needles, m.p. 131~134°, $[\alpha]_D$ −297° (c=0.48 in $CHCl_3$), UV : λ_{max}^{EtOH} 286.5 mμ (log ε 3.78). *Anal.* Calcd. for $C_{20}H_{21}O_4N$: C, 70.78; H, 6.24. Found : C, 70.81; H, 6.27. This compound was identical with (−)-canadine, m.p. 134~135.5°, $[\alpha]_D$ −300° (c=0.50 in $CHCl_3$), prepared from (±)-canadine according to the procedure reported by Gadamer,[*5] by comparison of IR spectra and mixed melting point determination.

b) From 13-epiophiocarpine acetate (VIIβ) : According to the procedure described above, a mixture of VIIβ (190 mg.), EtOH (35 ml.) and 5% Pd-C (600 mg.) was hydrogenolyzed at 100 kg./cm², 60° for 4 hr. in the same manner to afford 128 mg. of the crystalline product. This product was recrystallized from MeOH giving 80 mg. (49.3%) of (±)-canadine, m.p. 169~172°, which showed no depression on mixed melting point and an identical IR spectrum with an authentic sample. The mother liquor was evaporated, recrystallized from MeOH to further afford 8.5 mg. (5.2%) of (−)-canadine as pale yellow needles, 132~134.5°, $[\alpha]_D$ −296° (c=0.50 in $CHCl_3$). *Anal.* Calcd. for $C_{20}H_{21}O_4N$: C, 70.78; H, 6.24. Found : C, 70.55; H, 6.39. This material was identical with (−)-canadine by mixed melting point determination and IR spectra comparison.

The authors are very grateful to Prof. Emeritus E. Ochiai who gave us kind encouragement in pursuing this work. We are also indebted to Prof. T. Okamoto, Dr. S. Okuda and Dr. Y. Kawazoe for their helpful discussion. Thanks are also due to Dr. T. Suzuki, The Government Chemical Industrial Research Institute of Tokyo, for NMR measurement, Miss Shibata for UV and IR spectral measurements, and Miss N. Ohe and Miss A. Sugiyama for carrying out microanalyses.

Summary

The natural *l*-β-hydrastine (Iβ) was epimerized to *l*-α-hydrastine (Iα). Iα was converted to (−)-canadine (VIII), througth ophiocarpine (VIα), whereas Iβ transformed into VIII through 13-epiophiocarpine (VIβ). The absolute configration of ophiocarpine and 13-epiophiocarpine are represented by VIα (13*R*:13a*R*) and VIβ (13*S*:13a*R*), respectively. Accordingly, the absolute configuration of *l*-α-hydrastine and *l*-β-hydrastine are also designated as Iα (α*R*:1*R*) and Iβ (α*S*:1*R*), respectively.

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150. Michitoshi Ohta, Hideo Tani, Sekiko Morozumi, and Sachiko Kodaira : The Stereochemistry of Hydrastine, Narcotine, Ophiocarpine, and their Derivatives. II.[*1] Absolute Configuration of Narcotine and their Derivatives.[*2]

(*Kowa Chemical Laboratories, Kowa Co., Ltd.*[*3])

The preceding paper[*1] reported that hydrastine was chemically correlated with canadine *via* ophiocarpine and thus the absolute configuration of the alkaloids were established. In this connection, we here describe the absolute configuration of narcotine which is present only in opium and possesses clinically useful antitussive properties and derived alkaloids, analogously as reported in previous paper.[*1]

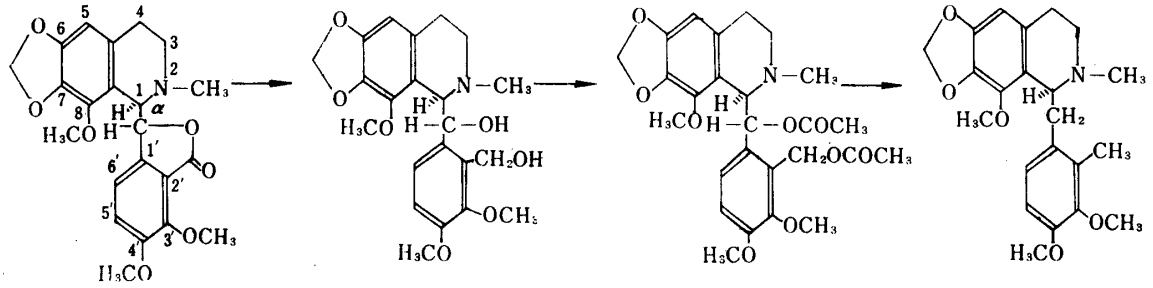
Marshall, Pyman, and Robinson[1] reported that the prolonged action of hot methanolic potassium hydroxide on natural *l*-α-narcotine results in the formation of an

*1 Part I : This Bulletin, **12**, 1072 (1964); Tetrahedron Letters, No. 13, 859 (1963).
*2 Preliminary communication. Tetrahedron Letters, No. 27, 1857 (1963).
*3 Shimotakaido 3-400, Suginami-ku, Tokyo (太田道敏, 谷 英郎, 両角積子, 小平早智子).
1) M. A. Marshall, F. L. Pyman, R. Robinson : J. Chem. Soc., **1934**, 1315.

equilibrium mixture of the original base (*l*-α-narcotine (Iα)) and a new optical active isomeride (*l*-β-narcotine (Iβ)) and naturally occuring *l*-α-narcotine differs from naturally occuring *l*-β-hydrastine in its stereochemical configuration by consideration of the $[\alpha]_{546}$ values of these alkaloids.

According to the procedure of Robinson,[2] lithium aluminum hydride reduction of natural *l*-α-narcotine (Iα) and the epimer *l*-β-narcotine (Iβ) readily afforded the corresponding *l*-α-narcotinediol (IIα), m.p. 133~134°, $[\alpha]_D$ +63.5° ($CHCl_3$) in 82% yield and an oily *l*-β-narcotinediol (IIβ), respectively.

Treatment of either diol with acetic anhydride in pyridine gave the corresponding diacetate (IIIα), m.p. 111~113°, $[\alpha]_D$ −68° ($CHCl_3$) or the epimeric diacetate (IIIβ), m.p. 124~125°, $[\alpha]_D$ −22° ($CHCl_3$). In the presense of 10% palladium on carbon at 95~100° *l*-α-diacetate (IIIα) was hydrogenolyzed at 55~70 kg./cm² to afford 1-(2-methyl-3,4-dimethoxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (IV), m.p. 99~101°, $[\alpha]_D$ +33° ($CHCl_3$) in 44% yield. In the same way, hydrogenolysis of the epimeric diacetate (IIIβ) gave the same product (IV) in 30% yield. This shows that C_α of Iα was epimerised under the influence of basic catalysis to Iβ, as previously indicated by Robinson, *et al.*[2]



Iα (α*S*:1*R*) Iβ (α*R*:1*R*) IIα (α*S*:1*R*) IIβ (α*R*:1*R*) IIIα (α*S*:1*R*) IIIβ (α*R*:1*R*) IV (1*S*)

Chart 1.

