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# 149. Michitoshi Ohta, Hideo Tani, and Sekiko Morozumi : The Stereochemistry of Hydrastine, Narcotine, Ophiocarpine, and their Derivatives. I. Absolute Configuration of Hydrastine and Ophiocarpine.*1

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The absolute configurations of hydrastine and narcotine, members of the phthalide group of isoquinoline alkaloids have not been established.

Ophiocarpine was shown to have the structure, 13-hydroxy-canadine by Manske[1] in 1939 and (±)-ophiocarpine was synthesized by Govindachari[2] and Takemoto, *et al.*,[3] but their stereochemistry has not been fully investigated.

The evident close relationship between hydrastine and (−)-canadine and their copresence in plants have often been a matter of comment. It is, therefore, of more than passing interest that the former is convertible into the latter without racemization by chemical means.[4]

In the present paper, we wish to report that hydrastine was chemically correlated with ophiocarpine and also (−)-canadine. Since the latter are of known absolute configuration, thus the absolute configurations of these alkaloids have been elucidated.

Marshall, Pyman, and Robinson[5] in 1934, observed that the prolonged action of hot methanolic potassium hydroxide on hydrastine results in the formation of an equilibrium mixture of the original base (*l*-β-hydrastine (Iβ)) and a new optically active isomeride (*l*-α-isomer (Iα)).

Mirza and Robinson[6] reported that lithium aluminum hydride reduction of *l*-β-hydrastine (Iβ) to a *l*-β-hydrastinediol (IIβ) followed by treatment with thionyl chloride gave dihydroanhydroberberinemethochloride, which afforded dihydroanhydroberberine on heating at 160~170° under diminished pressure. The final oxidation to berberine was easily accomplished.

Subsequently, Dúbravková, *et al.*[7] also succeeded in synthesizing 1-methoxy-7,8-dihydroberberine methiodide from narcotine through narcotinediol and its ditosyl derivatives.

Lithium aluminum hydride reduction of natural *l*-β-hydrastine (Iβ) and its epimer *l*-α-hydrastine (Iα) produced by prolonged action of hot methanolic potassium hydroxide on Iβ, gave the corresponding diols, a crystalline diol (IIβ), m.p. 145~146°, $[\alpha]_D$ +19° ($CHCl_3$), and an oily diol (IIα), respectively.[6]

Selective tosylation of *l*-β-diol (IIβ) with an equimolar amount of *p*-toluenesulfonyl chloride in pyridine afforded the monotosylate, due to expected lack of steric hindrance of the primary alcohol. Without isolation, the monotosylate was converted into the methotosylate (Vβ, X=OTs) by spontaneous intramolecular quaternarization. The corresponding methiodide (Vβ, X=I), m.p. 227~229° (decomp.) was obtained in a better yield

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*1 Preliminary communication : Tetrahedron Letters, No.13, 859 (1963).

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1) R. H. F. Manske : Can. J. Research, **17B**, 51 (1939).
2) T. R. Govindachari, S. Rajadurai : J. Chem. Soc., **1957**, 557.
3) T. Takemoto, Y. Kondo : Yakugaku Zasshi, **82**, 1413 (1962).
4) R. H. F. Manske, H. L. Holmes : "The Alkaloids," Vol. IV, 176 (1954), Academic Press, New York.
5) M. A. Marshall, F. L. Pyman, R. Robinson : J. Chem. Soc., **1934**, 1315.
6) R. Mirza, R. Robinson : Nature, **166**, 271 (1950).
7) L. Dúbravková, I. Ježo, P. Šefčovič, Z. Votický : Chem. Zvesti., 8, 576 (1954) (C. A., **50**, 374 (1956)).

(66%) by the action of sodium iodide in acetonitrile solution on the unpurified methotosylate, and then converted into methochloride (Vβ, X=Cl), m.p. 225~229° (decomp.), $[\alpha]_D$ −169.5° (EtOH), by passing through ion exchange column of Dowex 1-X 2 and treatment with an equivalent amount of 0.1*N* hydrochloric acid. Analogously, the *l*-α-diol (IIα) reacted with *p*-toluenesulfonyl chloride in pyridine and then the same procedure give the methiodide (Vα, X=I), m.p. 253~255° (decomp.), in 75% yield and which was converted into the methochloride (Vα, X=Cl), m.p. 191~193° (decomp.), $[\alpha]_D$ −166.5° (EtOH).

On the other hand, the *l*-β-diol (IIβ) also reacted with thionyl chloride or hydrogen chloride in chloroform smoothly at room temperature to afford the hydrochloride of monochloride (IIIβ), m.p. 160~163°, $[\alpha]_D$ +101.5° ($CHCl_3$), which cyclized to the quaternary methochloride (Vβ, X=Cl) by treatment with aqueous potassium carbonate or alcoholic ammonia solution at room temperature. In the same way, *l*-α-diol (IIα) was converted to the quaternary methochloride (Vα, X=Cl) *via* the hydrochloride of monochloride (IIIα). The quaternary salts were identical with the methochloride obtained from quaternarization of the monotosylate by mixed melting point determination and infrared spectra comparison.

Furthermore, catalytic hydrogenation of the hydrochloride (IIIβ) with 10% palladium on carbon at room temperature gave the dechloro compound (IVβ) in 78% yield, m.p. 84~86°, $[\alpha]_D$ +86° ($CHCl_3$). Analogously, the compound (IIIα) was hydrogenated with 20% palladium on carbon to give the dechloro compound (IVα) in 70% yield, m.p. 153~154°, $[\alpha]_D$ +80° ($CHCl_3$).

