[Chem. Pharm. Bull. 23(11)2560—2566(1975)]

UDC 547.94.02.05 : 581.192 : 548.73

Studies on Lupin Alkaloids. VI.*,[1] Isolation and Structure of (+)-Isomatrine[2]

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(Received May 2, 1975)

A new stereoisomer of matrine was isolated from "Ku-Shen," dry roots of *Sophora flavescens*, and named (+)-isomatrine. Epimerization of this compound into (+)-matrine (I) demostrated its flamework. X-Ray analysis of (+)-isomatrine hydrobromide was performed and its structure, [5*R*,6*R*,7*S*,11*R*]-17-oxomatridine (VI), was elucidated. The conformations of A, B, C and D ring in VI are chair, boat, boat and half-chair, respectively.

In the course of the studies on antitumor activity of *Leguminosae* plants constituents,[4] three of us in Shizuoka College of Pharmacy carried out the isolation of lupin alkaloids and pterocarpoids from Korean 'Ku-Shen(苦参)', dry roots of *Sophora flavescens*, and a new alkaloid was isolated. The alkaloid, corresponding to none of lupin alkaloids so far isolated,[5] is a new stereoisomer of (+)-matrine (I), as described below, and named (+)-isomatrine (VI). We investigated the isolation of (+)-isomatrine (VI) from various sources and the results are summarized in Table I, which suggests that this minor alkaloid might become isolable as a free base after a stock for a certain period although the reason is not clear.

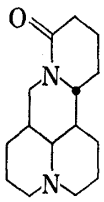
Table I. Source and Content of (+)-Isomatrine (VI)

Source	Time of extraction	Content of (+)-isomatrine
Korean Ku-Shen, purchased in 1970		0.02%
Korean Ku-Shen, purchased in 1971		0.0025%
Korean Ku-Shen, purchased in 1973		0.0031%
Dry root of *Sophora flavescens*, collected in Kakegawa, Shizuoka Prefecture, in May, 1972	May, 1972	none
The same material stocked	May, 1973	none
The same material stocked	May. 1974	0.0014%

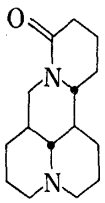
(+)-Isomatrine, mp 132—134°, $[\alpha]_D^{25}=+44°$ ($CHCl_3$), possesses an empirical formula, $C_{15}H_{24}ON_2$, determined by elementalanalysis and mass spectral data ($M^+=m/e$ 248). The infrared (IR) spectrum shows the presences of a lactam (1620 cm^{-1}) and a *trans* quinolizidine (Bohlmann Band,[6] 2740, 2760, 2780 cm^{-1}) and the absence of NH or OH. These data and the plant source of the alkaloid strongly suggest that this may be a C_{15}-lupin alkaloid of matridine- or sparteine-type.

* Dedicated to the memory of Prof. Eiji Ochiai.

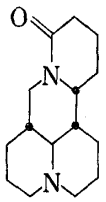
1) Part V: S. Okuda, M. Yoshimoto, K. Tsuda, and N. Utsugi, *Chem. Pharm. Bull.* (Tokyo), **14**, 314 (1966).
2) This work was presented at 93th (Tokyo, April, 1973) and 94th (Sendai, April, 1974) Annual Meeting of Pharmaceutical Society of Japan, Abstracts of Papers II-195 (1973) and II-194 (1974).
3) Location: *a) 2-2-1, Oshika, Shizuoka; b) 7-3-1, Hongo, Bunkyo-ku, Tokyo; c) 1-1-1, Yayoi, Bunkyo-ku, Tokyo.*
4) R. Kojima, S. Fukushima, A. Ueno, and Y. Saiki, *Chem. Pharm. Bull.* (Tokyo), **18**, 2555 (1970).
5) *a)* F. Bohlmann, D. Rahtz, and C. Arndt, *Chem. Ber.*, **91**, 2189 (1958); *b)* S. Okuda, I. Murakoshi, H. Kamata, Y. Kashida, J. Haginiwa, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **13**, 482 (1965).
6) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).


