 512 × 1 K data points per spectrum, each composed of 256 transients.

PLANT MATERIAL.—The plant material was collected in August 1987, in Mt. Wu-Lai, Taiwan. A voucher specimen was deposited in the Herbarium of the School of Pharmacy, National Taiwan University.

EXTRACTION AND ISOLATION.—The powdered bark (1.5 kg) was extracted with 95% EtOH (5 liters × 3). Concentration of the EtOH extract afforded a residue (203 g) that was triturated with 5% HOAc (500 ml × 3) and filtered. The combined acidic filtrate was extracted with Et_2O (500 ml × 3) and then basified with NH_4OH to pH 9. The total alkaloids were extracted with $CHCl_3$ (600 ml × 3). After concen-

tration the $CHCl_3$ extract (2.97 g) was partitioned between Et_2O (200 ml) and 2% NaOH (100 ml × 2). The Et_2O layer was evaporated to give a nonphenolic alkaloid fraction (1.65 g). The aqueous layer was adjusted to pH 9 with NH_4Cl and extracted with $CHCl_3$ (100 ml × 3). The $CHCl_3$ layer was dried ($MgSO_4$) and evaporated to give a phenolic alkaloid fraction (1.0 g). Tlc analysis (Si gel, 5% MeOH in $CHCl_3$ saturated with NH_4OH) of the phenolic fraction showed mainly two spots (R_f 0.39 and 0.25). Flash chromatography on a Si gel (50 g, 230–400 mesh) column eluting with Me_2CO (15–40%) in toluene yielded 323 mg of neocaryachine (R_f 0.39) and 589 mg of caryachine (R_f 0.25). Caryachine [**2**] was identified by comparison (ir, ^1H nmr, ^{13}C nmr, and mmp) with an authentic sample from this laboratory (4).

Neocaryachine [**1**].—Mp 95–97°; $[\alpha]^{25}D$ −197° (c = 0.36, MeOH); uv λ max (MeOH) (log ε) 286.5 (3.76), 294.0 (sh, 3.70) nm, λ max (MeOH + KOH) (log ε) 287.5 (3.90) nm; ir ν max (KBr) 3468 (m, OH), 2894 (s), 1619 (w), 1587 (m), 1495 (s), 1484 (s), 1439 (m), 1381 (w), 1279 (s), 1228 (s), 1085 (s), 1031 (m), 934 (m, $-OCH_2O-$), 866 (w), 778 (w) cm^{-1}; eims *m/z* (rel. int. %) $[M]^+$ 325 (17%) (found 325.1310, calcd for $C_{19}H_{19}NO_4$, 325.1314), 188 (100), 175 (5), 149 (7); ^1H nmr see Table 1; ^{13}C nmr see Table 2.

Caryachine N-*metho perchlorate* [**5**].—The sample of **5** was obtained previously in this laboratory (4). Its nOe data: in C_5D_5N H-1 to H-11β 3%, H-1 to H-12 7%, H-4 to H-5β 3%, H-7 to H-5β 2%, H-7 to H-6 8%, H-7 to 6-OMe 15%, H-10 to H-11β 3%; in DMSO-d_6 H-1 to H-11β 3%, H-1 to H-12 3%, H-4 to H-5β 4%, H-7 to H-5β 3%, H-7 to H-6 3%, H-7 to 6-OMe 11%, H-10 to 9-OH (δ 9.24) 13%, H-10 to H-11β 3%.

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