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Nuclear Magnetic Resonance Study of the Stereoisomeric 2-Oxazolidone and 2-Phenyl-2-oxazoline Derivatives of α-Amino-β-hydroxy Acids[1]

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NMR studies on β-substituted α-amino acids have revealed that the coupling constant ($J_{\alpha\beta}$) between C_α–H and C_β–H is larger in *erythro* form than in *threo* form in case of β-methylleucine[2] or isoleucine derivatives.[3] However, it is well known that the value of the coupling constant in such >CH–CH< system is considerably effected by the environmental linkage. In fact, in our experiment for comparison of $J_{\alpha\beta}$ value of free α-amino-β-hydroxy acids, the relationship was found to be reversed, that is, *threo* form always showed the relatively larger value than *erythro* form as shown in Table 1.

Furthermore, the small differences in $J_{\alpha\beta}$ values observed in a group of α-amino-β-hydroxy acids may not allow its use for assignment of relative configurations, even if a pair of pure diastereoisomeric compounds is obtained.

TABLE 1. CHEMICAL SHIFTS AND COUPLING CONSTANTS OF FREE α-AMINO-β-HYDROXY ACIDS IN D_2O

R–CH(OH)–CH(NH_2)–CO_2H

R	*threo*		*erythro*	
	H_α (ppm)	$J_{\alpha\beta}$ (Hz)	H_α (ppm)	$J_{\alpha\beta}$ (Hz)
CH_3	3.62	5.0	3.81	4.2
C_6H_5	3.88	4.5	4.83	4.2
CH_2CO_2H	3.70	4.1	3.92	3.8
$(CH_3)_2CH$–	a)		3.91	3.2
	4.05	5.0	4.10	4.6

a) Measurements of these values were impossible, since chemical shifts of H_α and H_β were overlapped.

Since the coupling constants in the aliphatic compounds as mentioned above are revealed as an average value contributed from relatively stable rotational isomers of each diastereomer, it is expected that a difference between J_{erythro} and J_{threo} could be enlarged if amino and hydroxy groups are fixed in an appropriate ring which prevents a free rotation of α-β carbon-carbon bond.

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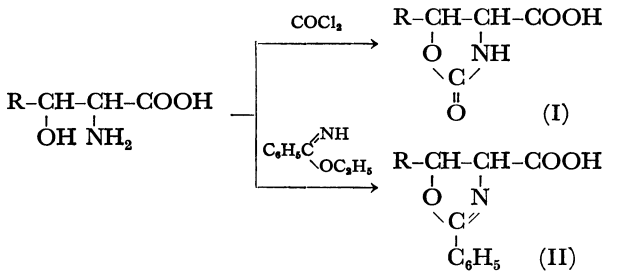
1) This study was partly presented at the 26th Annual Meeting of the Chemical Society of Japan, Kanagawa, April, 1972.

2) K. Okubo and Y. Izumi, This Bulletin, **43**, 1541 (1970).

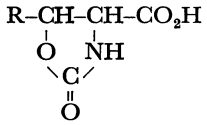
3) J. Shoji, K. Tori, and H. Otsuka, *J. Org. Chem.*, **30**, 2772, (1965).

α-Amino-β-hydroxy acids were known to be cyclized either with phosgene or with iminoether to the corresponding 2-oxazolidone (I) or 2-phenyl-2-oxazoline (II) derivatives respectively without any configurational changes.[4] We prepared 2-oxazolidone derivative of six diastereoisomeric pairs of α-amino-β-hydroxy acids, *i.e.*, DL-threonine, β-phenyl-DL-serine, β-hydroxy-DL-glutamic acid, β-hydroxy-DL-aspartic acid, β-hydroxy-DL-leucine and β-furyl-DL-serine, the configurations of which are known definitely. We also synthesized the diastereoisomeric pairs of 2-phenyl-2-oxazoline derivative of DL-threonine, β-phenyl-DL-serine and β-hydroxy-DL-leucine.



The coupling constants $J_{\alpha\beta}$ measured for those derivatives are summarized in Tables 2 and 3. The

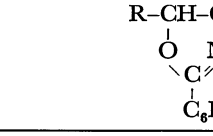
Table 2. Chemical shifts and coupling constants of 2-oxazolidone derivatives in CD_3OD



R	*cis* (*erythro*)		*trans* (*threo*)	
	H_α (ppm)	$J_{\alpha\beta}$ (Hz)	H_α (ppm)	$J_{\alpha\beta}$ (Hz)
CH_3[a]	4.39	9.0	4.04	5.0
C_6H_5[b]	4.55	9.6	4.29	5.0
CH_2CO_2H[c]	4.47	9.0	4.27	5.7
CO_2H[d]	4.70	10.2	4.37	4.0
$(CH_3)_2CH$–[e]			4.10	5.0
 [d]	5.90[f]	9.5	5.75[f]	6.0
CH_2CH_2NHZ[g,6]	4.33	9.0	4.08	5.2

a) T. Kaneko and T. Inui, This Bulletin, **35**, 1145 (1962).
b) T. Kaneko and T. Inui, *Nippon Kagaku Zasshi*, **82**, 1075 (1962); T. Inui, *ibid.*, **83**, 493 (1962).
c) R. Yoshida, Dissertation, Osaka University, 1961.
d) T. Inui, Y. Ohta, T. Ujike, H. Katsura, and T. Kaneko, This Bulletin, **41**, 2148 (1968).
e) *Cis* form was recrystallized from ethyl acetate and *n*-hexane, mp 144—146°C. Found: C, 48.62; H, 6.51; N, 7.98%. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09%. Assignment of H_α of this isomer was impossible, because of very close chemical shifts of H_α and H_β. *Trans* form was recrystallized from ethyl acetate and *n*-hexane, mp 118—119 °C. Found: C, 48.93; H, 6.38; N, 8.10%.
f) H_β value was mentioned, as H_α peak was masked by the solvent peak.
g) Z=$C_6H_5CH_2OCO$-

