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IMPROVED METHODS OF OBTAINING N^{im}-TRITYL-SUBSTITUTED HISTIDINE DERIVATIVES

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UDC 547.466.493

Two variants are proposed for the synthesis of N^{α}-Boc-N^{im}-tritylhistidiine. The first variant starts from N^{α},N^{im}-di-Boc-histidine, from which the N^{im}-Boc group is removed with hydrazine hydrate. The N^{α}-Boc-histidine formed is esterified with chlorotrimethylsilane, tritylated in the imidazole group, and, after the elimination of the trimethylsilyl protection from the carboxyl group, N^{α}-Boc-N^{im}-tritylglycine is obtained with a yield of 80%. The second variant starts from N^{α},N^{im}-ditritylhistidine, which, by treatment with hydrochloric acid in acetone and then with dilute ammonia, is converted into N^{im}-tritylhistidine. From this, by acylation with di-tert-butyl pyrocarbonate, N^{α}-Boc-N^{im}-tritylhistidine is obtained with a yield of 91%. The acylation of N^{im}-tritylhistidine with other alkoxycarbonylating reagents leads to N^{α}-tert-amyl-, N^{α}-benzyl-, and N^{α}-4-methoxybenzyloxycarbonyl derivatives of N^{im}-tritylhistidine.

The triphenylmethyl (trityl) group is not one of the amino-protective groupings that is most widely used in peptide chemistry [1]. The only exception is formed by trityl-substituted histidine derivatives, which have been studied since the fifties [2-5] and have been used in peptide synthesis even in recent years. It is known from various publications [2-4, 6] that the condensation of N^{α},N^{im}-ditritylhistidine with amino acid esters with the aid of dicyclohexylcarbodiimide leads to the formation of dipeptides with yields of 80-90%. Ditri-

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tylhistidine also adds to dipeptide esters completely satisfactorily, and the N^{α}-trityl group can be selectively removed with solutions of hydrogen chloride in organic solvents [7]. Later, methods were developed for obtaining a N^{α}-tert-butoxycarbonyl (N^{α}-Boc) derivative of N^{im}-tritylhistidine [8, 9]. In the peptides obtained from this histidine derivative the N^{α}-Boc group can also be eliminated fairly selectively [10, 11]. The N^{im}-trityl group is readily removed with trifluoroacetic or formic acid [8, 12], and also by heating with aqueous acetic acid [3, 6]. Thus, the information available in the literature leaves no doubt of the fact that trityl-substituted histidine derivatives and, particularly, derivatives with trityl protection of the nitrogen of the imidazole ring may be of definite practical interest for peptide synthesis. However, the known methods for obtaining trityl-substituted histidine derivatives are characterized by a high laboriousness and yields that are not always satisfactory.

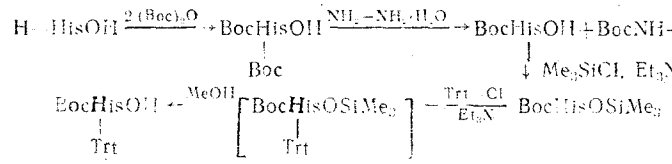
The tritylation of free histidine in an aqueous medium has no practical value because of the low yield of detritylhistidine [5]. More satisfactory results are obtained when the methyl ester of histidine is tritylated [2], but then saponification of the ester group is necessary in order to obtain ditritylhistidine. Two approaches have been used to obtain N^{α}-Boc-N^{im}-tritylhistidine. In one of them, the methyl ester of N^{im}-tritylhistidine, which is obtained either by the selective detritylation of the methyl ester of ditritylhistidine [5] or by the introduction of a trityl group into the imidazole ring of the methyl ester of histidine [8], is treated with Boc-azide and the carboxy group is then liberated by saponification [8, 9]. In another variant, N^{α}-Boc-histidine is tritylated [8]. In this process, both the imidazole ring and the carboxy group react, and the trityl ester of N^{α}-Boc-N^{im}-tritylhistidine that is formed is hydrolyzed with alkali. In this variant, onto the complications connected with the hydrolysis of the trityl ester are superposed the difficulties connected with the preparation of N^{α}-Boc-histidine [8, 13].

