A CARYACHINE *N*-METHOSALT FROM *CRYPTOCARYA CHINENSIS* AND PMR SPECTRAL CHARACTERISTICS OF SOME QUATERNARY PAVINE ALKALOIDS

CHUNG-HSIUNG CHEN, SHOEI-SHEN LEE, and CHUNG-FANG LAI

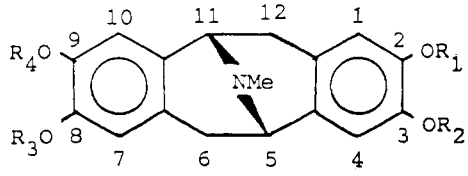
School of Pharmacy, National Taiwan University, Taipei, Taiwan, Republic of China,

and

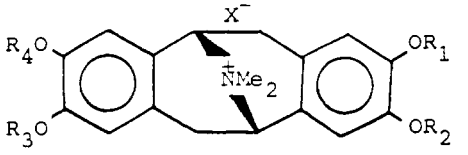
JINN WU and JACK L. BEAL

College of Pharmacy, The Ohio State University, Columbus, Ohio 43210

ABSTRACT.—From the powdered bark of *Cryptocarya chinensis*, a quaternary form of (−)-caryachine (**3**) was isolated as the *N*-methopercholorate salt (**5**). Its identity was confirmed by conversion to the iodide salt (**6**) and direct comparison with a synthetic sample of (±)-caryachine methiodide (**6a**). The positional isomer, (±)-isocaryachine methiodide (**7a**), was also synthesized; its pmr spectral properties were compared with (±)-caryachine methiodide and other quaternary pavine alkaloids.



1, $R_1+R_2=R_3+R_4=CH_2$
2, $R_1=R_2=Me$, $R_3+R_4=CH_2$
2a, An antipode of **2**
3, $R_1=H$, $R_2=Me$, $R_3+R_4=CH_2$
3a, A racemate of **3**
4, $R_1=Me$, $R_2=H$, $R_3+R_4=CH_2$
4a, A racemate of **4**
8, $R_1=R_2=R_3=R_4=Me$



5, $R_1=H$, $R_2=Me$, $R_3+R_4=CH_2$, $X^-=ClO_4^-$
6, $R_1=H$, $R_2=Me$, $R_3+R_4=CH_2$, $X^-=I^-$
6a, A racemate of **6**
7, $R_1=Me$, $R_2=H$, $R_3+R_4=CH_2$, $X^-=I^-$
7a, A racemate of **7**
9, $R_1=R_2=Me$, $R_3+R_4=CH_2$, $X^-=I^-$
10, $R_1=R_2=R_3=R_4=Me$, $X^-=Cl^-$