I

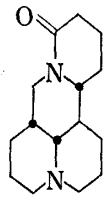
matrine
5*S*; 6*S*; 7*R*; 11*R*
5 : 6=*cis*, 6 : 7=*cis*
7 : 11=*trans*


II

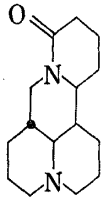
allomatrine
5*S*; 6*R*; 7*R*; 11*S*
5 : 6=*trans*, 6 : 7=*trans*
7 : 11=*trans*


III

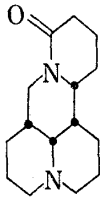
sophoridine[1)]
5 : 6=*trans*, 6 : 7=*trans*
7 : 11=*cis*


IV

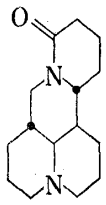
isosophoridine[1a,2)]
5 : 6=*cis*, 6 : 7=*trans*
7 : 11=*trans*


V

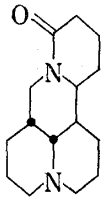
darvasamine[3)]
5 : 6=*trans*, 6 : 7=*cis*
7 : 11=*cis*


VI

isomatrine
5*R*; 6*R*; 7*S*; 11*R*
5 : 6=*cis*, 6 : 7=*cis*
7 : 11=*cis*


VII

5 : 6=*trans*, 6 : 7=*cis*
7 : 11=*trans*

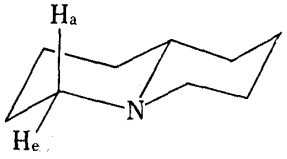

VIII

5 : 6=*cis*, 6 : 7=*trans*
7 : 11=*cis*

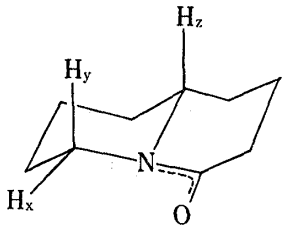
Chart 1. The Stereoisomers of Matrine Type Alkaloids

1) *a*) K.A. Aslanov, A.S. Sadykov, V.B. Leont'ev, and A.I. Begisheva, *Khim. Prir. Soedin.*, **5**, 93 (1969) [*C.A.*, **71**, 61616t (1969)]; *b*) A.I. Begisheva, Z.U, Petrochenko, K.A. Aslanov, and A.S. Sadykov, *ibid.*, **5**, 455 (1969) [*C.A.*, **72**, 67163k (1970)]; *c*) A.I. Begisheva, K.A. Aslanov, Z.U. Petrochenko, and A.S. Sadykov, *ibid.* **7**, 55 (1971) [*C.A.*, **74**, 112279g (1971)].
2) F. Rulko, and N.F. Proskurnina, Zh Obshch. Khim., **32**, 1965 (1962) [*C.A.*, **55**, 4609 (1963)].
3) A. Zunnunshanov, S. Iskandarov, and S.Y. Yunusov, and R. Shakirov, *Khim. Prir. Soedin.*, **7**, 851 (1971) [*C.A.*, **76**, 124144p (1972)].

In its nuclear magnetic resonance (NMR) spectrum (220 mHz, $CDCl_3$), three peak groups—A (a multiplet, δ 3.78, 1H), B (seven peaks, δ 3.47—3.69, 2H) and C (a deformed triplet, δ 2.64—2.93)—are characteristic. If this compound possesses a quinolizidine and a quinolizidone, A and B may be attributed to Hz-type proton in quinolizidone[7)] and two He-type protons in quinolizidine[8)] respectively. Although the shape of B is slightly different from that in the typical *trans* quinolizidine derivatives, this may be caused by distortion of ring structure. The spin-decoupling (100 mHz, C_6D_6) and the comparison between the signal patterns in 100 mHz (C_6D_6) and 220 mHz ($CDCl_3$) spectra reveal that B is due to geminal protons (X-$\overset{H^2}{\underset{H^1}{C}}$-$\overset{H}{C}$-C-, X possesses no proton), H^1; δ 3.63 ($CDCl_3$), 3.76 (C_6D_6), J=13.5, 12.8 Hz: H^2; δ 3.51 ($CDCl_3$), 3.63 (C_6D_6), J=13.5, 4.6 Hz. These chemical shifts are quite abnormal in comparison with the reported values of Hx (δ 4.88—4.35) and Hy (δ 3.00—2.2) in the various lupin alkaloids,[7)] in which the dihedral angle between Hx and amide group in quinolizidone is very small. However the



trans quinolizidine



quinolizidone

Chart 2

7) F. Bohlmann and D. Schumann, *Tetrahedron Letters*, **1965**, 2435.
8) *a*) F. Bohlmann, D. Schumann, and H. Schulz, *Tetrahedron Letters*, **1965**, 173; *b*) V.H.P. Hamlow, S. Okuda, and N. Nakagawa, *ibid.*, **1964**, 2553.

