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Studies on Lupin Alkaloids. VIII.[1] A New Stereoisomer of Sophocarpine[2]

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A new stereoisomer (I) of (−)-sophocarpine (II) was isolated from epigeal part of *Sophora flavescens*. The relative configuration and stereochemistry were determined by X-ray diffraction studies with monohydrate of free base. The absolute configuration was elucidated by chemical interrelation of I with (+)-matrine (III) and (+)-allomatrine (IV) of known absolute configuration.

Keywords——Alkaloid from *Sophora flavescens*; A new stereoisomer of (−)-sophocarpine; Structure determination by X-ray diffraction studies; Absolute configuration determined by chemical interrelation with (+)-matrine and (+)-allomatrine; Isomerization of dihydroderivative

We have investigated the structures[1] and biological activities[4] of the alkaloids of Japanese *Sophora flavescens* Aiton. In this paper we wish to report the isolation and structure (I) of a new stereoisomer of (−)-sophocarpine (II).

The alkaloidal fraction (71 g) obtained from the fresh epigeal parts (24 kg), collected in Shizuoka Prefecture in May of 1974, was subjected to repeated silica gel column chromatography, affording a new alkaloid (1.2 g), colorless prisms, mp 83—84° (*n*-hexane), $C_{15}H_{22}N_2O \cdot H_2O$, $[\alpha]_D^{13}$ −77° (c=1.00, EtOH), M^+ 246.173 (Calcd. for $C_{15}H_{22}N_2O$: 246.170), λ_{max}^{EtOH} nm (ε): 256 (2850), ν_{max}^{KBr} cm^{-1}: 2825, 2765 (*trans* quinolizidine), 1660, 1655, 1597 (α,β-unsaturated lactam), NMR (C_6D_6) δ_{TMS} ppm: 6.04 (C_{14}–H, d., $J_{13,14}$=10.5 Hz), 5.82 (C_{13}–H, d.q., $J_{13,14}$=10.5, $J_{12\alpha,13}$=3.5, $J_{12\beta,13}$=5.0 Hz), 3.69 ($C_{17\beta}$–H, q., $J_{17\alpha,17\beta}$=13.5, $J_{17\alpha,5\beta}$=5.0 Hz), 3.20 ($C_{17\alpha}$–H, q., $J_{17\alpha,17\beta}$=13.5, $J_{17\alpha,5\beta}$=11.0 Hz), 3.03 ($C_{11\beta}$–H, m.).

On refluxing the water solution of the alkaloid (I) with platinum catalyst under atmospheric pressure of hydrogen for 30 min, I was converted into (+)-matrine (III) and (+)-allomatrine (IV) in 67 and 12% yield respectively. This fact and its characteristics mentioned above exhibited that I should be a stereoisomer of (−)-sophocarpine (II).[5] The melting point and $[\alpha]_D$ value of I are different from those of II, monohydrate, mp 54°, $[\alpha]_D^{12}$ −32° (c=0.98, EtOH), but are similar to those of (+)-Δ^{13}-dehydrosophoridine (X), mp 83—84°, $[\alpha]_D^{22}$ +76.8° (c=0.266, EtOH, the sign is opposite), which was obtained by de-N-oxidizing osnovan 7 ((+)-Δ^{13}-dehydrosophoridine-N-oxide (IX)) isolated from Russian Sophora alopeculoides.[6]

1) Part VII: A. Ueno, K. Morinaga, S. Fukushima, and S. Okuda, *Chem. Pharm. Bull.* (Tokyo), **26**, 1832 (1978).
2) A part of this work was presented at the Annual Meeting of Pharmaceutical Society of Japan (Nagoya, April, 1976), Abstracts of papers, II-210.
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4) R. Kojima, S. Fukushima, A. Ueno, and Y. Saiki, *Chem. Pharm. Bull.* (Tokyo), **18**, 2555 (1970).
5) *a*) A.P. Orekhov and N. Proskurnina, *Chem. Ber.*, **67**, 77 (1934); *b*) S. Okuda, H. Kamata, and K. Tsuda, *Chem. Ind.* (London), **1962**, 1326.
6) S. Kuchkarov, Yu, K. Kushmuradov, Kh. A. Aslanov, and A.S. Sadykov, *Khim. Prir. Soedin.*, **1977**, 541. NMR-data of X (solvent was not mentioned) seems to be slightly different from those of I in $CDCl_3$, C_6D_6, and CS_2.