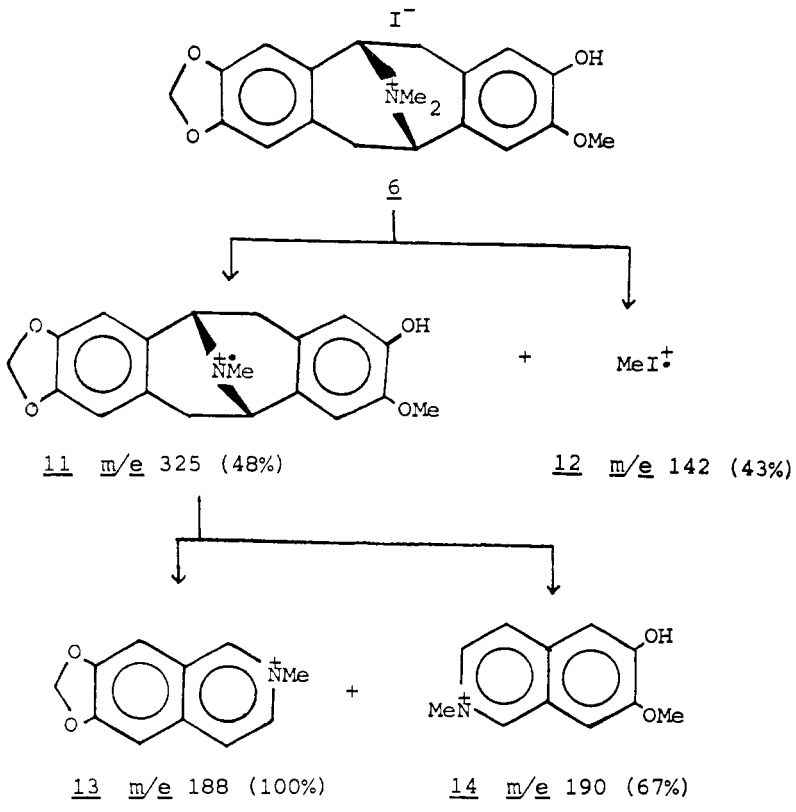
The Chinese cryptocarya, *Cryptocarya chinensis* Hemsl. (Lauraceae), is a perennial plant widely distributed in forests on lowlands of altitude 500 to 1000 meters in Taiwan and in southeastern China (1). The wood from the trunk of this tree is of high quality and useful as a building material. Past studies (2, 3) on the alkaloidal constituents of this species have revealed that it is a rich source of pavine alkaloids. So far, three tertiary pavine alkaloids have been isolated from this species, namely, crychine (**1**), (+)-*O*-methylcaryachine (**2a**), and (−)-caryachine (**3**), which also exists in racemic form (**3a**). Crychine is identical to

eschscholtzine isolated from *Eschscholtzia californica* (4, 5), and (+)-*O*-methylcaryachine is the optical antipode of (−)-eschscholtzidine (**2**) from the same source (6). Two alternate structures, 2-hydroxy-3-methoxy-8,9-methylenedioxy-*N*-methylpavinane (**3**) and 3-hydroxy-2-methoxy-8,9-methylenedioxy-*N*-methylpavinane (**4**), have been proposed for caryachine (2). Several synthetic studies (7, 8, 9) have established **3** to be the structure of caryachine, and the isomeric structure **4** has been named isocaryachine (7).

With our continuing interest in the pavine alkaloids, we have examined the quaternary alkaloid fraction of *Cryptocarya chinensis*, which, to our knowledge, has never before been investigated. We wish now to report here the isolation and characterization of a quaternary *N*-methosalt of (−)-caryachine from this species. This is the first report of the natural occurrence of this alkaloid.

The quaternary alkaloid fraction was separated from the tertiary alkaloid fraction by solvent partition and precipitation as the reineckate salt, which was then exchanged by an anionic resin into the chloride form. Fractionation of this chloride salt on a silica gel column provided a major alkaloid, which was crystallized as the perchlorate salt (**5**), mp 211–212°, $[\alpha]^{25}D-224°$ (MeOH). The uv spectrum of this salt showed a single maximum at 291.5 nm, which shifted to 295 nm upon treatment with base, suggesting the presence of a phenolic function. Both the uv and cd spectra showed strong resemblance to those of the pavine alkaloids (10). The pmr spectrum in deuteriomethanol revealed four aromatic protons as three singlets at δ 6.95, 6.82, and 6.60 (2H), the latter being split into two singlets of one proton each on addition of a trace of deuterium oxide. An AB quartet at δ 5.95 ($J=1$ Hz) indicated the presence of a methylenedioxy group, a conclusion which is also supported by an ir absorption at 930 cm^{-1}. Finally, one methoxyl group appeared at δ 3.92 as a singlet, and a quaternary *N*,*N*-dimethyl group appeared at δ 3.30 as a singlet. An iodide salt (**6**) was prepared from the perchlorate salt (**5**), and the mass spectrum of this iodide salt reflected the distinctive characteristics of the *N*,*N*-dimethylpavinane skeleton. As illustrated in scheme **1**, the major mode of fragmentation represents the result from thermolysis of the parent salt (**6**) giving the tertiary molecular ion (**11**) at *m/e* 325 and the methyl iodide ion (**12**) at *m/e* 142. The base peak (**13**) at *m/e* 188 and the major ion (**14**) at *m/e* 190 correspond to each half of the *N*,*N*-dimethylpavinane skeleton. The above data can be accommodated by two alternative structures, caryachine methiodide (**6**) or isocaryachine methiodide (**7**). Racemic forms of both compounds (**6a** and **7a**) were then synthesized from (±)-caryachine (**3a**) and (±)-isocaryachine (**4a**) obtained from our previous work (7, 11). A direct comparison of the uv, ir, pmr and mass spectra established the identity of the natural iodide salt to be (−)-caryachine methiodide (**6**). In a study by Barker and Battersby (12), the absolute configuaration of (−)-caryachine (**3**) was established as 5S,11S by correlation with (−)-argemonine (**8**) of proven configuration. The reported cd curves of the above two compounds (9) are similar to the curve of (−)-caryachine methoperchlorate (**5**), which should, accordingly, possess the same 5S,11S configuration.

