BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 3524—3528 (1969)

The N→O Acetyl Migration of 5-Substituted-2-pyrrolidinemethanols*[1]

Hisayuki SAKURAI and Toshiyasu ISHIMARU

The Institute of Scientific and Industrial Research, Osaka University, Suita, Osaka

(Received May 21, 1969)

In order to obtain information about the stereochemistry of a fused-ring system, *cis* and *trans* isomers of 5-methyl- and 5-phenyl-2-pyrrolidinemethanols were synthesized and rate constants for their N→O acetyl migrations were measured. Each product was a mixture of *cis* and *trans* isomers. For both 5-methyl and 5-phenyl derivatives, it was observed that *trans* isomers migrated faster than *cis* isomers. The results were discussed in relation to stereochemistry.

The configuration of penicillin containing a fused-ring system consisting of 4- and 5-membered rings was determined by X-ray diffraction.[1] Very little, however, has been reported about the stereochemical studies of such a fused-ring system as penicillin because of the unstability of the 4-membered ring containing a lactam bond. Welsh proposed[2] that the N→O acyl migration of α-aminoalcohols, which has been studied in our laboratory, proceeds *via* an oxazolidine intermediate. The authors synthesized *cis* and *trans* isomers of 5-methyl- and 5-phenyl-2-pyrrolidinemethanol and examined their N→O acetyl migration rates in relation to configuration. This system is supposed to form during migration a fused-ring intermediate consisting of 5- and 5-membered rings.

*1 Paper IX, Stereochemistry of α-aminoalcohols and related compounds. For the previous paper in this series, see T. Ishimaru, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **81**, 1592 (1960).

1) D. Crowfoot, C. W. Bunn, B. W. Roger-Low and A. Turner-Jones, "The Chemistry of Penicillin," H. T. Clarke, J. R. Johonson and Sir R. Robinson Princeton Univ. Press (1949), pp. 310-366.

2) L. Welsh, *J. Am. Chem. Soc.*, **71**, 3500 (1949).

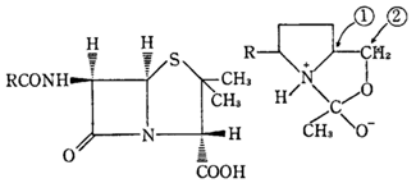
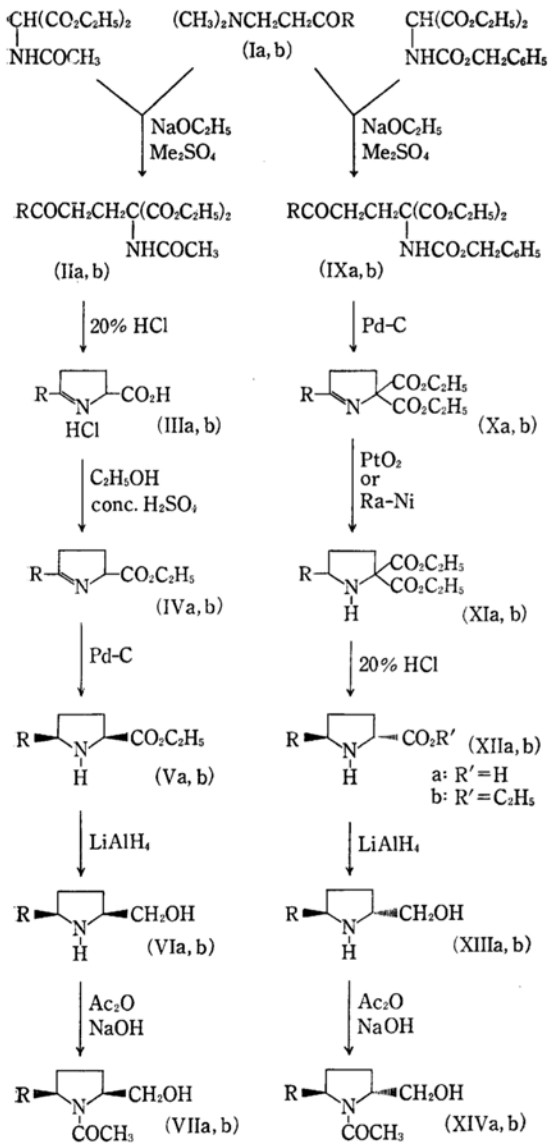


Fig. 1. Penicillin

Since the free rotation of the bond between C_1 and C_2 (Fig. 1) is possible, it was expected that the difference between *cis* and *trans* isomers in the effects which the configuration of the substituent R would produce on the N→O acetyl migration would be very little. However, a considerable difference was observed. The results and stereochemical discussion are described.