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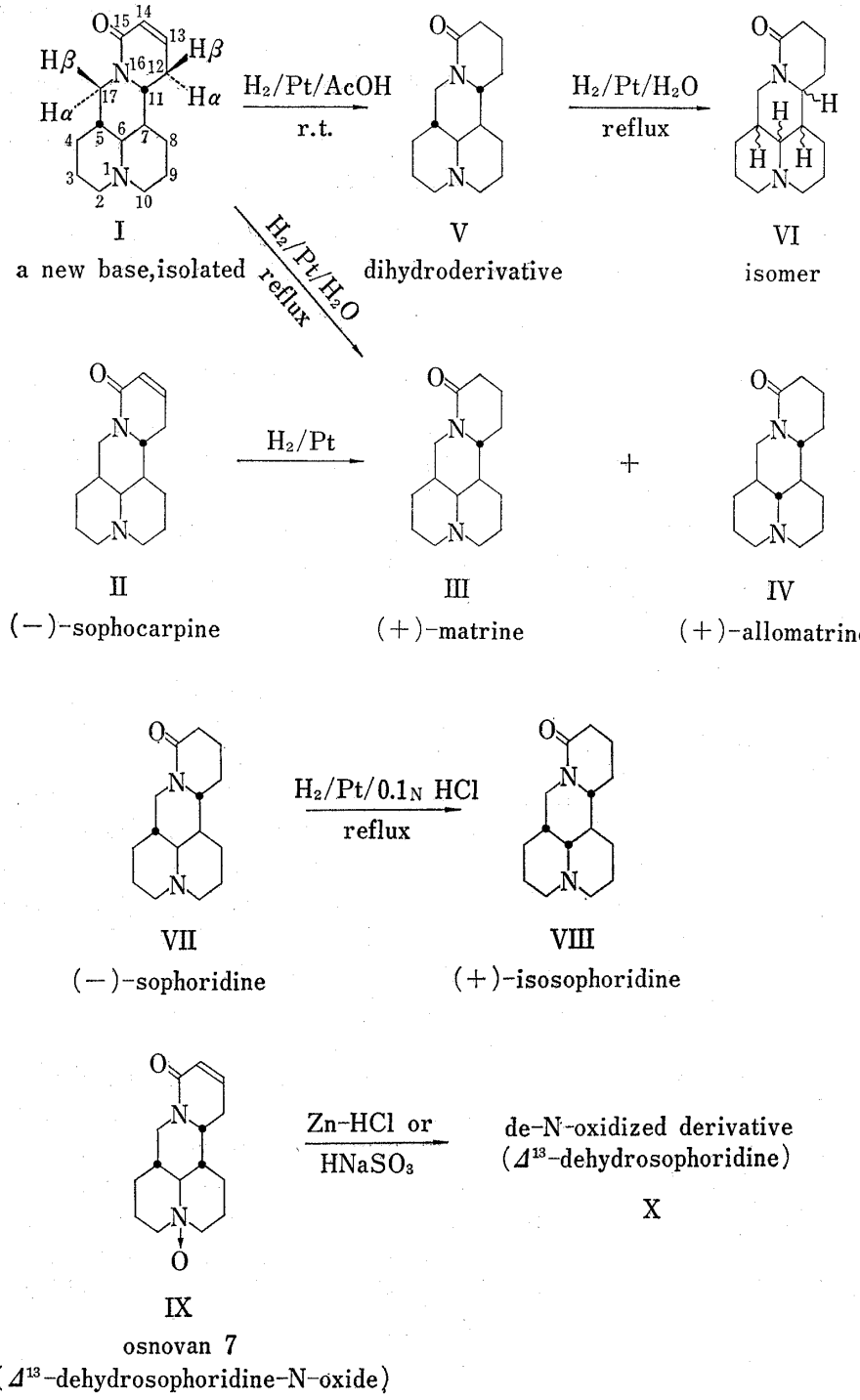

