Chem. Pharm. Bull.
16(9)1680–1685(1968)

UDC 547.834.2.02 : 541.653

Synthesis of Quinolizine Derivatives. XVIII.[1] Diastereoisomers of 3-(4-Chlorobenzyl)quinolizidine, an Uterus-contracting Agent, and 3-Lupinine

ICHIRO MATSUO,[2a] KAZURO SUGIMOTO,[2b]
and SADAO OHKI[2c]

Technical Research and Development Institute, Japan Defence Agency,[2a] *Medical Department, Self Defence Force,*[2b] *and Tokyo College of Pharmacy*[2c]

(Received October 26, 1967)

The configurations of the diastereoisomers (Ia and Ib) of 3–(4–chlorobenzyl)quinolizidine were determined from the retention time in gas chromatography, NMR spectra of their methiodides, and from their dipole moments, in comparison with those of 3–lupinine and 3–epilupinine.

Synthesis of 3–(4–chlorobenzyl)quinolizidine (I) was described in Part XVI[3] of this series. The diastereoisomeric mixture (Ia and Ib) of I has a sparteine–like uterus–contracting action and has been found to have some clinical effect.[4] In order to find the relationship between the steric structure and pharmacological activity of these compounds, configuration of Ia (mp 73°) and Ib (mp 60°) was determined, and some examinations were made on 3–lupinine (IIa), mp 59°, and 3–epilupinine (IIb), mp 30°, related to I.

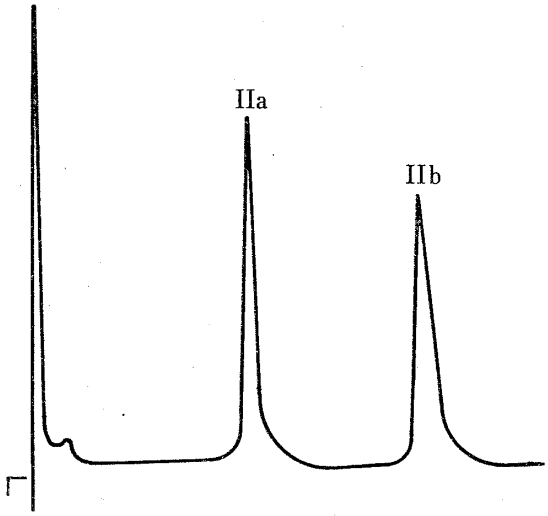


Fig. 1. Gas Chromatogram of IIa, b

stationary phase 10% N.P.G.S. 3 m
carrier gas: He
flow rate: 50 ml/min
column temp. 190°

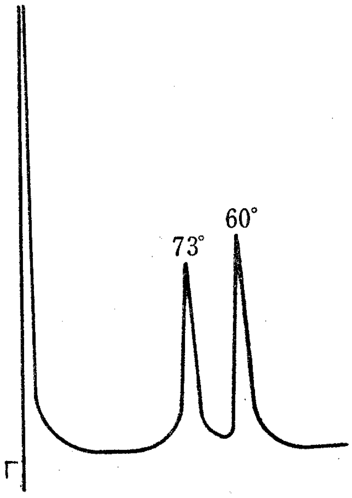


Fig. 2. Gas Chromatogram of Ia (mp 73°) and Ib (mp 60°)

stationary phase: XE–60 10% 2 m
carrier gas: He
flow rate: 35ml/min
column temp. 230°

---

[1] Part XVII: S. Ohki, *Yakugaku Zasshi*, **87**, 1359 (1967).

[2] Location: *a, b) Ikejiri-cho, Setagaya–ku, Tokyo; c) Women's Department, Ueno–Sakuragi 1–10–19, Daito–ku, Tokyo.*

[3] I. Matsuo, K. Sugimoto, and S. Ohki, *Chem. Pharm. Bull.* (Tokyo), **14**, 691 (1966).