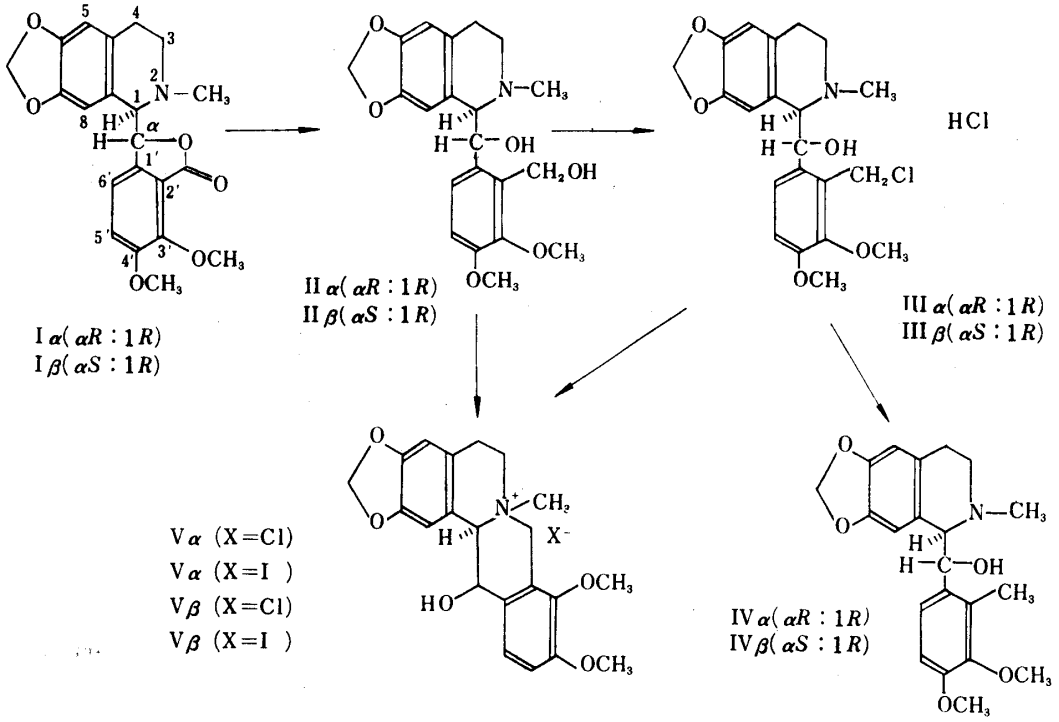



Chart 1.

Dry *l*-α-methochloride (Vα, X=Cl) was pyrolyzed at 205~210° under diminished pressure to give a small amount of isomeride of original methochloride and ophiocarpine (VIα), m.p. 186~188°, $[\alpha]_D$ −283° ($CHCl_3$) in 13% yield, whose melting point and infrared spectra were identical with the corresponding properties of the natural ophiocarpine*[2,1] as shown in Fig. 1.

*[2] We should like to thank Dr. Manske for his generous gift of ophiocarpine.

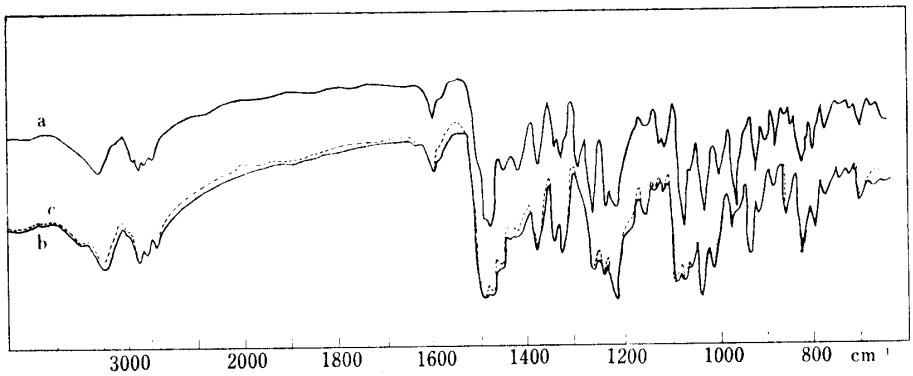



Fig. 1. Infrared Spectra

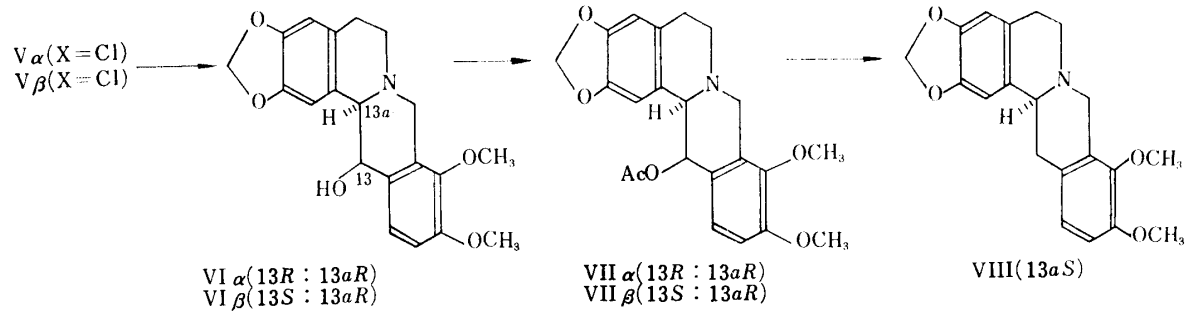
a : epiophiocarpine (Ⅵβ)
b : ophiocarpine (Ⅵα), obtained by author.
c : ophiocarpine (broken line), provided by Dr. Manske. (in KBr disc)

On the other hand, *l*-β-methochloride (Vβ, X=Cl) was refluxed in *o*-dichlorobenzene at 210~215° to afford the 13-epimer of ophiocarpine (Ⅵβ), m.p. 161~162°, $[\alpha]_D$ −282° ($CHCl_3$), in good yield (68%). Treatment of 13-epiophiocarpine (Ⅵβ) with methyl iodide furnished the original methiodide (Vβ, X=I) as expected. Ophiocarpine, however, did not gave the methiodide (Vα, X=I), but contrary to expectations afforded the isomeric methiodide, m.p. 271~272° (decomp.).*3

Govindachari, *et al.*,[8] previously, reported that the hydrogenolysis of ophiocarpine with 5% palladium on carbon promoted by perchloric acid in acetic acid afforded racemic (±)-canadine.

