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PREPARATION OF TRITYL DERIVATIVES OF AMINO ACIDS WITH THE AID OF THE SILYLATION REACTION

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A number of N-trityl-substituted amino acids (lysine, glutamine, tyrosine, valine, and proline) have been obtained with the aid of the silylation reaction. Bis(trimethylsilyl)acetamide was used as the silylating agent. The compounds were isolated with good yields and were distinguished by chromatographic homogeneity, and they were characterized by their angles of optical rotation, melting points, and elementary analyses. Their purity was checked by TLC and ^{13}C NMR.

One of the widely used methods of protecting amino groups in peptide chemistry is substitution by a triphenylmethyl (trityl) grouping. The usual method of obtaining trityl derivative of amino acids (AAs) is by the action of trityl chloride on hydrochlorides of the methyl (or ethyl) esters of the AAS in the presence of a tertiary base (triethylamine) followed by alkaline hydrolysis of the compounds obtained [1]. Disadvantages of this method include the necessity for a special stage of obtaining and isolating the corresponding AA ester which is associated in a number of cases with certain difficulties; for example, the methyl ester of N^{ε}-tert-butoxycarbonyl-L-lysine is obtained by using diazomethane. Furthermore, the process of hydrolyzing the esters is complicated by the steric hindrance connected with the large volume of the trityl radical. Consequently, to hydrolyze the esters of a number of tritylamino acids severe conditions are necessary (elevated temperature, excess of alkali), and this has an adverse effect on the quality of the desired product (partial racemization, degradation). The tritylation of free AAs in aqueous organic media considerably simplifies the process, but the hydrolysis of the trityl chloride, competing with the main reaction, leads to a large consumption of this reagent and, as a rule, the trityl derivatives are obtained in relatively low yield (40-50%). Recently, the trityl derivative of histidine has been obtained via the trimethylsilyl ester of the AA, which was subjected to tritylation with triphenylmethyl chloride without isolation [2].

Our task was to obtain trityl derivatives of a number of AAs (lysine, tyrosine, glutamine, valine, proline) with the aid of the silylation reaction in order to determine the possibilities of the method (to what extent this transformation has a general nature). The corresponding AA was first silylated in methylene chloride (or DMFA) solution and the trimethylsilyl ester so obtained, without isolation, was then treated with trityl chloride in the presence of trimethylamine:

$$H\text{--}A\text{--}OH \xrightarrow{BSA} [Me_3Si\text{--}A\text{--}OSiMe_3] \xrightarrow{(C_6H_5)_3CCl} Trit\text{--}A\text{--}OSiMe_3 \xrightarrow{H_2O} Trit\text{--}A\text{--}OH,$$

where A is an amino acid residue.

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In contrast to [2] we used as the silylating agent not chlorotrimethylsilane but a more universal silylating agent — bis(trimethylsilyl)acetamide (BSA) [3]. All the trityl derivatives of AAs were obtained with fairly high yields (70-80%) and a high degree of purity. Some physicochemical characteristics of the compounds synthesized were determined (angles of optical rotation, melting points, elementary compositions).

We used the ^{13}C NMR method to confirm the structures and check the purities of the compounds obtained. It proved to be particularly useful in the case of tyrosine. Thus, the presence of a $(C_6H_5)_3C-N-$ bond was confirmed by the well-defined signal in the spectra at 71.0 ± 0.2 ppm corresponding to the radical of a quaternary carbon atom. The spectra of all the compounds lacked signals corresponding to a trimethylsilyl grouping. In the spectra of the tritylated tyorsine derivative there was no signal in the 75-90 ppm region, which shows the absence of substitution of the hydroxy of the tyrosine by a trityl radical. Consequently, under the given conditions tritylation takes place only at the amino group with the formation of the corresponding monotrityl derivative even with a twofold excess of trityl chloride. No other impurities whatever were detected in appreciable amounts in the spectra.

For convenience of isolation, the individual compounds were obtained and characterized in the form of their diethylammonium salts. All the products were chromatographically homogeneous and their characteristics were identical with those of analogous compounds described in the literature.

EXPERIMENTAL

Dry freshly distilled solvents were used. Melting points were determined in open capillaries without correction, and angles of optical rotation on a polarimeter. The chromatographic purities and mobilities were determined by the TLC method on Silufol plates in the chloroform—methanol system. The analyses of all the compounds corresponded to the calculated figures. The ^{13}C NMR spectra of solutions in hexadeuterodimethyl sulfoxide (c = 100 mg/ml) were recorded on a WP-80DS spectrometer with a working frequency of 20.115 MHz. The conditions of recording the spectra and the calculations of the chemical shifts were similar to those given previously [4]. All the AAs used had the L configuration.