[4] R. Nagashima, A. Takano, T. Tamura, and S. Shinoya, *Japan. J. Pharmacol.*, **16**, 353 (1966).

(1) Gas Chromatography of the Diastereoisomers (Ia,b and IIa,b)

Gas chromatograms of I and II are respectively shown in Fig. 1 and 2. In general, the retention time of the compounds having an axial substituent tends to be shorter than that of the compounds with equatorial group, and the fact is apparent in II, the retention time of IIa being shorter than that of IIb. If this relation were to be applied to I, the substance of mp 73° should have axial chlorobenzyl group and that of mp 60°, the equatorial group, corresponding respectively to Ia and Ib. That both Ia,b and IIa,b are the *trans*-quinolizidine compounds has been recognized from their infrared absorptions (2700—2800 cm^{-1}).

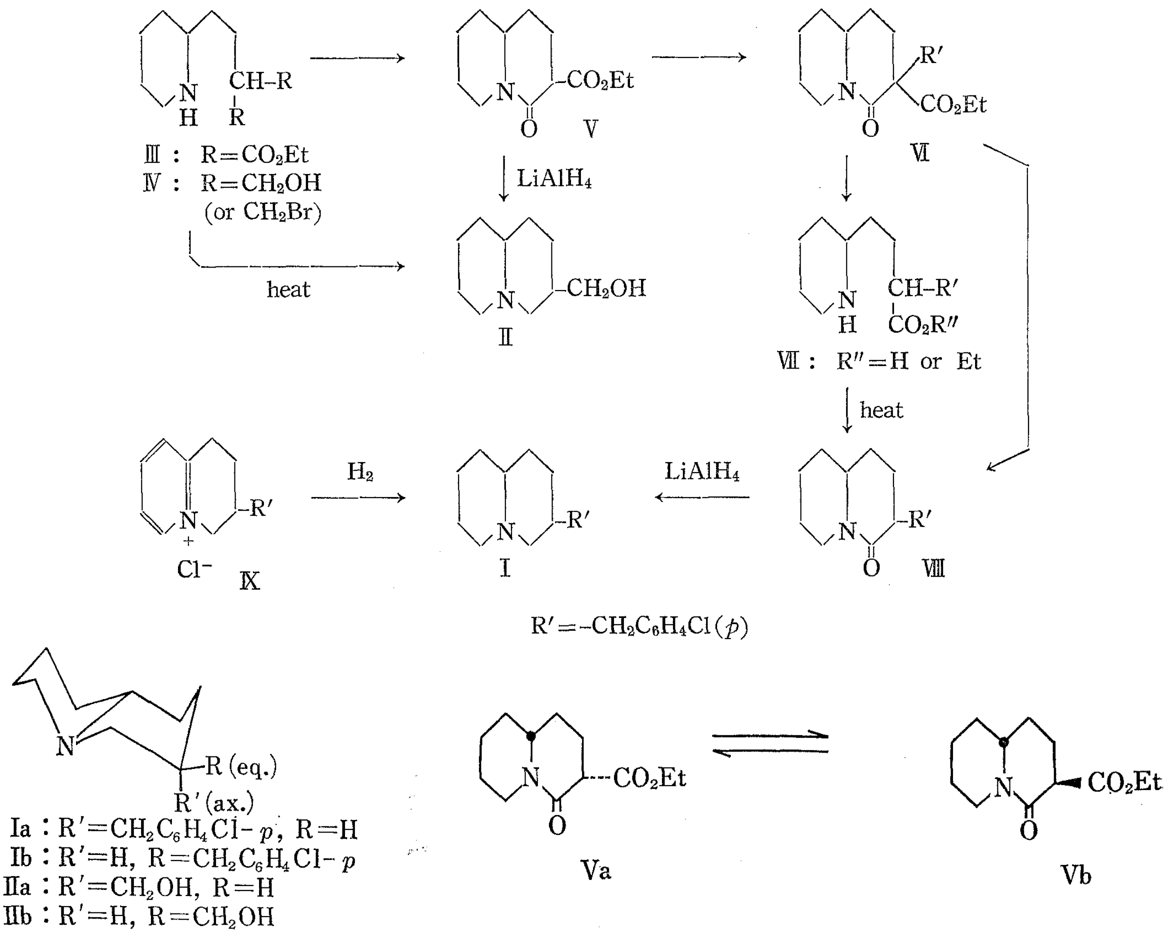


Chart 1

With respect to the formation ratio of Ia:Ib and IIa:IIb, it had been shown earlier³⁾ that the formation ratio of Ia and Ib differed markedly according to the method of their preparation (*cf.* Chart 1). In gas chromatography, this formation ratios were 4:6 to 6:4 by both methods (a) (V→VI→VII→VIII→I) and (b) (IX→I), the ratio being approximately 1:1, one example of which is shown in Fig. 2. The formation ratios reported in the previous paper³⁾ were calculated after isolation of each isomer by fractional crystallization of their picrates. This procedure may have harbored some ambiguity and the earlier report on the formation ratio is hereby corrected.