Chart 1

Hydrogenation of I on platinum catalyst in acetic acid gave the corresponding dihydroderivative (V), colorless prisms, mp 107.5—108.5° (*n*-hexane), $C_{15}H_{24}N_2O$, $[\alpha]_D^{16}$ −67° (*c*=1.03, EtOH), M^+ 248.183 (Calcd. for $C_{15}H_{24}N_2O$: 248.182), ν_{max}^{KBr} cm^{-1}: 2795, 2745 (*trans* quinolizidine), 1620 (lactam). The characteristics, including the superimposable NMR spectrum (Fig. 1), bear a close resemblance to those of (−)-sophoridine (VII),[7] mp 109—110° (*n*-hexane), $[\alpha]_D^{18}$ −63.75° (*c*=0.53, H_2O), ν_{max}^{KBr} cm^{-1}: 2795, 2750 (*trans* quinolizidine).

7) *a*) A. Orechoff, *Chem. Ber.*, **66**, 948 (1933); *b*) T.Y. Yunusov, A.P. Matveeva, V.B. Leont'ev, F.G. Kamaev, Kh. A. Aslanov, and A.S. Sadykov, *Khim. Prir. Soedin.*, **1972**, 200; *c*) F.G. Kamaev, V.B. Leont'ev, Kh. A. Aslanov, Yu. A. Ustynyuk, and A.S. Sadykov, *Khim. Prir. Soedin.*, **1974**, 744.

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Refluxing (−)-sophoridine (VII) with platinum catalyst in 0.1 N hydrochloric acid under atmospheric pressure of hydrogen gave (+)-isosophoridine (VIII),[8] mp 111—112° (ether), $C_{15}H_{24}N_2O$, $[\alpha]_D^{16}$ +101.5° (c=3.21, EtOH), ν_{max}^{KBr} cm^{-1}: no *trans* quinolizidine band. Under the similar conditions employing water in place of 0.1 N hydrochloric acid, the dihydroderivative (V) was quantitatively converted into a stereoisomer (VI), colorless prisms, mp 110—111° (ether), $[\alpha]_D^{23}$ +108° (c=0.53, EtOH), M$^+$ 248.184 (Calcd. for $C_{15}H_{24}N_2O$: 248.182), ν_{max}^{KBr} cm^{-1}: no *trans* quinolizidine band, 1635 (lactam).

The data described above strongly suggest that I might be (−)-Δ^{13}-dehydrosophoridine (X). The stereochemistry of sophoridine was determined by the extensive NMR studies and the structure VII was proposed.[7c] On the other hand, very recently the same research group proposed IX as the structure of osnovan 7 ((+)-Δ^{13}-dehydrosophoridine-N-oxide).[6] This discrepancy puzzled us.

To obtain the definite information of the structure of I, X-ray diffraction studies were carried out. Crystals grown from *n*-hexane were prisms elongated along c axis, mp 83°, $C_{15}H_{22}N_2O\cdot H_2O$, MW=264.34, orthorhombic, space group $P2_12_12_1$, Z=4, a=22.567, b=8.239, c=7.645 Å, V=1421 Å^3. 1279 Independent reflections with $I>2\sigma(I)$ were collected on a Philips PW1100 four-circle diffractometer with CuKα radiation monochromated by a graphite plate. The intensities were measured by a θ–2θ scan method with a scan speed of 6° (θ)min^{-1}. The scans were repeated twice when the total number of counts measured during a single scan were less than 1000. The background was measured at each end of the scan for half the total scan time. The intensities were corrected for Lorentz-polarization factors but not for absorption. The size of the crystal used for the intensity measurement was about 0.3 ×0.3×1.5 mm.