Scheme 1. Synthetic route.

Experimental*2

Ethyl 5-Substituted-2-pyrrolidinecarboxylate (Va, b and XIIa, b). The compounds were prepared by the method reported by Sanno[3] (Table 1). Esterification of Δ^1-2-substituted-pyrroline-5-carboxylic acid hydrochlorides (IIIa, b) was carried out by the method of Leonard.[4]

5-Substituted-2-pyrrolidinemethanol (VIa, b and XIIIa, b). To an ice-cooled suspension of 2.5 g (0.066 mol) of lithium aluminum hydride in 50 cc of anhydrous tetrahydrofuran (THF), 11.0 g (0.05 mol) of Vb in 50 cc of anhydrous THF was added dropwise with stirring. After refluxing for 2 hr, 50 cc of THF containing 5 cc of water was added dropwise and the reaction mixture was refluxed for an hour with stirring. Precipitate was filtered and washed three times with THF. The filtrate and washings were combined and dried over anhydrous sodium sulfate. Distillation under reduced pressure gave 6.2 g (70 %) of VIb, bp 148—149°C/4.5 mmHg. Picrate, mp 138—138.5°C (EtOH). Other materials were obtained in the same manner as described above (Tables 2 and 3).

***N*-Acetyl-5-substituted-2-pyrrolidinemethanol (VIIa, b and XIVa, b).** To an ice-cooled and mechanically stirred solution of 2.9 g (0.025 mol) of VIa in 20 cc of acetone, 5 cc (0.053 mol) of acetic anhydride was added dropwise and the 2 N sodium hydroxide solution (containing 3.4 g of sodium hydroxide) was added. When necessary, an appropriate amount of sodium hydroxide solution was added to keep the reaction mixture alkaline. After concentration *in vacuo*, the residue was extracted with chloroform. The extract was dried over anhydrous sodium sulfate, concentrated *in vacuo* and distilled under reduced pressure. Three grams (75.8 %) of viscous oil, bp 153.5—154.5°C/5 mmHg was obtained. Other materials were prepared in the same manner as described above (Table 4).

Kinetic Procedure of N→O Acetyl Migrations. Measurement was carried out according to the method of Ishimaru[5] at 50±0.1°C in 15 cc of 90 % aqueous dioxane containing an equivalent amount of 0.1 N hydrochloric acid to the sample which was weighed accurately. At regular intervals, 2 cc of reaction mixture was pipetted into 10 cc of ice-cooled 20% aqueous acetone and titrated with 0.02 N barium hydroxide using bromophenol blue as indicator. The pH of the end point is about 3.5.

No linear relationship was shown on the second-order plots. Therefore rate constants were estimated from the gradients of the lines drawn over the first three points. Each constant is an average of 2–4 measurements.

Measurement of pK_a values. pK_a values of 5-substituted-2-pyrrolidinemethanols were measured by the method reported by Parke and Davis.[6] About 10 mg

*2 Melting and boiling points are uncorrected.

3) Y. Sanno, *Yakugaku Zasshi (J. Pharm. Soc. Japan)*, **78**, 1113 (1958).

4) F. Leonard, U. S. Pat, 3164597; *Chem. Abstr.*, **62**, 16194, 9108 (1965).

5) T. Ishimaru, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **81**, 648 (1960).

6) T. V. Parke and W. W. Davis, *Anal. Chem.*, **26**, 642 (1954).

TABLE 1. ETHYL 5-R-2-PYRROLIDINECARBOXYLATE

	R	R'	Bp °C/mmHg	Elemental analyses, Found (Calcd) C	H	N
cis	CH_3	C_2H_5	59/3[a]	61.20 (61.12	9.34 9.64	8.80 8.91)
trans	CH_3	H	mp 197—199[b]	55.70 (55.80	8.60 8.58	10.80 10.84)
cis	C_6H_5	C_2H_5	141—143/3.3[c]	71.42 (71.21	7.92 7.81	6.50 6.39)
trans	C_6H_5	C_2H_5	150—151/4.8	71.24 (71.21	8.01 7.81	6.32 6.39)

a) Bp 94—95°C/19 mmHg has been reported.[3]
b) Mp 207°C has been reported.[3]
c) Bp 95—97°C/0.07 mmHg has been reported.[4]

TABLE 2. 5-R-2-PYRROLIDINEMETHANOL

	R	Bp °C/mmHg	pK_a
cis	CH_3	75—81/4.5	10.5
trans	CH_3	88—91/7	10.5
cis	C_6H_5	148—149/4.5	9.38
trans	C_6H_5	135—137/2	9.29
	H	73—76/5[a]	10.6

a) Bp 98°C/10 mmHg[7] and bp 100—105°C/9 mmHg[8] have been reported.