II is obtained by various methods of synthesis and the general tendency for their formation ratio of IIa:IIb is that IIa, considered to be the less stable form, is unexpectedly more predominant. For exmaple, in the case of the two synthetic methods, (i) (III→V→II)⁵⁻⁷⁾ and (ii) (IV→II)⁸⁾ shown in Chart 1, IIa has been obtained predominantly.

This time, method (i) forms IIa and IIb in 1:1.2 ratio (Fig. 1) and method (ii) in 1:2.7 ratio, showing IIb to be formed in a relatively greater amount. In the past, separation of IIa and IIb has been effected by alumina column chromatography or by fractional distillation. However, IIb is more liable to undergo resinification and more difficult to crystallize than IIa, and the amount of IIb obtained must have been less than that actually formed. Since IIb seems to be more predominant, as shown above, the equilibrium $\mathrm{Va} \leftrightarrows \mathrm{Vb}$[9] tends towards Vb with the equatorial $-COOC_2H_5$, and IIb was formed in larger amount by the reduction of V with lithium aluminum hydride. The reaction from IV to II is also considered to have tended towards a more facile cyclization to form IIb.

(2) Nuclear Magnetic Resonance Spectra of I and II

Configuration of IIa and IIb has been clarified through their infrared spectra,[10,11] dipole moments,[12] and the intramolecular cyclization of their tosyl esters,[11] but it can also be determined from their nuclear magnetic resonance (NMR) spectra (Fig. 3 and 4).