The crystal structure was determined by the direct method based on 190 reflections with |E| greater than 1.4. The correct solution was found for the set giving R value 0.285 and figure of merit 1.06. Almost all the atoms could be located on the E-map. The final structure was determined by subsequent Fourier synthesis. A molecule of crystallization water coordinated to N(1) was found on the electrondensity map. The refinement of the structure was carried out by the block-diagonal least-squares method with anisotropic thermal parameters for all atoms. No hydrogen atoms were taken into account in the present structure

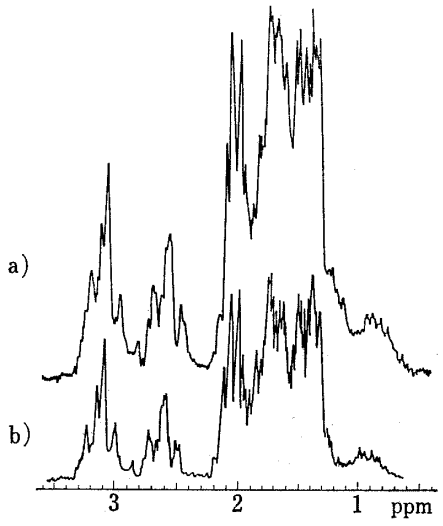

Fig. 1. a) NMR Spectrum (CS_2) of Dihydroderivative (V), b) NMR Spectrun (CS_2) of Sophoridine (VII)[7c]

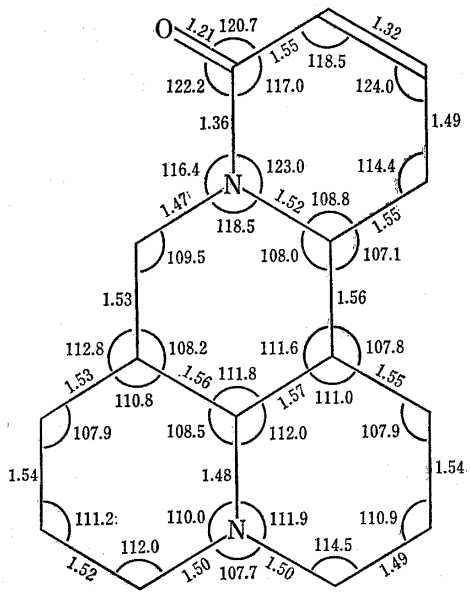

Fig. 2. Bond Lengths (Å) and Bond Angles (°)

8) F. Rulko, *Zh. Obshch. Khim.*, **32**, 1695 (1962).

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Table I. Final Atomic Parameters

