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ADDITIONAL ALKALOIDS FROM *CRYPTOCARYA CHINENSIS*

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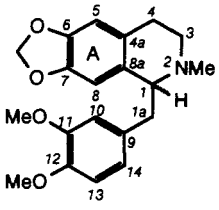
ABSTRACT.—Two alkaloids, (±)-romneine [**1**], a benzylisoquinoline, and (+)-cryprochine [**2**], a new proaporphine, were isolated from the leaves and bark, respectively, of *Cryptocarya chinensis* (Lauraceae).

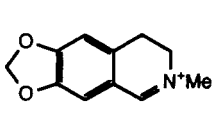
Past studies on the alkaloidal constituents of *Cryptocarya chinensis* Hemsl. (Lauraceae), a perennial widely distributed in forests in the lowlands of Taiwan and in southeastern China (1), have revealed that it is a good source for pavine alkaloids (2–5). So far, four tertiary and one quaternary pavine alkaloid, namely (−)-caryachine, (−)-eschscholtzine, (+)-eschscholtzidine, (−)-neocaryachine, and (−)-caryachine *N*-metho salt, have been isolated from this species. We now report the isolation and characterization of two additional bases, (±)-romneine [**1**] and (+)-cryprochine [**2**], from the leaves and stem bark, respectively.

(±)-Romneine [**1**], isolated from the nonphenolic alkaloidal fraction of the leaves, showed, in its fabms spectrum, $[M+H]^+$ at *m/z* 342. Its ^{1}H-nmr spectrum displayed two singlets (δ 6.50, 6.25) and a complicated ABX pattern between δ 6.59 and 6.77 in the aromatic region, a methylenedioxy singlet at δ 5.82, two methoxys at δ 3.83 and 3.77, and one *N*-Me at δ 2.46. These data are identical to those of (−)-romneine (6). Its ^{13}C-nmr spectrum showing signals of 12 aromatic carbons, one methylenedioxy carbon (δ 100.7), one methine (δ 65.6), three methylenes (δ 47.6, 41.5, and 26.5), and three methyls (δ 56.2, 56.2, 2× O-CH_3 and δ 43.0, N-CH_3), is also consistent with the structure. The fabms included the major ion, *m/z* 190, which is in accord with fragment **A**, confirming the location of the methylenedioxy function on ring A. The lack of optical activity and the nOe studies, which enhanced signals of H-13 (δ 6.77, d, $J=8.8$ Hz) and H-10 (δ 6.59, d, $J=1.5$ Hz), upon irradiation of the MeO singlets at δ 3.83 (12-OMe) and 3.77 (11-OMe), respectively, further proved **1** to be (±)-romneine. This is the first natural occurrence of the racemate of romneine. Both (−)-romneine and (+)-romneine had been isolated previously from *Laurelia novae-zelandiae* (6) and *Romeneya coulteri* (7), respectively.

Romneine is apparently biogenetically related to the pavine eschscholtzidine, via the iminium intermediate **B** (8). The intramolecular cyclization from C-14 to C-3 leads to eschscholtzidine, while reduction of the iminium leads to romneine [**1**].

