The subunits of the 11S globulin of variety Tashkent-1 differ in their primary structures from the corresponding subunits of variety 108-F.

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PREPARATION OF HYDRAZIDES OF AMINO ACIDS AND PEPTIDES

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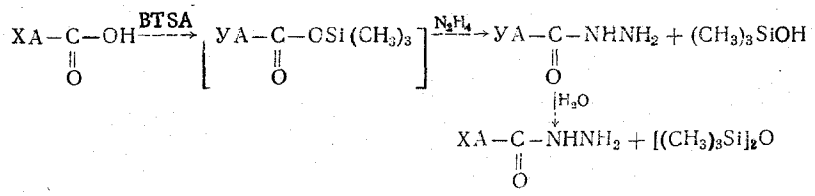
A new method of synthesizing hydrazides of amino acids and peptides is considered which involves the hydrazinolysis of the silyl esters of the corresponding compounds. A number of hydrazides of derivatives of amino acids and peptides has been obtained in high purity with yields close to quantitative. The physicochemical characteristics of the compounds synthesized are given.

The usual method of obtaining hydrazides of amino acids and peptides, which are used mainly for the synthesis of azides, is the hydrazinolysis of the methyl or ethyl esters of the corresponding compounds [1]. As a rule, the process is performed under mild conditions (at room temperature) in ethanol or dimethylformamide (DMFA). The hydrazine is used in the form of hydrazine hydrate or, more rarely, as anhydrous hydrazine, the hydrazine being taken in excess to prevent the formation of symmetrical bishydrazides. A disadvantage of this method is the necessity for the previous synthesis of the methyl or ethyl ester of the corresponding compound which, in a number of cases, is associated with certain difficulties. Thus, for example, esters of derivatives of N^{ε}-tert-butoxycarbonyl-L-lysine can be obtained only by using diazomethane [2].

We have developed a convenient method for obtaining hydrazides of amino acids or peptides which consists in the preliminary silylation of the corresponding amino acid or peptide followed by the hydrazinolysis of the trimethylsilyl ester with anhydrous hydrazine [3]. The reaction is performed at room temperature in DMFA or methylene chloride in accordance with the following scheme:



where X represents a protective group or a hydrogen atom; Y, a trimethylsilyl or protective group; A, an amino acid or peptide residue; and BTSA represents bis(trimethylsilyl)acetamide.

Bis(trimethylsilyl)acetamide is used as the silylating agent [4]. The hydrazides of the corresponding amino acids and peptides are obtained in yields of 80-98% and in high purity.

It is interesting that the process under consideration differs from known reactions of nucleophilic substitution at a silicon atom in acyloxysilanes [5]. In spite of the fact that

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the molecule of the silyl derivative of an amino acid or peptide has two potential centers for nucleophilic attack in the hydrazinolysis reaction (the carbon atom of the carboxy group and the silicon atom), in contrast to the reactions mentioned above the process takes place selectively at this carbon atom.*

A number of hydrazides of amino acids and peptides† have been obtained by the method that we have developed and some of their physicochemical characteristics (angle of optical rotation, melting point, elementary composition) have been determined. The compounds synthesized were characterized by chromatographic homogeneity and had characteristics identical with those of the analogous hydrazides obtained via the methyl (or ethyl) ester.

EXPERIMENTAL

All operations with silyl derivatives were performed in hermetically sealed systems using dry reagents. The DMFA was made absolute by azeotropic distillation with benzene. The methylene chloride was dried over calcium chloride and was then redistilled and stored over calcium hydride. Anhydrous hydrazine was obtained by distilling hydrazine hydrate over solid caustic soda.

Melting points were determined in open capillarities without correction.

The chromatographic purities and mobilities of the compounds synthesized were determined by thin-layer chromatography on "Silufol" plates in methanol–chloroform systems (ratios by volume). Samples for elementary analysis were recrystallized from methanol and were dried in a vacuum drying chest over phosphorus pentoxide and potassium hydroxide.

1. Preparation of Z-Phe-$NHNH_2$. A. A solution of 1 g (3.34 mmole) of benzyloxycarbonyl-L-phenylalanine in 2 ml of DMFA was treated with 1.3 g (6 mmole) of BTSA, and the reaction mixture was kept at room temperature (20-25°C) for 3 h. Then 0.53 ml of anhydrous hydrazine was added and the new reaction mixture was kept at room temperature for 12 h. The resulting hydrazide was precipitated with an excess of water and it was carefully washed on a glass filter and was dried in vacuum. This gave 1 g of product in the form of a white crystalline powder. Yield 95% of theory. The product was chromatographically homogeneous (R_f 0.47 (9:1 system, run twice), R_f 0.32 (9:1 system, run once)), mp 168-169°C $[\alpha]_D^{22}$ −7.0° (c 1.0; CH_3OH).

