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Conformational Changes in Fused Hydrazines, 2,3,5,10-Tetrahydro-1H-pyrazolo[1,2-*b*]phthalazines[1]

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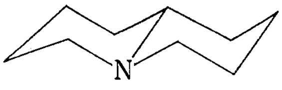
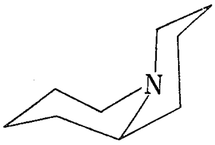
Conformational changes of 2,3,5,10-tetrahydro-1H-pyrazolo[1,2-*b*]phthalazines (Va, Vb), which have a 6/5 fused ring system with two bridgehead nitrogen atoms, were studied by means of variable-temperature nuclear magnetic resonance (NMR) spectroscopy. It is concluded that they exist as the conformer VI with *trans*-fused configuration, converting between the two antipodes (IX, IX′) *via* synchronous inversion of both nitrogens. The activation parameters (Ea, log A, ΔFc^*) for the inversion were also determined as follows. For Va; $Ea=16.9$ kcal/mole, log $A=16.7$, $\Delta Fc^*=12.4$ kcal/mole. For Vb; $Ea=18.7$ kcal/mole, log $A=18.3$, $\Delta Fc^*=12.5$ kcal/mole.

The quinolizidine moiety is present in a number of biologically active alkaloids, and much attention has been collected to conformational analysis of quinolizidine derivatives because they have a conformationally mobile sp$_3$ nitrogen atom at a ring fusion. It is also well known that quinolizidine compounds exist as a mixture of two most important conformations as I and II, in which, under ordinary conditions, the former predominates.[3] In connection with quinolizidine derivatives the stereochemistry of bridgehead nitrogen compounds containing an indolizidine[4] or a pyrrolizidine[5] moiety have been also studied.



I



II

In addition to these conformational studies, stereochemical stability of trivalent nitrogen compounds has been of interest for several decades. Separation of ordinary tertiary amines into the corresponding optical antipodes at room temperature is prevented by rapid nitrogen inversion. However, considerable attention has been focussed on aziridines,[6] because possibility for their successful resolution into the optical forms had been predicted from the fact that the nitrogen inversion is slow due to a large ring strain in such a three-membered ring. Recently, conformation and conformational equilibrium of the fused hydrazine derivatives, III with a 6/6 ring system and IV with a 5/5 ring system, were studied by means of variable-temperature nuclear magnetic resonance (NMR) spectroscopy.[7] As the results, it was concluded that they have a *trans* configuration for the 6/6 system and a *cis* configuration for the 5/5 system, converting between two antipodes by synchronous inversion at the two nitrogens. Later, this concept of synchronous inversion is extended to other hydrazine deriva-

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[1] A part of this work was presented at the 2nd Symposium on Heterocyclic Chemistry (Nagasaki, November 11, 1969).

[2] Location: *Kamiyoga 1-18-1, Setagaya-ku, Tokyo.*

[3] E.L. Eliel, "Conformational Analysis," Interscience Publishers, New York, 1965, p. 250; T.M. Moynehan, K. Schoefield, R.A. Jones, and A.R. Katritzky, *J. Chem. Soc.*, **1962**, 2637.

[4] C.P. Rader, R.L. Young, Jr., and H.S. Aaron, *J. Org. Chem.*, **30**, 1536 (1965).

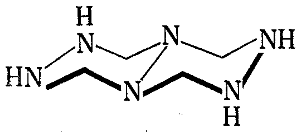
[5] G. Foder, *Chem. Ind.* (London), **1954**, 1424.

[6] "Inversion of Nitrogen in Heterocyclic Systems" was reviewed by T. Murayama in *Kagaku no Ryoiki*, 23, 578 (1969).

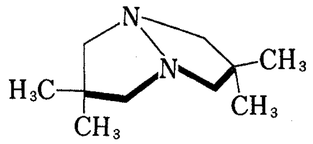
[7] J.P. Kintzinger, J.M. Lehn, and J. Wagner, *Chem. Comm.*, **1967**, 206.

tives,[8] but there is no literature about conformational exchange of fused hydrazine derivatives having a 6/5 fused system.

