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ASYMMETRIC TRANSFORMATION OF ALANINE

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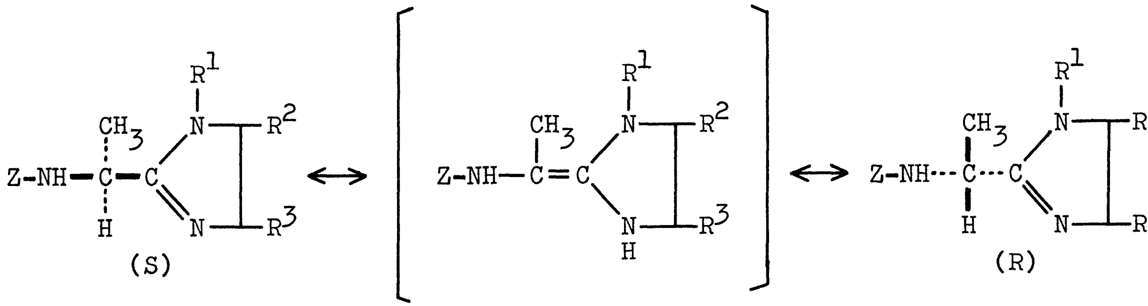
Hydrolysis of an imidazoline derived from (S)-alanine and (S)-aminomethylpyrrolidine afforded (R)-alanine in the optical yield of 93.8 % (e.e.). When the same procedure was applied to (R)-alanine, (R)-alanine (93.2 % e.e.) was obtained. This fact confirms that the asymmetric transformation does not proceed with inversion. Asymmetric transformation of alanine *via* other imidazolines was also examined.

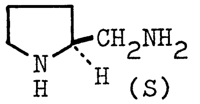
In an optical resolution the theoretical yield of one pure enantiomer is 50 per cent, but in an ideal asymmetric transformation a racemic material would be converted into one of the isomers in 100 per cent yield.[1)] The applications of this asymmetric transformation to optically stable racemic compounds have been reported. The asymmetric transformation of amino acids, ketones, and aldehydes were presented by Yoshikawa *et al.*[2)] However, a general method of asymmetric transformation of optically stable α-substituted carboxylic acids has not been reported.

We have studied a new method of the asymmetric transformation of α-substituted carboxylic acids. This paper deals with the asymmetric transformation of alanine which is used as a model of α-substituted carboxylic acids. (S)-alanine and (R)-alanine were converted to the imidazoline derivatives. When a chiral diamine is used as a diamine component to form the imidazoline ring, it is expected that the epimerization of C-2 *exo* methine of the imidazoline ring[3)] changes the ratio of two epimers (Scheme 1).

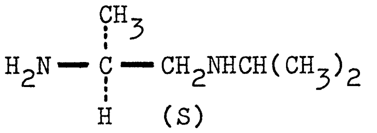


Scheme 1

Imidazoline derivatives were prepared by the iminoether coupling method.[4)] (S)-2-Benzyloxycarbonylaminopropioimino ethyl ether (a) was prepared from (S)-alanine, and corresponding (R)-iminoether (b) was prepared from (R)-alanine according to the methods described by Hirotsu et al.[4)] and Yamada et al.[5)] Three diamines were used to prepare the imidazoline derivatives; (S)-aminomethylpyrrolidine (I), 2(S)-2-amino-5-methyl-4-azahexane (II), and N-isopropylethylenediamine (III).



I



$$H_2N-\overset{CH_3}{\underset{H}{C}}-CH_2NHCH(CH_3)_2 \quad (S)$$

II

$H_2NCH_2CH_2NHCH(CH_3)_2$

III

Imidazolines (Ia, IIa, and IIIa) were synthesized from the (S)-iminoether (a) and the diamines (I, II, and III) respectively, and imidazolines (Ib, IIb, and IIIb) were synthesized from the (R)-iminoether (b) and diamines (I, II, and III) respectively. The yields and the physical data of the imidazoline derivatives were shown in Table 1.