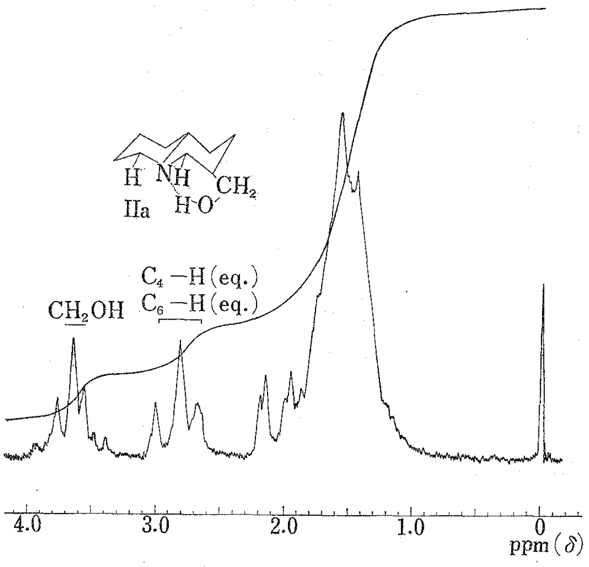


Fig. 3

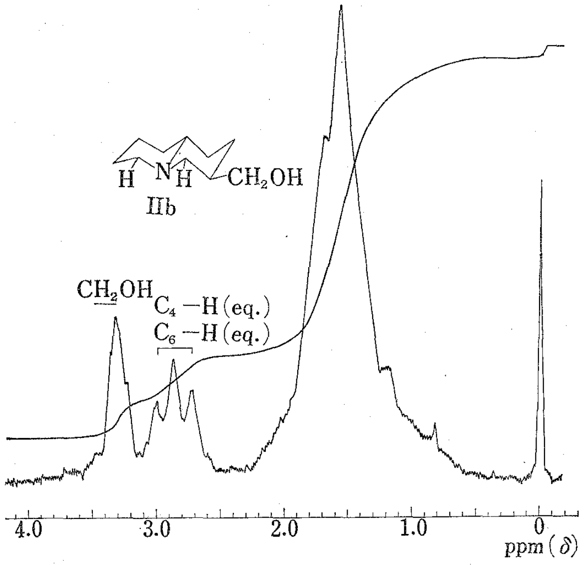


Fig. 4

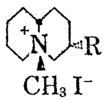
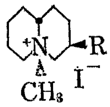
The signal for CH_2OH of IIa is shifted to a lower field than that of IIb and this is assumed to be due to the axial CH_2OH in IIa which can form an intramolecular hydrogen bonding ($\rightarrow N\cdots HOCH_2-$). The reason why the signal for CH_2OH of IIa appears as a multiplet is thought to be because the two methylene protons are not equivalent by the hydrogen bond formation.

The NMR spectra of Ia and Ib do not show such a marked difference as those of IIa and IIb, and it is difficult to make a decisive assignment. However, their distinction was obtained by examining the signals for $\overset{+}{N}-CH_3$ of their methiodides (Table I).

---

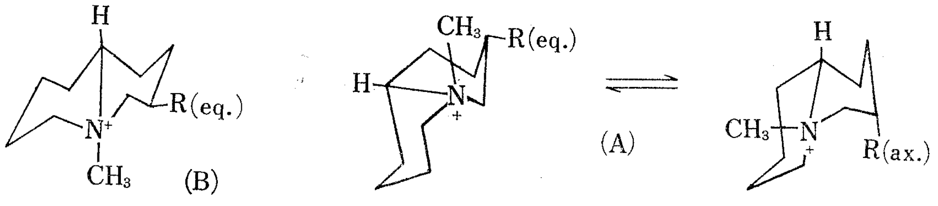
5) I. Matsuo, *Yakugaku Zasshi*, **81**, 1078 (1961).
6) K. Winterfeld and G. Schulz, *Arch. Pharm.*, **291**, 610 (1958).
7) H.R. Lewis and C.W. Shoppee, *J. Chem. Soc.*, **1956**, 313.
8) K. Winterfeld and C. Heinen, *Ann.*, **573**, 7, 85 (1951).
9) Lewis and Shoppee (ref. 7) assumed the presence of diastereoisomers Va and Vb which respectively gave rise to IIa and IIb, but the presence of Va and Vb was not proved by either gas-liquid chromatography or other methods (ref. 5). Enolization of $>\mathrm{NCO}\underset{|}{\mathrm{C}}\mathrm{HCOOC_2H_5}$ in V may be prevented but Va and Vb are thought to be in equilibrium.
10) A. Reiser, I. Ratuský, and F. Šorm, *Chem. Listy*, **47**, 1491 (1953).
11) S. Ohki and Y. Noike, *Chem. Pharm. Bull.* (Tokyo), **7**, 708 (1959).
12) I. Ratuský and F. Šorm, *Collection Czech. Chem. Commun.*, **20**, 798 (1955).