In order to elucidate the absolute configuration of IV, optical methods were used successfully. As shown in Fig. 1, optical rotatory dispersion curve of the IV showed a positive Cotton-effect, a*[4] = +83°, whereas the curve for (−)-laudanosine which was assigned by Corrodi and Hardegger[3] as infrared configuration was essentially a mirror image, the a-values being −96°.

It is known[4] that the optical rotations of several 1,2,3,4-tetrahydroisoquinoline derivatives having the same absolute configuration are shifted in the same direction as polarity of the solvent is increased, and Corrodi and Hardegger's recent chemical studies[3] have shown that these bases have 1*S*-configurations.

As shown in Table I, the IV exhibited a shift in positive direction as the polarity of the solvent increased. This suggests that IV should have *S*-configuration at C_1, and consequently C_1 of Iα and Iβ should also have the same configuration.

On the other hand, according to the same synthetic routes reported previously,*[1] IIα and IIβ on treatment with thionyl chloride or hydrogen chloride in chloroform at

*4 The molecular amplitude a=[(molecular rotation at first extremum)−(molecular rotation at second extremum)]×10^{-2}.

2) *a*) R. Mirza, R. Robinson: Nature, **166**, 271 (1950). *b*) W. Awe, W. Wiegrebe: Arch. Pharm., **295**, 817 (1962).

3) H. Corrodi, E. Hardegger: Helv. Chim. Acta., **39**, 889 (1956).

4) W. Leithe: Ber. **63**, 1498 (1930); *Ibid.*, **67**, 1261 (1934); A.R. Battersby, T.P. Edwards: J. Chem. Soc., **1960**, 1214; A. Brossi, F. Burkhardt: Helv. Chim, Acta., **44**, 1558 (1961); M. Tomita, J. Kunitomo: Yakugaku Zasshi, **82**, 734 (1962).

Table I. Specific Optical Rotation ($[\alpha]_D$) of (+)-Laudanosine and IV in Different Solvents

	CCl_4	C_6H_6	$CHCl_3$	EtOH	IV HCl
(+)-Laudanosine[4]	—	+2.2°	+52°	+90°	+102°
IV	+22°	—	+33°	+57°	+ 62°

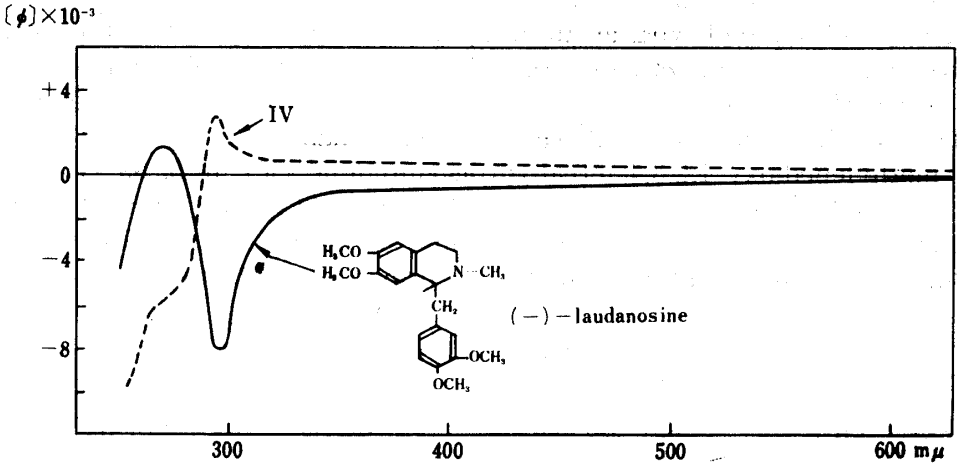


Fig. 1. Optical Rotatory Dispersion Curves of (−)-Laudanosine and IV in Dioxane

room temperature yielded the monochloro hydrochloride (Vα), m.p. 175~175.5° (decomp.), and Vβ, m.p. 155° (decomp.), respectively. Catalytic hydrogenation of the compounds (Vα and Vβ) with palladium on carbon gave the dechloro compound (VIα), m.p. 101~102°, $[\alpha]_D$ −35.5° ($CHCl_3$) and VIβ, m.p. 100~102°, $[\alpha]_D$ +24.5° ($CHCl_3$), respectively.

The diols, IIα and IIβ respectively, were reacted with 1 mole of *p*-toluenesulfonyl chloride in pyridine followed by treatment with sodium iodide in acetonitrile to afford the corresponding *l*-α-methiodide (VIIα, X=I), m.p. 240~242° (decomp.) in 62% yield and *l*-β-methiodide (VIIβ, X=I), m.p. 168~170° (decomp.) in 37% over-all yield from Iβ. Subsequent conversion into the chloride salts (VIIα, X=Cl), m.p. 241~242° (decomp.) and VIIβ (X=Cl), m.p. 235~238° (decomp.), was effected by using a column of Dowex 1-X2 ion