In recent years, we have worked on the development and simplification of methods for obtaining trityl-substituted histidine derivatives. Some of this work has been published previously [14]. The present paper gives a detailed description of the methods developed.

In spite of the successful use of ditritylhistidine for the production of dipeptides, N^{α}-Boc-N^{im}-tritylhistidine is of greater practical importance for peptide synthesis [9-12]. We have considered two variants of the synthesis of this histidine derivative, using different starting materials. In the first variant N^{α},N^{im}-di-Boc-histidine [15] was used, this being converted into N^{α}-Boc-histidine and tritylated in the imidazole residue.

It is known that the N^{im}-Boc group is fairly readily split out under the action of nucleophilic reagents. Previously, to convert di-Boc-histidine into N^{α}-Boc-histidine use has been made of the action of ammonia [16], caustic soda [8], or methanol in an alkaline medium [13]. We have found that in practice it is most desirable to use hydrazine hydrate to this conversion. When the treatment of di-Boc-histidine with hydrazine hydrate was carried out in boiling ethanol, the reaction time was shortened to a few minutes, and the N^{im}-Boc group was converted quantitatively into Boc-hydrazine, which is of practical importance [1, 17], and which, after the evaporation of the solvent was extracted with a yield of about 75%. Then its residues and the hydrazine residues were converted into acetone hydrazones by heating with acetone, these were eliminated by extraction with ether, and the residual N^{α}-Boc-histidine was crystallized from ethanol with a yield of about 90%.

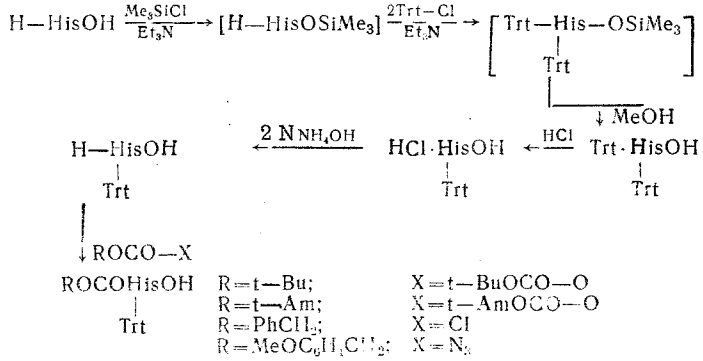
As mentioned above, in the tritylation of N^{α}-Boc-histidine the undesirable esterification of the carboxy group takes place [8]. In order to avoid this complication, we have converted the carboxy group of N^{α}-Boc-histidine into the trimethylsilyl ester. Such esterification takes place readily and quantitatively when N^{α}-Boc-histidine is treated with chlorotrimethylsilane in the presence of triethylamine in a mixture of chloroform and acetonitrile. The subsequent addition to a solution of the ester obtained of a tritylating reagent (chlorotriphenylmethane or bromotriphenylmethane) leads to the formation of trimethylsilyl ester of N^{α}-Boc-N^{im}-tritylhistidine which, in the presence of ethanol, is converted in a few minutes into N^{α}-Boc-N^{im}-tritylhistidine, obtained after purification with a yield of 80%.



Another variant of the synthesis of N^{α}-Boc-N^{im}-tritylhistidine is based on the use of N^{α},N^{im}-ditritylhistidine as the initial compound. As in the tritylation of N^{α}-Boc-histidine, in the production of ditritylhistidine the histidine was first converted into the trimethylsilyl ester by the action of chlorotrimethylsilane and triethylamine and was then tritylated with two equivalents of tritylating reagent. After the removal of the protection from the carboxyl with ethanol, ditritylhistidine precipitated from the reaction mixture in the crystalline form with a yield of 85-100%.