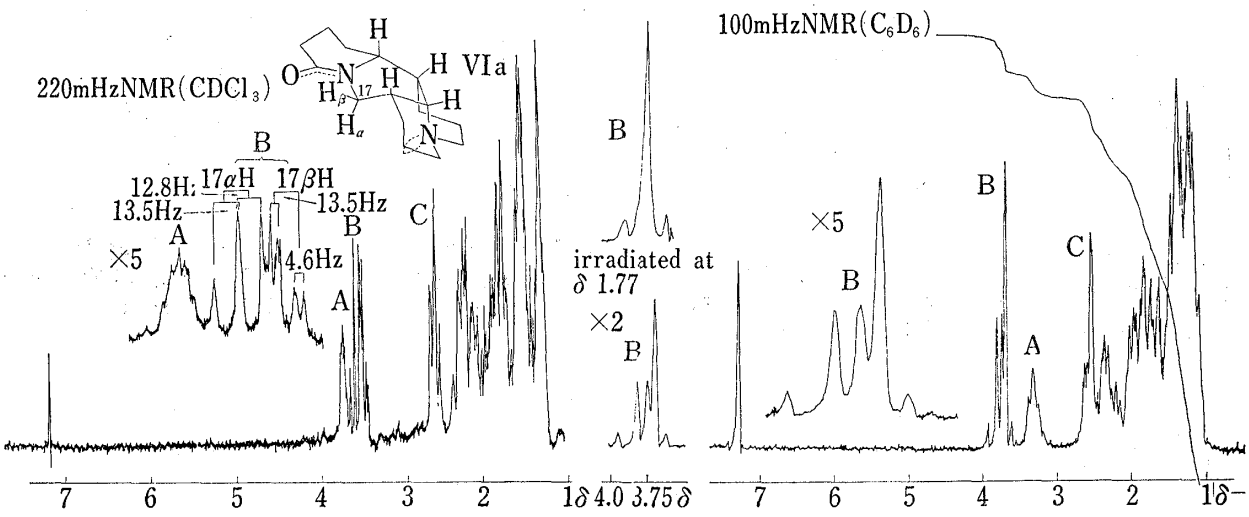


Fig. 1. The NMR Spectra of (+)-Isomatrine (VI)

chemical shifts of Hx and Hy may close to each other in the quinolizidone whose amide group is forced to hold the bisectional position between these two hydrogens.

This compound should not be a C_{15}-lupin alkaloid of sparteine-type from the following reasons. 1) If amide carbonyl is located at C_{10} or C_{17}, the NMR signals due to Hx and Hy become more complex as in the case of 10-oxo- or 17-oxosparteine. 2) In the case of 2-oxosparteine (or 15-oxosparteine) derivative, the difference of δ-value between Hx and Hy should not be small[9] since the dihedral angle between amide group and one of two protons on C_{10} (or C_{17}) is quite small regardless of the ring junction (6H,7H: *cis* or *trans*, or 9H,11H: *cis* or *trans*) as seen in Chart 3.