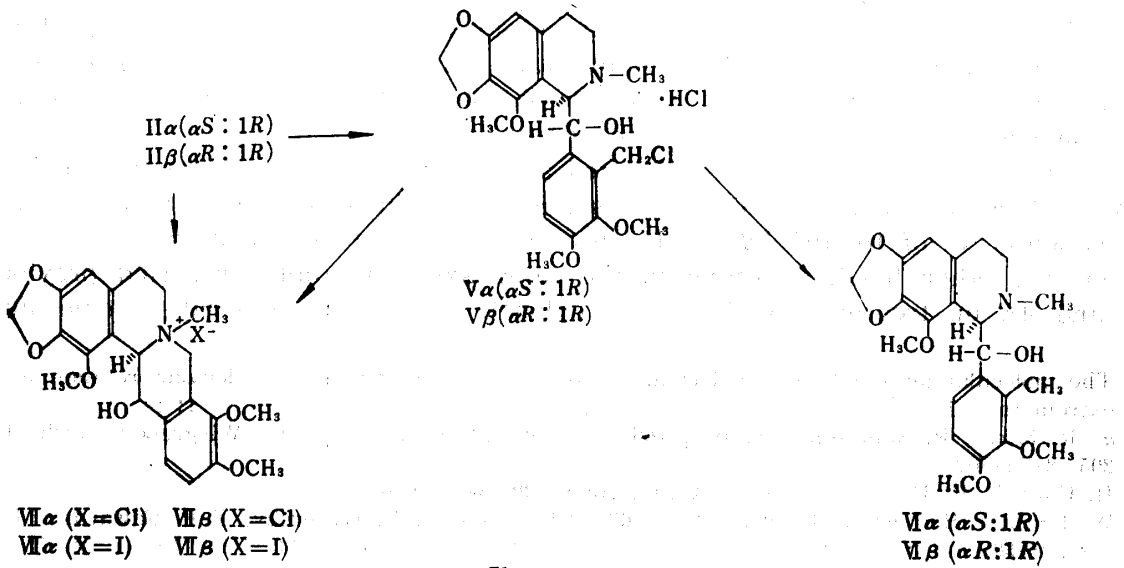
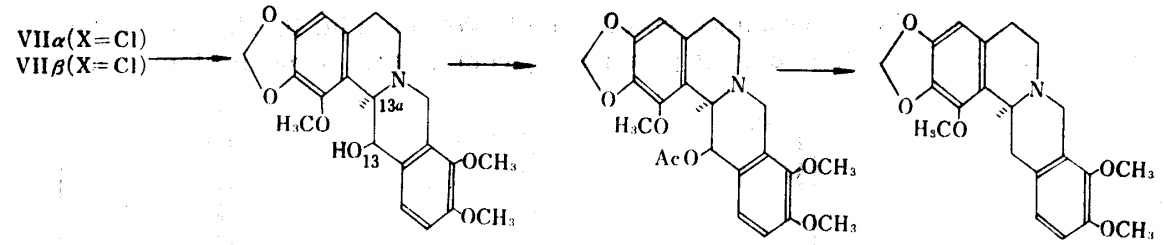


Chart 2.

exchange resin. Furthermore, treatment of Vα and Vβ with aqueous potassium carbonate or alcoholic ammonia solution at room temperature gave VIIα (X=Cl), m.p. 241~242° (decomp.), $[\alpha]_D$ −191.5° (EtOH), and VIIβ (X=Cl), m.p. 235~238° (decomp.), $[\alpha]_D$ −184° (EtOH), respectively. These compounds were identical with the above obtained materials by infrared spectra comparison and mixed melting point.

Pyrolysis of VIIα (X=Cl) or VIIβ (X=Cl) in *o*-dichlorobenzene at 210° gave the corresponding compound (VIIIα), m.p. 165~166°, $[\alpha]_D$ −195° ($CHCl_3$) in 78% yield and VIIIβ, m.p. 190~191°, $[\alpha]_D$ −290° ($CHCl_3$) in 74% yield, respectively. These compounds, (VIIIα and VIIIβ) were treated with methyl iodide in methanol to furnish methiodides, VIIα (X=I) and VIIβ (X=I), having melting points and infrared spectra in agreement with the above described methiodides, respectively.

Acetylation of VIIIα and VIIIβ gave the corresponding acetates, Xα, m.p. 169~170°, $[\alpha]_D$ −106° ($CHCl_3$) in 59% yield and Xβ, m.p. 172.5~173.5°, $[\alpha]_D$ −389° ($CHCl_3$) in 86% yield. Further, hydrogenolysis of Xα at 80~90° at 50 kg./cm² with 10% palladium on carbon in ethanol gave a mixture of (−)-1-methoxycanadine (X), m.p. 150~152°, $[\alpha]_D$ −270° ($CHCl_3$), in 48% yield and (±)-1-methoxycanadine, m.p. 139~141°, in 18% yield. From VIIIβ (±)-1-methoxycanadine also was prepared by reduction with zinc powder in hydrochloric acid, and was identical with the material obtained above. Similarly, hydrogenolysis of Xβ afforded (−)-1-methoxycanadine (X), m.p. 150~152°, $[\alpha]_D$ −271° ($CHCl_3$), in 43% yield, and its racemate in 17% yield, identical in melting point and infrared spectra with the above material. The infrared spectrum of (−)-1-methoxycanadine (X) showed bands at 2837, 2789, and 2750 cm^{-1}, indicating the presense of C/D *trans* fused quinolizidine system and also specific rotation of X had large negative value ($[\alpha]_D$ −270°) similar to that of (−)-canadine ($[\alpha]_D$ −299° (EtOH)).[5]



VIIIα (13*S*:13a*R*) Xα (13*S*:13a*R*) X (13a*S*)
VIIIβ (13*R*:13a*R*) Xβ (13*R*:13a*R*)

Chart 3.

It is known that hydroxyl and methoxy groups attached to aromatic rings do not influence the optical rotation in protoberberine alkaloids: all of the (−)-tetrahydroberberine alkaloids with only one asymmetric carbon possess almost equal [M] values averaging ca. −1000 and have the same configurations as (−)-norcoralydine. Consequently, (−)-1-methoxycanadine (X) should have the same *S*-configuration at C_{13a} as at C_{13a} of (−)-canadine.

Infrared spectra of VIIIα and VIIIβ showed bands in the region near 3500 cm^{-1}, indicating the presence of hydrogen bonding. Apparently more extensive hydrogen bonding is present in VIIIα than VIIIβ, as shown by a comparison of spectra of the same concentration in carbon tetrachloride, cf. Fig. 2. Moreover, the infrared spectra of VIIIβ showed bands at 2805, 2774, and 2753 cm^{-1} due to characteristic band of *trans* B/C fused quinolizidine system, according to Bohlmann's and Wenkert and Roychaudhuri's infrared criterion,[5] whereas VIIIα did not exhibit prominant bands at 2760~2750 cm^{-1}. Similarly,

5) F. Bohlmann: Chem. Ber., **91**, 2157 (1958); *Ibid.*, **92**, 1798 (1959); E. Wenkert, D. K. Roychaudhuri: J. Am. Chem. Soc., 78, 6417 (1956).

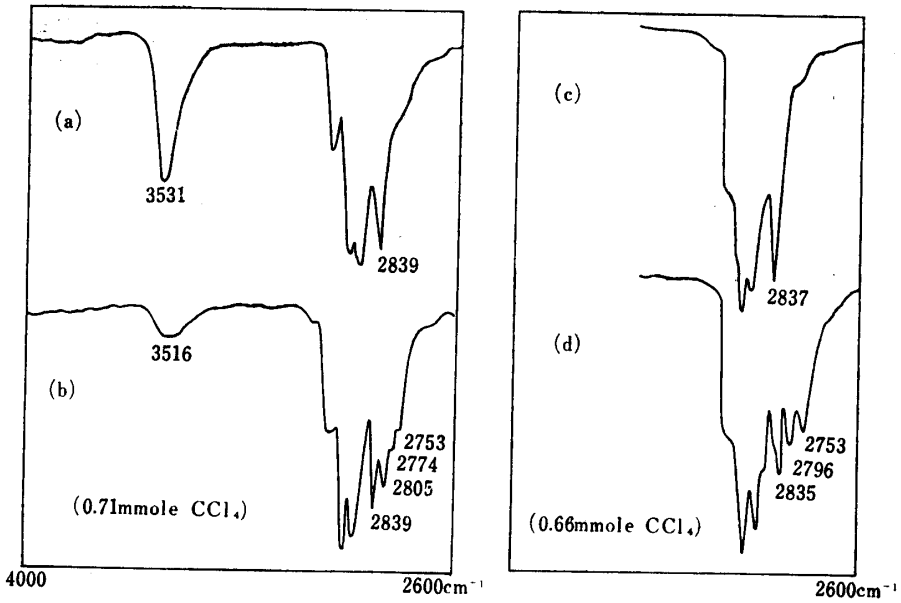


Fig. 2. Infrared Spectra in the 4000~2600 cm^{-1} Regions
a : Ⅷα b : Ⅷβ c : Ⅸα d : Ⅸβ (LiF prism)