It is known [7, 8] that a N^{α}-trityl group in histidine is readily split out by solutions of hydrogen chloride, while a N^{im}-trityl group is fairly stable under these conditions. On this basis, we have developed a simple and convenient method for converting ditritylhistidine into N^{im}-tritylhistidine, which is the first time this has been obtained in the form of a free base, although it has been characterized previously in the form of the picrate [8]. To obtain N^{im}-tritylhistidine, hydrochloric acid was cooled to a cooled suspension of ditritylhistidine in acetone, whereupon, from the solution formed initially, N^{im}-tritylhistidine hydrochloride precipitated. It was filtered off and, after being washed to eliminate triphenyl carbinol, it was treated on the filter with dilute ammonia solution. After washing and drying, N^{im}-tritylhistidine was obtained with a yield of 80-90%.

By the acylation of N^{im}-tritylhistidine with di-tert-butyl pyrocarbonate [18, 19] under the conditions used previously for obtaining Boc derivatives of other amino acids [18, 20, 21], N^{α}-Boc-N^{im}-tritylhistidine was obtained with a yield of 91%, its purification in this case being simpler than in the tritylation of N^{α}-Boc-histidine.



N^{im}-Tritylhistidine is a convenient starting material for the preparation of a series of various N^{α}-protected derivatives. To introduce N^{α}-alkoxycarbonyl protective groupings it is possible to use pyrocarbonates and alkoxycarbonyl chlorides or azides. The acylation conditions are determined by the properties of the acylating reagent and do not differ from the conditions for the acylation of ordinary amino acids. Thus, the treatment of N^{im}-tritylhistidine with d-tert-amyl pyrocarbonate [22] and with benzyloxycarbonyl chloride and p-methoxybenzyloxycarbonyl azide [23] in alkaline aqueous organic solutions led to the corresponding N^{α}-substituted derivatives with high yields.

EXPERIMENTAL

Reanal L-histidine, Biokhimreaktiv di-tert-butyl pyrocarbonate, and Aldrich p-methoxybenzyloxycarbonyl azide were used. Angles of optical rotation were determined on a Perkin-Elmer 241 polarimeter.

Extracts were dried with anhydrous sodium sulfate and were evaporated in a rotary evaporator in vacuum at 40°C.

N^{α}-tert-Butoxycarbonylhistidine. A solution of 3.1 g of histidine in 20 ml of 1 M K_2CO_3 solution and 5 ml of isopropanol was treated with 10 ml of Boc_2O and 5 ml of isopropanol and the mixture was stirred at 30-40°C for 1 h. Then it was diluted with water to 70-80 ml, acidified with citric acid solution to pH 3, and extracted with benzene (2 × 20 ml). The extract was washed with water and evaporated, the residue was dissolved in ethanol, and the solution was boiled for 10 min. The ethanol was evaporated off and the residue was dissolved by distilling 25 ml of toluene off from it in vacuum and was then triturated in a mixture of ether and methylene chloride (1:1; four times with 15-20 ml of the mixture of solvents each time). After drying, the combined extracts were evaporated to give 1.8-2.0 g (69-76%) of

crystalline Boc-hydrazine with mp 35-37°C. The viscous residue after the extraction of the Boc-hydrazine was dissolved in 20-25 ml of acetone, and the solution was heated at 50°C for 10-15 min and evaporated. The residue was triturated with ether (3-4 portions of 15 ml each) and was crystallized from ethanol (10-15 ml). The crystalline mass was diluted with ether and the precipitated was filtered off, washed with ether, and dried in vacuum to give 4.5-4.7 g (88-92%) of N^{α}-Boc-histidine with mp 194-195°C, $[\alpha]_D^{20}$ +26.5° (c 1, CH_3OH).