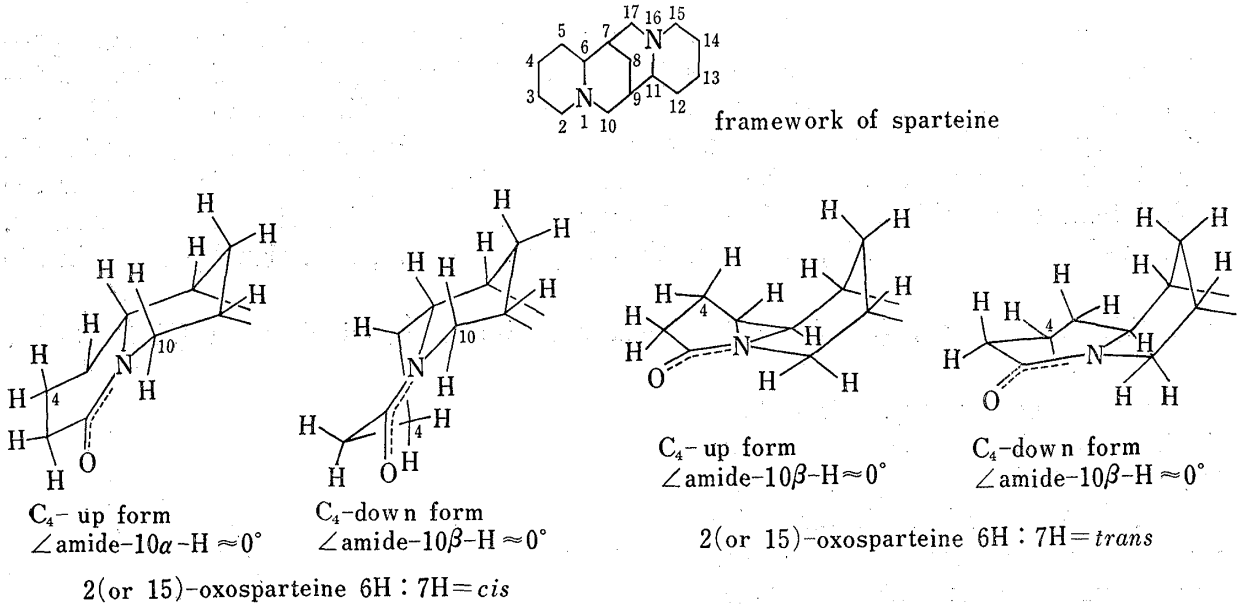
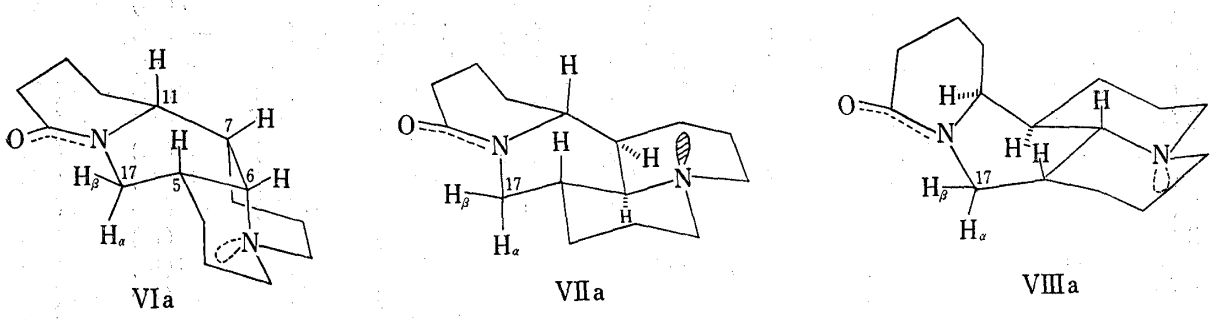


Chart 3

Consequently the possibility that the new alkaloid might be a C_{15}-lupin alkaloid of matridine framework increased. If this is the case, amide carbonyl should be at C_{15} since otherwise NMR signals of Hx and Hy are more complex. To confirm this assumption, the epimerization of this alkaloid was performed by heating its water solution with Adams catalyst in atmosphere

9) Usually the difference is about 2 ppm.[7]

of hydrogen and (+)-matrine (I) and allomatrine (II) were obtained besides a starting material. This clearly demonstrated that this is one of three unknown stereoisomers of matrine as seen in Chart 1 and 4. Among them VIII is excluded since amide group is not located at the bisectional position between 17α- and 17β-H, as seen in Chart 4. The structure VI and VII, whose A, B, C, and D rings are chair, boat, boat, and half-chair in both cases, may satisfy the requirements discussed above. $J_{7,11}$ is a key to distinguish these two stereoisomers, since 7-H and 11-H are *cis* in VI but *trans* in VII. However it seemed to be extremely difficult to find out the correct value.



VIa VIIa VIIIa

(+)-isomatrine
5*R* : 6*R* : 7*S* : 11*R*

∠amide-17β-H≈0°

Chart 4

The hydrobromide of this new alkaloid, (+)-isomatrine, was crystallized from methanol-acetone solution as colourless transparent prisms. The crystals were so deliquescent that they were sealed in thin-walled glass capillaries for the X-ray diffraction studies. The lattice constants and intensity data were obtained by the measurements on Rigaku four-circle X-ray diffractometer using Ni-filtered Cu$K\alpha$ radiation. For the measurement of anomalous dispersion effect, Zr-filtered Mo$K\alpha$ radiation was used. The crystal data are: (+)-isomatrine hydrobromide, $C_{15}H_{24}ON_2 \cdot HBr$, mol. wt.=329.30, mp=166.5°—168°. Orthorhombic, $P2_12_12_1$. a=7.830 (4), b=14.940 (7), c=12.930 (7) Å. U=1512.6 Å^3, Z=4, Dx=1.446 gcm^{-3}.