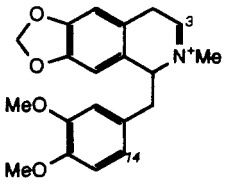


1



m/z 190

A

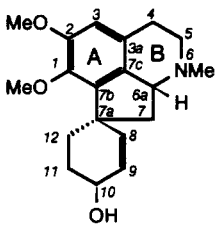


B

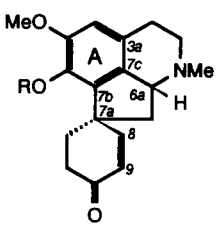
Cryprochine [**2**], an amorphous solid, $[\alpha]^{24}D$ +40.0° (*c* = 0.48, MeOH), gave, in its hreims spectrum, the molecular ion at *m/z* 315.1833, corresponding to $C_{19}H_{25}NO_3$ (calcd 315.1834). The ir absorption at 3468 cm^{-1} suggested the presence of an OH function. The lack of bathochromic shift of the uv band under alkaline conditions indicated further that it is an alcoholic function. The ^{1}H-nmr spectrum exhibited one aromatic proton singlet (δ 6.53), two olefinic protons (δ 5.88 d, δ 5.84 dd), a double doublet at δ 4.13 (dd, *J* = 4.8, 3.2 Hz), two MeO singlets (δ 3.77 and 3.73), and an *N*-Me singlet (δ 2.31). Treatment of **2** with MnO_2 yielded the enone product **3**; H_α and H_β at δ 5.94 (d, *J* = 10.1 Hz) and 6.89 (dd, *J* = 10.1, 1.3 Hz), respectively, both shifted downfield compared to the corresponding signals in the parent compound. This result suggested that **2** contains an allylic alcohol moiety (11). The presence of eight signals belonging to aromatic and olefinic carbons (δ >110 ppm), of which three are protonated (CH) and five are fully substituted, two oxygenated (δ > 140 ppm), and three nonoxygenated, further suggested that **2** contains an aromatic ring together with a double bond, which is part of the allylic alcohol. The rest of the ^{13}C-nmr signals reveal a quaternary carbon (δ 48.3), two methines (δ 65.1 and 63.8), five methylenes, two MeO's (δ 60.8 and 56.3), and an *N*-Me (δ 43.3). The above structural fragments constitute the structure of **2** as an isomer of amuroline [**4**] (9), which was revised to the current structure in 1975 by correlation with the X-ray crystallographic structure of 11,12-dihydroglaziovine (10), leaving the stereochemistry at C-6a, C-7a, and C-10 to be determined.

From the reported ^{1}H-nmr data of reduced proaporphines possessing an enone moiety, the shift difference of the olefinic protons is about 0.70–0.76 ppm in the anti isomers (11–13) such as amuronine [**5**] and about 0.90–0.95 ppm ($\Delta\delta_{8\text{-}9}$ of $\Delta\delta_{12\text{-}11}$) in the syn isomers (H-6a and the double bond in ring D are on the same side) as in (+)-8,9-dihydrostepharine [**6**] (Table 1). The shift difference of the olefinic protons in **3** is 0.95 ppm. Consequently, H-6a and the double bond in ring D are syn to each other. Other supportive evidence is deduced from ^{13}C-nmr analysis; the signal of C-7 in the syn and anti reduced proaporphines bearing an allylic alcohol in ring D is observed around 50.2 ppm and 45.0 ppm, respectively. In the syn and anti reduced enone proaporphines, the signal for C-7 is, however, observed around 49.0 and 43.0 ppm, respectively (14) (Table 2). The signal of C-7 in **2** and **3** appearing at δ 50.2 and 49.1 ppm, respectively, assigned from 2D nmr analysis described later, confirms the syn relationship between H-6a and the olefinic double bond. This relationship and the dextrorotatory optical property of **3**, $[\alpha]^{24}D$ +75.4° (*c* = 0.15, MeOH), point to the stereochemistry of C-6a and C-7a as *R* and *S*, respectively (11).

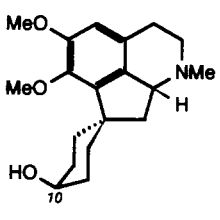
Detailed analysis of the ^{1}H-nmr spectrum of **2**, as assisted by a COSY experiment, helped to locate the AMX system composed of H-6a and H-7's at δ 3.22 (dd, *J* = 11.0,



2



3 R=Me
5 R=Me, 6a-αH
6 R=H, (+)-form of racemate



7

4 6a-αH, 10-αOH

TABLE 1. ^{1}H-nmr Data of Compounds **2**–**6** (13) in $CDCl_3$ (δ in ppm, *J* in Hz).