N^{α}-Boc-N^{im}-tritylhistidine. In an atmosphere of dry nitrogen, 0.9 ml of chlorotrimethylsilane was added to a solution of 1.3 g of N^{α}-Boc-histidine in a mixture of 5 ml of chloroform, 3 ml of acetonitrile, and 2 ml of triethylamine, and the mixture was stirred for 25-30 min. Then 1.5 g of chlorotriphenylmethane was added and stirring was continued for another hour. After the addition of 10-15 ml of methanol the resulting mixture was stirred for 15 min and was evaporated in vacuum. The residue was mixed with water (30 ml) and benzene (20 ml), and, after the addition of 3 ml of 1 M H_2SO_4 solution, the aqueous layer was extracted with benzene (2 × 20 ml) and the extract was washed with water and evaporated. The residue was dissolved in 10 ml of ethanol and after the addition of 10 ml of 1 M NaOH and 30 ml of water the solution was kept at 20°C for 1-2 h, filtered if necessary, and neutralized with 12 ml of 1 M acetic acid solution. The mixture was kept in the refrigerator for 1-2 h, and the precipitate was filtered off, washed on the filter with water and with ether and was dried in vacuum over $CaCl_2$. This gave 2.0 g (80%) of chromatographically homogeneous N^{α}-Boc-N^{im}-tritylhistidine with mp 118-120°C, $[\alpha]_D^{20}$ +16.6° (c 1; C_2H_5OH) [8, 9]. Found, %: C 72.6; H 6.2; N 8.3. $C_{30}H_{31}N_3O_4$. Calculated, %: C 72.4; H 6.3; N 8.4.

Similarly, 1.3 g of N^{α}-Boc-histidine and 1.8 g of bromotriphenylmethane gave 2.0 g (80%) of N^{α}-Boc-N^{im}-tritylhistidine with the same characteristics.

N^{α},N^{im}-Ditritylhistidine. In an atmosphere of dry nitrogen, with stirring, 6 ml of triethylamine and 2 ml of chlorotrimethylsilane were added to a suspension of 1.55 g of finely ground histidine in a mixture of 5 ml of dimethylformamide and 10 ml of chloroform, whereupon the temperature of the mixture rose to 30-35°C. It was stirred at this temperature for 15-20 min, and 7.1 g of bromotriphenylmethane was added and stirring was continued for another 1 h. Then the mixture was diluted with benzene (20-25 ml), the precipitate was filtered off and washed with benzene, and the filtrate was evaporated to a viscous semicrystalline residue. This was treated with 15-20 ml of methanol and, after a few minutes' stirring, the precipitate was filtered off and was washed with methanol, benzene, and acetone (15-20 ml portions) and dried in vacuum. This gave 6.2-6.4 g (97-100%) of ditritylhistidine with mp 181-182°C. After reprecipitation from chloroform with methanol, a product was obtained with mp 183-185°C, $[\alpha]_D^{20}$ +9.5 (c 1; chloroform) [2].

Similarly, 10 mmole of histidine and 22 mmole of chlorotriphenylmethane yielded 6.0-6.2 g (94-97%) of ditritylhistidine with mp 182-184°C.

N^{im}-Tritylhistidine. With stirring, 5 ml of concentrated hydrochloric acid was added to a suspension of 11 g of ditritylhistidine in 40 ml of acetone cooled to 5°C, which led to a solution from which, on further stirring, a crystalline precipitate of N^{im}-tritylhistidine gradually deposited. After 30-40 min, the mixture was diluted with ether (30 ml), and the precipitate was filtered off, washed with acetone and with ether, and again with acetone. After a sample of the product had been dried in vacuum, it had mp 192-193°C, $[\alpha]_D^{20}$ +32° (c 1; CH_3OH). The product was unstable on storage. To the precipitate on the filter was added 15-20 ml of 2 M ammonia solution, the mixture was stirred for 2-3 min, the solution was separated off, and the precipitate was once more washed with ammonia solution, water, acetone, and ether, and was dried in vacuum over P_2O_5 to constant weight. This gave 6.0 g (89%) of N^{im}-tritylhistidine with mp 186-187°C (decomp.), $[\alpha]_D^{20}$ + 10.5° (c 1; C_2H_5OH — 1 M acetic acid (1:1)). R_f 0.3 (Silufol plates, chloroform—methanol—concentrated ammonia (40:10:1) system). Found, %: C 75.6; H 5.7; N 10.6. $C_{25}H_{23}N_3O_2$. Calculated, %: C 75.5; H 6.0; N 10.6.