TABLE 3. PICRATES OF 5-R-2-PYRROLIDINEMETHANOL

	R	Mp °C	Elemental analyses, Found (Calcd) C	H	N
cis	CH_3	112.5—114[a]	41.88 (41.87	4.58 4.68	16.20 16.27)
trans	CH_3	118—119.5[a]	41.90 (41.87	4.67 4.68	16.04 16.27)
cis	C_6H_5	138—138.5[b]	50.33 (50.25	4.29 4.46	13.97 13.79)
trans	C_6H_5	139.5—140[b]	50.39 (50.25	4.47 4.46	14.08 13.79)
	H	106.5—108[a,c]	40.13 (40.01	4.26 4.27	16.92 16.96)

a) Recrystallization from EtOH-Et_2O.
b) Recrystallization from EtOH.
c) Mp 106—107°C has been reported.[9]

of a sample was dissolved in 10 cc of water and 0.1 N hydrochloric acid (equivalent or a little more) was added. The solution was titrated with 2 N potassium hydroxide at 18°C. "Hitachi Horiba pH meter D-5" was used for the measurement.

Results and Discussion

The authors intended to obtain *cis* isomers, Va and Vb, from IVa and IVb by catalytic reduction. It was confirmed by gas chromatography that Va and Vb were pure respectively. However, *cis*-5-phenyl-2-pyrrolidinemethanol (VIb) obtained from Vb turned out to be a mixture of *cis* and *trans* isomers (*cis* : *trans*=8.5 : 1.5).[10] It is supposed

7) P. Karrer, P. Portmann and M. Suter, *Helv. Chim. Acta*, **31**, 1617 (1948).
8) W. Oelofsen and Choh Hao Li, *J. Am. Chem. Soc.*, **88**, 4257 (1966).
9) F. P. Doyle, M. D. Mehta, G. S. Sach and J. L. Pearson, *J. Chem. Soc.*, **1958**, 4458.
10) "Du Pont 310 Curve Resolver" was used for the analyses of the chromatograms.

TABLE 4. *N*-ACETYL-5-R-2-PYRROLIDINEMETHANOL

	R	Bp °C/mmHg	Elemental analyses Found (Calcd) C	H	N
cis	CH_3	153.5—154.5/5	61.32 (61.12	9.75 9.62	9.01 8.91)
trans	CH_3	157.5—159.5/6.5	61.10 (61.12	9.77 9.62	9.00 8.91)
cis	C_6H_5	203—205/5	70.92 (71.21	8.06 7.81	6.24 6.39)
trans	C_6H_5	175—176/2	70.99 (71.21	8.00 7.81	6.32 6.39)
	H	139—142/2.1	58.48 (58.72	9.31 9.15	9.85 9.78)

that the presence of *trans* isomer in VIb is due to isomerization by heating during isolation since the *trans* peak of VIb increased after heating at about 180°C for 2 hr (*cis* : *trans*=6.6 : 3.4). *N*-Acetyl-*cis*-5-methyl-2-pyrrolidinemethanol (VIIa) was also recognized to be mixed with a little of *trans* isomer (*cis* : *trans*=9.0 : 1.0).

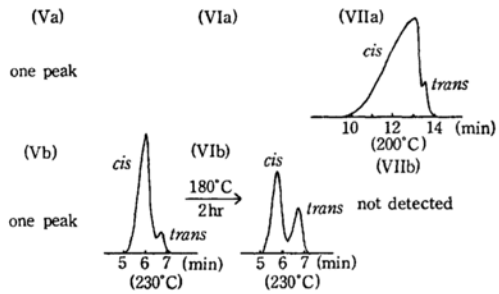


Fig. 2. Gas chromatograms of *cis* isomers.