In order to correlate both stereoisomers (Ⅵα and Ⅵβ) with (−)-canadine, the following experiments were carried out. Both Ⅵα, Ⅵβ were acetylated with acetic anhydride at room temperature to give the ophiocarpine acetate (Ⅶα), m.p. 141~143°,*4 $[\alpha]_D$ −357.5° ($CHCl_3$) and 13-epiophiocarpine acetate (Ⅶβ), m.p. 170~171°, $[\alpha]_D$ −129° ($CHCl_3$), respectively.

Finally, catalytic hydrogenolysis of both acetates with 5% palladium on carbon at 60° at 80~100 kg./cm² hydrogen pressure yielded (−)-canadine (Ⅷ), m.p. 131~134°, $[\alpha]_D$ −297° ($CHCl_3$) and (±)-canadine, m.p. 169~172°, $[\alpha]_D$ ±0° ($CHCl_3$), whose melting point




VI α(13*R* : 13a*R*)
VI β(13*S* : 13a*R*)
VII α(13*R* : 13a*R*)
VII β(13*S* : 13a*R*)
VIII(13a*S*)

Chart 2.

*3 lit.[1] ophiocarpine methiodide, m.p. 271° (decomp.). The isomerism due to the introduction of another center of asymmetry at the N atom in tetrahydroberberine derivatives had been studied. (J. Gadamer : Arch. Pharm., **248**, 47 (1910); C. Tani, *et al.* : Yakugaku Zasshi, **72**, 447 (1952); *Ibid.*, **74**, 315 (1954); P. B. Russell : J. Am. Chem. Soc., **78**, 3115 (1956)).

*4 T. R. Govindachari, *et al.*[2] reported m.p, 165~167°, but the acetate from the sample of ophiocarpine provided by Dr. Manske melted at 133~137°, undepressed on admixture with a sample obtained above and the IR spectra of the two compounds were identical.

8) T. R. Govindachari, S. Rajadurai, N. Viswanathan : J. Sci. Ind. Research (India), **18B**, 176 (1959) (C. A., **54**, 1582 (1960)).

and infrared spectra were identical with the authentic sample*[5] in each case, as shown Fig. 2. Ophiocarpine acetate gave (−)-canadine in 13% yield and (±)-canadine in 42% yield and 13-epiophiocarpine acetate gave the former in 5% and the latter in 49% yield, respectively.

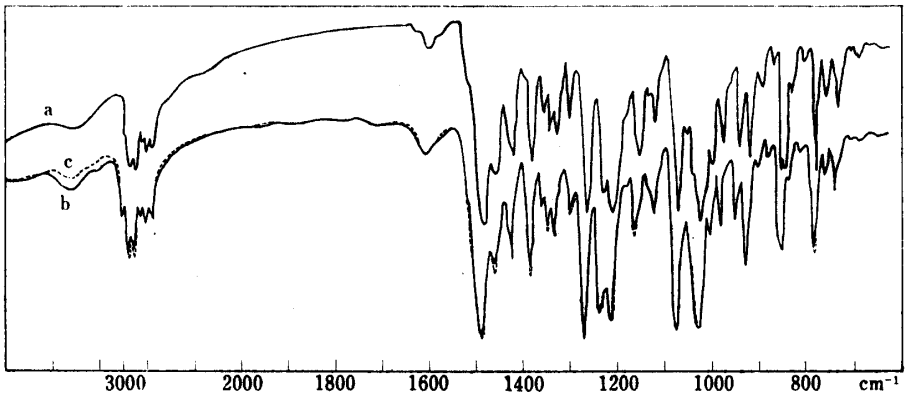



Fig. 2. Infrared Spectra

a : (−)-canadine
b : (−)-canadine, obtained from ophiocarpine.
c : (−)-canadine, obtained from epiophiocarpine. (in KBr disc)

The configuration of ophiocarpine (Ⅵα) and 13-epiophiocarpine (Ⅵβ) were confirmed as follows. An interesting method of studying the stereochemistry at $C_{13a}$ is by means of the infrared bands between 2700 and 2800 $cm^{-1}$. Wenkert's original contributions[9] to this subject were further refined by Bohlmann,[10] who pointed out that the relative simplicity or complexity of these peaks is due to the interaction between the lone-pair electrons of nitrogen and at least two axial C-H bonds which are adjacent to the nitrogen atom and trans to the nitrogen lone-pair. In the present work this idea was extended to tetrahydroberberine series in which the B/C ring system can be considered as a substituted quinolizidine. As shown in Fig. 3, the infrared spectra of ophiocarpine and 13-epiophiocarpine near 2800 $cm^{-1}$ exhibit complex patterns, so that both isomers should have a trans quinolizidine system. In OH stretching region, a broad band near 3520 $cm^{-1}$, showing strong hydrogen bond, is observed with ophiocarpine, on the other hand, only a sharp, free OH absorption band near 3600 $cm^{-1}$, with 13-epiophiocarpine. Apparently more extensive intramolecular hydrogen bonding is present in ophiocarpine than in 13-epimer.