the acetate (Ⅸβ) exhibited typical bands at 2836, 2796, and 2753 cm^{-1} characteristic of the *trans*-quinolizidine system, but Ⅸα did not absorb in this region as shown in Fig. 2.

Furthermore, differences in the pK_a-values between Ⅷα, pK_a : 5.60 (80% methylcellosolve); 5.90 (70% EtOH), and Ⅷβ, pK_a : 5.62 (80% methylcellosolve); 6.06 (70% EtOH), could not be observed.

The nuclear magnetic resonance spectrum of Ⅷα, cf. Fig. 3, showed rather sharp peaks at ca. 2.9 p.p.m. due to ring protons adjacent to the nitrogen atom, whereas the

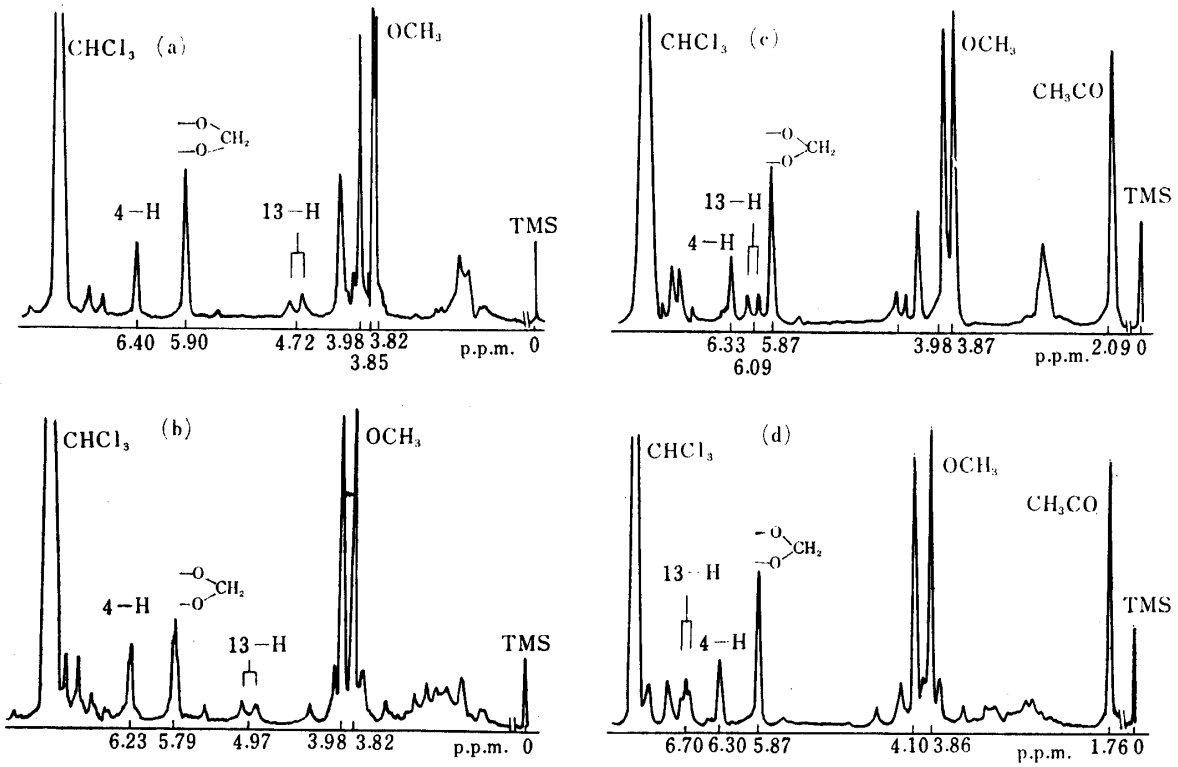
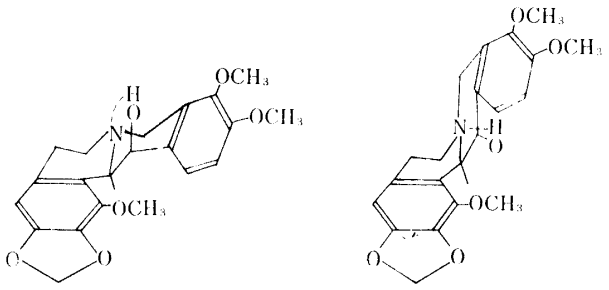


Fig. 3. Nuclear Magnetic Resonance Spectra
a : Ⅷα b : Ⅷβ c : Ⅸα d : Ⅸβ (in $CHCl_3$)

ring proton signals of Ⅷβ appeared as broad peaks at 3.3~2.4 p.p.m. similar to that of ophiocarpine and epiophiocarpine, fused *trans*-quinolizidine system. Musher and Richards[6] observed that *cis*-decalins give a sharp resonance peaks due to the ring protons, in contrast to the broad signals shown by *trans*-decalins. Similar behaviour has already been reported for *cis-trans* isomers of systems containing fused rings.[7] Recently, Katriztky, *et al.*[8] reported that this behaviour is not simply related to the *cis* or *trans* arrangement of the ring in the quinolizidine series. However, nuclear magnetic resonance spectra of Ⅷα, Ⅸα, and Ⅷβ, Ⅸβ were found to be significantly different in appearance in contrast to the Katriztky's criterion in quinolizidine series.

From these results, it can be concluded that Ⅷβ exists in the *trans*-fused quinolizidine conformation, which must contain a hydrogen bonding axial hydroxyl group. On the contrary, it is highly unlikely that the B/C ring fusion in Ⅷα could be other than *cis*. The C_{13} hydroxyl group in Ⅷα should be axial for hydrogen bonding.



Ⅷβ (13*R*:13*aR*) Ⅷα (13*S*:13*aR*)

Chart 4.

The absolute configuration of Ⅷα and Ⅷβ, based on the preceding correlations, can be assigned as 13*S*:13*aR* and 13*R*:13*aR*, respectively.