It is considered that hydrolyses of XIa and XIb afford *trans* isomers, which are expected to be more stable thermodynamically, but *cis* isomers are also likely to be produced. As expected the ethyl esters of XIIa and XIIb were mixtures of *cis* and *trans* isomers (XIIa, *cis* : *trans*=1.0 : 9.0; XIIb, *cis* : *trans*=5.8 : 4.2). It was recognized that *trans*-5-phenyl-2-pyrrolidinemethanol (XIIIb) (*cis* : *trans* =5.6 : 4.4) and *N*-acetyl-*trans*-5-methyl-2-pyrrolidinemethanol (XIVa) (*cis* : *trans*=5.7 : 4.3) were also mixtures.

The reaction rate constants were calculated by second-order equation. (Table 5)

If it is assumed that each sample is pure, the ratio $k(trans)/k(cis)$ equals about 4–5. Considering the gas chromatographic results, it seems that the ratio $k(trans)/k(cis)$ is high in practice and *cis* isomers migrate much more slowly than *trans* isomers. Neglecting *cis* isomers, we obtained the initial concentrations of *trans* isomers from the results of gas chromatographic analyses and calculated the rate constants for *trans* isomers. The results of the calculations for two samples in which the ratios of isomers are different agree with each other. Thus the migration rates of *cis* isomers are considered to be negligible.

In *N*-acetyl derivatives there seem to be two forms, (A) and (B), which are in equilibrium. (A) is considered favorable for forming the intermediate proposed for N→O acyl migration (Fig. 1). Taking the steric hindrance into consideration, it

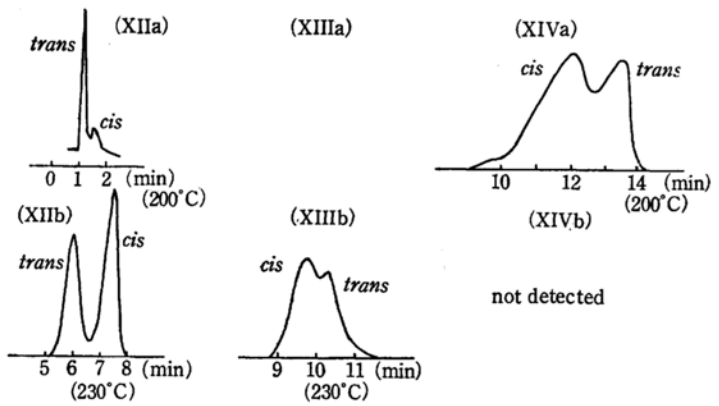


Fig. 3. Gas chromatograms of trans isomers.

Table 5. Migration rate constants

		k_2* mol l^{-1} sec^{-1}	k_2 mol l^{-1} sec^{-1}
5-CH_3	*trans*	7.22×10^{-4} a)	1.9×10^{-4}
	cis	1.48×10^{-4} b)	
5-C_6H_5	*trans*	5.86×10^{-4} c)	1.7×10^{-4}
	cis	1.51×10^{-4} d)	

* Rate constants when the samples are assumed to be pure. In practice a) *cis* : *trans*=5.7 : 4.3
b) *cis* : *trans*=9.0 : 1.0
c) *cis* : *trans*=5.6 : 4.4
d) *cis* : *trans*=8.5 : 1.5

seems that (B) predominates in *cis* and that the two forms can easily interchange in *trans*. Consequently, it is understood that *trans* isomers migrate faster than *cis* isomers.

It is difficult to discuss the difference of substituent effects between methyl and phenyl groups. The ratios of isomers were obtained on the basis of the results of gas chromatography, although isomerization may occur during the operation due to high temperature of the columns. In addition, in 5-phenyl derivatives gas chromatographic analyses were performed for 5-phenyl-2-pyrrolidinemethanols (VIb, XIIIb), and not for *N*-acetyl-5-phenyl-2-pyrrolidinemethanols (VIIb, XIVb).

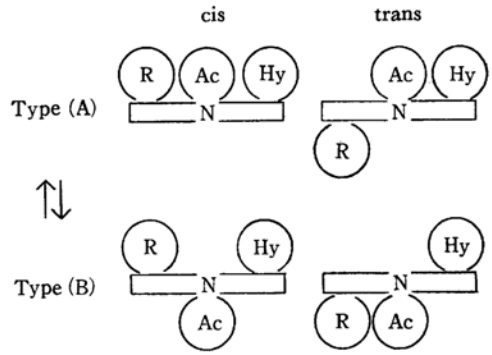


Fig. 4. *N*-Acetyl derivatives.
R=CH_3 or C_6H_5
Ac=$COCH_3$ Hy=CH_2OH

We were unsuccessful in synthesizing pure isomers, but we found from the measurements of their N→O acetyl migration that *trans* isomers migrated faster than *cis* isomers.