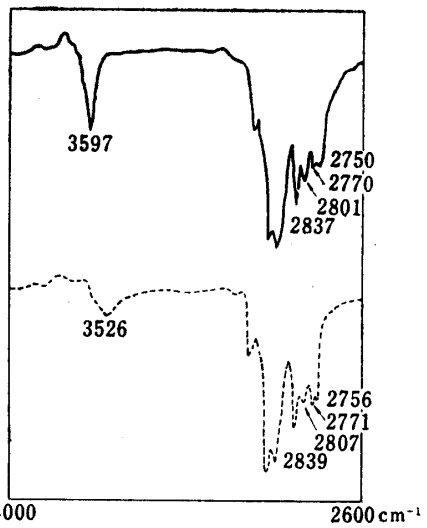



Fig. 3. Infrared Spectra of Epiophiocarpine (Ⅵβ) (——) and Ophiocarpine (Ⅵα) (------) (4000~2600 $cm^{-1}$ in 0.7 mmole $CCl_4$ solution, 2 cm. cell, LiF prism)

Prelog and Häfliger[11] showed that distinct differences exist in the $pK_a$ values of isomeric 1,2-aminoalcohols, the *cis-oid* isomer being the stronger base and the possibility of hydrogen bonding between the amino

*[5] The sample of (−)-canadine melted at 134~135.5°, $[\alpha]_D$ −300° ($CHCl_3$) : it was prepared according to Gadamer's procedure (Arch. Pharm., **239**, 659 (1901)) from (±)-tetrahydroberberine, m.p. 170~172°.

9) E. Wenkert, D. K. Roychaudhuri : J. Am. Chem. Soc., **78**, 6417 (1956).
10) F. Bohlmann : Chem. Ber., **91**, 2157 (1958); *Ibid.*, **92**, 1798 (1959).
11) V. Prelog, O. Häfliger : Helv. Chim. Acta., **33**, 2021 (1950).

and hydroxyl groups increases the base strength. This $pK_a$ difference between ophiocarpine ($pK_a^{80\%MCS}$ 5.57) and 13-epiophiocarpine ($pK_a^{80\%MCS}$ 5.15) was now also apparent and the former is a stronger base than the latter by about 0.42 $pK_a$ unit.

From these results we concluded that the hydroxyl group in ophiocarpine should have an axial configuration whereas in 13-epimer it should be equatorial, respectively.

The nuclear magnetic resonance spectra of both isomers were studied to further support this conclusion. As shown in Fig. 4, nuclear magnetic resonance spectrum of ophiocarpine in chloroform solution shows a doublet at 4.69 p.p.m. for the $C_{13}$-proton, whereas the peak for 13-epiophiocarpine appeared further upfield at 4.44 p.p.m. (in deuterochloroform, doublet). This downward shift in ophiocarpine is caused by the diamagnetic anisotropy which arises from electronic ring currents of ring A and probably ring D. The $C_1$-proton signal (6.70 p.p.m. in chloroform) in ophiocarpine absorbs at higher field than in 13-epimer (7.34 p.p.m. in deuterochloroform). This might be explained by the presence of spatial interaction effect.[12] Moreover, the $C_1$-proton signal in ophiocarpine acetate (6.72 p.p.m. in deuterochloroform) occurred very close to that of 13-epimer acetate (6.75 p.p.m. in deuterochloroform), probably due to the characteristic acetylation shift.[12] The methyl proton signal of the axial acetoxy group in ophiocarpine acetate appears at higher field as singlet (1.78 p.p.m.) because of the shielding effect of ring D, whereas the equatorial 13-epimer acetate absorbs at 2.23 p.p.m., as usual.

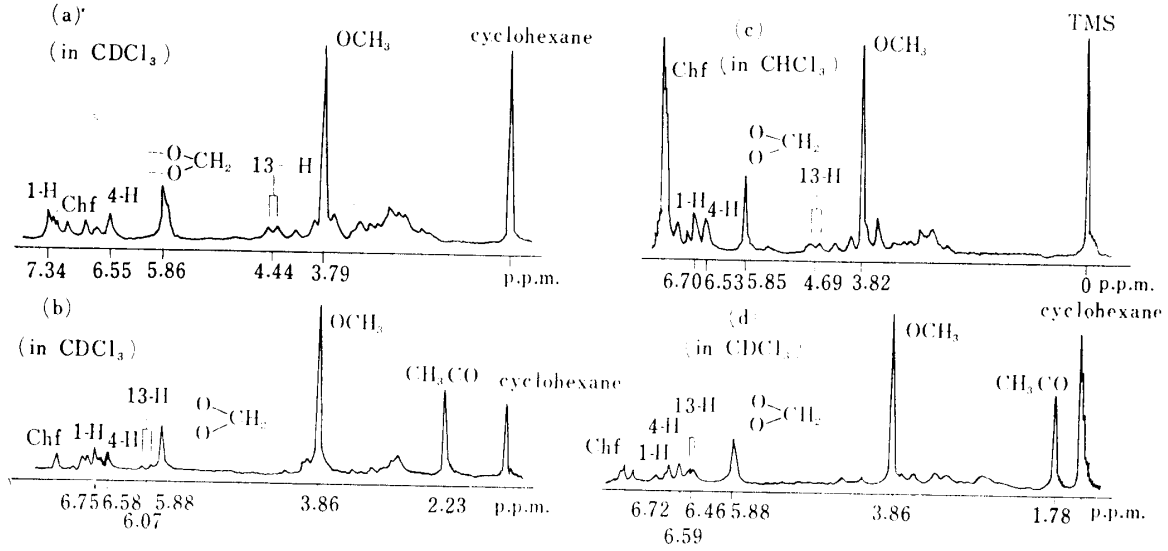



Fig. 4. Nuclear Magnetic Resonance Spectra

a : epiophiocarpine (Ⅵβ) b : epiophiocarpine acetate (Ⅶβ)
c : ophiocarpine (Ⅵα) d : ophiocarpine acetate (Ⅶα)

