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CONVERSION OF AMINO HYDROXYACIDS TO OXAZOLIDINE-4-CARBOXYLIC ACIDS, OXAZOLIDINE-5-CARBOXYLIC ACIDS AND TETRAHYDROOXAZINE-4-CARBOXYLIC ACIDS

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Summary. The title compounds are stable in aqueous solution above pH 7, and can be isolated following N-acylation.

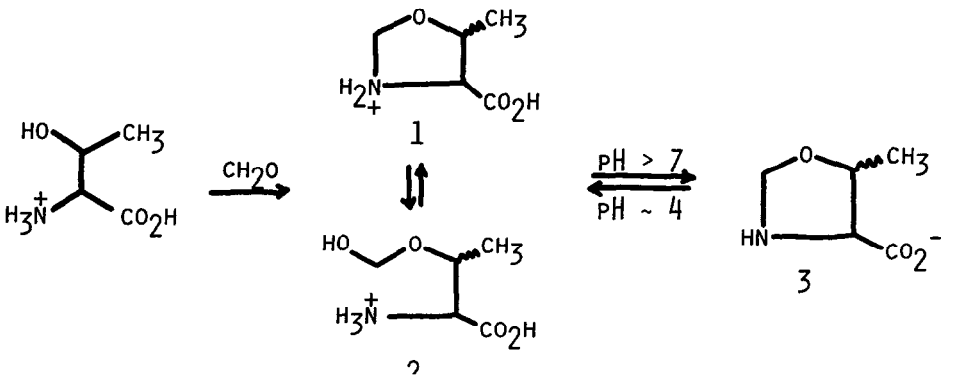
The conversion of mercaptoamino acids to thiazolidinecarboxylic acids in aqueous solution is a well established synthetic operation[1]. However, an analogous reaction, beginning with an amino *hydroxy*acid and leading to *oxygen*-containing heterocyclic rings, is virtually unknown in the literature. In the work of Emoto and Ando[2], no product could be isolated from the reaction of serine with formaldehyde or benzaldehyde, but threo and erythro-β-phenylserine formed oxazolidines in 93% and 43% yields, respectively, upon treatment with alkaline formaldehyde, the structures of the two compounds being based upon infrared measurements. β-Hydroxy-α-amino acid esters have been found to react with aromatic aldehydes in non-aqueous media to give Schiff bases, which cyclize to N-acyloxazolidinecarboxylic acid esters under acylation conditions[3]. Pivaldehyde reacted with the ethyl esters of serine and threonine to form ethyl oxazolidine-4-carboxylates with no evidence of Schiff base formation[4].

In this Letter, we report on the nature of the reactions which take place between aldehydes and amino hydroxyacids in aqueous solution, and we describe a general procedure for the conversion of such amino acids to five- and six-membered heterocyclic rings containing oxygen and nitrogen.

Slow evaporation of a solution of DL-threonine hydrochloride (10 mmoles) and 37% formaldehyde (10 mmoles) in water (10 ml) yielded an oily residue, which crystallized following successive triturations with ether and isopropyl alcohol, m.p. 125-138°C. The pmr spectrum of this crystalline material in D_2O indicated it to be a 1.3/1 mixture of two hydrochlorides. One of these compounds showed δ 5.12 (2H, ABq, 10 Hz), 4.30 (1H, dq, J = 5, 6 Hz), 3.61 (1H, d, 5 Hz), 1.53 (3H, d, 6 Hz). The second compound showed δ 4.83 (2H, s), 4.28 (1H, dq, J = 7.0, 8.0 Hz), 3.80 (1H, d, 8.0 Hz), 1.34 (3H, s, 7.0 Hz). Addition of solid sodium carbonate to the pmr sample to bring the pH to 7.5 led immediately to the formation of a single new material having δ 4.59 (2H, ABq, J = 6 Hz), 3.89 (1H, dq, J = 6.0, 7.0 Hz), 3.32 (1H, d, J = 7.0 Hz), 1.39 (3H, d, J = 6.0 Hz). Reacidification of the solution restored the original spectrum, except that the relative

intensities of the two doublets at high field were slightly different from the original. A similar set of observations was made beginning with DL-allothreonine.

Scheme 1 shows the interpretation proposed to account for these results. According to this scheme, formaldehyde reacts with these amino hydroxyacids under mildly acidic conditions to form a protonated oxazolidinecarboxylic acid 1, which is unstable and in equilibrium with the protonated methylol 2. Deprotonation leads to an oxazolidinecarboxylate (3), which is stable in aqueous solution.



Scheme 1

It was expected that N-acylation of 3 under Schotten-Baumann conditions would lead to acid stable oxazolidinecarboxylic acids, and this expectation was confirmed. Addition of benzoyl chloride and additional sodium bicarbonate to the pH 7.5 solution derived from DL-threonine led to 4A, m.p. 123.0-124.0°; the pH 7.5 solution derived from allothreonine led, similarly, to 4B, m.p. 153.5-155.5°.

