The Rearrangement of Acid Anhydride by a *t*-Amine. The Preparation of Glycylglycine from *N*-Benzyloxycarbonylglycine Anhydride

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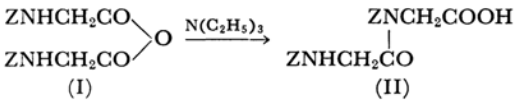
In a previous paper,[1] it was reported that β-hydroxy-α-amino acid *N*-carboxy anhydrides rearrange to 2-oxazolidone-4-carboxylic acid 5-derivatives in the presence of triethylamine. The reaction presumes the possibility of an analogous rearrangement reaction between other acid anhydrides and a *t*-amine.

In this communication, a new method for the preparation of dipeptide via the rearrangement reaction of *N*-benzyloxycarbonylamino acid anhydride with *t*-amine, followed by reduction, will be described. *N*-Benzyloxycarbonylglycine anhydride (I) (m. p. 122—123°C, IR: $\nu_{C=O}$ 1825 cm^{-1} and 1765 cm^{-1}), prepared from *N*-benzyloxycarbonylglycine (m. p. 120°C) by the use of dicyclohexylcarbodiimide,[2,3] was rearranged by the reaction of a *t*-amine, e. g., triethylamine in an inactive solvent such as dioxane or tetrahydrofuran at room temperature, to *N'*-(*N*-benzyloxycarbonylglycyl) *N'* - benzyloxycarbonylglycine (II) (yield 85%; m. p. 135°C, IR: $\nu_{C=O}$ 1685 cm^{-1}, 1720 cm^{-1}, and 1745 cm^{-1}. Found: C, 60.00; H, 4.94; N, 6.91; equiv. wt. 398, Calcd. for $C_{20}H_{20}O_7N_2$: C, 59.99; H, 5.04; N, 7.00%; equiv. wt. 400.4).



$$\begin{matrix}\text{ZNHCH}_2\text{CO}\\ \text{ZNHCH}_2\text{CO}\end{matrix}\!\!>\text{O} \xrightarrow{N(C_2H_5)_3} \begin{matrix}\text{ZNCH}_2\text{COOH}\\ |\\ \text{ZNHCH}_2\text{CO}\end{matrix}$$

(I) (II)

$$\xrightarrow{H_2/Pd} \text{H-(-NHCH}_2\text{CO-)}_2\text{-OH}$$

(III)

Z: $C_6H_5CH_2OCO$

Even if the amount of the base added was less than the equivalent of I (1—1/10 mol. per mol. of I), the reaction gave satisfactory yields (about 85%). This result indicates that the base reacted with I as a catalyst. Since II has the molecular formula, $C_{20}H_{20}O_7N_2$, which agreed with that of I, it should be an isomer of I. The product II dissolved when a portion of it was heated with aqueous sodium hydrogen carbonate. On acidification, a crystalline product, which was found to be identical with the starting material (II) by means of a mixed melting point procedure (m. p. 135°C), was deposited from the solution. Therefore, II must contain a free carbonyl group. The fact mentioned above led us to conclude that II must be a rearranged product. Another piece of evidence relating to the II structure was also obtained by the reduction producing glycylglycine (III) (yield 97%; m. p. 215—220°C (decomp.), Found: C, 36.51; H, 5.99; N, 21.03; equiv. wt. 134, Calcd. for $C_4H_8O_3N_2$: C, 36.36; H, 6.10; N, 21.20%; equiv. wt. 132.1) from II with palladium black in ethanol.

The infrared spectrum of III was identical with that of an authentic sample in all regions. Thus, this reaction will be extended as a new method of preparing dipeptides. One further investigations of the rearrangement reaction will be reported in the future.

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[3] H. Schüssler and H. Zahn, *Chem. Ber.*, **95**, 1076 (1962).