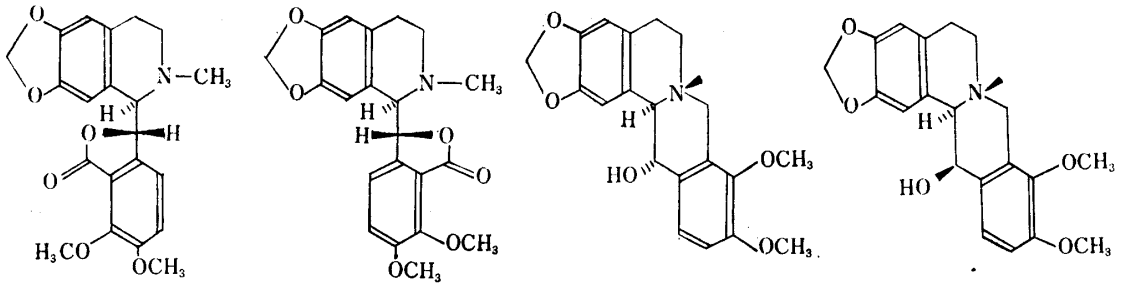
Corrodi and Hardegger[13] established the absolute configuration of (−)-norcoralydine chemically by correlating this compound with (−)-tetrahydropapaverine and they proved that all (−)-tetrahydroberberine alkaloids with only one asymmetric carbon have the same configuration as (−)-norcoralydine by means of Leithe's method.

As mentioned above, both these compounds were chemically correlated with the naturally occuring (−)-canadine, which has the same configuration as (−)-norcoralydine. Therefore, the configuration of the ophiocarpine and 13-epiophiocarpine is

12) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, K. Tsuda : This Bulletin, **10**, 338 (1962).
13) H. Corrodi, E. Hardegger : Helv. Chim. Acta., **39**, 889 (1956).

represented by VI$\alpha$ (13*R*:13a*R*) and VI$\beta$ (13*S*:13a*R*), respectively, in which the asymmetric carbon ($C_{13a}$) is designated as the *R*-configuration.

Accordingly, the absolute configuration of *l*-$\alpha$-hydrastine and *l*-$\beta$-hydrastine should be represented by I$\alpha$ ($\alpha R$:1*R*) and I$\beta$ ($\alpha S$:1*R*), respectively.



I$\beta$($\alpha S$ : 1*R*) I$\alpha$($\alpha R$ : 1*R*) VI$\beta$(13*S* : 13a*R*) VI$\alpha$(13*R* : 13a*R*)

Chart 3.

## 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.

***l*-$\beta$-Hydrastine (I$\beta$)**——Commercial samples (California Corporation for Biochemical Research) were used after recrystallization from EtOH, m.p. 133~135°, $[\alpha]_D$ −61° (c=1.00 in $CHCl_3$), UV $\lambda_{max}^{EtOH}$ mμ (log ε) : 297.5 (3.86). (lit.[14] m.p. 132°, $[\alpha]_D$ −67.8° (c=2.55 in $CHCl_3$)).

***l*-$\alpha$-Hydrastine (I$\alpha$)**——The compound (I$\alpha$) was prepared according to the procedure of Robinson[5] in 77% yield, m.p. 162~163.5°, $[\alpha]_D$ −141° (c=1.00 in $CHCl_3$), UV $\lambda_{max}^{EtOH}$ mμ (log ε) : 297.5 (3.86). (lit.[5] m.p. 162°, $[\alpha]_{546}$ −163° (c=1.2 in $CHCl_3$)).

***l*-$\beta$-Hydrastinediol (II$\beta$)**——According to the procedure reported by Robinson[6] : A solution of I$\beta$ (5.0 g.) in dry benzene (75 ml.) was gradually added to a stirred suspension of $LiAlH_4$ (0.5 g.) in dry $Et_2O$. The mixture was then refluxed for 1 hr., cooled in an ice-bath, the excess of reagent decomposed by dropwise addition of $H_2O$. The two phase were separated and the aqueous layer was extracted with benzene. The benzene solution was washed with aqueous NaCl solution and $H_2O$, dried over $Na_2SO_4$, evaporated, the resulting residue recrystallized from EtOH to give 4.38 g. (86.7%) as prisms; m.p. 145~146°, $[\alpha]_D$ +19° (c=1.00 in $CHCl_3$). (lit.[6] m.p. 143~144°). Diacetate : m.p. 128~130° (from $Me_2CO$). *Anal.* Calcd. for $C_{25}H_{29}O_8N$ : C, 63.68; H, 6.20; N, 2.97. Found : C, 63.45; H, 6.24; N, 3.11.

***l*-$\alpha$-Hydrastinediol (II$\alpha$)**——Compound (I$\alpha$) was reduced with $LiAlH_4$ in the same manner as described above giving a colorless oily material. Diacetate : m.p. 126~127° (from $Me_2CO$). *Anal.* Calcd. for $C_{25}H_{29}O_8N$ : C, 63.68; H, 6.20; N, 2.97. Found : C, 63.43; H, 6.30; N, 3.07.