This paper describes the observation of conformational changes in 2,3,5,10-tetrahydro-1H-pyrazolo[1,2-*b*]phthalazines, Va and Vb, which were both synthesized in this laboratory.[9]



III



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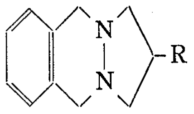
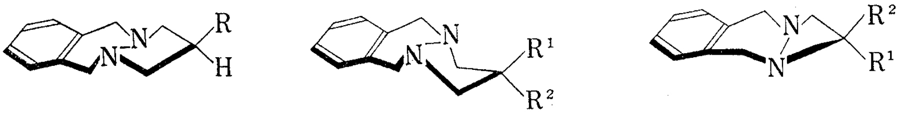


Va : R=H
Vb : R=CH_3

Results and Discussion

Conformation of V

The possible conformations for *trans* and *cis* 2,3,5,10-tetrahydro-1H-pyrazolo[1,2-*b*]-phthalazines (Va, Vb) are shown in Chart 1.



VIa : R=H
VIb : R=CH_3

VIIa : $R^1=R^2=H$
VIIb : $R^1=CH_3$, $R^2=H$
VIIb' : $R^1=H$, $R^2=CH_3$

VIIIa : $R^1=R^2=H$
VIIIb : $R^1=CH_3$, $R^2=H$
VIIIb' : $R^1=H$, $R^2=CH_3$

Chart 1

The conformer VI has a half-chair conformated six-membered ring and a *trans* ring fusion. On the other hand, VII and VIII have a *cis* ring fusion, but the conformation of the six-membered ring of the former is half-chair and that of the latter half-boat. On the basis of the strong Bohlmann bands in infrared (IR) spectra of Va and Vb, possibility of the conformation VII can be ruled out, because they have only one *trans*-axial hydrogen to the lone pair of electrons on each nitrogen.[9,10]

According to their NMR spectra, this conclusion was also supported, and finally VI could be confirmed to be the prefered.

As shown in Fig. 1a, the NMR spectrum (at 100 MHz) of Vb in CS_2 at 20° shows a sharp singlet at 6.35 τ (4H) for the six-membered ring CH_2, two multiplets centered at 7.04 τ (2H) and 7.62 τ (3H), where the signal of methine proton is included, for the five-membered ring CH_2, and a doublet centered at 8.91 τ (3H) for the CH_3. As the temperature drops these signals except those of methyl and aromatic protons are broadened. At $-50°$ the spectrum (Fig. 1b) shows a fine structure again, namely a single AB pattern centered at 6.42 τ and four multiplets centered at 6.66 τ (1H), 7.23 τ (1H), 7.55 τ (2H) and 8.10 τ (1H). Even at this temperature, the signal of methyl protons does not change and the signal centered at 7.55 τ contains that of the methine proton. Since VII demands two AB quartets of the six-membered ring CH_2 signal, VII can be ruled out. If Vb has a *cis* ring fusion, it must exist as a mixture of a large amount of VIIIb and a small amount of VIIIb', since the former having a methyl

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8) J.E. Anderson and J.M. Lehn, *J. Am. Chem. Soc.*, **89**, 81 (1967); J. Wagner, W. Wojnarowski, J.E. Anderson, and J.M. Lehn, *Tetrahedron*, **25**, 657 (1969); J.M. Lehn and J. Wagner, *ibid.*, **25**, 677 (1969).

9) A. Nakamura and S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), in press.

10) F. Bohlmann and C. Arndt, *Chem. Ber.*, **91**, 2167 (1958).

group with a quasi-equatorial conformation should be more stable than the latter having a quasi-axially conformated methyl group.[11] Therefore, two doublets for the CH_3 and two pairs of multiplets with unequal intensities for the five-membered ring CH_2 are expected in the spectra at low temperatures. On the other hand, since the conformer VI with a *trans* ring fusion has a twofolds ymmetry axis passing through the carbon atom bearing the methyl group, four multiplets of equal intensities for the five-membered ring CH_2 and a single doublet for the CH_3 are expected. The spectrum at −50° (Fig. 1b) is in accord with this expectation, hence it is concluded that Vb exists as the conformer VIb and accordingly Va must exists as the conformer VIa with a *trans* ring junction.