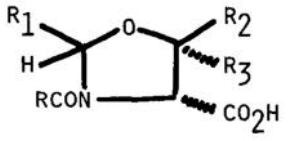
The following general procedure, illustrated for D-serine, was then employed to prepare the compounds shown in Table I from the amino acids threonine, allo-threonine, β-hydroxyvaline, serine, isoserine, homoserine and β-phenylserine.

A solution of the amino acid (0.02 mole) and 37% formaldehyde (0.02 mole) in 2N NaOH (10 ml) was allowed to stand overnight at 4°, and was then treated dropwise at 0-5° with a solution of benzoyl chloride (0.02 mole) in acetone (8 ml). Solid sodium bicarbonate was added during the benzoylation to maintain the pH above 7. The reaction mixture was diluted with water, extracted with ether, the ether extract discarded, and the aqueous phase acidified to pH 1. Extraction with ether afforded

2.63 g of crude material, which gave 2.26 g (51%) of 4C following recrystallization from ethyl acetate[5].

Part of the pmr spectrum of 4G (D_2O, Na_2CO_3, 37°) is shown in Figure 1. Under these conditions, the compound exists as a 1:1 mixture of conformational isomers corresponding to restricted rotation about the amide bond. The C2 methylene protons are anisochronous in both isomers, and have different coupling constants. A detailed account of the nmr spectra of these compounds as a function of pH, solvent and temperature, and comparison with the analogous thiazolidinecarboxylic acids will be published elsewhere.

Table I. Synthesis of five-membered and six-membered rings from amino hydroxyacids



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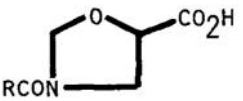

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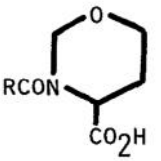

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Compound	Configuration of Amino Acid	R	R_1	R_2	R_3	Yield (%)[a]	m.p.(°C)
4A	DL	Ph	H	CH_3	H	75	123.0-124.0
4B	DL	Ph	H	H	CH_3	65	153.5-155.5
4C	D	Ph	H	H	H	51	101.5-103.5
4D	L	Ph	H	CH_3	CH_3	61[b]	130.0-131.5
4E	DL	Ph	H	H	H	79	122.5-123.5
4F	DL	Ph	H	CH_3	CH_3	92	141.5-142.5
4G	DL	p-NO_2-C_6H_4	H	CH_3	CH_3	37	221.0-222.0
4H	DL	p-Cl-C_6H_4	H	CH_3	CH_3	81	183.0-185.0
4I	DL	p-CH_3O-C_6H_4	H	CH_3	CH_3	55	127.5-128.5
4J	DL	p-CH_3-C_6H_4	H	CH_3	CH_3	82	135.5-136.5
4K	DL	Ph	H	Ph	H	93[c]	d
4L	DL	t-BuOCOCH_2	H	CH_3	CH_3	51[e]	120.0-121.0
4M	DL	Ph	Ph	H	H	34[f]	132.0-134.0
5	D	Ph				63	138.0-139.0
6A	DL	Ph				59	147.0-148.0
6B	DL	t-BuOCOCH_2				18[e]	125.0-127.0

[a]All yields refer to recrystallized material of analytical purity. [b]Refers to the dibenzylamine salt. [c]Refers to the barium salt. [d]Not taken. [e]Acylation performed at 0-5°C by addition of t-butyl hydrogen malonate, DCC and THF to the amino acid-formaldehyde reaction mixture. [f]Reaction performed in aqueous DMF.

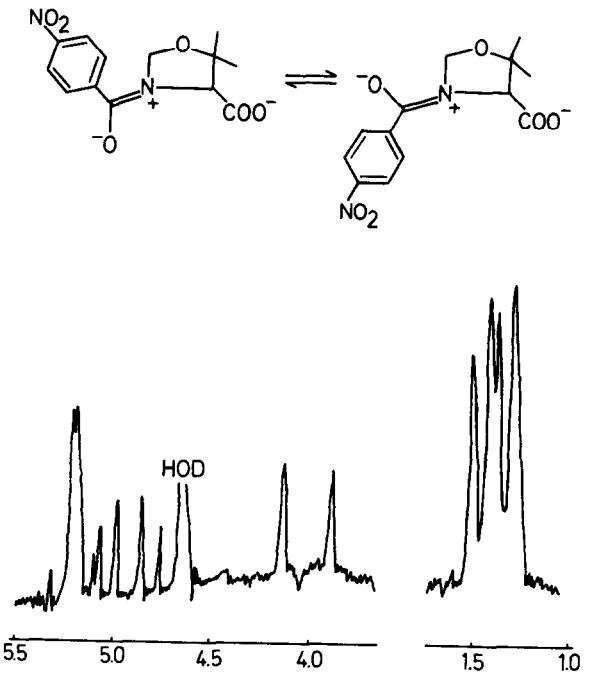

Figure 1. The pmr spectrum of 4G in D_2O at 37°C.

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REFERENCES AND NOTES

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[5]Satisfactory microanalytical data (C, H, N) were secured for each of the compounds shown in Table I.

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