***l*-$\beta$-1-($\alpha$-Hydroxy-2′-chloromethyl 3′,4′-dimethoxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (III$\beta$)**——a) By treatment with HCl in $CHCl_3$: II$\beta$ (2.3 g.) was mixed with $CaCl_2$ (0.6 g.) in $CHCl_3$ (46 ml.) and then dry HCl passed through the mixture at room temperature for 3 hr., the solid separated, and extracted with $CHCl_3$. Filtration and evaporation of the filtrate *in vacuo* left a solid, which was recrystallized from MeOH-$Me_2CO$, m.p. 158~161°, yield, 2.39 g. (87.6%). The analytical sample was recrystallized from MeOH-$Me_2CO$, m.p. 160~163°, $[\alpha]_D$ +101.5° (c=1.00 in $CHCl_3$), UV : $\lambda_{max}^{EtOH}$ 288 mμ (log ε 3.84). *Anal.* Calcd. for $C_{21}H_{24}O_5NCl \cdot HCl \cdot H_2O$ : C, 54.79; H, 5.91; N, 3.04. Found : C, 54.78; H, 5.55; N, 3.21.

b) By treatment with $SOCl_2$ in $CHCl_3$ : A solution 0.40 g. of II$\beta$ in 7 ml. of $CHCl_3$ was cooled in an ice-bath. A solution 0.1 ml. of $SOCl_2$ in 3 ml. of $CHCl_3$, was then added portionwise with stirring. After the addition was completely the reaction solution was allowed to stand at room temperature 3 hr., the solvent was evaporated and the resulting residue recrystallized from MeOH-$Me_2CO$ to afford 0.25 g. (52.6%) of crystalline product, m.p. 156~161°. This compound was not depressed by admixture with the sample prepared from the procedure (a).

14) M. Freund, W. Will : Ber., **19**, 2797 (1886).

***l*-α-1-(α-Hydroxy-2′-chloromethyl-3′,4′-dimethoxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (IIIα)**—By treatment with $SOCl_2$ in $CHCl_3$: The oily compound (IIα) was treated with $SOCl_2$ in $CHCl_3$ in the same manner as described above to give the solid (IIIα) after recrystallization from $Me_2CO$–$Et_2O$. The product melted at 138~141°; yield, 97.3% (over-all yield from Iα). *Anal.* Calcd. for $C_{21}H_{24}O_5NCl \cdot HCl$: C, 57.02; H, 5.70; N, 3.17. Found: C, 56.59; H, 5.90; N, 2.99.

***l*-β-1-(α-Hydroxy-2′-methyl-3′,4′-dimethoxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (IVβ)**—A solution of IIIβ (1.02 g.) in MeOH (30 ml.) was hydrogenated over 10% Pd-C (0.1 g.) at atmospheric pressure. The catalyst was removed, the filtrate was evaporated, and the resulting solid was dissolved in $H_2O$ and treated with $Na_2CO_3$, extracted with $Et_2O$. After evaporation of solvent the residue was recrystallized from isopropyl ether to give 0.64 g. (77.7%), colorless prisms, m.p. 84~86°, $[\alpha]_D$ +86° (c=1.00 in $CHCl_3$), UV: $\lambda_{max}^{EtOH}$ 287 mμ (log ε 3.67). *Anal.* Calcd. for $C_{21}H_{25}O_5N$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.61; H, 7.04; N, 3.50.

***l*-α-1-(α-Hydroxy-2′-methyl-3′,4′-dimethoxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (IVα)**—IIIα was hydrogenated over 20% Pd-C in the same manner as described above affording colorless needles which crystallized from EtOH, m.p. 153~154°, $[\alpha]_D$ +80° (c=1.00 in $CHCl_3$), UV: $\lambda_{max}^{EtOH}$ 290 mμ (log ε 3.66); yield, 70.3%. *Anal.* Calcd. for $C_{21}H_{25}O_5N$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.98; H, 6.74; N, 3.82.

**13-Epihydroxy-7-methyl-2,3-methylenedioxy-9,10-dimethoxy-5,6,13,13*a*-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizinium Chloride (Vβ, X=Cl)**—a) By treatment of IIIβ with $K_2CO_3$: To a suspension of IIIβ (0.23 g.) in $H_2O$ (0.3 ml.) was added a saturated $K_2CO_3$ solution (5 ml.). After several minutes the solution was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $K_2CO_3$, evaporated *in vacuo*, the resulting solid was recrystallized from MeOH–$Me_2CO$ to yield 0.13 g. (64.2%), m.p. 225~229° (decomp.). UV $\lambda_{max}^{EtOH}$ mμ (log ε): 236 (4.25), 286.5 (3.89). *Anal.* Calcd. for $C_{21}H_{24}O_5NCl$: C, 62.14; H, 5.96; N, 3.45. Found: C, 62.35; H, 5.88; N, 3.63.

b) By treatment of IIIβ with $NH_3$: An ethanolic solution (4 ml.) containing 9.2 w/v% $NH_3$ was added to a suspension of IIIβ (2.19 g.) in EtOH (40 ml.). After standing at room temperature overnight the solvent was removed, the residue extracted with $CHCl_3$–MeOH (4:1), filtered and evaporated. Recrystallization of the residue from MeOH–$Me_2CO$ afforded 1.52 g. (78.7%) of crystalline product, m.p. 225~228° (decomp.). For analysis the substance was recrystallized from MeOH–$Me_2CO$, m.p. 225~229° (decomp.), $[\alpha]_D$ −169.5° (c=0.99 in EtOH), undepressed on admixture with the above sample.