Table 1. Imidazoline Derivatives of Alanine

Imidazoline	R^1	R^2	R^3	Yield %	mp °C	$[\alpha]_D^{23}$	IR cm^{-1}	M^+ obs. (calc.)
Ia	$-(CH_2)_3-$		H	86	86-87.5	-94.1°	1710 1620	287.1634 (287.1633)
Ib	$-(CH_2)_3-$		H	75	86-87.5	-94.9°	1710 1620	287.1643 (287.1633)
IIa	$-CH(CH_3)_2$	H	$-CH_3$	57	71.5-73	-57.9°	1710 1610	303.1930 (303.1945)
IIb	$-CH(CH_3)_2$	H	$-CH_3$	64	120-122.5	-36.2°	1695 1600	303.1955 (303.1945)
IIIa	$-CH(CH_3)_2$	H	H	50	99.5-101	-0.1°	1710 1615	289.1799 (289.1789)
IIIb	$-CH(CH_3)_2$	H	H	36	99.5-101	0°	1710 1615	289.1771 (289.1789)

The configuration and the optical purity of the alanine residues of the imidazoline derivatives were determined as DNP-alanine prepared after hydrolysis of the derivatives according to the method described by Yonetani et al.[3)] (hydrolysis condition: 6N HCl, 110°C, 20 h). The specific rotation of the prepared DNP-alanine was observed at 546 nm and the concentration of the solution was calculated from the extinction coefficient at 360 nm; authentic DNP-(S)-alanine: $[\alpha]^{32}_{546}$ +221° (c=0.22, 1 % $NaHCO_3$); $\lambda_{max}^{1\%\ NaHCO_3}$ 360 nm (ε=1.72×10^4). The results are shown in Table 2.

Imidazolines (Ia and Ib) were obtained as crystals in the form of plates, and both the crystalline compounds (Ia and Ib) had a melting point of 86-87.5°C. From the spectral data (IR, UV, and NMR) and specific rotation shown in Table 1, Ia and Ib were considered to be identical. Hydrolysis of Ia and Ib afforded (R)-alanine

Table 2. Configuration and Optical Purity of Alanine Residues of Imidazoline Derivatives

Imidazoline	Config. of DNP-Alanine[a]	Optical Purity (% e.e.)	Yield of DNP-Alanine[b] (%)
Ia	(R)	93.8	89.2
Ib	(R)	93.2	90.1
IIa	(S)	91.9	5.6
IIb	(R)	91.8	4.3
IIIa	(S)	8.2	11.1
IIIb	(R)&(S)	0	9.9

a) The configuration of DNP-alanine prepared by the reaction of the hydrolyzate of imidazoline with 2,4-dinitrofluorobenzene was compared with that of an authentic sample, DNP-(S)-alanine.

b) DNP-alanine is prepared almost quantitatively from alanine.[6] The yield of DNP-alanine represents the yield of alanine residue on the hydrolysis of the imidazoline derivatives.

(Table 2). This fact confirms that the bond between proton and C-2 exo methine carbon is labile enough to occur epimerization, and that the asymmetric transformation does not proceed with inversion.

Imidazoline (IIa) was isolated as crystals in the form of columns by recrystallization from petroleum ether, and imidazoline (IIb) was isolated as fine needles by recrystallization from acetone-petroleum ether. The physical data of IIa and IIb were clearly different from each other. Table 2 shows that (S)-alanine was obtained by hydrolysis of IIa, and (R)-alanine was obtained from IIb. The configurations of the obtained alanines were those of the starting alanines. Asymmetric transformation of alanine via IIa or IIb was unsuccessful.

The achiral diamine (III) was used as an amine component to prepare imidazolines (IIIa and IIIb). The imidazolines were isolated as fine needles and showed a specific rotation of around zero at 589, 577, 546, 435, and 365 nm. Table 2 shows that optically active alanine appreciably racemized via IIIa or IIIb.

It is explicable that the alanine was obtained in low yield by the hydrolysis of IIa, IIb, IIIa, and IIIb (Table 2). The existence of an isopropyl group on nitrogen atom in diamine moiety is common to these imidazolines. The difficulty of the hydrolysis is explained on the basis of the steric hindrance of this isopropyl group. Similar description was given in the case of hydrolysis of proteins containing valine or isoleucine residue.[7]

By a preliminary experiment, the ratio of the two epimers of Ia and Ib with respect to C-2 exo methine of the imidazoline ring in methanol was shown to be (S):(R)= 3:7. Because the imidazolines were isolated as crystalline form, high optical yields of obtained alanine (93.8, 93.2 % in the case of Ia and Ib, respectively) are considered to be due to a combination of resolution by preferential crystallization of one diastereoisomer and epimerization.[8)]

This is a new method for the asymmetric transformation of alanine *via* optically labile imidazoline derivatives. Application of this methods to other amino acids and α-substituted carboxylic acids will be reported elsewhere.

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