ATOM	X	Y	Z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
N (1)	4308 (3)	3146 (10)	4909 (11)	16 (2)	142 (15)	154 (16)	7 (4)	−2 (5)	−4 (16)
C (2)	4868 (4)	2229 (14)	5255 (19)	13 (2)	158 (21)	338 (33)	10 (6)	−4 (8)	4 (26)
C (3)	4759 (4)	711 (15)	6342 (18)	13 (2)	199 (23)	314 (33)	14 (6)	−17 (7)	38 (27)
C (4)	4302 (5)	−406 (13)	5459 (17)	18 (2)	144 (20)	285 (30)	15 (6)	−2 (8)	−7 (24)
C (5)	3741 (4)	589 (12)	5128 (14)	13 (2)	133 (18)	158 (19)	3 (5)	−4 (6)	24 (19)
C (6)	3881 (4)	2096 (12)	3964 (13)	15 (2)	100 (15)	153 (20)	0 (5)	−1 (6)	−5 (17)
C (7)	3304 (4)	3037 (12)	3448 (16)	19 (2)	95 (16)	219 (24)	−4 (5)	−9 (7)	19 (20)
C (8)	3367 (5)	4872 (13)	3849 (18)	24 (3)	117 (18)	314 (33)	4 (6)	−7 (9)	1 (24)
C (9)	3953 (6)	5462 (15)	3048 (20)	31 (3)	146 (22)	369 (38)	−19 (8)	5 (11)	34 (28)
C (10)	4467 (5)	4629 (14)	3872 (17)	22 (3)	150 (20)	287 (31)	−14 (7)	8 (8)	55 (25)
C (11)	2754 (5)	2395 (12)	4464 (14)	21 (2)	122 (16)	175 (22)	5 (6)	−4 (7)	9 (18)
C (12)	2203 (4)	3232 (14)	3674 (17)	14 (2)	172 (20)	299 (30)	11 (6)	−19 (8)	−1 (24)
C (13)	1647 (5)	2361 (15)	4157 (16)	20 (3)	208 (23)	217 (26)	6 (7)	−5 (7)	−38 (24)
C (14)	1612 (5)	773 (17)	4382 (14)	20 (3)	293 (29)	139 (21)	3 (8)	4 (7)	−54 (26)
C (15)	2188 (4)	−248 (13)	4251 (13)	20 (2)	173 (19)	115 (18)	−4 (7)	−8 (6)	14 (18)
N (16)	2709 (3)	582 (10)	4150 (10)	17 (2)	132 (14)	135 (15)	−5 (4)	−5 (5)	−25 (15)
C (17)	3253 (4)	−392 (12)	4237 (15)	12 (2)	110 (16)	246 (25)	−1 (5)	−2 (6)	31 (21)
O	2167 (3)	−1712 (9)	4163 (10)	22 (2)	177 (13)	218 (16)	−26 (5)	−7 (5)	7 (15)
O (S)	3848 (3)	3726 (11)	8572 (11)	26 (2)	251 (18)	250 (19)	−20 (6)	3 (6)	−85 (18)

The values are multiplied by 10^4. The estimated standard deviations are given in parentheses denoting the least sighificant digits. Anisotropic temperature factors are of the form: $T=exp\{-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)\}$

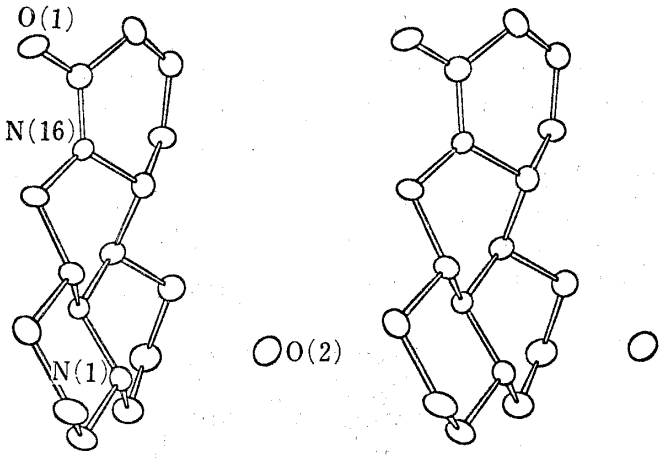
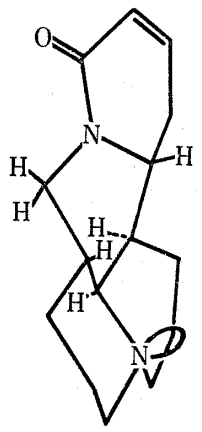
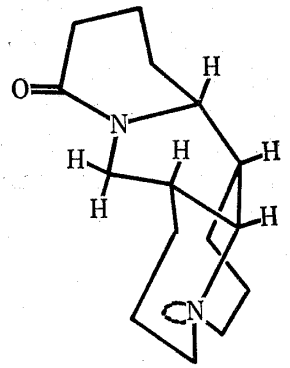