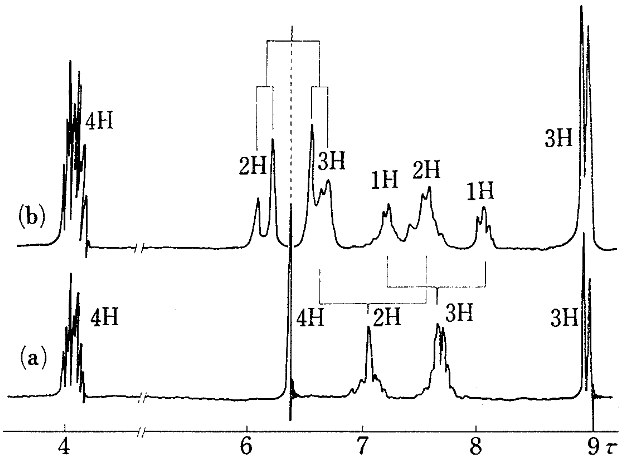


Fig. 1. The 100 MHz NMR Spectrum of Vb in CS_2 at (a) +20° and (b) −50°

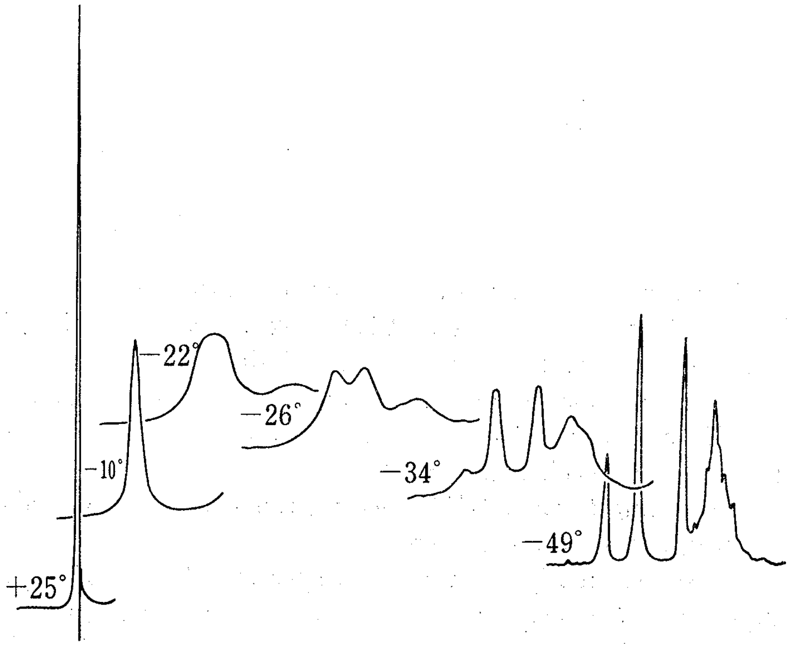
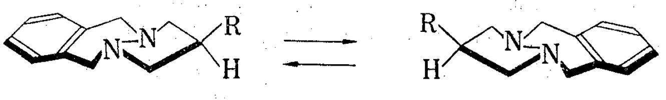


Fig. 2. The NMR Spectrum of Six-Membered Ring CH_2 Protons of Va in CS_2 at Various Temperatures (at 60 MHz)

Rates of Synchronous Inversion of the Two Nitrogens

As mentioned above, the signal of the six-membered ring CH_2 of Va or Vb changes from a AB type to a sharp singlet as the temperature rises (Fig. 2). These temperature-dependent spectral changes show that they exist in an enantiomeric set of time-averaged conformations which are separated by a substantial energy barrier. This barrier may be associated with inversion of configuration of the hydrazine nitrogen atoms, all other possible conformational changes being unlikely to involve energy barrier of the observed magnitude. Thus the changes must be the type IX⇄IX′ *via* synchronous inversion[8] of both nitrogens. By the changes of the CH_2 signal with temperature, the nitrogen inversion rate can be successfully determined.



IX IX

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[11] E.L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, p. 251.

The exchange broadening of the two interacting nuclear spin resonance signals has been written by Alexander,[12] and under slow-exchange limit at low temperature, the observed change in line-width is correlated to the half-life (τ) by Eq. (1).

$$\tau=\frac{1\pm J_{AB}/(\delta_{AB}^2+J_{AB}^2)^{1/2}}{\pi(w-w_0)} \qquad (1)$$

At the very point of coalescence of the AB-quartet signal, τ_c is given by Eq. (2).

$$\tau_c=\frac{\sqrt{2}}{\pi(\delta_{AB}^2+6J_{AB}^2)^{1/2}} \qquad (2)$$

And above the coalescence temperature, Eq. (3) is used to calculate τ.

$$\tau=\frac{2(w-w_0)}{\pi\delta_{AB}^2} \qquad (3)$$

Eqs. (1) to (3) were employed to calculate the exchange life-time listed in Table I and II.