As described above, Marshall, Pyman, and Robinson[1] reported that natural *l*-α-narcotine (Iα) corresponds to *l*-α-hydrastine (Ⅺα), obtained by epimerization of natural *l*-β-hydrastine (Ⅺβ), in its stereochemical configuration by consideration of the optical rotatory power at 546 mμ. It is known, however, that configurational assignments based on rotations obtained at the D-line are at times equivocal.[9] Therefore, the rotatory dispersion curves of these alkaloids were measured, cf. Fig. 4. The optical rotatory dispersion curves of Iα and Ⅺβ showed the negative Cotton-effect, centered near 310 mμ, whereas Iβ and Ⅺα exhibited the positive Cotton-effect in the same region. This suggests that the configuration at the asymmetric $C_{1,\alpha}$ positions of Iα and Iβ correspond to Ⅺβ and Ⅺα, designated as the αS:1*R* and αR:1*R*, respectively. Therefore, *l*-α-narcotine (Iα) and *l*-β-narcotine (Iβ) should have the absolute configuration assigned as αS:1*R* and αR:1*R*, respectively.

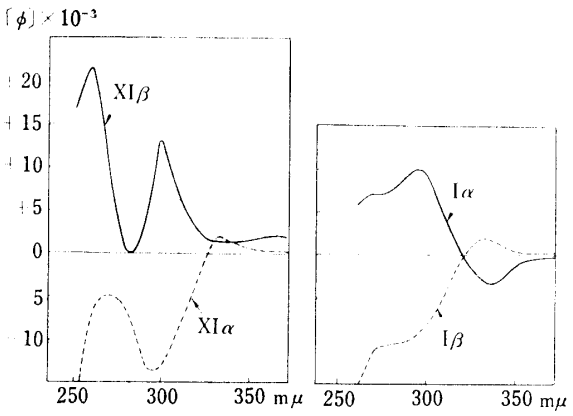
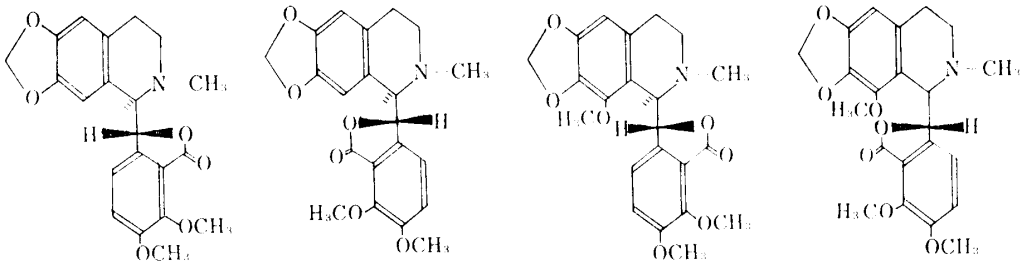


Fig. 4. Optical Rotatory Dispersion Curves of *l*-α-Hydrastine (Ⅺα), *l*-β-Hydrastine (Ⅺβ), *l*-α-Narcotine (Iα) and *l*-β-Narcotine (Iβ) in 2*N* Hydrochloric Acid

Interestingly the absolute configuration of natural *l*-α-narcotine at C_1 has the same configuration as that at the C_9 of morphine, codeine and thebain, which are accompanied by narcotine and (+)-laudanosine in *papaver somniferum* L.

6) J. Musher, R. E. Richards : Proc. Chem. Soc., **1958**, 230; J. I. Musher : J. Am. Chem. Soc., **83**, 1146 (1961).
7) W. B. Moniz, J. A. Dixon : J. Am. Chem. Soc., **83**, 1671 (1961); H. Booth : Tetrahedron, **19**, 91 (1963).
8) T. M. Moynehan, K. Schofield, R. A. Y. Jones, A. R. Katritzky : J. Chem. Soc., **1962**, 2637.
9) H. G. Leemann : Chimia (Switz.), **14**, 8 (1960); C. Djerassi : "Optical Rotatory Dispersion," 236 (1960), McGraw-Hill Book Comp. Inc., New York.



l-α-Hydrastine (αR:1R) (XIα) | *l*-β-Hydrastine (αS:1R) (XIβ) | *l*-β-Narcotine (αR:1R) (Iβ) | *l*-α-Narcotine (αS:1R) (Iα)

Chart 5.

Experimental

All melting points are uncorrected. The NMR spectra were measured in $CHCl_3$ or $CDCl_3$ with tetramethylsilane or cyclohexane as internal standard, using a Varian instrument, operating at 60 Mc.p.s. IR spectra were obtained on a Hitachi EPI-2 double-beam spectrophotometer using either rock salt prism or LiF prism using polystyrene for calibration. UV spectra were determined on a Hitachi EPS-2 automatic recording spectrophotometer in EtOH solution. RD curves were measured with the Rudolph automatic recording spectropolarimeter.

***l*-α-Narcotine (Iα)**——Commercial samples were recrystallized from EtOH, m.p. 176~177°, $[\alpha]_D$ −195° (c=1.05, $CHCl_3$), −175° (c=1.00, dioxane), UV λ_{max}^{EtOH} mμ (log ε): 291 (3.62), 310 (3.70); $\lambda_{max}^{dioxane}$ mμ (log ε): 291.5 (3.65), 309 (3.69).

***l*-β-Narcotine (Iβ)**——According to the procedure reported by Robinson,[1] a solution of Iα (70 g.) and benzoyl peroxide (2.5 g.) and KOH (70 g.) in MeOH (1 L.) was refluxed 48 hr. and then diluted with H_2O (500 ml.) and acidified with 20% HCl. The MeOH solution was evaporated under reduced pressure and the bases precipitated from the cooled solution by 20% NH_4OH. After filtration and washing with H_2O, the resulting crystalline product was extracted with EtOH (400 ml.) at 60° for 2 min. and filtered, the crystal residue was recrystallized from AcOEt to yield 24 g. (34.3%), m.p. 177~179°, $[\alpha]_D$ −86° (c=1.00, $CHCl_3$), $[\alpha]_D$ −110° (c=1.00, dioxane), UV λ_{max}^{EtOH} mμ (log ε): 290 (3.58), 312 (3.68); $\lambda_{max}^{dioxane}$ mμ (log ε): 290 (3.63), 310 (3.67). *Anal.* Calcd. for $C_{22}H_{23}O_7N$: C, 63.91; H, 5.61; N, 3.39. Found: C, 64.01; H, 5.62; N, 3.51.

***l*-α-Narcotinediol (IIα)**——IIα was prepared according to the directions of Robinson[2] in 81.5% yield, m.p. 133~134°, $[\alpha]_D$ +63.5° (c=1.00, $CHCl_3$), UV: λ_{max}^{EtOH} 284 mμ (log ε 3.60).