With the availability of both positional isomers, caryachine methiodide (**6a**) and isocaryachine methiodide (**7a**), it would be of some interest to compare their spectral properties. Both compounds showed only minor differences in their ir and mass spectra. However, a pronounced difference was observed in their pmr spectra in the aromatic region. Previously, in our analyses (7, 13) of the pmr spectra of *N*-methylpavinane alkaloids, a complementary and additive relation-



SCHEME 1. *Mass spectral fragmentation of (−)-caryachine methiodide.*

ship was noted for the chemical shifts of aromatic protons. Additive rules were deduced that can be used to predict the spectra of *N*-methylpavinanes with similar substitution patterns. It was established that the chemical shifts for the pair of aromatic protons adjacent to the C–N bond, H_4 and H_{10}, appear at a lower field than that of H_1 and H_7; in addition, aromatic protons *ortho* or *meta* to a phenolic function experience a definite range of upfield shift. To ascertain whether the same conclusion could be applied to the quaternary *N*,*N*-dimethylpavinane system, a cross comparison was made between several quaternary alkaloids and their corresponding tertiary counterparts, including (±)-caryachine (**3a**) and its methiodide (**6a**); (±)-isocaryachine (**4a**) and its methiodide (**7a**); (−)-eschscholtzidine (**2**) and its methiodide (**9**); and (−)-argemonine (**8**) and its methochloride (**10**). All the pertinent data analyzed are shown in *table* **1**. It is quite obvious from comparison of each pair that a general trend of a downfield shift was observed for each proton on the *N*-methylpavinane skeleton upon quaternization of the nitrogen atom. Except for this phenomenon of downfield shift, the general absorption pattern of the quaternary bases strongly resembles that of their tertiary counterparts. Thus, it can be assumed that the complementary and additive relationship deduced from the tertiary system still holds in the quaternary system. It is based on this assumption that assignment of each proton was made for all quaternary bases in table 1. These data should be useful in the event other similar alkaloids are observed in nature.

TABLE 1. *PMR data for some* N,N-*dimethylpavinanes in comparison with corresponding* N-*methylpavinanes.*

	H_1	H_5	H_7	H_{10}	OCH_2O AB q.	OMe C_2	OMe C_3	OMe C_5	OMe C_9	$+NMe_2$	NMe	Solvent
6a	6.53	6.88	6.69	6.92	6.02	——	3.80	——	——	3.22	——	DMSO-d_6
3a[a]	6.38	6.71	6.49	6.71	5.89	——	3.78	——	——	——	2.38	DMSO-d_6
7a	6.66	6.72	6.66	6.89	5.98	3.76	——	——	——	3.32	——	DMSO-d_6-$CDCl_3$(2:1)
4a[a]	6.48	6.58	6.48	6.71	5.89	3.71	——	——	——	——	2.38	DMSO-d_6
9[b]	6.52	6.82	6.52	6.79	5.93	3.81	3.90	——	——	3.59	——	$CDCl_3$
2[c]	6.42	6.58	6.42	6.58	5.80	3.75	3.83	——	——	——	2.52	$CDCl_3$
10[b]	6.52	6.83	6.52	6.83	——	3.80	3.89	3.80	3.89	3.56	——	$CDCl_3$
8[d]	6.46	6.62	6.46	6.62	——	3.77	3.84	3.77	3.84	——	2.54	$CDCl_3$