Of the 1185 reflections with 2θ angles less than 110°, intensities of 1105 independent reflections were measured along with 270 Friedel pairs ($h\ k\ l$ and $h\ \bar{k}\ l$) which were used for the determination of absolute configuration. Scanning was made with θ—2θ mode and the background was measured for 10 sec. at each end of the scan. No absorption correction was applied since the crystal was small enough to neglect the absorption effect.

The structure was solved by the heavy atom method and refined by the method of least-squares with block-diagonal approximations. The R factor was reduced to 0.067 including anisotropic thermal parameters for each atom. Unit weight was assumed for each reflection. The final difference electron-density map showed no anomalous feature. The atomic parameters are give in Table II.

The absolute configuration was determined by the anomalous dispersion method. $\Delta f'$=−0.3 and $\Delta f''$=2.6 were used as the value of the dispersion corrections for bromine for Mo$K\alpha$ radiation. The structure factors for Bijvoet pairs of the reflections were calculated and compared with the observed values by assuming a right-handed set of axes. The results are shown in Table III. A comparison between the observed and calculated intensities indicated that assumed configuration was correct. The absolute configuration (+)-isomatrine (VI) hydrobromide is established as shown in Fig. 2, Chart 1 and 4.

Bond lengths and angles are shown in Chart 5 and Chart 6, respectively. The average standard deviations of these values were estimated to be about 0.02 Å and 1.2°. The short C(15)-N(16) distance of 1.37 Å and the planar trigonal conformation of N(16) indicate the presence of amide group at this part.

TABLE II. Atomic Parameters and Their Estimated Standard Deviations ($\times 10^4$)

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
BR	705(2)	558(1)	753(1)	196(3)	65(1)	61(1)	0(2)	−33(2)	2(1)
N(1)	1197(15)	5888(7)	6398(9)	145(25)	33(6)	61(8)	15(10)	8(13)	1(6)
C(2)	1747(23)	6837(10)	6195(14)	221(38)	30(8)	96(14)	4(15)	16(20)	−4(9)
C(3)	3113(28)	6834(11)	5380(15)	368(53)	36(9)	104(16)	−31(20)	−47(26)	8(10)
C(4)	4737(22)	6290(10)	5767(17)	217(36)	40(8)	136(17)	−27(15)	12(26)	7(11)
C(5)	4218(21)	5336(9)	6183(12)	132(27)	40(8)	84(12)	−17(14)	3(18)	−6(8)
C(6)	2688(18)	5355(9)	6892(10)	106(25)	41(8)	49(9)	4(13)	−22(14)	−2(7)
C(7)	2068(17)	4406(10)	7196(9)	127(24)	33(7)	40(8)	6(14)	7(13)	−4(8)
C(8)	246(24)	4215(13)	6771(15)	113(39)	49(12)	77(17)	−6(20)	−4(24)	5(12)
C(9)	−966(22)	4930(12)	7172(13)	176(35)	80(11)	114(13)	33(16)	40(18)	12(10)
C(10)	−327(21)	5888(10)	7073(11)	163(32)	72(8)	75(9)	35(14)	0(15)	−8(7)
C(11)	3415(25)	3707(10)	6838(13)	184(42)	41(8)	42(13)	26(16)	24(21)	10(8)
C(12)	2856(30)	2751(12)	7144(13)	292(58)	28(10)	70(12)	29(22)	38(25)	7(9)
C(13)	3933(25)	2090(10)	6599(14)	399(43)	53(8)	62(14)	10(17)	43(22)	6(9)
C(14)	3353(21)	2150(11)	5357(14)	285(32)	37(10)	88(14)	−7(16)	−1(20)	7(10)
C(15)	3486(14)	3116(7)	4958(9)	159(21)	52(5)	89(8)	6(10)	11(13)	3(6)
N(16)	3553(21)	3789(9)	5670(11)	146(36)	32(7)	52(10)	12(13)	14(18)	0(7)
C(17)	3875(18)	4682(10)	5219(12)	212(28)	28(9)	65(12)	−1(13)	20(16)	−2(8)
O	3561(16)	3233(7)	4021(8)	284(27)	61(6)	47(7)	1(12)	42(12)	0(6)

To represent the absolute configuration, the right-handed coordinate system should be taken. The temperature factors are of the form: $T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$.