Fig. 3. A Stereoscopic View of I. This is drawn by the plotter program ORTEP (C. K. Johnson, 1965, Report ORNL-3794, Oak Ridge National Laboratry, Oak Ridge, Tenessce) O(1): Oxygen of Lactam Carbonyl, O(2): Oxygen of Water



stereo structure of I



Stereo structure of (+)-isomatrine (XI)

Fig. 4

determination. The final R factor was 0.094 for 1279 observed reflections. The atomic parameters are listed in Table I. No attempt has been made to determined the absolute configuration by X-ray diffraction method because too small intensity difference by anomalous dispersion was expected to measure the difference with certainty. The bond lengths and bond angles are shown in Fig. 2. The standard deviations are estimated to be about 0.017 Å for C–C bonds and 0.9° for C–C–C angles. The relative configuration (A/B: *trans*, A/C: *trans*, B/C: *cis*) and stereochemistry (A-ring: chair, B- and C-ring: boat) of I were thus clarified as seen in Fig. 3 and 4. This stereostructure is the same to that of sophoridine (VII) proposed previously.[7c]

As mentioned above, I could be converted into (+)-matrine (III) and (+)-allomatrine (IV). The similar treatment in deuterium oxide under atmospheric pressure of deuterium, gave the corresponding deuterioderivatives. In the NMR spectra of deuterated III and IV thus

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obtained (Fig. 5), the signals due to 17α- and 17β-H were not quartet but doublet respectively and this indicates the replacement of $C_{5\alpha}$–H in these compouns by deuterium. On the other hand, the signal intensities due to $C_{11\beta}$–H are not decreased and this means that this position was not affected under the conversion conditions. Consequently the absolute configuration at C_{11} of I, III and IV, are the same and the absolute configuration of I (5*R*: 6*S*: 7*R*: 11*R*) were concluded.

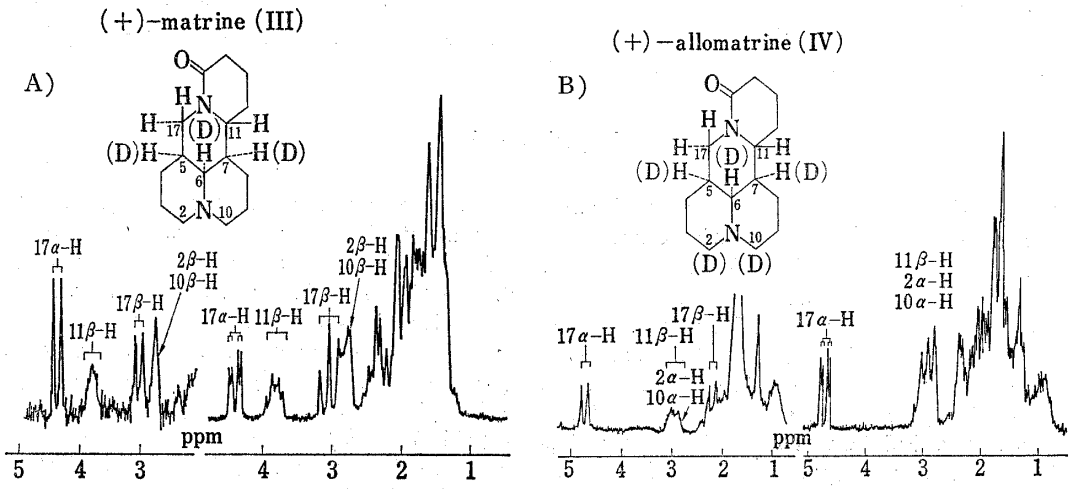

Fig. 5. A) Right and left NMR spectra ($CDCl_3$): (+)-matrine (III) and its deuterated derivative in which 5α-H is replaced by D. Decrease of signal intensities due to 2β- and 10β-H (equatorial type, δ: *ca.* 2.8) and the reduced signal width of 11β-H in the left spectrum suggest the partial replacements with D at 2β-, 10β- and 7α-positions.
B) Right and left NMR spectra ($CDCl_3$): (+)-allomatrine (IV) and its deuterated derivative in which 5α-H is completely and 2α-, 10α-H (equatorial type, δ:*ca.* 2.8) are largely replaced with D.