[a]Values for **3a** and **4a** were taken from *Refence* 7.
[b]Values for **9** and **10** were taken from *Reference* 14.
[c]Values for **2** were taken from *Reference* 2.
[d]Values for **9** were taken from *Reference* 15.

EXPERIMENTAL[1]

PLANT MATERIAL.—The bark from *Cryptocarya chinensis* Hemsl. was collected during the summer of 1975 in Nantou County, Taiwan. A specimen of this plant was authenticated by Mr. Muh-Tsuen Kao, Department of Botany, National Taiwan University; and a voucher specimen was deposited in the School of Pharmacy of the same university. The bark was dried in an oven at 40° C and milled to a fine powder.

EXTRACTION AND INITIAL FRACTIONATION PROCEDURES.—The powdered bark (0.95 Kg) was extracted in a Soxhlet extractor with 95% ethanol. The ethanolic extract was evaporated, *in vacuo,* to give a dark brown residue (136 g). This was triturated with 5% acetic acid and filtered. The process was continued until the filtrate showed a negative Valser's test. The combined acidic solution (2.6 liters) was adjusted to pH 9–10 with ammonium hydroxide solution. A heavy precipitate occurred immediately, which was removed by filtration. The filtrate was extracted with chloroform (5 x 400 ml) to remove the neutral and tertiary base fractions. The aqueous solution was adjusted to pH 2–3 with 10% hydrochloric acid solution. Addition of a saturated aqueous solution of reineckate salt (2%) to this acidic solution yielded a precipitate of quaternary alkaloids as reineckate salts (26 g). The precipitate was dissolved in a mixed solvent of methanol-acetone-water (3:1:1) and then filtered. The filtrate was mixed with anion-exchange resin (IRA-400, Cl^- form, 480 g) and stirred for three days. The resin was removed by filtration, and the filtrate was evaporated under reduced pressure to give the quaternary chloride salts as a pale brown solid (4.6 g). This crude quaternary salt mixture was chromatographed on a silica gel (E. Merck No. 7734, 150 g) column and eluted with chloroform-methanol mixture increasing from 5% to 20% in methanol. Each fraction of 15 ml was collected and analyzed by tlc.

ISOLATION OF (−)-CARYACHINE METHOPERCHLORATE (**5**).—The residue (1.86 g) from column fraction 68–98 eluted with 20% methanol in chloroform was dissolved in a minimum amount of hot distilled water. The resulting solution was then treated with a 20% sodium perchlorate solution until complete precipitation of the perchlorate salt was achieved. The precipitate was collected by filtration and crystallized from distilled water to yield (−)-caryachine methoperchlorate (**5**) as colorless needles (450 mg), mp 211–212°, $[\alpha]^{25}D$ −224° (c 0.13, MeOH); ir ν max (KBr): 3440 (m), 1628 (m), 1600 (w), 1506 (s), 1485 (s), 1447 (s), 1392 (m), 1355 (m), 1303 (sh, m), 1270 (s), 1246 (s), 1112 (s), 1036 (s), 950 (m), 930 (m), 908 (m), 879 (m), and 625 (s) cm^{-1}; uv (MeOH) λ max (log ϵ): 225 (sh, 4.07), and 291.5 (3.95) nm, λ max (MeOH–0.1 N NaOH):

[1]The melting points were taken with a Thomas-Hoover apparatus without correction. The uv spectra were determined with a Hitachi model 200–20 spectrophotometer. The ir spectra were taken with a Perkin-Elmer 577 spectrophotometer in KBr pellets. The pmr spectra were recorded in suitable solvents, with tetramethylsilane as an internal standard, on a Varian model A60–A instrument; all the chemical shifts are reported in δ (ppm) units. CD spectra were determined on a Durrum-Jasco ORD/UV–5 spectrophotometer with the Sproul Scientific SS–20 modification and were determined in methanol. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. Mass spectra and high resolution mass spectral analysis were determined on an A.E.I. MS–902 instrument with a direct inlet system.