TABLE III. Comparison of the Observed and Calculated Intensity Ratio used to Establish the Absolute Configuration

h k l	$\frac{\lvert Fc(hkl)\rvert^2}{\lvert Fc(h\bar{k}\bar{l})\rvert^2}$	$\frac{\lvert Fo(hkl)\rvert^2}{\lvert Fo(h\bar{k}\bar{l})\rvert^2}$	h k l	$\frac{\lvert Fc(hkl)\rvert^2}{\lvert Fc(h\bar{k}\bar{l})\rvert^2}$	$\frac{\lvert Fo(hkl)\rvert^2}{\lvert Fo(h\bar{k}\bar{l})\rvert^2}$
2 1 1	0.90	0.83	2 1 2	0.89	0.84
4 1 1	0.80	0.72	3 1 2	1.37	1.59
6 1 1	1.06	1.15	6 2 2	0.81	0.83
5 2 1	1.25	1.37	3 3 2	1.14	1.27
3 3 1	0.89	0.87	3 7 2	1.21	1.51
4 3 1	1.25	1.21	3 2 3	1.17	1.38
2 6 1	0.78	0.73	2 3 3	0.82	0.85
3 7 1	1.16	1.34	3 4 3	1.28	1.56
1 8 1	0.75	0.71	2 5 3	1.13	1.31
2 10 1	1.12	1.21	1 8 3	0.87	0.90

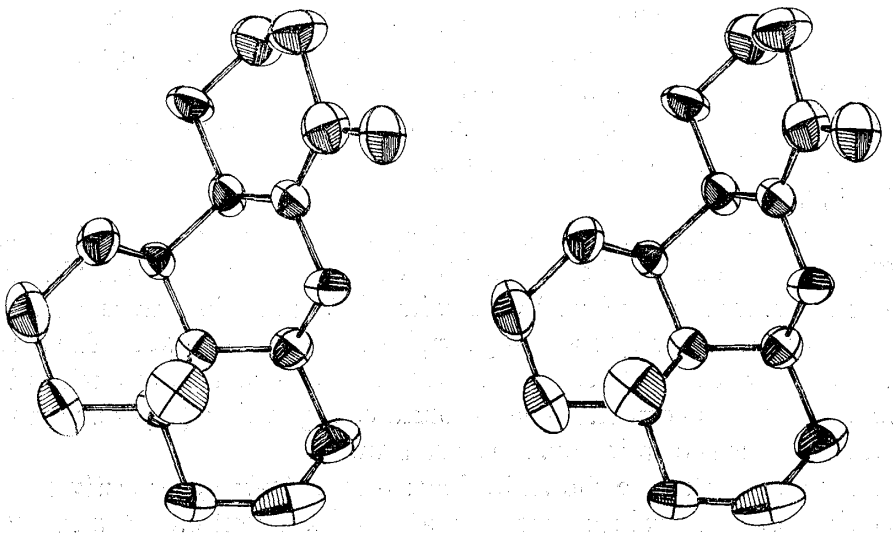


Fig. 2. A Stereoscopic View of the (+)-Isomatrine (VI) Hydrobromide

This is drawn by the plotter program ORTEP (C.K. Johnson, 1965, Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tennessee).

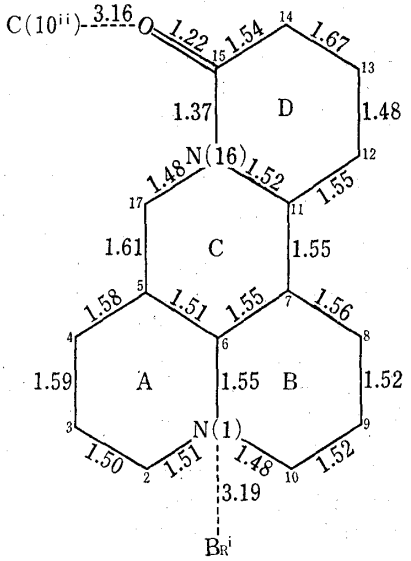


Chart 5. Bond Lengths (in Å Unit)

The shortest intermolecular interatomic distances are also shown. Symmetry operations are: i at $-x, 1/2+y, 1/2-z$; ii at $1/2-x, 1-y, -1/2+z$.

