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**Abstract**

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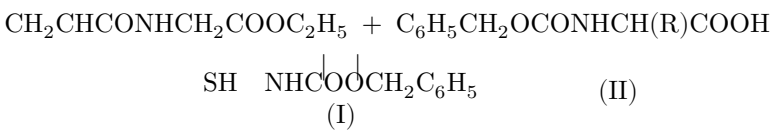
# A New Method for Obtaining S-Aminoacyl Derivatives of Cysteine Peptides

*(Presented by Academician M. M. Shemyakin, 21 IX 1960)*

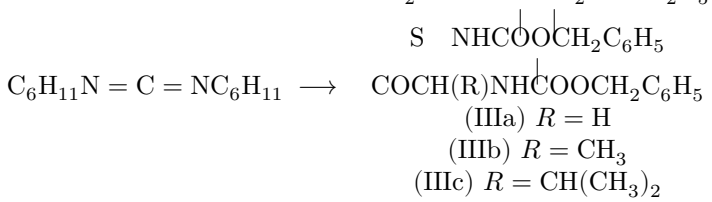
Earlier we showed ([1]) that the carbodiimide method of peptide synthesis can be successfully applied to the synthesis of O-aminoacyl derivatives of serine and tyrosine peptides, belonging to the type of compounds that have recently received the name depsipeptides ([2,3]). In the present communication we give data concerning the use of N,N′-dicyclohexylcarbodiimide for the synthesis of S-aminoacyl derivatives of cysteine peptides, which it is expedient to consider as representatives of thiodepsipeptides. The latter are of interest because the considerable lability of the S–CO bond of the mercaptoacyl group accounts for their capacity for various rearrangements, which may prove of interest from the biochemical point of view ([4,5]).

Up to the present time, the principal method for obtaining certain thiodepsipeptides has been the reversible reaction of transfer of aminoacyl residues from S-aminoacyl derivatives of thiophenol to compounds containing a free sulfhydryl group ([4])*. By this method S-acyl, S-aminoacyl, and S-peptide derivatives of cysteamine ([4]), glutathione ([4]), and coenzyme A ([10]) were obtained. To obtain S-aminoacyl derivatives of cysteamine, fusion of cysteamine hydrochloride with amino acid chlorohydrides was also used ([11]). In addition, the literature describes the synthesis of an S-aminoacyl derivative of an N-formyl derivative of cysteine by the chlorohydride method ([12]).

In the method proposed by us, formation of the mercaptoacyl group is effected by condensation, with the aid of N,N′-dicyclohexylcarbodiimide, of an ester of a cysteine-containing peptide (I) with carbobenzoxyamino acids (II). By this method the esters of S-carbobenzoxyaminoacyl-N-carbobenzoxy-*L*-cysteinylglycine (IIIa–IIIc) were obtained.



(I) (II)



(IIIa) $R = H$
(IIIb) $R = CH_3$
(IIIc) $R = CH(CH_3)_2$

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* The starting S-aminoacyl derivatives of thiophenol were obtained by the reaction of chlorohydrides of amino acid hydrochlorides with thiophenol ([6]), or by the mixed-anhydride method using chloroformic ester ([7]). The latter was also used for the synthesis of a series of S-aminoacyl derivatives of thioglycolic, thiopropionic, and certain other thio acids ([8,9]).

The synthesis of compounds (IIIa–IIIc) was carried out under conditions analogous to those described by us earlier ([1]) for the preparation of O-aminoacyl derivatives of serine peptides (equimolecular amounts of reagents, presence of pyridine, room temperature). In all cases the thio-depsipeptides formed were isolated in the crystalline state in good yield.

Thus, N,N′-dicyclohexylcarbodiimide makes it possible to synthesize compounds in which amino-acid residues are linked not only by an amide or ester bond, but also by a thioester bond.

## Experimental Part

**1. Ethyl ester of N-carbobenzoxy-L-cysteinylglycine (I)** (cf. ([12])). 5.7 g (0.008 mole) of diethyl dicarbobenzoxy-L-cystinylglycine ([13], [14]) in 125 ml of methanol, 2.5 g of zinc dust, and 10 ml of 4 N sulfuric acid are boiled for 4 hours. The still-warm solution is then filtered, the precipitate on the filter is washed with methanol, and the filtrate is evaporated in vacuo. The precipitated substance is filtered off and washed with water. Compound (I) is obtained in quantitative yield; m.p. 118–120° (from aqueous ethanol); $[\alpha]_D^{20} - 21.3°$ ($c = 2\%$ in glacial acetic acid).

| | |
|---|---|
| Found, %: | C 53.22; H 6.14; N 8.20 |
| $C_{15}H_{20}N_2O_5S$. Calculated, %: | C 52.92; H 5.91; N 8.23 |

**2. Preparation of S-aminoacyl derivatives of ethyl ester of N-carbobenzoxy-L-cysteinylglycine.** To a solution of equimolecular amounts

of ethyl ester of N-carbobenzoxy-L-cysteinylglycine (I) and the corresponding N-carbobenzoxyamino acid (II), dissolved in a minimal amount of acetone, are added equimolecular amounts of pyridine and N,N′-dicyclohexylcarbodiimide, dissolved in a minimal amount of acetone. The reaction mixture is left for 24 hours at room temperature. The precipitated N,N′-dicyclohexylurea is filtered off and washed with acetone. The filtrate is evaporated in vacuo to dryness, and the residue is recrystallized from the appropriate solvent.

Data are given below for compounds (IIIa–IIIc) obtained by this method.

Ethyl ester of S-carbobenzoxyglycyl-N-carbobenzoxy-L-cysteinylglycine (IIIa). Yield 86%; m.p. 120–122° (aqueous acetone); $[\alpha]_D^{20} - 21.2^\circ$ ($c = 2\%$ in glacial acetic acid).

| | |
|---|---|
| Found, %: | C 56.80; H 5.54; N 8.16 |
| $C_{25}H_{29}N_3O_8S$. Calculated, %: | C 56.48; H 5.49; N 7.90 |

Ethyl ester of S-carbobenzoxy-L-alanyl-N-carbobenzoxy-L-cysteinylglycine (IIIb). Yield 68%; m.p. 113–115° ($CCl_4$); $[\alpha]_D^{20} - 32.9^\circ$ ($c = 2\%$ in glacial acetic acid).

| | |
|---|---|
| Found, %: | C 56.96; H 5.83; N 7.62 |
| $C_{26}H_{31}N_3O_8S$. Calculated, %: | C 57.23; H 5.72; N 7.68 |

Ethyl ester of S-carbobenzoxy-L-valyl-N-carbobenzoxy-L-cysteinylglycine (IIIc). Yield 65%; m.p. 105–106° ($CCl_4$); $[\alpha]_D^{23} - 41.0^\circ$ ($c = 2\%$ in glacial acetic acid).

| | |
|---|---|
| Found, %: | C 58.70; H 6.27; N 7.35 |
| $C_{28}H_{35}N_3O_8S$. Calculated, %: | C 58.62; H 6.15; N 7.32 |

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