296 nm; cd (MeOH): $[\theta]_{297}$ −39,400, $[\theta]_{279}$ +82,000, $[\theta]_{238}$ −380,400; pmr δ (CD_3OD): 3.30 (s, $\overset{+}{N}Me_2$), 3.92 (s, OMe), 5.95 (AB q, J=1 Hz, OCH_2O), 6.60 (s, 2 Ar*H*), 6.82 and 6.95 (2s, 1 Ar*H* each), δ (CD_3OD–D_2O): 6.61, 6.65, 6.86 and 6.98 (4s, 1 Ar*H* each). This compound was identified by conversion to (−)-caryachine methiodide (**6**) and a direct comparison of the latter with synthetic (±)-caryachine methiodide (**6a**).

(−)-CARYACHINE METHIODIDE (**6**) FROM (−)-CARYACHINE METHOPERCHLORATE (**5**).—A 40 mg. sample of (−)-caryachine perchlorate (**5**) was dissolved in a minimum amount of hot distilled water and treated with an excess amount of saturated potassium iodide solution. The resulting solution was extracted with chloroform (5 × 50 ml). After drying over anhydrous sodium sulfate, the chloroform solution was evaporated under reduced pressure to give a residue which was crystallized from methanol, mp 174–175°, $[\alpha]^{24}D$ −160° (c 0.12, MeOH); mass spectrum, *m/e* (%): 339 (9.6), 338 (7.4), 326 (11.4), 325 (48), 324 (34.8), 311 (6.1), 310 (11.2), 309 (8.4), 204 (11.9), 191 (10.2), 190 (67), 189 (16), 188 (100), 176 (7.9), 175 (10.5), 142 (43), and 127 (18); high resolution mass measurement of *m/e* 339 (M^+-1), calculated mass for $C_{20}H_{21}NO_4$, 339.1470, found, 339.1473. This compound is identical with (±)-caryachine methiodide (**6a**) in terms of ir, uv, and pmr spectral data.

PREPARATION OF (±)-CARYACHINE METHIODIDE (**6a**).—A solution of 30 mg of (±)-caryachine (**3a**) (7, 11) in methanol (5 ml) was mixed with freshly distilled methyl iodide (5 ml). The resulting solution was refluxed for 4 hr and then evaporated under reduced pressure to give a pale brown residue. The residue was triturated with anhydrous ether and crystallized from methanol to yield (±)-caryachine methiodide (**6a**) as yellow needles, mp 205–206°, uv (MeOH) λ max (log ε): 290 (4.00) nm, λ max (MeOH–0.1 N NaOH) 297.5 nm; pmr δ (DMSO-d_6): 3.22 (s, $\overset{+}{N}Me_2$), 3.80 (s, OMe), 4.96 (m, *H*-5 and *H*-11), 6.02 (AB q, J=1 Hz, OCH_2O), 6.53, 6.69, 6.88, and 6.92 (4s, 1 Ar*H* each); mass spectrum, *m/e* (%): 339 (10), 338 (7), 326 (11.6), 325 (52.5), 324 (37.8), 311 (7), 310 (10), 309 (7.7), 204 (13), 191 (11), 190 (71.2), 189 (14.6), 188 (100), 176 (8.8), 175 (10.5), 142 (46.4), and 127 (18); high resolution mass measurement of *m/e* 339 (M^+-1), calculated mass for $C_{20}H_{21}NO_4$, 339.1470, found, 339.1473.