***l*-β-Narcotinediol (IIβ)**——IIβ was obtained from Iβ as an oil, in the same manner as described for IIα. The picrate was recrystallized from H_2O, m.p. 97~107°. *Anal.* Calcd. for $C_{28}H_{30}O_{14}N_4$: C, 52.01; H, 4.68. Found: C, 52.36; H, 4.62.

***l*-α-Narcotinediol Diacetate (IIIα)**——A solution of IIα (3.00 g.) and Ac_2O (6 ml.) in anhyd. pyridine (6 ml.) was kept overnight at room temperature. The solvent was evaporated *in vacuo*, the residue extracted with $CHCl_3$, washed with 10% $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4. The solvent was removed and the product recrystallized from Me_2CO-MeOH to give 2.79 (75.8%) of crystals, m.p. 111~113°, $[\alpha]_D$ −68° (c=1.00, $CHCl_3$). *Anal.* Calcd. for $C_{26}H_{31}O_9N$: C, 62.26; H, 6.23; N, 2.79. Found: C, 62.30; H, 6.35; N, 2.96.

***l*-β-Narcotinediol Diacetate (IIIβ)**——Similar to IIIα as above, IIIβ was prepared in 38% yield from IIβ obtained by reduction of Iβ, recrystallized from Me_2CO-MeOH, m.p. 124~125°, $[\alpha]_D$ −22° (c=1.00, $CHCl_3$). *Anal.* Calcd. for $C_{26}H_{31}O_9N$: C, 62.26; H, 6.23; N, 2.79. Found: C, 62.20; H, 6.19; N, 2.84.

1-(2-methyl-3,4-dimethoxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (IV)——a) From IIIα: A mixture 1.00 g. of IIIα, 1.0 g. of 10% Pd-C and 40 ml. of EtOH was heated in an autoclave at initial H_2 pressure of 55 kg./cm² and constantly stirred at 95° for 5.5 hr. and then allowed to stand overnight at room temperature. After filtration, the residue on evaporation was extracted with $CHCl_3$. The extract was washed with 10% Na_2CO_3, and H_2O, dried, and evaporated giving 0.70 g. of the residue. The residue was recrystallized from MeOH to give 0.34 g. (44.3%) of crystalline product, m.p. 99~101°, $[\alpha]_D$ +33° (c=1.00, $CHCl_3$), UV: λ_{max}^{EtOH} 282 mμ (log ε 3.39). *Anal.* Calcd. for $C_{22}H_{27}O_5N$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.71; H, 7.17; N, 3.60.

b) From IIIβ: As in (a) above, a mixture of IIIβ (700 mg.), EtOH (30 ml.) and 10% Pd-C (1.0 g.) was hydrogenolysed at 70 kg./cm², 100° for 4 hr. in the same manner to afford 160 mg. (30%) of recrystallized product (MeOH) melting at 99~101°, $[\alpha]_D$ +33° (c=1.00, $CHCl_3$). *Anal.* Calcd. for $C_{22}H_{27}O_5N$: C, 68.55;

H, 7.06; N, 3.63. Found : C, 68.65; H, 7.02; N, 3.79. This product showed no mixed melting point depression and an identical IR spectra with Ⅳ obtained in (a).

***l*-α-1-(α-Hydroxy-2′-chloromethyl-3′,4′-dimethoxybenzyl)-2-methyl-8-methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (Vα)**——a) By treatment with HCl in $CHCl_3$: Dry HCl was passed through a mixture 8.0 g. of Ⅱα, 2.0 g. of $CaCl_2$ and 80 ml. of $CHCl_3$ at room temperature for 4 hr., then filtered. The residue was recrystallized from MeOH-Me_2CO to give 6.6 g. (70.3%) of crystalline product, m.p. 175~175.5°, $[\alpha]_D$ +10° (c=1.00, $CHCl_3$), UV : λ_{max}^{EtOH} 285 mμ (log ε 3.55). *Anal.* Calcd. for $C_{22}H_{26}O_6NCl \cdot HCl \cdot H_2O$: C, 53.88; H, 5.96; N, 2.86. Found : C, 54.19; H, 5.77; N, 2.89.

b) By treatment with $SOCl_2$ in $CHCl_3$: A solution 20.85 g. of Ⅱα in 160 ml. of $CHCl_3$ was cooled in ice-bath. A solution 3.80 ml. of $SOCl_2$ in 20 ml. of $CHCl_3$ was then added portionwise with stirring. After the addition was completed the solution was allowed to stand at room temperature for 3 hr., the solvent was then evaporated and the resulting residue recrystallized from MeOH-Me_2CO to afford 7.5 g. (30.6%) of crystalline product, m.p. 174~175°, identical with Vα obtained in (a) by mixture melting point determination and IR comparison.

***l*-β-1-(α-Hydroxy-2′-chloromethyl-3′,4′-dimethoxybenzyl)-2-methyl-8-methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (Vβ)**——a) By treatment with HCl in $CHCl_3$: The oily material (Ⅱβ) was treated with dry HCl in $CHCl_3$ in the same manner as described in Vα (a), to give a solid (Vβ). After recrystallization from MeOH-Me_2CO, the product melted at 147~152° (39.7% over-all yield from Iβ). *Anal.* Calcd. for $C_{22}H_{26}O_6NCl \cdot HCl$: C, 55.94; H, 5.76; N, 2.97. Found : C, 55.69; H, 5.42; N, 2.91.

b) By treatment with $SOCl_2$ in $CHCl_3$: The oily material (Ⅱβ) was treated with $SOCl_2$ in $CHCl_3$ in the same manner as described in Vα (b) to afford a solid, which was recrystallized from MeOH-Me_2CO, m.p. 57~86°. After drying over P_2O_5 *in vacuo* at 110° for 2 hr., the product melted at 155° (56% over-all yield from Iβ), $[\alpha]_D$ −35.5° (c=1.00, $CHCl_3$), UV : λ_{max}^{EtOH} 285 mμ (log ε 3.47). *Anal.* Calcd. for $C_{22}H_{26}O_6NCl \cdot HCl$: C, 55.94; H, 5.76; N, 2.97. Found : C, 56.11; H, 5.88; N, 3.24. This product was identical with Vβ obtained in (a) by mixed melting point determination.

