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THE SYNTHESIS OF N-HYDROXY PEPTIDES

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During the past decade a substantial number of natural products which contain N-hydroxy amide group -CONH(OH)- have been found, mainly from microbial sources. These substances act variously as potent growth factors, antibiotics, tumor inhibitors or cell division factors (1). Thus, so far no N-hydroxy peptides containing optically active compounds have been obtained by chemical synthesis. A synthesis of glycyl-N-hydroxyglycine was reported lately (2) in a low yield. Conventional methods for acylation of N-hydroxyamino acids are ineffective (3).

In this paper we wish to report on a general method for the preparation of N-hydroxy peptides derived from N-hydroxyglycine. We achieved the synthesis of dipeptides containing an optically active amino acid, e.g.: L-alanyl-N-hydroxyglycine, L-phenylalanyl-N-hydroxyglycine and L-γ-benzylglutamyl-N-hydroxyglycine, in addition to the inactive glycyl-N-hydroxyglycine. This method is based on the fact that the N-hydroxyamino group is a very weak base, that even in low pH its hydrochloride undergoes dissociation and reacts with N-carboxy anhydride of an amino acid (4). The acidic conditions prevent polymerization of the N-carboxy anhydride as well as racemization.

N-Hydroxyglycine was prepared by a method which was developed lately (5) or better by a slight modification (2). The peptide formation was carried out as follows: N-hydroxy glycine (0.91 g, 0.01 mole) was dissolved in ethanol, THF or dioxane by the addition of hydrogen chlorides (0.01 mole) either in the form of concentrated hydrochloric acid or as 12% ethanolic HCl. After filtration N-carboxy anhydride (0.01 mole) was added and the reaction mixture kept first for 24 hrs at room temperature and then overnight in ice box. In case the hydrochloride of the product precipitated (either as a solid or as an oil) the supernatant liquid was withdrawn by decantation. In case that it did not precipitate the solution was evaporated to dryness in vacuum. In both cases the residue was dissolved in ethanol and precipitated by the addition of triethyl-

amine (1.5 ml). In the preparation of the L-phenylalanine derivative, chloroform was also added after the addition of triethylamine. All the N-hydroxy dipeptides were recrystallized by dissolving in a small amount of hot water, and the addition of ethanol. The results are summarized in the Table. Elementary results (C,H,N) of all compounds as well as molecular weights (by potentiometric titrations) were satisfactory.

The N-hydroxy peptides prepared gave the hydroxamic test with $FeCl_3$. The wavelength and the intensity of the absorbance of the ferric complex depend on the pH and on the ratio between the components. Optical rotations and dissociation constants were also determined and are given in the Table.

Table N-Hydroxy Peptides $RCH(NH_2)CON(OH)CH_2COOH$

R	Reaction solvent	Yield	Decomp. temp.	$\alpha\|D\|_{25}^{o}$	pKa COOH	pKa N-OH	pKa NH_3^+
H	ethanol[a]	67%	215°c	-	2.9[d]	8.2[e]	9.8[f]
CH_3	THF[a]	55%	190°	35.0°	2.9	8.4	10.0
CH_2Ph	THF[b]	38%	213°	32.2°	2.9	7.7	9.7
CH_2CH_2 | $PhCH_2OCO$	dioxane[a]	53%	183°	49.4°	2.85	7.65	9.6

a) With aqueous HCl. b) With ethanolic HCl. c) Lit. (2) 195°, darkens at 185°. d) Lit. (2) 2.9. e) Lit. (2) 8.25. f) Lit. (2) 9.9.

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