PREPARATION OF (±)-ISOCARYACHINE METHIODIDE (**7a**).—Treatment of (±)-isocaryachine (**4a**) (7, 11) with methyl iodide in methanol in the same manner as described above yielded (±)-isocaryachine methiodide (**7a**) as yellow needles from methanol, mp 180.5–182°, uv (MeOH) λ max (log ε): 290 (3.76) nm, λ max (MeOH–0.1 N NaOH): 296 nm; pmr δ (DMSO-d_6–$CDCl_3$ 2:1): 3.32 (s, $\overset{+}{N}Me_2$), 3.76 (s, OMe), 5.02 (m, *H*-5 and *H*-11), 5.98 (AB q, J=1 Hz, OCH_2O), 6.66 (s, 2 Ar*H*), 6.72 and 6.89 (2s, 1 Ar*H* each); mass spectrum *m/e* (%): 339 (11.7), 338 (9.3), 326 (10.3), 325 (37.4), 324 (29), 311 (13.7), 310 (14.4), 309 (6), 191 (8.3), 190 (48), 189 (15.8), 188 (100), 176 (18), 175 (8.8), 142 (51), and 127 (17.6); high resolution mass measurement of *m/e* 339 (M^+-1), calculated mass for $C_{20}H_{21}NO_4$, 339.1470, found 339.1473.

ACKNOWLEDGMENTS

This investigation was supported by the National Science Council, Republic of China, and in part by the National Institutes of Health, U.S. Public Health Service (Grant GM 20968). The authors wish to thank Dr. Kuo-Hsiung Lee, School of Pharmacy, University of North Carolina at Chapel Hill, for measurement of high resolution mass spectra.

Received 6 September 1978.

LITERATURE CITED

1. H.-L. LI, T.-S. LIU, T.-C. HUANG, T. KOYAMA, and C. E. DEVOL, "Flora of Taiwan", *Vol. II*, Epoch Publishing Co., Ltd., Taipei, Taiwan, Republic of China, p. 422.
2. S.-T. LU and P.-K. LAN, *Yakugaku Zasshi*, **86**, 177 (1966).
3. S.-T. LU, *Yakugaku Zasshi*, **86**, 296 (1966).
4. R. H. F. MANSKE and K. H. SHIN, *Can. J. Chem.*, **43**, 2180 (1965).
5. R. H. F. MANSKE, K. H. SHIN, A. R. BATTERSBY, and D. F. Shaw, *Can. J. Chem.*, **43**, 2183 (1965).
6. R. H. F. MANSKE and K. H. SHIN, *Can. J. Chem.*, **44**, 1259 (1966).
7. C.-H. CHEN, J. WU, N. A. SHAATH, and T. O. SOINE, *Taiwan Yao Hsueh Tsa Chih*, **28**, 43 (1976).
8. S. NATARAJAN and B. R. PAI, *Indian J. Chem.*, **12**, 550 (1974).
9. S. F. DYKE, R. G. KINSMAN, P. WARREN, and A. W. C. WHITE, *Tetrahedron*, **34**, 241 (1978).
10. R. P. K. CHAN, J. C. CRAIG, R. H. F. MANSKE, and T. O. SOINE, *Tetrahedron*, **23**, 4209 (1967).
11. C.-H. CHEN, J. WU, N. A. SHAATH, and T. O. SOINE, *Taiwan Yao Huseh Tsa Chih*, **29**, 19 (1977).
12. A. C. BARKER and A. R. BATTERSBY, *J. Chem. Soc.*, **C**, 1317 (1967).
13. C.-H. CHEN and T. O. SOINE, *J. Pharm. Sci.*, **61**, 55 (1972).
14. J. WU, J. L. BEAL, and R. W. DOSKOTCH, to be published.
15. J. WU, J. L. BEAL, W.-N. WU, and R. W. DOSKOTCH, *Lloydia*, **40**, 294 (1977).