***l*-α-1-(α-Hydroxy-2′-methyl-3′,4′-dimethoxybenzyl)-2-methyl-8-methoxy-6,7-methylenedioxy-1,2,3,-4-tetrahydroisoquinoline (VIα)**——A solution Vα (4.9 g.) in EtOH (180 ml.) was hydrogenated over 20% Pd-C (0.98 g.) at atmospheric pressure. After H_2 absorption, the catalyst was removed, the filtrate was evaporated and the resulting solid was dissolved in H_2O and decomposed with Na_2CO_3, extracted with Et_2O. After evaporation the residue was recrystallized from iso-PrOH to yield 2.7 g. (67.3%) of crystalline product, m.p. 101~102°, $[\alpha]_D$ −35.5° (c=1.00, $CHCl_3$), UV : λ_{max}^{EtOH} 282 mμ (log ε 3.42). *Anal.* Calcd. for $C_{22}H_{27}O_6N$: C, 65.82; H, 6.78; N, 3.49. Found : C, 65.59; H, 6.88; N, 3.53.

***l*-β-1-(α-Hydroxy-2′-methyl-3′,4′-dimethoxybenzyl)-2-methyl-8-methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (VIβ)**——Vβ was hydrogenenated over 5% Pd-C in the same manner as described for Ⅵα to afford a crystalline product. After recrystallization from EtOH, the product melted at 100~102°, yield 82%, $[\alpha]_D$ +24.5° (c=1.00, $CHCl_3$), UV : λ_{max}^{EtOH} 282.5 mμ (log ε 3.36). *Anal.* Calcd. for $C_{22}H_{27}O_6N$: C, 65.82; H, 6.78; N, 3.49. Found : C, 65.76; H, 6.84; N, 3.39.

***l*-α-13-Hydroxy-2,3-methylenedioxy-1,9,10-trimethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizinium Chloride (VIIα, X=Cl)**——a) From Vα by treatment with K_2CO_3 : To saturated K_2CO_3 solution (2.5 ml.) was added Vα (0.76 g.). After several minutes the solution was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over K_2CO_3, evaporated *in vacuo*, and the residue was recrystallized from MeOH-Me_2CO to yield 0.37 g. (54.7%), m.p. 235~236° (decomp.). The analytical sample was recrystallized from MeOH-Me_2CO twice, m.p. 241~242° (decomp.), $[\alpha]_D$ −191.5° (c=1.00, EtOH), UV : λ_{max}^{EtOH} 282.5 mμ (log ε 3.57).

b) From Vα by treatment with NH_3 : A ethanolic solution (4 ml.) containing NH_3 (9.2 w/v%) was added to a suspension of Vα (2.0 g.) in EtOH (30 ml.). After standing at room temperature overnight, the solvent was evaporated and then the residue extracted with $CHCl_3$. The extract was dried, evaporated yielding a solid residue. After recrystallization from MeOH-Me_2CO the product melted at 239~240° (decomp.), 1.5 g. (84.4%). This product was identical with the sample obtained in (a) by mixture melting point determination and IR spectra comparison. *Anal.* Calcd. for $C_{22}H_{26}O_6NCl$: C, 60.62; H, 6.01; N, 3.21. Found : C, 60.34; H, 6.12; N, 3.19.

c) From Ⅱα by treatment with TsCl in pyridine : To a solution of Ⅱα (1.00 g.) in dry pyridine (5 ml.) was added portionwise *p*-toluenesulfonyl chloride (0.46 g.) in an ice-bath. The reaction mixture was kept at room temperature overnight, and then the solvent was removed *in vacuo*. The residue was dissolved in acetonitrile (25 ml.), and mixed with a hot solution of NaI (2.5 g.) in acetonitrile (25 ml.). Filtration and evaporation of the filtrate left a solid which was triturated with H_2O. After recrystallization from MeOH-H_2O, the product melted at 240~242° (decomp.), 0.81 g. (62.0%). A mixture of 0.50 g. of this methiodide and Dowex 1-X 2 anion exchange resin (OH form, 10 ml.) in H_2O (100 ml.) was stirred fo 1 hr,, and filtered, washed with H_2O. The combined filtrates were neutralized with an equivalent ammount of 0.1*N* HCl, and then the solvent removed *in vacuo*, the resulting residue was recrystallized from MeOH-Me_2CO to yield 0.36 g. (88.8%) of crystalline product, m.p. 241~242° (decomp.), which was identical with the product obtained in (a) by mixed melting point determination and IR comparison.

***l*-β-13-Hydroxy-2,3-methylenedioxy-1,9,10-trimethoxy-5,6,13,13*a*-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizinium Chloride (VIIβ, X=Cl)**——a) From Vβ by treatment with K_2CO_3 : To a saturated K_2CO_3 solution was added Vβ in the same manner as described above. After recrystallization from MeOH-Me_2CO the crystalline product melted at 235~238° (decomp.), yield. 77.5%, $[\alpha]_D$ −184° (c=1.00, EtOH), UV : λ_{max}^{EtOH} 282.5 mμ (log ε 3.54). *Anal.* Calcd. for $C_{22}H_{26}O_6NCl$: C, 60.62; H, 6.01; N, 3.21. Found : C, 60.58; H, 6.16; N, 3.23.

b) From Vβ by treatment with NH_3 : Vβ was treated with EtOH-NH_3 in the same manner as described above to yield crystalline product (78.0%), m.p. 235~238° (decomp.) after recrystallization from EtOH. This product was identical with that obtained in (a) by mixed melting point determination.

c) From IIβ by treatment with TsCl in pyridine : The oily material (IIβ), prepared from *l*-β-narcotine (Iβ) (1.10 g.) by reduction of $LiAlH_4$ was dissolved in dry pyridine (5 ml.), and treated with *p*-toluenesulfonyl chloride (0.51 g.) and then with NaI (2.7 g.) in acetonitrile. The usual work up gave 0.54 g. (37.2% from Iβ) of crystalline methiodide (VIIβ, X=I), m.p. 168~170° (decomp.). This methiodide was converted into a methochloride (VIIβ, X=Cl), m.p. 235~238° (decomp.) by treatment with Dowex 1-X 2 (OH form) anion exchange resin and then 0.1*N* HCl in the usual way, yield 70.9%. The methochloride was identical with that obtained in (a) by mixed melting point determination and IR spectra comparison.

***l*-α-13-Hydroxy-2,3-methylenedioxy-1,9,10-trimethoxy-5,6,13,13*a*-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine (VIIIα)**——A mixture of the methochloride (VIIα, X=Cl) (1.5 g.) and *o*-dichlorobenzene (6 ml.) was refluxed 3 hr. and then evaporated *in vacuo*, the resultng residue recrystallized from MeOH to yield 1.04 g. (78.3%) of crystalline product, m.p. 165~166°, $[\alpha]_D$ −195° (c=1.00, $CHCl_3$), UV : λ_{max}^{EtOH} 282 mμ (log ε 3.51). *Anal.* Calcd. for $C_{21}H_{23}O_6N$: C, 65.44; H, 6.02; N, 3.63. Found : C, 65.40; H, 6.10; N, 3.84. Methiodide : A solution of VIIIα (100 mg.) and MeI (0.1 ml.) in MeOH (2.5 ml.) was refluxed 4 hr. After evaporation of the solvent, the residue was recrystallized from MeOH-H_2O to give 45 mg. of crystalline product, m.p. 242~243° (decomp.), which was identical with the methiodide (VIIα, X=I) obtained above by mixed melting point determination and IR spectra comparison.

