SYNTHESES OF β-HYDROXY-α-AMINO ACIDS BY SUBSTITUTION REACTIONS OF THIAZOLINE AND IMIDAZOLINE COMPOUNDS

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β-Hydroxy-α-amino acids were newly synthesized by the aldol condensation of 2-benzyloxycarbonylaminomethyl-2-thiazoline (II) or -2-imidazoline (VI) with aldehydes followed by acid hydrolysis.

It has been known that, in the molecule of the peptide antibiotic bacitracin A, *N*-terminal isoleucine residue adjacent to the thiazoline ring is very susceptible to racemization.[1,2] In our previous work, this peculiar behavior led to the general understanding that such racemization is a common character of an exo methine group attached to *C*-2 atom of either thiazoline, oxazoline, or imidazoline ring, the reaction proceeding presumably through a protonation followed by a carbanion formation.[3] If the reaction mechanism *via* the carbanion is considered, it can be

expected that an electrophilic substitution will occur at the anionic carbon atom under a mild condition without an addition of any base. In the present investigation, we established a novel synthetic method of β-hydroxy-α-amino acids utilizing a newly exploited substitution reaction, based on the above assumption, of the heterocyclic compounds derived from glycine with the various kinds of aldehydes followed by acid hydrolysis.

2-Benzyloxycarbonylaminomethyl-2-thiazoline (II) was prepared by coupling of benzyloxycarbonylaminoacetimino ethyl ether (I) with 2-mercaptoethylamine.[2-4] A simple addition of an aldehyde such as formaldehyde, acetaldehyde,or propionaldehyde to the thiazoline compound (II) in dimethyl sulfoxide or dimethylformamide at room temperature afforded the desired products (IIIa-c) of the aldol condensation in a fairly good yield after long period as shown in Table 1.

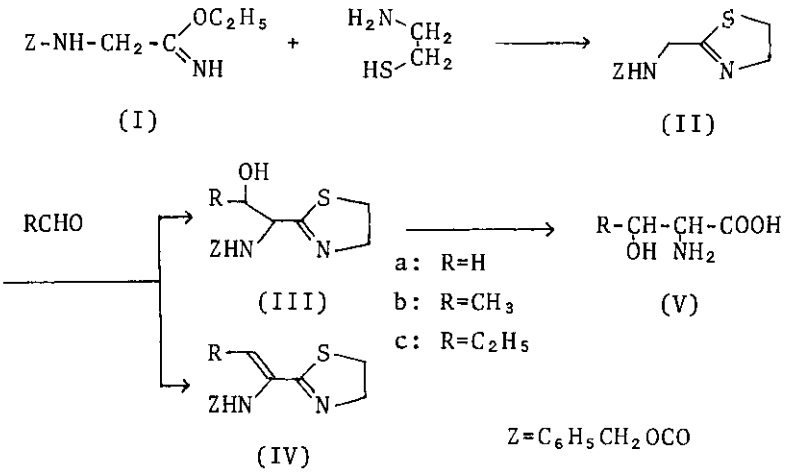

Table 1. Reaction conditions and yields in formations of thiazoline compounds III

	solvent	temperature	reaction time	yield (%)
IIIa	DMSO	r.t.	1 week	71
IIIb	DMSO	r.t.	2 weeks	72
IIIc	DMSO	r.t.	24 hr	82

The reaction in tetrahydrofuran or methylene chloride did not proceed at room temperature except on acetaldehyde. Refluxing of the reaction mixture in these solvents gave the dehydrated products (IV) in rather poor yields. An advantage in use of the polar solvent like dimethyl sulfoxide or dimethylformamide to secure the hydroxy compound (III) may be arisen from a possible contribution of a polarity of the solvent to a stability of the intermediate carbanion resulting in an acceleration of the aldol condensation. However, in the cases of isobutylaldehyde and benzaldehyde, only the dehydrated products (IV) were obtained even in the polar solvent at room temperature.

A similar reaction of aldehydes with the imidazoline derivative (VI) which was prepared from the same imino ether (I) and ethylenediamine [3], proceeded more smoothly in dimethylformamide giving the corresponding products (VIIa-d) by the aldol condasation as shown in Table 2. All the aldehydes used, *i.e.*, acetaldehyde, propionaldehyde, isobutylaldehyde, and benzaldehyde, afforded the desired products in good yields after the reaction

period within either 4 hr or 24 hr.

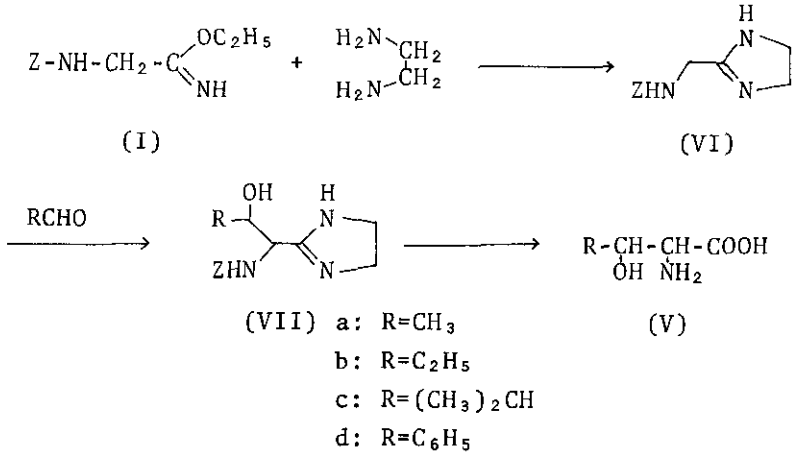

Table 2. Reaction conditions and yields in formations of imidazoline compounds VII

	solvent	temperature	reaction time	yield (%)
Va	DMF	r.t.	4 hr	85
Vb	DMF	r.t.	4 hr	83
Vc	DMF	r.t.	24 hr	84
Vd	DMF	r.t.	24 hr	94

Hydrolyses of the thiazoline compounds (IIIa-c) with 1N HCl in sealed tubes at 110° for 24 hr gave serine, threonine and β-hydroxynorvaline, respectively in 60-80 % yields. Ratios of threo and erythro forms were found to be 1.7-2.1 : 1 in threonine, and 3.2 : 1 in β-hydroxynorvaline by means of colorimetric analyses after separation of each 2,4-dinitrophenylated product

of the hydrolyzates (IV) through the high speed liquid chromatography. The solvent (dimethyl sulfoxide or dimethylformamide) and the temperature (room temperature or 60°) of the coupling reaction did not affect significantly to the ratio of the diastereomers in the case of threonine. Since severe racemization could never occur in the hydrolysis procedure, a relation between thermodynamical stabilities of two diastreomers in each coupling product (III) must be reflected to the preferable formation of threo form in both amino acids.

On the other hand, the imidazoline products (Va-d) could not be hydrolyzed with HCl or even with HBr at various concentrations. Such resistance of the imidazoline (V) to the acid hydrolysis may be due to a resonance stabilization of imidazoline ring by a protonation at the nitrogen atom. Therefore, we attempted the hydrolysis of the imidazoline compound (V) after an introduction of benzenesufonyl group to the ring imino nitrogen. Hydrolysis of the benzenesulfonyl derivative of VIIa with 1N HCl at 110° for 24 hr gave threonine in 55% yield in 5 : 1 ratio of threo and erythro forms. Although the yield in the hydrolysis of the imidazoline derivative was not satisfactory, the predominant formation of threo form of the β-hydroxy-α-amino acid should be noteworthy.

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Received, 3rd October, 1978