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**Abstract**

**Full Text**

**Chemistry**

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## Phosphine Derivatives of Amino Acids and Peptides

The physiological activity of organophosphorus compounds has attracted the attention of researchers to this field. Recently many classes of organophosphorus substances have been obtained, including phosphinic analogs of  $\alpha$ -amino acids. The phosphinic analog of glycine is known, and a method for the synthesis of aliphatic amino acids of the general formula  $\text{NH}_2-(\text{CH}_2)_n-\text{PO}(\text{OH})_2$  has also been elucidated and described simultaneously <sup>(1)</sup>. Later a paper appeared on the phosphinic analog of a dicarboxylic amino acid (glutamic acid) <sup>(2)</sup>.

M. I. Kabachnik and T. Ya. Medved' described the synthesis of  $\alpha$ -aminomethylphosphinic acid from esters of halogen-substituted methylphosphinic acid <sup>(3)</sup>; they also developed a method for the synthesis of  $\alpha$ -aminoalkylphosphinic acid <sup>(4,5)</sup> from aldehydes, diethyl phosphite, and ammonia. This method proved to be the most convenient.

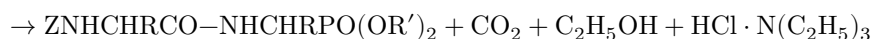
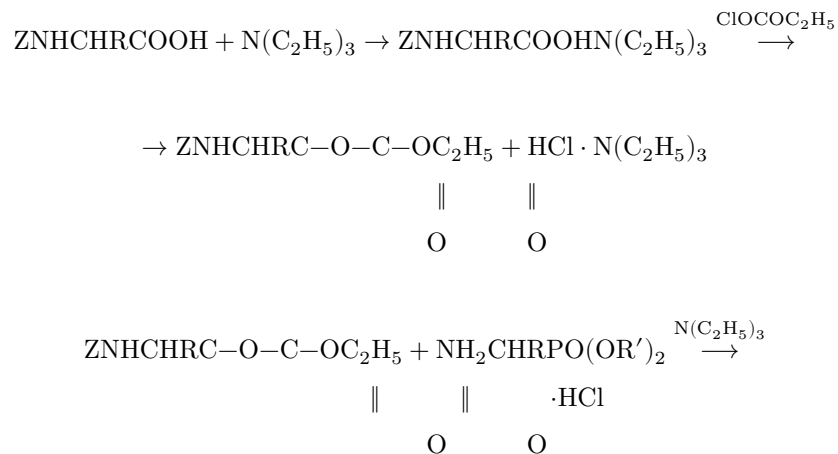
Phosphinic  $\alpha$ -amino acids are phosphinic analogs of  $\alpha$ -aminocarboxylic acids, whose biological importance is great. Asparagine acid is one of the very rare specific compounds necessary for the development of tubercle bacilli, and its phosphinic analog is of interest for the study of possible antagonistic action.

It should also be noted that organophosphorus compounds are anticholinesterase substances or are converted into such substances in the organisms of animals and plants. The phosphinic analog of glutamic acid is an inhibitor of the enzymatic synthesis of glutamine <sup>(2)</sup>.

It was natural to turn attention to the synthesis of phosphinic analogs of peptides consisting of  $\alpha$ -amino acid residues and a phosphinic analog of an amino acid.

For the formation of the peptide bond we used the "mixed anhydrides" method <sup>(6)</sup>. The amino group of the first component was protected by the carbobenzyloxy group  $Z$  ( $Z = \text{C}_6\text{H}_5\text{CH}_2\text{OCO}-$ ); the second component was prepared by the known method <sup>(4,5)</sup> and was the hydrochloride of the diethyl ester of  $\alpha$ -aminobenzylphosphinic acid.

The general scheme of the synthesis is as follows:



According to the scheme described, we obtained a series of compounds that are phosphinic analogs of  $\alpha$ -amino acids and peptides.

To carry out peptide synthesis from the amino end, it is necessary to remove the carbobenzyloxy protection. The carbobenzyloxy group was removed with 40% HBr in glacial acetic acid according to Ben-Ishai (7), and a series of bromohydrates was obtained.

## Experimental Part

Carbobenzyloxy derivatives of glycine and alanine were prepared by a known method (8). Carbobenzyloxy derivatives of glycyglycine and glycyalanine were obtained by saponification of the methyl ester of the carbobenzyloxydipeptide or by protection of the amino group of the dipeptide with the carbobenzyloxy group by the usual method under Schotten-Baumann conditions (8, 9). The hydrochloride of the diethyl ester of  $\alpha$ -aminobenzylphosphinic acid was obtained from diethyl phosphite (10), 10% ammonia in absolute ethanol, and benzaldehyde (4).

**Diethyl ester of carbobenzyloxy- $\alpha$ -aminobenzylphosphinic acid** was obtained by the gradual addition of carbobenzyloxy chloride (0.34 g) to 0.554 g (0.002 mol) of the hydrochloride of the diethyl ester of  $\alpha$ -aminobenzylphosphinic acid in 10 ml of 2 N NaOH at  $-10^\circ$ , with the pH of the medium 8-9. On vigorous shaking, a white precipitate formed, which was washed with water, dried in a vacuum pistol, and washed with ether. Yield 98.8%; m.p.  $112^\circ$ .