N^{α}-Boc-N^{im}-Tritylhistidine from N^{im}-Tritylhistidine. A suspension of 1.0 g of N^{im}-tritylhistidine in 3 ml of 1 M K_2CO_3 solution and 3 ml of isopropanol was treated with 0.6 ml of Boc_2O and the mixture was stirred at 30-35°C for 40 min, by which time the N^{im}-tritylhistidine had dissolved completely. The solution was diluted with water to 20 ml and was acidified with 3.5 ml of 2 M HCl, and the resulting crystalline precipitate was filtered off, washed with water, and dried in vacuum to constant weight. This gave 1.1 g (88%) of N^{α}-Boc-N^{im}-tritylhistidine with mp 118-120°C, $[\alpha]_D^{20}$ + 16.0 (c 1; C_2H_5OH).

N^{α}-tert-Amyloxycarbonyl-N^{im}-tritylhistidine. A solution of 1.2 g of N^{im}-tritylhistidine in 4 ml of 1 M NaOH solution and 5 ml of isopropanol was treated with 0.8 ml of di-tert-amyl pyrocarbonate and the mixture was stirred for 20 min at 25°C, after which another 0.1 ml of the pyrocarbonate was added and stirring was continued for another 15 min. Then the mixture was diluted with water to 30 ml and was acidified with 5% citric acid solution, and the white friable precipitate was filtered off, washed with water (3 × 10 ml) and dried. For final purification, the product was triturated in petroleum ether at 40°C and the residue was washed with petroleum ether and with pentane and was dried in vacuum over P_2O_5 and paraffin wax. This gave 1.4 g (91%) of N^{α}-tert-amyloxycarbonyl-N^{im}-tritylhistidine with mp 105-107°C (decomp.), $[\alpha]_D^{20}$ +12.0° (c 1; C_2H_5OH). Found, %: C 72.6; H 6.6; N 8.2. $C_{31}H_{33}N_3O_4$. Calculated, %: C 72.8; H 6.5; N 8.2.

N^{α}-Benzyloxycarbonyl-N^{im}-tritylhistidine. With stirring and ice cooling, a solution of 0.7 ml of benzyloxycarbonyl chloride in 2 ml of dioxane was added dropwise to a suspension of 1.1 g of N^{im}-tritylhistidine in 5 ml of 1 M K_2CO_3 solution and 5 ml of dioxane, and the mixture was stirred at ~20°C for 30 min. Then it was diluted with water to 50 ml and 0.5 ml of glacial acetic acid was added, and after a few minutes the aqueous solution was poured off from the resinous precipitate. The precipitate was triturated in fresh water until it had crystallized completely and its was then filtered off, washed with water, and dried. For purification, the product was triturated in hot petroleum ether and was washed on the filter with a mixture of petroleum ether and diethyl ether and was dried in vacuum. This gave 1.4 g (95%) of chromatographically homogeneous Nα-benzyloxycarbonyl-N^{im}-tritylhistidine with decomp. 95-100°C, $[\alpha]_D^{20}$ +9.7° (c 1; C_2H_5OH). Found, %: 74.7; H 5.7; N 7.8; $C_{33}H_{29}N_3O_4$. Calculated, %: 74.6; H 5.5; N 7.9.