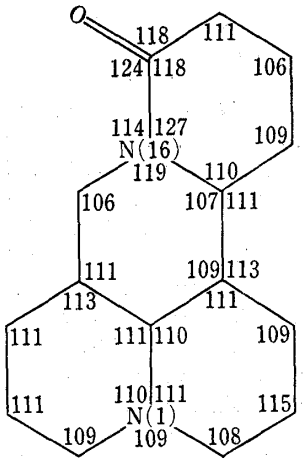


Chart 6. Bond Angles (in Degrees)

The conformation of the molecule may be seen from Fig. 2. To illustrate the conformation more quantitatively, the endocyclic torsion angles were calculated for each ring and are given in Chart 7, which clearly shows the ring A adopts chair conformation while B and C are in boat form. The conformation of D ring can be described as half-chair as shown in Chart 8.

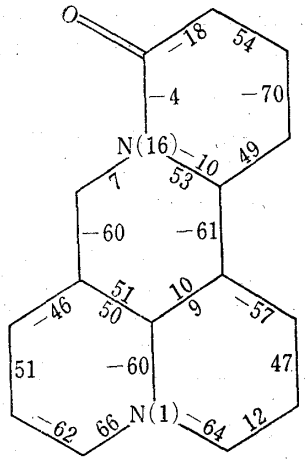


Chart 7. Endo Cyclic Torsion Angles (in Degrees)

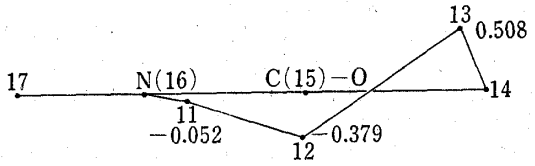


Chart 8. Conformation of D Ring as seen along the C(15)-O Bond

The deviation of atoms from the carbonyl plane are shown in Å unit.

The structure of (+)-isomatrine is established to be [5*R*, 6*R*, 7*S*, 11*R*]-17-oxomatridine (VI). If the epimerization of VI into (+)-matrine (I) involves only the inversion of 11-H, the absolute configuration of (+)-matrine should be [5*R*, 6*R*, 7*S*, 11*S*], the antipode of the absolute configuration proposed previously.[1] The studies in this regard is now in progress.

Experimental

All melting points were taken in H_2SO_4 bath and were uncorrected. IR spectra were recorded for KBr tablet with Hitachi EPI G_{21} spectrometer. NMR spectra were measured on JEOL 4H-100 or Varian HR 220 NMR spectrumeter in $CDCl_3$ or C_6D_6 with TMS as an internal standard and chemical shifts were given in

δ value. Mass spectra were determined at 80 eV with Hitachi RMU-7 spectrometer and optical rotations with an automatic polarimeter, Yanaco OR-50.

TLC was performed on Kiesel gel G nach Stahl using $CHCl_3$–CH_3OH (9: 1) as a developing solvent and H_2PtCl_6-KI solution for detecting a spot. Column chromatography was effected with Mallinckrodt silica gel (100 mesh). Gas-liquid chromatography (GLC) was carried on Hitachi K-53 gaschromatograph using 10% SE-30 column (100 cm, column temp., 240°).

Isolation of (+)-Isomatrine (VI)——Several isolation experiments were made with the various samples as shown in Table I. A typical procedure was as follows. "Ku-Shen," 1 kg, was chopped in small pieces and extracted twice with 10 liters of water for a week at room temp. under stirring several times a day. The combined water extract was passed through a column of Amberite IRC-50 (H^+ type, 250 ml) and the absorbed alkaloid fraction was eluted with 1 liter of 2N aq. NH_3. pH of the eluate was made at about 4 with conc. aq. HCl and the solution was concentrated *in vacuo* to a paste. This paste was made alkaline with a large excess of solid K_2CO_3 under cooling with ice and extracted with $CHCl_3$ repeatedly. After drying over Na_2SO_4, the combined $CHCl_3$ extract was evaporated to leave an alkaloid fraction (15—20 g). This was dissolved in 15—20 ml of $CHCl_3$ and 150—200 ml of ether were added. The mixture was allowed to stand for several hours to precipitate a fraction insoluble in ether which contained mainly N-oxide type alkaloids. The slightly yellow upper solution was evaporated and the residual yellow oil (6—8 g) was treated with three 100 ml of hot *n*-hexane. The *n*-hexane extract gave an oil (3—4 g) whose thin-layer chromatography (TLC) showed a small but clear spot characteristic to (+)-isomatrine (VI). Repeated column chromatography on silica gel (30—50 times the weight of the sample) finally afforded about 30—50 mg of VI, eluted after allomatrine (II) with $CHCl_3$ containing 0.5—1% CH_3OH. Recrystallization from acetone gave fine colourless prisms, mp 132—134°. *Anal.* Calcd. for $C_{15}H_{24}ON_2$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.43; H, 9.67; N, 11.34. *Rf*: VI, 0.45 (blue green spot with H_2PtCl_6-KI solution); I, 0.60; II, 0.52. t_R: VI, 10.5; I, 9.3; II, 8.3 min.