c) By treatment with TsCl in pyridine: To a solution of IIβ (0.40 g., 1.03 mmol.) in dry pyridine (2 ml.) was added portionwise *p*-toluenesulfonylchloride (0.197 g., 1.03 mmol.) in an ice-bath. The reaction mixture left at room temperature overnight, and then the solvent was removed *in vacuo*, the residue dissolved in $CH_3CN$ (12 ml.) and mixed with a solution of NaI (1.15 g.) in $CH_3CN$ (10 ml.). Filtration and evaporation of the filtrate left a solid on trituration with warmed water (2 ml.). After recrystallization from MeOH the product melted at 227~229° (decomp.); yield, 0.34 g. (66.2%). *Anal.* Calcd. for $C_{21}H_{24}O_5NI$: C, 50.71; H, 4.86; N, 2.82. Found: C, 50.73; H, 4.90; N, 2.78. A mixture of 0.25 g. of this methiodide and Dowex 1-X 2 anion exchange resin (OH form, 5 ml.) in $H_2O$ (60 ml.) was stirred for 1 hr., and filtered, washed with $H_2O$. The combined filtrates were neutralized with an equivalent amount of 0.1*N* HCl, and then the solvent was removed *in vacuo*. The resulting residue was recrystallized from MeOH–$Me_2CO$ to yield 0.185 g. (90.6%) of crystals, m.p. 225~229° (decomp.), which were identical with above methochloride in melting point and by IR spectra comparison.

**Ophiocarpine Methochloride (Va, X=Cl), 13-Hydroxy-7-methyl-2,3-methylenedioxy-9,10-dimethoxy-5,6,13,13*a*-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizinium Chloride**—a) By treatment of IIIα with $K_2CO_3$: To an aqueous solution (0.5 ml.) of unpurified material (IIIa), prepared from Iα (0.91 g.) with treatment by $LiAlH_4$ and then HCl, was added saturated $K_2CO_3$ solution. Working up as in the above procedure gave 0.20 g. (20% over-all yield from Iα), m.p. 185~190° (decomp.).

b) By treatment of IIIα with $NH_3$: Unpurified IIIα, prepared from Iα (0.59 g.), was treated with EtOH–$NH_3$ to give a crystalline product (0.17 g., 26.1% over-all yield from Iα) with m.p. 188~191° (decomp.). For analysis a sample was recrystallized from MeOH–$Me_2CO$ melting at 191~193° (decomp.), UV $\lambda_{max}^{EtOH}$ mμ (log ε): 235 (4.07), 287 (3.73). *Anal.* Calcd. for $C_{21}H_{24}O_5NCl \cdot H_2O$: C, 59.50; H, 6.18; N, 3.31. Found: C, 59.51; H, 6.28; N, 3.60.

c) By treatment with TsCl in pyridine: The oily material (IIα), prepared from Iα (2.93 g.) by reduction of $LiAlH_4$, was dissolved in dry pyridine (16 ml.), and treated with *p*-toluenesulfonyl chloride (1.46 g.) and then with NaI in $CH_3CN$. The usual work up gave 2.83 g. (74.5%) of crystalline product, m.p. 252~254° (decomp.). An analytical sample had m.p. 253~255° (decomp.) (from $H_2O$). *Anal.* Calcd. for $C_{21}H_{24}O_5NI$: C, 50.71; H, 4.86; N, 2.82. Found: C, 50.55; H, 4.90; N, 3.10. The methiodide was converted to a methochloride by treatment with Dowex 1-X 2 anion exchange resin (OH form) and then 0.1*N* HCl in usual way. The methochloride melted at 191~193° (decomp.); yield, 96.3%, $[\alpha]_D$ −166.5° (c=1.00 in EtOH), UV $\lambda_{max}^{EtOH}$ mμ (log ε): 235 (4.11), 287 (3.80). The IR spectra was identical with

above sample by procedure (b), which did not depress the melting point of this sample.

**13-Epiophiocarpine (VIβ), 13-Epihydroxy-2,3-methylenedioxy-9,10-dimethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine**——A suspension of 1.02 g. of the methochloride (Vβ, X=Cl) in *o*-dichlorobenzene (6 ml.) was refluxed in an oil bath kept at 210~215° for 6.5 hr. untill homogeneous. The solvent was removed *in vacuo* and the resulting residue recrystallized from MeOH to give 0.61 g. (68.1%) of VIβ, m.p. 161~162°, $[\alpha]_D$ −282° (c=1.00 in $CHCl_3$), UV : $\lambda_{max}^{EtOH}$ 286 mμ (log ε 3.76). *Anal.* Calcd. for $C_{20}H_{21}O_5N$ : C, 67.59; H, 5.96; N, 3.94. Found : C, 67.42; H, 5.99; N, 4.09. Methiodide : A solution of 13 epiophiocarpine (77 mg.) and $CH_3I$ (0.1 ml.) in MeOH (2 ml.) was refluxed for 2.5 hr. After evaporation of the solvent, the residue was recrystallized from MeOH to give 57 mg. (53%) of 13-epiophiocarpine methiodide, m.p. 227~229° (decomp.), which was also identical with Vβ (X=I) by mixed melting point determination and IR spectra comparison.