***l*-β-13-Hydroxy-2,3-methylenedioxy-1,9,10-trimethoxy-5,6,13,13*a*-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine (VIIIβ)**——A mixture of the methochloride (VIIβ, X=Cl) and *o*-dichlorobenzene was refluxed for 6 hr. Work up in the same manner as VIIIα gave a crystalline product (74.2%), m.p. 190~191° (from MeOH), $[\alpha]_D$ −290° (c=1.00, $CHCl_3$), UV : λ_{max}^{EtOH} 281.5 mμ (log ε 3.47). *Anal.* Calcd. for $C_{21}H_{23}O_6N$: C, 65.44; H, 6.02; N, 3.63. Found : C, 65.59; H, 5.96; N, 3.65. Methiodide : A solution of VIIIβ (200 mg.) and MeI (0.2 ml.) in MeOH (10 ml.) was refluxed for 4 hr., and then evaporated, the residue was recrystallized from H_2O affording 178 mg. of crystalline product, m.p. 170~173° (decomp.), which was identical with methiodide (VIIβ, X=I) obtained above by mixed melting point determination and IR comparison.

***l*-α-13-Acetoxy-2,3-methylenedioxy-1,9,10-trimethoxy-5,6,13,13*a*-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine (IXα)**——A solution of VIIIα (380 mg.) in Ac_2O (0.5 ml.) and pyridine (10 ml.) was kept overnight at room temperature and then concentrated to dryness *in vacuo*. The residue was extracted with $CHCl_3$ and washed with 10% Na_2CO_3, H_2O and then dried over Na_2SO_4, evaporated to give a crystalline product. Recrystallization from EtOH gave 250 mg. (59.3%), m.p. 169~170°, $[\alpha]_D$ −106° (c=1.00, $CHCl_3$), UV : λ_{max}^{EtOH} 282 mμ (log ε 3.44). *Anal.* Calcd. for $C_{23}H_{25}O_7N$: C, 64.62; H, 5.90; N, 3.28. Found : C, 64.65; H, 6.04; N, 3.42.

***l*-β-13-Acetoxy-2,3-methylenedioxy-1,9,10-trimethoxy-5,6,13,13*a*-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine (IXβ)**——VIIIβ was similarly acetylated with Ac_2O in pyridine as described above. After recrystallization from EtOH the crystalline product melted at 172.5~173.5°, yield, 85.5%, $[\alpha]_D$ −389° (c=1.00, $CHCl_3$), UV : λ_{max}^{EtOH} 281 mμ (log ε 3.42). *Anal.* Calcd. for $C_{23}H_{25}O_7N$: C, 64.62; H, 5.90; N, 3.28. Found : C, 64.52; H, 5.98; N, 3.45..

2,3-Methylenedioxy-1,9,10-trimethoxy-5,6,13,13*a*-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine (X)——a) From Xα : A mixture of Xα (700 mg.), EtOH (40 ml.) and 10% Pd-C (700 mg.) was heated in an autoclave at 50 kg./cm² of initial H_2 pressure and constantly stirred at 90° for 4 hr., and then allowed to stand overnight at room temperature. After filtration, the residue on evaporation was extracted with $CHCl_3$. The extract was washed with 10% Na_2CO_3 and H_2O, dried, evaporated. After recrystallization from MeOH twice the product melted at 150~152°, 290 mg. (48%), $[\alpha]_D$ −270° (c=1.00, $CHCl_3$), UV : λ_{max}^{EtOH} 283.5 mμ (log ε 3.47), IR ν cm^{-1} : 2837, 2789, 2750 (CCl_4, LiF prism 2.0 cm. cell). *Anal.* Calcd. for $C_{21}H_{23}O_5N$: C, 68.28; H, 6.28; N, 3.79. Found : C, 68.55; H, 6.28; N, 4.04. The mother liquors were evaporated to dryness, the residue was chromatographed on neutral alumina (Woelm.). The first $CHCl_3$ elute containing MeOH (2 v/v%) afforded a crystalline material, recrystallized from MeOH to give 110 mg. (18.2%) of racemic X, m.p. 139~141°, identical with the sample (m.p. 140~141.5°) synthesized by another route by mixed melting point determination.

b) From Xβ : According to the procedure described above in (a), a mixture of Xβ (400 mg.), EtOH (30 ml.) and 10% Pd-C was hydrogenolyzed at 78° and 50 kg./cm² initial pressure for 4 hr. Work up in the same manner gave 150 mg. (43.3%) of (−)-X, m.p. 150~152°, $[\alpha]_D$ −271° (c=1.00, $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{23}O_5N$: C, 68.23; H, 6.28; N, 3.79. Found : C, 68.13; H, 6.36; N, 3.84. This product

was identical with a sample obtained above by mixed melting point determination and IR spectra comparison (KBr disk). Work up in the same manner gave 60 mg. (17.3%) of racemic X, m.p. 139~141°, which was identified by comparison with sample (m.p. 140~141.5°) synthesized by another route.

c) From VIIIβ : A mixture of VIIIβ (300 mg.) and 20% HCl (10 ml.) and Zn powder (1.0 g.) was heated in water bath for 1.5 hr. and then filtered, evaporated *in vacuo*, made basic with NH_4OH. The solid was extracted with $CHCl_3$, and the extract dried over Na_2SO_4, evaporated, the residue recrystallized from MeOH yielding 170 mg. (44%) of crystalline product, m.p. 140~141.5°, $[\alpha]_D$ ±0° (c=1.00, $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{23}O_5N$: C, 68.28; H, 6.28; N, 3.79. Found : C, 68.14; H, 6.12; N, 3.63.

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Summary

The natural *l*-α-narcotine (Iα) and its epimer *l*-β-narcotine (Iβ) were stereospecifically converted into 1-(2-methyl-3,4-dimethoxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (IV) and (−)-1-methoxycanadine (X), respectively. According to these results, the absolute configuration of Iα and Iβ were established as (α*S*:1*R*) and (α*R*:1*R*), respectively.

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〔Added in proof〕 This paper was presented at the Kanto Branch Meeting of Pharmaceutical Society of Japan, Tokyo, April, 1963. After submission of this paper, the report of the stereochemistry and absolute configuration of narcotine (A. R. Battersby, H. Spencer : Tetrahedron Letters, No. 1, 11 (1964)) was seen. They described the same configuration as our results by a method similar to the present one. However, the stereochemistry of VIIIα was different from our results.