Table 3. Chemical shifts and coupling constants of 2-phenyl-2-oxazoline derivatives in $CDCl_3$



R	R′	*cis* (*erythro*)		*trans* (*threo*)	
		H_α (ppm)	$J_{\alpha\beta}$ (Hz)	H_α (ppm)	$J_{\alpha\beta}$ (Hz)
CH_3	C_2H_5	5.50	11.2	5.11	7.0
C_6H_5[a]	CH_3	5.28	11.0	4.80	7.5
$(CH_3)_2CH$–[b]	CH_3	4.95	10.0	5.01	6.0

a) S. H. Pines, M. A. Kozlowsky, and S. Karaday, *J. Org. Chem.*, **34**, 1621 (1969).
b) S. Futagawa, M. Nakahara, T. Inui, H. Katsura, and T. Kaneko, *Nippon Kagaku Zasshi*, **92**, 374 (1971).

erthro form corresponds to *cis* H_α–H_β relationship concerning with the ring plane and *threo* form to *trans* one. The $J_{\alpha\beta}$ values for both isomers of 2-oxazolidone derivatives converged within narrow range as far as tested, that is, *cis* isomers are centered to 9.6±0.6 Hz and *trans* one to 5.0±1.0 Hz. Similar separation of $J_{\alpha\beta}$ values for *cis* and *trans* compounds are observed in cases of 2-phenyl-2-oxazoline derivatives.

Although the couplings in such heterocyclic systems cannot be satisfactorily explained,[5] the observed values in this experiment indicated that the configurational relationship of *threo* and *erythro* isomers of α-amino-β-hydroxy acids can be assigned undoubtedly by the analysis of NMR spectra of their 2-oxazolidone or 2-phenyl-2-oxazoline derivatives. Furthermore, formation and purification of 2-oxazolidone derivative from a small amount of the sample of α-amino-β-hydroxy acid can be carried out very easily. Therefore, this procedure will present a convenient and practical method for determination of configurational isomerism of α-amino-β-hydroxy acid.

A criterion on an advantage of this method was tested in the case where only one form of two diastereoisomeric isomers of α-amino-β-hydroxy acid was obtained. In our another synthetic study of the new amino acid, *i.e.* β-hydroxyornithine, first we obtained only one unknown form of its derivative.[6] Thus 5-(2-benzyloxycarbonylaminoethyl)-2-oxazolidone-4-carboxylic acid prepared from synthetic DL-β-hydroxyornithine showed the coupling constant $J_{\alpha\beta}$ of 9.0 Hz. From this single value, we assigned this isomer to *cis*, namely, *erythro* form, and this conclusion was successfully applied to further synthetic study.[6] Later we could obtain the other form of DL-β-hydroxyornithine and its 2-oxazolidone derivative gave the expected value of $J_{\alpha\beta}$ of 5.2 Hz as *trans* type, namely, *threo* isomer.[6]

Experimental

The NMR spectrum was obtained at room temperature

4) a) D. F. Elliot, *J. Chem. Soc.*, **1949**, 589; b) T. Kaneko and T. Inui, *Nippon Kagaku Zasshi*, **82**, 1075 (1961).

5) R. J. Abraham and K. Parry, *J. Chem. Soc. B*, **1971**, 446.

6) T. Wakamiya, T. Teshima, T. Shiba, and T. Kaneko, This Bulletin, to be published in detail.

with a Varian T-60 spectrometer at 60 MHz. Sodium 2,2-dimethyl-2-silapentane-5-sulfonate was used as an internal reference in deuterium oxide solution and tetramethylsilane was used for tetradeuteromethanol and deuterochloroform solutions. The chemical shifts are expressed as ppm from the reference peak.

Preparation of 2-Oxazolidone Carboxylic Acid Derivatives of α-Amino-β-hydroxy Acid. α-Amino-β-hydroxy acid (30 mg) was dissolved in 1M potassium hydroxide solution (10 ml) and was cooled to 5 °C. Then, a solution of phosgene (1.5 g) in toluene (10 ml) was added all at once. After stirring for an additional hour, the aqueous layer separated from the toluene layer was acidified with concentrated hydrochloric acid and extracted three times with 10 ml portion of ethyl acetate. The combined extract was dried and evaporated to dryness. The residue was dissolved in CD_3OD and the solution was directly analyzed by NMR.

Preparation of 2-Phenyl-2-oxazoline Ester Derivatives of α-Amino-β-hydroxy Acid. α-Amino-β-hydroxy acid methyl ester hydrochloride (50 mg) was dissolved in ethanol (10 ml) in a 30 ml flask and mixed with a solution of benziminoethyl ether (1.0 g) in ethyl ether (5 ml). The mixture was stirred vigorously at 20 °C for 1 hr. After addition of water (10 ml), the reaction mixture was extracted three times with each 10 ml portion of ethyl ether, and then evaporated to dryness. The residue was dissolved in $CDCl_3$ and the solution was directly analyzed by NMR.