N^{α}-4-Methoxybenzyloxycarbonyl-N^{im}-tritylhistidine. A suspension of 1.1 g of N^{im}-tritylhistidine in 5 ml of 1 M K_2CO_3 solution and 3 ml of isopropanol was treated with 0.5 g of 4-methoxygenzyloxycarbonyl azide, and the mixture was stirred at 25-30°C for 5 h, a solution being formed. This was diluted with water and acidified with citric acid solution, and the resulting crystalline precipitate was filtered off, washed with water, and dried. Then the product was triturated in petroleum ether, washed on the filter with a mixture of petroleum ether and diethyl ether, and again dried in vacuum. This gave 1.3 g (83%) of N^{α}-4-methoxybenzyloxycarbonyl-N^{im}-tritylhistidine with decomp. p. 75-80°C, $[\alpha]_D^{20}$ + 11.0 (c 1; C_2H_5OH). Found, %: 72.9; H 5.6; N 7.6. $C_{34}H_{31}N_3O_5$. Calculated, %: 72.7; H 5.6; N 7.5.

SUMMARY

Two variants of the synthesis of N^{α}-tert-butoxycarbonyl-N^{im}-trityl-L-histidine are proposed which start from di-tert-butoxycarbonyl-L-histidine and from dityrityl-L-histidine, respectively, with the use as intermediate compounds of N^{α}-tert-butoxycarbonyl-L-histidine and N^{im}-trityl-L-histidine, respectively, the syntheses of these compounds being performed by improved methods. New N^{α}-alkoxycarbonyl derivatives of N^{im}-trityl-L-histidine have been synthesized from N^{im}-trityl-L-histidine.

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CORRELATION OF THE C-1' CHEMICAL SHIFTS WITH THE VICINAL SPIN–SPIN COUPLING CONSTANTS OF THE H-1' AND H-2' PROTONS IN NUCLEOSIDES.

II. 2'-, 3'-, AND 5'-O-SUBSTITUTED NUCLEOSIDES

É. L. Kupche

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The existence of a correlation has been established for pyrimidine but not for purine, nucleosides. It is suggested that the change in the chemical shift of the anomeric carbon is a consequence of 1,2-eclipsing interaction between O-2' and N-1' in the S type of conformation of the ribose ring. Possible reason for the absence of a correlation in the case of purine nucleosides are discussed. It is shown that the chemical shift of the anomeric carbon can be used in the conformational analysis of the ribose rings of pyrimidine nucleosides.

Continuing a study of the correlation of the parameters of the NMR spectra for pyrimidine nucleosides that we established previously [1], we have investigated derivatives of pyrimidine nucleosides (I-IX) and of purine nucleosides (X-XVII). To study the correlation over a wider range and to exclude a possible influence of the considerable electronic effects on the (CSs) C-1' chemical shifts, we considered derivatives not containing substituents in the base part of the molecule. Because of substantial deviations for aqueous solutions [1], we used only aprotic solvents — dimethyl sulfoxide-d_6 (DMSO-d_6), pyridine-d_5, deuterochloroform ($CDCl_3$), and acetone-d_6.

A linear correlation is observed in the dependence obtained of the C-1' CSs for uridine derivatives (I-IX) on the vicinal spin–spin coupling constants (SSCCs) of the H-1' and H-2' protons (Fig. 1). The equation of the straight line was derived by the method of least squares and is described by the formula

$$\delta_{C\text{-}1'} = kJ_{1'-2'} + C, \quad (1)$$

where k = −1.07 ppm/Hz and C = 94.36 ppm (correlation coefficient, r = −0.987). It can be seen from Fig. 1 that no appreciable deviations from the correlation due to the influence of the solvent and of the electronic effects of the substituents are observed. The increase in the slope of the straight line in the case of 2',3',O-cyclic derivatives (k = −3.5 ppm/Hz and C = 100.9 ppm) is, as shown below, a consequence of the flattening of the ribose ring [2].

We initially suggested that the reason for the change in the C-1' CSs was formed by the dissimilar contributions of the α effect as a consequence of changes in the position of the conformational equilibrium of the ribose ring. However, it is known [3] that because of steric perturbations the α- and γ-carbon atoms usually give a resonance absorption line in a stronger field if the substituent is axial. In particular, this has been used previously

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