Hydrobromide of VI——VI, 48 mg, was dissolved in 2 ml of 0.1N aq. HBr and the mixture was allowed to stand overnight in a vacuum desiccator containing KOH pellets and P_2O_5. The residual solid was recrystallized twice from acetone–C_2H_5OH (99%) to give colourless prisms, mp 166.5—168°, after drying *in vacuo* over P_2O_5 for 24 hr. These prisms were recrystallized again from the same solvent and utilized for X-ray analysis.

Methiodide of VI——VI, 50 mg, was dissolved in 10 ml of ether and 1 ml of CH_3I was added. The mixture was allowed to stand overnight at room temperature and no precipitate of methiodide was observed. Under the similar conditions allomatrine (II) methiodide precipitates quantitatively. The mixture was refluxed and a slow precipitation of methiodide was observed after about 3 hr. Refluxing was continued for further 7 hr and the reaction mixture was evaporated. The residue was recrystallized from C_2H_5OH (99%) to give 36 mg of needles, mp 213° (decomp.). *Anal.* Calcd. for $C_{15}H_{24}ON_2 \cdot CH_3I$: C, 49.23; H, 6.97; N, 7.18. Found: C, 49.51; H, 7.01; N, 7.02.

N-Oxide of VI——The mixture of VI, 30 mg, and 5 ml of 3% H_2O_2 was allowed to stand at room temperature overnight. On TLC plate, the spot of VI disappeared and a dark blue spot, *Rf*: 0.10, newly appeared. The reaction mixture was evaporated *in vacuo* to dryness and the residue was recrystallized from acetone–CH_3OH to give amorphous powder, mp 220° (decomp., colouring at about 195°). *Anal.* Calcd. for $C_{15}H_{24}O_2N_2$: C, 68.15; H, 9.15; N, 10.60. Found: C, 67.98; H, 9.41; N, 10.47. *Rf*: 0.10.

The N-oxide, 2 mg, was dissolved in 2 ml of CH_3OH containing SO_2 and allowed to stand at room temperature overnight. The spot due to N-oxide disappeared and that of VI was recovered on TLC. The base, obtained from the reaction mixture by usual work up, showed the same *Rf*- and t_R-value as those of VI.

Epimerization of (+)-Isomatrine (VI) into (+)-Matrine (I) and Allomatrine (II)——VI, 50 mg, was dissolved in 5 ml of water and 50 mg of PtO_2 was added. The mixture was heated at 95—98° under vigorous stirring in an atmosphere of H_2 for 15 min. GLC of the reaction mixture showed a component ratio (I: II: VI = 48: 25: 27). If heating is continued further, a content of II increases and those of I and VI decrease. Catalyst was filtered and the filtrate was evaporated *in vacuo*. The residue was chromatographed on silica gel column (5 g) and eluted with $CHCl_3$ containing 1% CH_3OH. The fraction of matrine (I), 19 mg, was obtained and recrystallized from petroleum ether to give 14 mg of prisms, mp 73—75°, $[\alpha]_D^{25} = +33°$ (H_2O), which was identified with authentic (+)-matrine (I) by mixed melting point test and by the comparison of NMR and IR spectra. After the matrine fraction allomatrine (II) and a starting material (VI) were eluted and identified by means of TLC and GLC, but the pure specimens were not isolated.

Acknowledgement The authors wish to express their sincere thanks to Professor A. Tatematsu, Faculty of Pharmacy, Meijo University, and Professor I. Morishima, Department of Hydrocarbon Chemistry, Faculty of Engineering, Kyoto University, for measuring Mass and NMR (220 mHz) spectra.

Added in Proof (October 28, 1975) Recently X-ray analyses of chloroderivatives of (+)-matrine were performed in our laboratories and the absolute configuration (I: 5*S*; 6*S*; 7*R*; 11*R*) proposed previously was confirmed.