Found, %: C 60.67, 60.68; H 6.57, 6.40; N 3.80, 3.82; P 8.00, 8.03  
 $C_{19}H_{24}O_5NP$ . Calculated, %: C 60.5; H 6.36; N 3.7; P 8.22

**Diethyl ester of carbobenzoxyglycyl- $\alpha$ -aminobenzylphosphinic acid.**

To 0.75 g (0.00357 mol) of carbobenzoxyglycine in 10–15 ml of dry chloroform and 0.5 ml of triethylamine at  $-15^\circ$  was added 0.39 g (0.00357 mol) of ethyl chloroformate. The mixture was kept with stirring at  $-10$ – $5^\circ$  for 40 min and again cooled to  $-10^\circ$ . To the cooled mixture was added 1 g (0.00357 mol) of the hydrochloride of the diethyl ester of  $\alpha$ -aminobenzylphosphinic acid, in the form of a suspension in 10–15 ml of chloroform with 0.5 ml of triethylamine. The reaction, with vigorous stirring, was kept at  $-10^\circ$  for 40 min, at  $20^\circ$  for 2 h, and at  $50^\circ$  for 15 min. The mixture was then washed successively with water, 1 N HCl, water, 0.5 N  $NaHCO_3$ , and water, dried over anhydrous  $Na_2SO_4$ ; the chloroform was removed in vacuo, and an oil was obtained. The oil crystallized from a mixture of methanol and water. After recrystallization from alcohol, a substance was obtained in 50% yield; m.p.  $81$ – $82^\circ$ .

Found, %: N 6.76, 6.66; P 6.95, 6.99  
 $C_{21}H_{27}O_6N_2P$ . Calculated, %: N 6.44; P 7.14

**Diethyl ester of carbobenzoxyglycylglycyl- $\alpha$ -aminobenzylphosphinic acid** was obtained analogously to the diethyl ester of carbobenzoxyglycyl- $\alpha$ -aminobenzylphosphinic acid. Carbenzoxyglycylglycine was taken as the first component. After removal of chloroform, the oil was dissolved in ethyl acetate, and, upon addition of dry ether, a white precipitate formed; yield 48%, m.p.  $73^\circ$ .

Found, %: C 55.92, 55.93; H 6.15, 6.20; N 8.80, 8.75; P 6.24, 6.28  
 $C_{23}H_{30}O_7N_3P$ . Calculated, %: C 56.21; H 6.11; N 8.55; P 6.31

**Diethyl ester of carbobenzoxyalanil- $\alpha$ -aminobenzylphosphinic acid** was obtained analogously to the diethyl ester of carbobenzoxyglycyl- $\alpha$ -aminobenzylphosphinic acid. The oil crystallized from a mixture of methanol and water when the wall of the flask was rubbed with a rod. Yield 33%; m.p.  $103$ – $105^\circ$ .

Found, %: N 6.50, 6.52; P 6.80, 6.81  
 $C_{22}H_{29}O_6N_2P$ . Calculated, %: N 6.25; P 6.91

**Diethyl ester of carbobenzoxyglycylalanil- $\alpha$ -aminobenzylphosphinic acid.** To obtain this product, carbobenzoxygly-

cycloalanil. The oil crystallized from an ethyl acetate–ether mixture. Yield 31.35%; m.p.  $93^\circ$ .

Found, %: N 8.30, 8.30; P 6.13, 6.15  
 $C_{24}H_{32}O_7N_3P$ . Calculated, %: N 8.30; P 6.13

**Hydrobromide of the diethyl ester of glycyl- $\alpha$ -aminobenzylphosphinic acid.** To 0.52 g (0.0012 mole) of the diethyl ester of carbobenzoxyglycyl- $\alpha$ -aminobenzylphosphinic acid was added 0.5 ml of a 40% solution of HBr in

glacial acetic acid. The reaction mixture was left for 24 hours, until complete dissolution of the diethyl ester of carbobenzoxyglycyl- $\alpha$ -aminobenzylphosphinic acid. On addition of 15 ml of dry ether, a white precipitate of the hydrobromide obtained separated, which was recrystallized twice from methanol. Yield 52.2%; m.p. 220° (dec.),  $R_f = 0.67$ . The following hydrobromides were obtained analogously.

**Hydrobromide of the diethyl ester of glycyglycyl- $\alpha$ -aminobenzylphosphinic acid.** Yield 55%; m.p. 270° (dec.),  $R_f = 0.35$ .

**Hydrobromide of the diethyl ester of alanyl- $\alpha$ -aminobenzylphosphinic acid.** Yield 60%; m.p. 300° (dec.),  $R_f = 0.43$ .

**Hydrobromide of the diethyl ester of glycyalanyl- $\alpha$ -aminobenzylphosphinic acid.** Yield 58.4%; m.p. 350° (dec.),  $R_f = 0.34$ .

Chromatographic determination was carried out in the system butanol–water–acetic acid (4 : 5 : 1), using “Leningrad” paper of type “M.” The chromatograms were developed with a 0.5% solution of ninhydrin in 95% aqueous acetone.

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*Note: Figure translations are in progress. See original paper for figures.*

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