TABLE I. Exchange Life-Time for Va $\delta_{AB}=31.0$ Hz, $J_{AB}=13.20$ Hz (at 60 MHz)

T (°K)	τ (*sec*)	T (°K)	τ (*sec*)
231	0.23	253	0.0101
236	0.0796	257	0.0058
239	0.0478	259	0.0044
242	0.030	263	0.0026
247	0.0178	267	0.0011
251	0.0133		

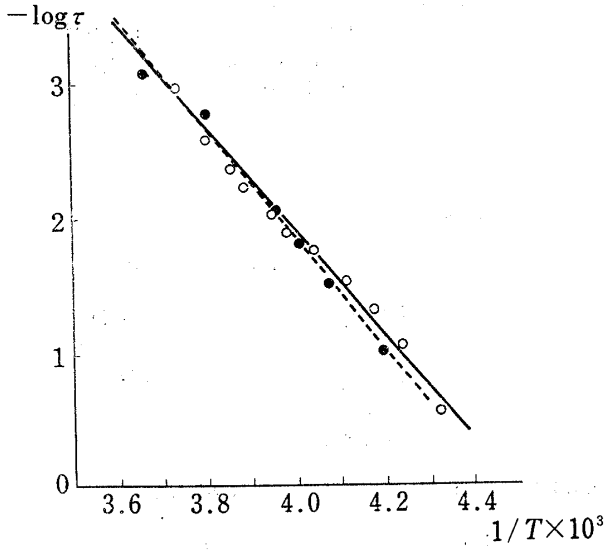

Fig. 3. Plots of −log τ *vs.* $1/T$ for Inversion of Va and Vb

—○—: Va ---●---: Vb

Arrhenius plots of which are shown in Fig. 3.

From the Eyring rate equation the rate constant k is

$$k=\frac{1}{2\tau}=\frac{\kappa\cdot f\cdot T}{h}e^{-\Delta F^*/RT} \qquad (4)$$

Incorporating a transmission coefficient $f=1/2$, Eq. (4) can be rewritten as

$$\Delta F^*=4.57T[10.02+\log T/k] \qquad (5)$$

Activation parameters thus obtained for Va and Vb, and also those for III and IV are listed in Table III.

In order to compare these ΔFc^* values with each other, it is necessary to take into account the solvent effects, because hydrogen bonding to the lone pair of nitrogen decreases the rate of nitrogen inversion by stabilization of the ground state.[8,13]

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[12] S. Alexander, *J. Chem. Phys.*, **37**, 967 (1962); M. Oki and H. Iwamura, *Tetrahedron*, **24**, 2377 (1967).

[13] A.T. Bottini and J.D. Roberts, *J. Am. Chem. Soc.*, **78**, 5126 (1956).

Table II. Exchange Life-Time for Vb $\delta_{AB}=28.0$ Hz, $J_{AB}=14.0$ Hz (at 60 MHz)

T (°K)	τ (*sec*)	T (°K)	τ (*sec*)
238	0.0995	253	0.0095
245	0.0312	263	0.0017
249	0.0157	273	0.00085

Table III. Activation Parameters for Va and Vb

Compound	Solvent	Ea (kcal/mole)	log$A$	ΔFc^* (kcal/mole)	Tc (°C)
Va	CS_2	16.9	16.7	12.4	−22
Vb	CS_2	18.7	18.3	12.5	−24
III[a]	D_2O			16.6	58
IV[a]	$CDCl_3$			12.1	−29

[a] from the reference 7)

In the case of N,N'-dimethyl-2,3-diazabicyclo[2.2.1]-5-heptene,[8] the ΔF^* value for D_2O solution is 2.3 kcal/mole higher than that for pentane solution. Comparing the ΔFc^* values of Va and Vb with those of III and IV by considering the solvent effects, it is clear that the value of V are approximate to that of IV and smaller than that of III. This fact should be ascribed to the large energy of ring strain in the 6/5 system in the ground state.

Experimental

Materials——The synthetic methods of Va and Vb were reported in a separate paper.[9]

Spectral Measurement——The NMR spectra were measured by a Japan Electron Optics JNM C-60HL (60 MHz) and JNM 4H-100 (100 MHz) instruments equipped with NT-C-60HL variable-temperature accessories. Tetramethylsilane was used as an internal standard. The spectral data for Va are shown below (at 60 MHz, in CS_2).

Temp. (°C)	Chemical shift (τ)			
	Aromatic H	Six-membered ring CH_2	Five-membered ring	
			N-CH_2	C-CH_2
+25	3.06 (m) 4H	6.31 (s) 4H	7.18 (t) 4H $J=7.6$ Hz	8.06 (m) 2H
−49	3.08 (m) 4H	6.11 (d) 6.63 (d) 2H $J=13.2$ Hz $J=13.2$ Hz	6.78 (m) 4H	7.87 (m) 4H

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