Proton	Compound				
	2	**3**	**4**[a]	**5**[b]	(+)-**6**[b]
H-3	6.55 s	6.60 s	6.50 s	6.60 s	6.54 s
H-4α	2.93 ddd (16.8, 11.4, 6.7)				
H-4β	2.77 br dd (16.8, 5.0)				
H-5α	3.07 br dd (11.4, 6.7)				
H-5β	2.44 ddd (11.4, 11.4, 5.0)				
H-6a	3.22 dd (11.0, 6.4)				
6-Me	2.32 s	2.35 s	2.38 s	2.37 s	2.36 s
H-7α	1.80 dd (11.0, 11.0)				
H-7β	2.39 dd (11.0, 6.4)				
H-8	5.83 d (10.0)	6.89 dd (10.1, 1.3)	5.54 dd (10.0, 1.2)	6.77 d (10.0)	6.85 dd (10.0, 1.0)
H-9	5.77 dd (10.0, 3.9)	5.94 d (10.1)	5.70 dd (10.0, 1.8)	6.04 d (10.0)	5.94 d (10.0)
H-10	4.13 dd (7.7, 3.9)				
H-11α	1.90 ddd (13.8, 12.5, 3.6)				
H-11β	2.00 dddd (12.5, 7.7, 5.6, 3.8)				
H-12α	1.55 ddd (13.7, 5.6, 3.6)				
H-12β	2.72 ddd (13.8, 13.7, 3.8)				
1-OMe	3.73 s	3.70 s	3.70 s	3.73 s	—
2-OMe	3.77 s	3.80 s	3.78 s	3.80 s	3.82 s

[a]Data for this compound are from Döpke *et al.* (9).
[b]Data for these compounds are from Casagrande *et al.* (13).

6.4 Hz), 2.39 (dd, J = 11.0, 6.4 Hz, H-7β) and 1.80 (t, J = 11.0 Hz, H-7α), respectively. The assignments of these protons were further confirmed by a hetero-COSY spectrum. An nOe difference study showing signal enhancement of H-6a (δ 3.22) upon irradiation of H-8 (δ 5.88, d) further supported the conclusion that H-6a and the olefinic protons are syn to each other. The stereochemistry of the allylic alcohol at C-10 was resolved from ^{1}H-nmr analysis of **7**, a product obtained by treatment of **2** with H_2-Pd/C. The ring D in **7** is presented in chair form as the stable conformation, in which the signal of H-10 appears as a broad multiplet at δ 4.08 with $W_{1/2}$ = 7.5 Hz, suggesting an equatorial proton. Thus, the OH group in **2** is in a pseudoaxial position and C-10 possesses the *S* configuration. The structure of **2**, therefore, is (6a-*R*, 7a-*S*, 10-*S*)-amuroline. To our knowledge, **2** represents the first isolation of this natural product, and **2** is named cryprochine.

Complete ^{13}C-nmr assignments of **1** and **2** were made and detailed in the Experimental section and Table 2, respectively. The ^{13}C-nmr spectrum of **1** was assigned from direct correlation with the reported data for laudanosine (15) and also from partial

TABLE 2. ^{13}C-nmr Data of Compounds **2**, **3**, **5**, and **6** in $CDCl_3$ (δ in ppm, m).

Carbon	Compound				Hetero-long range-COSY data of **2**	
	2	**3**	**5**[a]	(+)-**6**[a]	δ_C	δ_H
C-1	144.7 s	144.9 s	143.7 s		144.7	3.73 (1-OMe), 6.55 (H-3)
C-2	153.2 s	153.4 s	152.6 s		153.2	3.77 (2-OMe)
C-3	110.9 d	111.3 d	111.3 d			
C-3a	126.8 s	127.1 s	126.8 s[b]		126.8	2.77 (H-4β), 3.07 (H-5α)
C-7b	138.4 s	136.5 s	137.1 s[b]		138.4	2.39 (H-7β)
C-7c	134.2 s	133.9 s	133.9 s[b]		134.2	6.55 (H-3)
C-4	27.4 t	27.3 t	27.0 t	26.8 t	27.4	6.55 (H-3)
C-5	54.9 t	54.8 t	54.4 t	54.6 t	54.9	2.32 (N-Me)
C-6a	65.1 d	64.9 d	65.0 d	64.6 d	65.1	1.80 (H-7α), 2.32 (N-Me)
C-7	50.2 t	49.1 t	43.2 t	48.8 t	50.2	2.72 (H-12b)
C-7a	48.3 s	48.8 s	47.3 s	47.8 s	48.3	1.80 (H-7α), 5.83 (H-9)
C-8	136.0 d	154.7 d	156.9 d	155.1 d	136.0	1.80 (H-7α)
C-9	127.5 d	127.5 d	126.8 d	126.8 d		
C-10	63.8 d	199.3 s	198.7 s	198.5 s		
C-11	29.3 t	35.5 t	35.2 t	35.2 t	29.3	2.72 (H-12b)
C-12	29.3 t	33.9 t	31.5 t	33.1 t	29.3	1.80 (H-7α)
1-OCH_3	60.8 q	60.9 q	60.3 q	—		
2-OCH_3	56.3 q	56.5 q	56.0 q	56.4 q		
N-CH_3	43.3 q	43.4 q	43.2 q	43.4 q		