Table I. NMR Spectra of $\overset{+}{N}$–CH_3

cis Form  R	ppm (δ)	*trans* Form  R	ppm (δ)
H[a]	3.30	H[a]	3.09
CH_2OH[b] (IIa–CH_3I)	3.22	CH_2OH[b] (IIb–CH_3I)	3.02
$CH_2C_6H_4Cl$-*p*[b] (Ia–CH_3I)	3.17	$CH_2C_6H_4Cl$-*p*[b] (Ib–CH_3I)	2.97

a) solvent: D_2O *b*) solvent: $(CD_3)_2SO$

In quinolizidine derivatives in general, $\overset{+}{N}$–CH_3 signal of the *cis*–fused ring lies in a lower field than that of the *trans*–fused ring.[13,14] It was found by this examination that the $\overset{+}{N}$–CH_3 signals of the methiodides of Ia and Ib, and of IIa and IIb were in a similar relation to that of *cis*– and *trans*–quinolizidine methiodides,[13,15] as will be seen in Table I. In this case, the methiodide of IIa would take the *cis* form (A: R=CH_2OH) due to the steric hindrance of axial CH_2OH and $\overset{+}{N}$–CH_3, and the methiodide of IIb, the *trans* form (B: R=CH_2OH). If this relationship were to be applied to the methiodides of Ia and Ib, the compound exhibiting the $\overset{+}{N}$–CH_3 signal in the lower field would be the derivative having axial $CH_2C_6H_4Cl$ (*p*) group and that with the signal in the higher field would have the equatorial group. This conclusion agrees with the result deduced from the retention time in gas–liquid chromatography.



R=CH_2OH or $CH_2C_6H_4Cl$-*p*

Chart 2

(3) Dipole Moment

Dipole moments of IIa, IIb,[12] Ia, and Ib were measured by the Guggenheim–Smith method (Table II).

Table II. Dipole Moment of Ia,b and IIa,b

Compound	Dipole moment (D)
Ia (mp 73°)	2.50
Ib (mp 60°)	2.31
IIa (3–lupinine, mp 59°)	2.70 (2.83[a])
IIb (3–epilupinine, mp 30°)	2.27 (2.42[a])

a) values measured by Šorm, *et al*[14]

---

13) T.M. Moynehan, K. Schofield, R.A.Y. Jones, and A.R. Katritzky, *J. Chem. Soc.*, **1962**, 2637.

14) M. Uskoković, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Am. Chem. Soc.*, **86**, 3364 (1964).

15) K. Schofield and R.J. Wells, *Chem. Ind.* (London), **1963**, 572.

The partial moments of quinolizidine, chlorobenzene, and *p*–chlorotoluene are 0.74, 1.58, and 1.76D, respectively. In derivatives having axial $CH_2C_6H_4Cl$, the direction of the lone-pair electrons of nitrogen and that of $ClC_6H_4CH_2$ are in parallel and their moments would reinforce each other. On the other hand, in the derivatives with equatorial $CH_2C_6H_4Cl$, these moments would compensate each other. Consequently, the former would have a larger μ value than the latter. The partial moment of the primary alcohol group is 1.7 D, close to that of *p*–chlorotoluene, and the μ values of IIa,b and Ia,b would be approximately of the same order, if the factors due to the hydrogen bonding in IIa were to be subtracted. The result of the measurement showed the crystals of mp 73° to have a larger μ value, endorsing the conclusions drawn in the foregoing (1) and (2).

Results of the foregoing three methods enabled the determination of the substance of mp 73° as the derivative (Ia) with axial chlorobenzyl group and that of mp 60° as the derivative (Ib) with equatorial chlorobenzyl group, in comparison with IIa,b. The use of NMR spectra as outlined in (2) is considered to be a convenient and effective method for determining the configuration of 1– and 3–substituted quinolizidine derivatives.

Uterus–contracting action of Ia and Ib is now being examined by a different group and will be reported elsewhere.