1. Trit-Lys(BOC)-OH. The silyation of 2.46 g (10 mmole) of N^{ε}-tert-butoxycarbonyllysine in 10 ml of methylene chloride was carried out with 4.8 ml (20 mmole) of BSA as described previously [5], and then the reaction solution was cooled to 0°C and 1.45 ml (10.5 mmole) of triethylamine and 2.92 g (10.5 mmole) of trityl chloride were added successively. The reaction mixture was stirred at 0°C for 2 h and at room temperature for 6 h, and then 25 ml of methylene chloride was added and the reaction solution was washed successively with 0.1 N HCl (3 × 20 ml) to pH 3 and with H_2O (3 × 20 ml). The organic layer layer was dried with sodium sulfate, and the solvent was driven off in vacuum. The residue was dissolved in 10 ml of benzene and the product was precipitated with 50 ml of petroleum ether. After drying in vacuum, 3.5 g of product was obtained in the form of a white power, $C_{30}H_{36}N_2O_4$, yield 72%, chromatographically homogeneous, R_f 0.53-0.55 in the (9:1) system; mp 75-77°C, $[\alpha]_D^{20}$ + 35,0° (*c* 1; MeOH).

2. Trit-Glu(OtBu)-OH·Et_2NH. A trityl derivative was obtained by the method of paragraph 1 from 8 g (39 mmole) of the γ-tert-butyl ester of glutamic acid, 19.2 ml (80 mmole) of BSA, 11.2 g (40 mmole) of trityl chloride, and 5.6 ml (40 mmole) of triethylamine. It was dissolved in 100 ml of dry ethyl ether, 12.3 ml (120 mmole) of diethylamine was added, and the resulting precipitate of the salt was washed with ether and dried in vacuum. This gave 15.3 g of product in the form of a white powder, $C_{32}H_{42}N_2O_4$, yield 75%, chromatographically homogeneous, R_f 0.42-0.44 in the (9:1) system; mp 136-138°C, $[\alpha]_D^{20}$ + 19,0 (*c* 5; MeOH). Here and below, R_f values were determined for the free trityl derivatives of the AAs.

3. Trit-Val-OH·Et_2NH. The corresponding derivative was obtained by the method of paragraph 1 from 1.17 g (10 mmole) of valine, 4.8 ml (20 mmole) of BSA, 2.79 g (10 mmole) of trityl chloride, and 1.38 ml (10 mmole) of triethylamine in DMFA. The "crude" product was dissolved in 10 ml of ether, 3.08 ml (30 mmole) of diethylamine was added, and the salt that precipitated was washed with ether and dried in vacuum. This gave 3.5 g of product in the form of a white powder, $C_{28}H_{36}N_2O_2$, yield 80%, chromatographically homogeneous, R_f 0.73-0.75 in the (9:1) system and 0.60-0.65 in the (12:1) system; mp 158-160°C, $[\alpha]_D^{20}$ + 6,4° (*c* 5; MeOH).

4. Trit-Tyr-OH·Et_2NH. The trityl derivative was obtained by the procedure of paragraph 1 from 3.6 g (20 mmole) of tyrosine, 9.6 ml (40 mmole) of BSA, 5.6 (20 mmole) of trityl chloride, and 2.8 ml (20 mmole) of triethylamine in DMFA, and it was dissolved in 50 ml of ether and treated with 6.16 ml (60 mmole) of diethylamine, giving a salt which was washed with ether and dried in vacuum. The amount of product in the form of a white powder, $C_{32}H_{36}N_2O_3$, was 7.3 g or 74%; it was chromatographically homogeneous, R_f 0.70-0.73 in the (9:1) system; mp 188-190°C (decomp.), $[\alpha]_D^{20} + 18°$ (c 1; MeOH).

5. Trit-Pro-OH·Et_2NH. The trityl derivative was obtained by the method of paragraph 1 from 1.15 g (10 mmole) of proline, 4.8 ml (20 mmole) of BSA, 2.79 g (10 mmole) of trityl chloride, and 1.38 ml (10 mmole) of triethylamine in methylene chloride and it was dissolved in 30 ml of ether and treated with 2 ml (20 mmole) of diethylamine, and the resulting salt precipitate was washed with ether and dried in vacuum. The amount of product in the form of a white powder, $C_{28}H_{34}N_2O_2$, was 2.8 g or 65%; it was chromatographically homogeneous with R_f 0.68-0.70 in the (8:2) system; mp 161-163°C, $[\alpha]_D^{20} - 54.4°$ (c 5; chloroform).

SUMMARY

Using the synthesis of the trityl derivatives of various amino acids as examples, it has been shown that trityl protection can be conveniently introduced into the amino group of an amino acid with the aid of the silylation reaction.

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