B. To a mixture of 1 g (3.34 mmole) of benzyloxycarbonyl-L-phenylalanine in 2 ml of methylene chloride was added 1.3 g (6 mmole) of BTSA and the mixture was stirred with a magnetic stirrer at room temperature for 1 h. Then 0.53 ml of anhydrous hydrazine was added and after 30 min the reaction mixture was treated with an excess of water. The resulting hydrazide was washed on a glass filter and was dried in vacuum. This gave 0.9 g of product in the form of a white crystalline powder the physicochemical characteristics of which were identical with those of the product obtained by method A. Yield 85% of theory.

2. Preparation of Z-Pro-$NYNH_2$. By the method of paragraph 1, 2g (8.05 mmole) of benzyloxycarbonyl-L-proline, 2.4 g (12 mmole) of BTSA, and 1.3 ml of hydrazine yielded 1.7 g of product in the form of an oil. Since the hydrazide obtained was soluble in water, it was extracted from the aqueous solution with ethyl acetate. Yield 80% of theory; chromatographically homogeneous (R_f 0.57 (9:1 system, run twice)), $[\alpha]_D^{22}$ −36.0° (c 1.0; CH_3OH).

3. Preparation of Z-Glu(NH_2)-$NHNH_2$. Using the method of paragraph 1, 2 g (7.15 mmole), of benzyloxycarbonyl-L-glutamine, 3.8 g (18.6 mmole) of BTSA, and 1.2 ml of hydrazine yielded 1.7 g of product in the form of a white crystalline powder. Yield 80% of theory. The product was chromatographically homogeneous (R_f 0.26 (7:3 system)); mp 175-176°C; $[\alpha]_D^{22}$ −16.0° (c 1.0; CH_3OH).

4. Preparation of BOC-β-Ala-$NHNH_2$. By the method of paragraph 1, 1.89 g (10 mmole) of tert-butoxycarbonyl-β-alanine, 4.1 g (20 mmole) of BTSA, and 1.6 ml of hydrazine yielded 1.73 g of a product in the form of a white crystalline powder. Yield 85% of theory. The product was chromatographically homogeneous (R_f 0.23 (9:1 system, run twice)); mp 110-112°C.

5. Preparation of BOC-Val-Tyr-$NHNH_2$. By the method of paragraph 1, 2 g (5.25 mmole) of tert-butoxycarbonyl-L-valyl-L-tyrosine, 2.7 g (13.1 mmole) of BTSA, and 0.84 ml of hydrazine

*In the work cited [5], lithium tetrahydroaluminate, solid caustic potash, and methanol were used as nucleophilic reagents.

†All the amino acids used in the work had the L configuration.

gave 1.8 g of product. Yield 87% of theory. The product was chromatographically homogeneous (R_f 0.22 (9:1 system, run twice), mp 210-212°C; $[\alpha]_D^{22}$ −39°, (1.0; CH_3OH).

6. Preparation of BOC-Val-Lys(Z)-$NHNH_2$. By the method of paragraph 1, 1.5 g (3.14 mmole) of tert-butoxycarbonyl-L-valyl-N^{ε}-benzyloxycarbonyl-L-lysine, 1.3 g (6.28 mmole) of BTSA, and 0.51 ml of hydrazine gave 1.5 g of product in the form of a white crystalline substance. Yield 97% of theory. The product was chromatographically homogeneous (R_f 0.38 (9:1 system, run twice)), mp 163-165°C; $[\alpha]_D^{22}$ −39°, (c 1.0; CH_3OH).

7. Preparation of Z-Val-Gly-Lys(BOC)-Lys(BOC)-$NHNH_2$. By the method of paragraph 1, 1.0 g (1.31 mmole) of benzyloxycarbonyl-L-valylglycyl-N^{ε}-tert-butoxycarbonyl-L-lysyl-N^{ε}-tert-butoxycarbonyl-L-lysine, 0.54 g (2.62 mmole) of BTSA, and 0.21 ml of hydrazine gave 1 g of product in the form of a white crystalline powder. Yield 98% of theory. The product was chromatographically homogeneous (R_f 0.55 (7:3 system)), mp 202-205°C; $[\alpha]_D^{22}$ −18.0° (c 1.0; CH_3OH).

8. Preparation of Z-Val-Lys(BOC)-$NHNH_2$. Using the method of paragraph 1, 6.1 g (13 mmole) of benzyloxycarbonyl-L-valyl-N^{ε}-tert-butoxycarbonyl-L-lysine, 3.13 g (15 mmole) of BTSA, and 3.05 ml of hydrazine in 5.1 ml of DMFA gave 5.6 g of a white crystalline powder. Yield 89% of theory. The product was chromatographically homogeneous (R_f 0.27 (9:1 system, run twice), R_f 0.57 (8:2 system)), mp 170-172°C; $[\alpha]_D^{22}$ −26.0° (c 1.0; CH_3OH).

SUMMARY

1. A new convenient method has been developed for obtaining hydrazides of amino acids and peptides by the hydrazinolysis of the trimethylsilyl esters of the corresponding compounds.

2. The proposed method can be a general method of transforming carboxy groups of organic compounds into carbohydrazide groups under mild conditions.

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