Experimental

Formation of 3-Hydroxymethylquinolizidine (II)——Method (i) (III→V→II): This method was described earlier.[5] Method (ii) (IV→II): Five grams of 4–(2–piperidyl)–2–(hydroxymethyl)butanol[8] was heated in an oil bath (220—240°) at a pressure of 4 mmHg and the fraction of bp 146° (4 mmHg) was collected. Yield: 1.4 g (30.5%). The formation ratio of 3–lupinine (IIa) and 3–epilupinine (IIb) was 1:2.7 according to gas chromatography.

Methiodide of II: Prepared from MeI and II in MeOH by the usual method. IIa–MeI: mp 258—260° (from EtOH–Ether). IIb–MeI: uncrystallised.

Methiodide of Quinolizidine——*trans*–Quinolizidine methiodide,[13] mp 318° (from EtOH). *cis*–Quinolizidine methiodide,[13,15] mp 312° (from EtOH).

Dipole Moment of Ia and Ib——Molecular polarization P_0 of the solute was obtained according to the method of Guggenheim–Smith and the dipole moment μ was calculated from following equation.

$$\mu=0.0128\sqrt{P_0T} \tag{1}$$

$$P_0=\frac{\varepsilon}{(\varepsilon_1+2)^2}\;\frac{M_2}{d_6}\;\frac{(\varepsilon_{12}-\varepsilon_1)-(n_{12}{}^2-n_1{}^2)}{w_2} \tag{2}$$

where		
	ε_1,d_1,n_1	dielectric constant, density, and refractive index of the solvent
	ε_{12},n_{12}	dielectric constant and refractive index of the solution
	w_2	weight ratio of solute and solution
	M_2	molecular weight of the solute

Purified benzene was used as the solvent and ε_{12} was measured at 30°.

a) μ of Ia (mp 73°): A sample of 0.2299 g was dissolved in 22.8075 g of benzene and ε_{12} was measured at 30°. $\varepsilon_{12}=2.28756$. ε_1 and d_1 of benzene at 30° are as follows: $\varepsilon_1=2.26245$, $d_1=0.868445$

$w_2=0.2299/23.0374$, $M_2=263.5$, $n_{12}{}^2-n_1{}^2\doteq 0$

According to (2) $P_0=126.09$

According to (1) $\mu=2.50$ (D)

b) μ of Ib (mp 60°): Measured under the same condition as above.

Sample, 0.0370 g; benzene, 30.4539 g.

$\varepsilon_{12}=2.26580$, $w_2=0.0370/30.4909$, $M_2=263.5$

Accoding to (2) $P_0=107.80$

Accoding to (1) $\mu=2.31$ (D)

Dipole Moment of IIa and IIb——μ was measured by the same method as above.

a) μ of IIa (3–lupinine): A sample of 0.0398 g was dissolved in 31.8940 g of benzene and ε_{12} was measured at 14°.

$\varepsilon_{12}=2.3002$, $w_2=0.0398/31.9338$, $M_2=169.26$

$P_0=155.505$, $\mu=2.70$ (D)

b) μ of IIb (3-epilupinine): Sample, 0.0449 g; benzene, 30.5012 g.
$\varepsilon_{12}=2.2998$
$P_0=109.91$, $\mu=2.27$ (D)

Acknowledgement The authors express their gratitude to Dr. K. Kamiko, Director of the Research Institute, and Dr. I. Hirafuku, Assistant Director of the Central Hospital, both of the Japan Defence Agency, for their encouragement throughout the course of the present work. They are indebted to Dr. Y. Kishida and members of the Physicochemistry Division, Central Research Laboratories of Sankyo Co., Ltd., for the measurement of gas chromatography, and NMR and IR spectra, to Prof. A. Aihara of the Electro-communications College for the use of facilities for the measurement of dipole moments, and to Dr. Y. Arata of the same College for his co-operation in this measurement. Thanks are also due to Dr. K. Sasaki of the Shionogi Research Laboratories for the analysis of dipole moments.