[a]^{13}C-nmr spectra of **5** and **6** were recorded in DMSO-d_6 and only partial ^{13}C nmr of **6** are shown. Data are from Ricca and Casagrande (14).

[b]These data are revised from correlation with those of **2**.

comparison (ring A) with those of caryachine (5). The ^{13}C-nmr spectrum of **2** was assigned on the basis of 2D nmr analysis. The COSY spectrum of **2** established the coupling relationship of the AMX spin system (H-6a and H-7's), and that of H-4's and H-5's and those protons in ring D. These assignments were further confirmed by the hetero-COSY spectrum and are listed in Table 1. For example, two proton signals (δ 2.39 and 1.80) of the AMX system coupled to C-7 (δ 50.2) are designated to H-7's. In an nOe study, the MeO singlet at δ 3.77 was enhanced by irradiation of H-3 (δ 6.55), which served to locate the signals of 1-OMe and 2-OMe at δ 3.73 and 3.77, respectively. While the chemical shifts of proton-attached carbons could be assigned from the hetero-COSY data, those of the quaternary carbons were assigned by analysis of the hetero-long range-COSY spectrum (Table 2). Thus, the signals of C-3a (δ 126.8), C-7b (δ 138.4), and C-7c (δ 134.2) were distinguished by their long range couplings to H-4β (δ 2.77) (C-3a), H-5α (δ 3.07) (C-3a), H-3 (δ 6.55) (C-7c), and H-7β (δ 2.39) (C-7b). The ^{13}C-nmr spectrum of **3** was assigned by correlation with that of **2** (rings A and B) and reported data of related compounds (14). Among these, the signals of C-3a, C-7b, and C-7c in ring A were assigned differently as compared to those of **4**, which is a C-6a epimer of **3**. Since the moiety in ring D is expected to be of little influence on the chemical shifts of ring A carbons, these three signals are reasonably revised as shown in Table 2.

EXPERIMENTAL

INSTRUMENTAL.—Optical rotation was measured on a JASCO DIP-181 Digital Polarimeter. The ir spectra were recorded on a Perkin Elmer 1760-X infrared FT spectrometer. ^{1}H and ^{13}C nmr were recorded on Bruker AC-80 and AM-300 spectrometers and were measured in $CDCl_3$ (99.5%) (reference peak 7.24 ppm for ^{1}H and 77.0 ppm for ^{13}C nmr). The 2D nmr spectra were recorded by using Bruker's standard

pulse program. In the hetero-COSY and hetero-long range-COSY experiments a 1-sec delay was allowed between each scan, and the coupling constant was optimized for $J = 125$ Hz and 8 Hz, respectively. The homo-COSY correlation maps consisted of 512 × 1K data points per spectrum, each composed of 32 transients. The hetero-COSY and hetero-long range-COSY correlation maps consisted of 512 × 1K data points per spectrum, each composed of 256 transients. Uv spectra were recorded on a Hitachi 150-20 spectrophotometer. Ms was recorded on a Finnigan MAT 4500 series GC/MS and JEOL JMS-HX 110 spectrometer.