**Ophiocarpine (VIα), 13-Hydroxy-2,3-methylenedioxy-9,10-dimethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine**——The methochloride (Vα, X=Cl) (0.82 g.) was placed in an oil bath kept at 205~210° and heated under reduced pressure (2~3 mm. Hg) for 25 min. : this procedure was repeated with four samples. The residual material was combined, $H_2O$ (12 ml.) added and then extracted thoroughly with $Et_2O$. A crystalline powder was precipitated from the ethereal extract, after filtration the extract was combined with following extract. The aqueous phase was evaporated to dryness *in vacuo*, and the residue heated at 205~210° for 15 min., and then extracted with $Et_2O$ in the same manner as described above. The crystalline powder was recrystallized from MeOH-$Me_2CO$ to give 0.14 g. of colorless material, m.p. 252~256° (decomp.). *Anal.* Calcd. for $C_{21}H_{24}O_5NCl$ (ophiocarpine methochloride) : C, 62.14; H, 5.96; N, 3.45. Found : C, 61.66; H, 5.53; N, 3.00. This material was treated with KI solution to obtain crystalline product which recrystallized from $H_2O$ giving colorless crystals, m.p. 272~273° (decomp.), $[\alpha]_D$ −166° (c=0.50 in EtOH). This material was identical with ophiocarpine methiodide, prepared from ophiocarpine by treatment with $CH_3I$, by IR spectra comparison. The ethereal extracts were combined, dried over $Na_2SO_4$ and evaporated. The residue (1.00 g.) was chromatographed on neutral alumina (Woelm, 30 g.). The first $CHCl_3$ elute (200 ml.) yield a small amount of a compound which recrystallized from $Me_2CO$ as prisms (0.07 g.), m.p. 207~209°, $[\alpha]_D$ ±0° (c=1.00 in $CHCl_3$), UV $\lambda_{max}^{EtOH}$ mμ : 285.5, 291. *Anal.* Found : C, 72.03; H, 6.72; N, 3.37. This product was not further investigated. Further elution of the column with $CHCl_3$ (250 ml.) gave also crystalline product which was recrystallized from MeOH yielding 0.34 g. (12.5%) of a colorless product, m.p. 186~188°, $[\alpha]_D$ −283° (c=1.00 in $CHCl_3$), (lit.[1] $[\alpha]_D$ −284° (c=0.4 in $CHCl_3$)), UV : $\lambda_{max}^{EtOH}$ 291 mμ (log ε 3.74). *Anal.* Calcd. for $C_{20}H_{21}O_5N$ : C, 67.59; H, 5.96; N, 3.94. Found : C, 67.26; H, 5.92; N, 3.96. This compound was identical with a natural ophiocarpine (m.p. 182~185°) supplied by Dr. Manske. Methiodide : A solution of 10 mg. of ophiocarpine and $CH_3I$ (0.02 ml.) in $CHCl_3$-MeOH (1:1) was kept at room temperature for 5 days. Evaporation of the solvent and crystallization of the residue from water gave a crystalline material, m.p. 271~272° (decomp.). (lit.[1] m.p. 271° (decomp.)). This compound showed apparently depression of melting point on admixture with Vα (X=I) obtained above.

**13-Epiophiocarpine Acetate (VIIβ)**——A solution of VIβ (0.61 g.) in $Ac_2O$ (1 ml.) and pyridine (10 ml.) was kept overnight at room temperature and then concentrated to dryness *in vacuo*. The residue was recrystallized from MeOH to give 0.58 g. (85.8%) of crystals, m.p. 170~171°, $[\alpha]_D$ −129° (c=1.00 in $CHCl_3$), UV : $\lambda_{max}^{EtOH}$ 290 mμ (log ε 3.75). *Anal.* Calcd. for $C_{22}H_{23}O_6N$ : C, 66.49; H, 5.83; N, 3.52. Found : C, 66.61; H, 5.84; N, 3.80.

**Ophiocarpine Acetate (VIIα)**——A solution of VIα (0.3 g.) in $Ac_2O$ (7 ml.) was allowed to stand overnight at room temperature. Work up in usual way gave 0.27 g. (79.1%) of crystalline product (VIIα) after recrystallization from $CH_2Cl_2$-petr. ether, m.p. 141~143° (lit.[2] m.p. 165~167°), $[\alpha]_D$ −357.5° (c=1.00 in $CHCl_3$), UV : $\lambda_{max}^{EtOH}$ 290 mμ (log ε 3.72). *Anal.* Calcd. for $C_{22}H_{23}O_6N$ : C, 66.49; H, 5.83; N, 3.52. Found : C, 66.23; H, 6.06; N, 3.31. This compound was identical with natural ophiocarpine acetate, m.p. 133~137°, prepared from natural ophiocarpine supplied by Dr. Manske by mixed melting point determination and IR spectra comparion.

**(−)-Canadine (VIII), (−)-2,3-Methylenedioxy-9,10-dimethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*, *g*]quinolizine**——a) From ophiocarpine acetate (VIIα) : A mixture of VIIα (100 mg.), EtOH (25 ml.) and 5% Pd-C(240 mg.) was heated in an autoclave at 80 kg./cm² of initial $H_2$ pressure and constantly stirred at 60° for 5 hr. and then kept at room temperature overnight. After filtration and evaporation the residue was extracted with $CHCl_3$, washed with 10% $Na_2CO_3$, and $H_2O$, dried, evaporated giving 60 mg. of residue. The residue was recrystallized from MeOH twice to give 36 mg. (42.2%) of crystalline product, m.p. 169~172°, $[\alpha]_D$ ±0° (c=1.00 in $CHCl_3$). *Anal.* Calcd. for $C_{20}H_{21}O_4N$ : C, 70.78; H, 6.24; N, 4.13. Found : C, 70.47; H, 6.06; N, 4.41. This product was identical with (±)-canadine, m.p. 170~172°, prepared from berberinium chloride by $NaBH_4$ reduction, by comparison of IR spectra and mixed melting point determination. The mother liquor was evaporated to dryness, extracted with $Et_2O$, filtered and the resulting residue was chromatographed on neutral alumina (Woelm). The first $CHCl_3$ elute containing MeOH (2% v/v) afford crystalline material, recrystallized from MeOH to give 11 mg. (12.9%) of pale yellow

needles, m.p. 131~134°, $[\alpha]_D$ −297° (c=0.48 in $CHCl_3$), UV : $\lambda_{max}^{EtOH}$ 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.

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## 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]

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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).
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1) M. A. Marshall, F. L. Pyman, R. Robinson : J. Chem. Soc., **1934**, 1315.