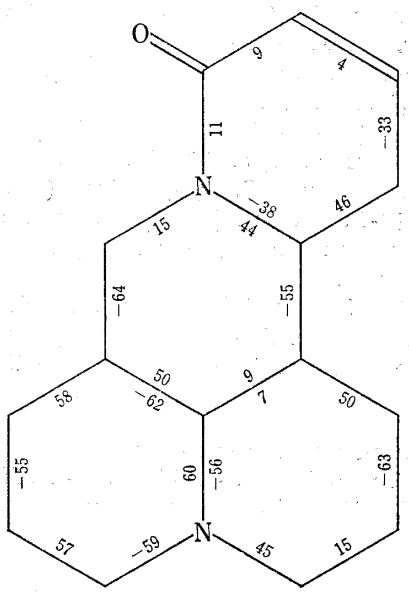

Fig. 6. Endo Cyclic Torsion Angles (°) of I

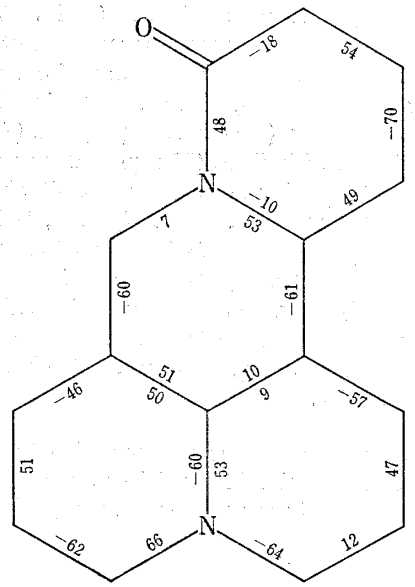

Fig 7. Endo Cyclic Torsion Angles (°) of (+)-Isomatrine (XI)

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The following facts are also noteworthy. As seen in Fig. 6 and 7, the endocyclic torsion angles of quinolizidine (C, D rings) of (+)-isomatrine (XI)[9] and I have the same sign mutually except those involving C_{14} and C_{15}. The atoms C_{14} and C_{15} of I lie on a plane and the signs of torsion angles involving them have no significant meaning. Thus the conformations of C/D rings resemble to each other. On the other hand, the endocyclic torsion angles in quinolizidine (A, B rings) of these compounds have reversed sign to each other. It is quite natural that the absolute configurations of C_6 and N_1 in I and XI are antipodal and that the quinolizidine structures (A, B rings) are of mirror image.

The studies on the conversion mechanisms from I into III or IV, the stereochemistry of VI and the direct comparison of I and V with the authentic samples of Δ^{13}-dehydrosophoridine (X) and sophoridine (VII) are now in planning.

Experimental

All the melting points were taken in a H_2SO_4 bath and are uncorrected. Infrared (IR), ultraviolet (UV), mass (MS) and nuclear magnetic resonance (NMR) spectral measurements were run on Hitachi EPI G_2 spectrometer, Hitachi EPS 3T spectrometer, Hitachi RMU 7 mass spectrometer and JEOL 4H-100 spectrometer using TMS as an internal standard. Optical rotations were measured with Yanaco OR-50 automatic polarimeter and GLC was carried out with Hitachi K-53 gas chromatograph. Conditions of TLC and GLC: Merck silica gel HF_{254}, $CHCl_3$: MeOH=4: 1, ascending development, visualized by H_2PtCl_6–KI solution; 2% Igepal CO-990 (nonyl phenoxypoly (ethyleneoxy) ethanol) on Gas-Chrom Q (80—100 mesh), 4 mm×1 m (spiral glass column), column temp. 220°, N_2 70 ml/min.