EXTRACTION AND ISOLATION.—The plant material was collected in August 1987 in Mt. Wu-Lai, Taiwan. A specimen was authenticated by Dr. Y.C. Shen, School of Pharmacy, National Taiwan University, and an herbarium specimen is deposited at the same institute. The powdered leaves (3.2 kg) were extracted with 95% EtOH (5 liters × 3). Concentration of the EtOH extract afforded a residue (305 g) which was triturated with 10% aqueous EtOH (pH 6.0, 1.5 liters). The filtrate was extracted with $CHCl_3$ (500 ml × 3). The condensed $CHCl_3$ extract (15.00 g) was then partitioned between Et_2O (200 ml) and 2% NaOH (100 ml × 2). The Et_2O layer was evaporated to give the nonphenolic alkaloid fraction (6.50 g). The aqueous layer was adjusted to pH 9 with NH_4Cl, and the resultant suspension was extracted with $CHCl_3$ (100 ml × 3). The $CHCl_3$ layer was dried ($MgSO_4$) and evaporated to give the phenolic alkaloids (1.32 g). Tlc analysis (Si gel, 3% MeOH in $CHCl_3$ saturated with NH_4OH) of the nonphenolic fraction showed an additional spot (R_f 0.42) besides the isolated eschscholtzine and eschscholtzidine. Flash chromatography of this fraction (6.00 g) on a Si gel (150 g, 70–230 mesh) column, eluted with MeOH (0.5%) in $CHCl_3$ saturated with NH_4OH, yielded two fractions. Fraction 1 (2.99 g) was rechromatographed on a Si gel column (230–400 mesh, 100 g), eluted with Me_2CO (10% to 20%) in toluene, to give (−)-eschscholtzine (2.11 g) and (+)-eschscholtzidine (258 mg); both compounds were identified by comparison (nmr, tlc) with authentic samples from this laboratory (4). Fraction 2 (58 mg) contained the additional spot and was purified via preparative tlc (Si gel, 20 × 20 cm, 1 mm, ×2) developed with 3% MeOH in $CHCl_3$ saturated with NH_4OH to give **1** (25 mg).

(±)-*Romneine* [**1**].—Amorphous solid: $[\alpha]^{25}D$ 0° ($c = 0.63$, MeOH); uv λ max (MeOH) (log ε) 287 nm (3.90), 250 nm (sh, 3.87); ir ν max (KBr) 2933 (s), 2838 (m), 2783 (m), 1516 (m), 1507 (m), 1488 (s), 1473 (w), 1456 (w), 1239 (w), 1034 (s), 934 (m, -OCH_2O-), 864 (w), 765 (w) cm^{-1}; fabms *m/z* (rel. int. %) $[M+H]^+$ 342 (100) (assigned to $C_{20}H_{23}O_4N + H$), 190 (92), 151 (35), 136 (11); ^1H nmr δ ($CDCl_3$) 6.77 (d, $J = 8.8$ Hz, H-13), 6.64 (br d, $J = 8.8$ Hz, H-14), 6.59 (d, $J = 1.5$ Hz, H-10), 5.82 (s, O-CH_2-O), 3.83 (s, 12-OMe), 3.77 (s, 11-OMe), 2.46 (s, NMe); nOe data 11-OMe to H-10 12%, 12-OMe to H-13 15%; ^{13}C nmr δ ($CDCl_3$) 65.6 (d, C-1), 43.0 (q, 2-Me), 47.6 (t, C-3), 26.5 (t, C-4), 128.0 (s, C-4a), 108.6 (d, C-5), 146.2 (s, C-6), 145.7 (s, C-7), 108.1 (d, C-8), 41.5 (t, C-1a), 133.8 (s, C-9), 111.9 (d, C-10), 149.2 (s, C-11), 148.1 (s, C-12), 113.9 (d, C-13), 122.1 (d, C-14), 100.7 (t, -OCH_2O-), 56.2 (q, 11-OMe, 12-OMe).

SEPARATION OF (+)-CRYPROCHINE [**2**].—Tlc analysis [Si gel, Me_2CO-$C_6H_5CH_3$ (2:3) saturated with NH_4OH] of the nonphenolic alkaloid fraction (1.65 g) obtained from the powdered bark (1.5 kg) (5) showed an additional spot **2** (R_f 0.26) besides the known eschscholtzine and eschscholtzidine. This fraction was chromatographed on a Si gel (50 g, 70–230 mesh) column, eluted with Me_2CO (5% to 20%) in toluene, to give (−)-eschscholtzine (565 mg) and (+)-eschscholtzidine (626 mg) and a fraction (208 mg) containing compound **2**. The latter fraction was further purified on a Si gel (11 g, 230–400 mesh) column eluted with MeOH (3% to 10%) in $CHCl_3$ to give **2** (30 mg): amorphous solid: $[\alpha]^{24}D$ +40.0° ($c = 0.48$, MeOH), uv λ max (MeOH) (log ε) 285 nm (3.67), 224 nm (sh, 420); ir ν max ($CHCl_3$) 3445 (m), 2950 (s), 2850 (m), 1600 (w), 1488 (s), 1455 (m), 1438 (m), 1375 (m), 1295 (m), 1265 (s), 1110 (m), 1000 (m), 850 (m) cm^{-1}; hreims *m/z* $[M]^+$ 315.1833 (calcd for $C_{19}H_{25}NO_3$, 315.1834); fabms *m/z* (rel. int. %) $[M+H]^+$ 316 (100), 298 (28), 284 (9), 272 (12), 204 (7), 190 (11), 165 (6), 152 (7); nOe data 1-OMe to H-12β 5%, 2-OMe to H-3 12%, H-3 to 2-OMe 11%, H-3 to H-4α 2%, H-3 to H-4β 1%, 6-Me to H-6a 11%, H-8 to H-6a 3%, H-9 to H-10 5%, H-10 to H-9 8%, H-10 to H-11α 8%; ^1H nmr see Table 1; ^{13}C nmr see Table 2.

MnO_2 OXIDATION OF **2**.—To a solution of **2** (15 mg) dissolved in CH_2Cl_2 (4 ml) was added MnO_2 (200 mg) at room temperature. The suspension was stirred for 4 h, and the precipitate was filtered via Celite. The filtrate was evaporated, and the residue was passed over Si gel (3 g, 70–230 mesh) eluted with CH_2Cl_2 to give **3** (10.5 mg): amorphous solid; $[\alpha]^{24}D$ +75.4° ($c = 0.1$, MeOH); uv λ max (MeOH) (log ε) 278 nm (3.15), 243 nm (sh, 3.58), 223 nm (sh, 3.95); ir ν max ($CHCl_3$) 1672 (s), 1600 (w), 1488 (s), 1462 (m), 1375 (m) cm^{-1}; eims *m/z* (rel. int. %) 313 $[M]^+$ (75) (assigned to $C_{19}H_{23}NO_3$), 312 (55) $[M-NC_2H_5]^+$ 270 (100), 149 (89), $[NC_2H_5]^+$ 43 (54), 42 (96); ^1H nmr see Table 1.

HYDROGENATION OF **2**.—To a solution of **2** (12 mg) dissolved in MeOH (4 ml) was added Pd/C (5%, 20 mg), and the mixture was reduced under H_2 (1 atmosphere) overnight. The suspension was then

filtered through a Celite pad. The filtrate was evaporated to give a pure product **7** (11 mg): amorphous solid; $[\alpha]^{27}D$ +46.7° (*c* = 0.45, MeOH); eims *m/z* (rel. int. %) $[M]^+$ 317 (35) (assigned to $C_{19}H_{27}NO_3$), 316 (100), 275 (11), 274 (72), 241 (12), 204 (15), 115 (16); ^1H nmr δ ($CDCl_3$) 6.51 (s, H-3), 4.08 (m, $W_{1/2}$ = 7.5 Hz, H-10), 3.82 (s, 2-OMe), 3.80 (s, 1-OMe), 2.35 (s, NMe).

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