Extraction and Isolation of I——Fresh epigeal parts (24 kg) of *Sophora flavescens* Aiton, collected at Awagatake in Kakegawa city, Shizuoka Prefecture, in May of 1974, were extracted with 90 *l* of MeOH and worked up as described in a previous paper.[1] The alkaloidal fraction (71 g) was chromatographed on silica gel column (300 g of Wakogel C-200) and eluted with *n*-hexane–benzene, benzene–$CHCl_3$, $CHCl_3$–MeOH and finally $CHCl_3$–MeOH–Et_2NH. The combined eluate with 1—10% MeOH–$CHCl_3$ gave 7.0 g of a heavy oil. Rechromatography of 6.0 g of this heavy oil on 300 g of Wakogel was performed eluting with 1% Et_2NH–benzene and then with 1% Et_2NH–benzene–MeOH in which MeOH content was gradually increased. The eluate with Et_2NH–benzene–MeOH (1: 98: 1) was evaporated and the residue was recrystallized from *n*-hexane to give 1.2 g of colorless prisms, mp 83—84°. *Anal.* Calcd. for $C_{15}H_{22}N_2O \cdot H_2O$: C, 68.15; H, 9.15; N, 10.60. Found: C, 68.48; H, 9.19; N, 10.32.

Hydrogenation of I——A solution of I (30 mg) in AcOH (2 ml) was hydrogenated with PtO_2 (30 mg) under atmospheric pressure of H_2 at room temperature. After filtering the catalyst and evaporating the solvent *in vacuo*, the residue was basified with K_2CO_3–H_2O followed by extraction with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and removal of solvent gave white solid which was recrystallized from *n*-hexane. Colorless prisms (V), 21 mg, mp 110—111°, M^+ 248.183 (Calcd. for $C_{15}H_{24}N_2O$: 248.182).

Isomerization of Dihydroderivative (V) into VI——A solution of V (50 mg) in H_2O (3 ml) was refluxed with PtO_2 (30 mg) under atmospheric pressure of H_2 for 1 hr. After filtering catalyst followed by evaporation of H_2O, the residue was recrystallized from ether to give 22 mg of colorless prisms (VI), mp 110—111°, $[\alpha]_D^{23}$ +108° (c=0.53, EtOH), M^+ 248.184 (Calcd. for $C_{15}H_{24}N_2O$: 248.182).

Conversion of I into (+)-Matrine (III) and (+)-Allomatrine (IV)——a) A solution of I (60 mg) in H_2O (5 ml) was refluxed with PtO_2 (50 mg) under atmospheric pressure of H_2 for 30 min. Evaporation of H_2O after filtering catalyst furnished 60 mg of oil which were purified by TLC. (+)-Matrine (III, 40 mg), mp 74—76°, $[\alpha]_D^{20}$ +40° (c=0.21, H_2O), R_f 0.57, t_R 5.9 min. (+)-Allomatrine (IV, 7 mg), mp 105—106°, $[\alpha]_D^{20}$ +46° (c=0.04, H_2O), R_f 0.41, t_R 5.1 min. These were identified with the authentic samples by comparison of their IR, NMR spectra, R_f, t_R and by mixed melting point test.

b) The similar treatment of 30 mg of I with 30 mg of PtO_2 in 4 ml of D_2O under atmospheric pressure of D_2 for 15 min, followed by treatment mentioned in a), afforded partially deuteriated (+)-matrine (III, 12 mg) and (+)-allomatrine (IV, 4 mg). Their R_f and t_R were not differentiated from those of the nonlabelled authentic samples.

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