# PREPARATION OF 1-BENZYL-1-METHYLETHOXYCARBONYL DERIVATIVES OF AMINO ACIDS

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The use of methods of purifying substituted peptides in acid media, such as gel filtration in aqueous acetic acid, gives rise to the necessity for finding accessible protective groupings with greater stability to acids than that of the tert-butoxycarbonyl (Boc) protective group. At the same time, it is desirable that such protection can be removed under comparatively mild conditions, permitting it to be combined with protective groups of the benzyl type [1].

One of the groupings that satisfies these requirements is apparently the 1-benzyl-1-methylethoxycarbonyl (2-benzylisopropoxycarbonyl, Pboc [2]) protective group, which is more resistant to the action of the protolytic reagents usually used for removing the tert-butoxycarbonyl protection [3].

We have synthesized a number of Pboc derivatives of amino acids in order to investigate more fully the properties of the Pboc protective group and the possibility of using these derivatives in peptide synthesis. The introduction of the Pboc grouping into the amino acid was effected with the aid of 1-benzyl-1-methylethyl pyrocarbonate (I) which was obtained from sodium 1-benzyl-1-methylethyl carbonate and trichloroacetyl chloride. We previously [4] obtained the pyrocarbonate (I) in the form of an oily mixture with the initial alcohol. As the result of further investigations we have succeeded in obtaining it in crystalline form (mp 44-44.5°C) after distilling off the initial alcohol in vacuum and crystallizing the residue from petroleum ether.

In the crystalline form, the pyrocarbonate (I) is distinguished by a high stability on storage. Its reactivity is practically the same as that of di-tert-butyl pyrocarbonate [5-7]. The reaction of the pyrocarbonate (I) with amino acids was carried out in aqueous organic solution in the presence of potassium carbonate as in the preparation of the Boc(amino acid)s from di-tert-butyl pyrocarbonate [5, 6]. The use of triethylamine in place of potassium carbonate gave no advantages, and with magnesia the reaction took place considerably less well.

TABLE 1. 1-Benzyl-1-methylethoxycarbonyl Derivatives of Amino Acids

| Amino acid | Reaction conditions | | | Solvent for crystallization | Yield, % | mp, °C | $[\alpha]_D^{20}$, c 1; $CH_3OH$ |
|---|---|---|---|---|---|---|---|
| | base | temperature, °C | time, h | | | | |
| *L*-Ala* | $K_2CO_3$ | 23—25 | 2 | $CH_2Cl_2$—hexane | 92 | 129—130 | —0.8 |
| *L*-Ala*† | MgO | 23—25 | 4 | $CH_2Cl_2$—hexane | 88 | 129—130 | —0.8 |
| *L*-Ala* | $Et_3N$ | 23—25 | 2 | Ether—hexane | 89 | 129—130 | |
| *L*-Asn | $K_2CO_3$ | 18—25 | 26 | Ether | 77 | 149—150 | |
| *L*-Asn | $K_2CO_3$ | 40—43 | 2 | Ether | 77 | 150—151 | —2.2 |
| Gly [2] | $K_2CO_3$ | 20—23 | 2 | Ether—hexane | 88 | 109—110 | |
| *L*-Leu [2] | $K_2CO_3$ | 23—25 | 2 | Hexane | 83 | 86—88 | —24.0 |
| *L*-Phe* | $K_2CO_3$ | 20—23 | 2 | Ether | 81 | 126—127 | +17.5 |
| *L*-Pro* | $K_2CO_3$ | 20—23 | 2 | Ether—hexane | 85 | 132—134 | —35.8 |
| *L*-Ser* | $K_2CO_3$ | 43—45 | 1.5 | $CH_2Cl_2$—hexane | 84 | 137—138 | +10.8 |
| *L*-Thr* | $K_2CO_3$ | 43—45 | 2 | $CH_2Cl_2$—hexane | 74 | 103—104 | —8.0 |
| *L*-Trp | $K_2CO_3$ | 20—23 | 2 | Ether—hexane | 95 | 147—148 | —12.5 |
| *D*-Trp | $K_2CO_3$ | 20—23 | 2 | Ether—hexane | 89 | 155—156 | +12.0 |
| *L*-Tyr | $K_2CO_3$ | 23—25 | 2 | Ether—hexane | 86 | 147—149 | —0.5 |

*The derivative was crystallized in the form of the dicyclohexylammonium salt.
†After 3 h, 0.25 equivalent of (I) was added.

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$$[C_6H_5CH_2C(CH_3)_2OCO]_2O+H_2NCHRCO_2^- \rightarrow C_6H_5CH_2C(CH_3)_2OCONHCHRCO_2^- + C_6H_5CH_2C(CH_3)_2OH+CO_2$$

The pyrocarbonate (I) was taken 20% excess and was added to the reaction mixture in the form of a 1 M solution in acetone. The time and temperature of the reaction was varied according to the reactivity of the amino acid. The Pboc derivatives of the amino acids were isolated by the method generally used in similar cases [5, 6] and were crystallized from the solvent mixtures shown in Table 1 or were converted into the dicyclohexylammonium salts.

Table I gives the reaction conditions and the characteristics of the compounds obtained. The melting points were determined in capillaries and are not corrected. The angles of optical rotation were determined on a Perkin–Elmer 141 polarimeter. The results of elementary analysis for C, H, and N corresponded to the calculated figures.

## LITERATURE CITED


1. R. Hirschmann and D. Veber, in: The Chemistry of the Polypeptides [in Russian], Moscow (1977), pp. 143-165.
2. V. F. Pozdnev, Khim. Prirodn. Soedin., 384 (1971).
3. V. F. Pozdnev, Khim. Prirodn. Soedin., 402 (1972).
4. V. F. Pozdnev, Zh. Organ. Khim., 7, 1078 (1971).
5. V. F. Pozdnev, Khim. Prirodn. Soedin., 764 (1974).
6. V. F. Pozdnev, Bioorg. Khim., 3, 1605 (1977); V. F. Pozdnev, Zh. Org. Khim., 13, 2531 (1977).


# SYNTHESIS OF ANALOGS OF THE C-TERMINAL PART OF FIBRINOPEPTIDE A


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The role of the configuration of the amino-acid residues of substrates (inhibitors) in the manifestation of the catalytic properties of thrombin have been studied little [1]. To investigate the stereospecificity of thrombin and to analyze the influence of the configurations of the amino acids of the immediate surroundings of the bond sensitive to hydrolysis by thrombin we have performed the synthesis of all the possible steroisomers of esters of tosylvalyl- (or tosylphenylalanyl)arginine of the L-L, D-D, L-D, and D-L types.

The hydrochlorides of Tos-X-Arg-$OCH_3$ (where X = Val, Phe, Z-Pro-Ala) were synthesized by condensing free arginine with the N-hydroxysuccinimide esters of the corresponding tosylamino acids obtained similarly to the N-hydroxysuccinimide esters of benzyloxycarbonylamino acids [2]. The condensation products were converted into the corresponding esters by treatment by thionyl chloride in absolute ethanol. The method of synthesizing peptides with unsubstituted C-terminal arginine, which possesses a number of advantages, has been widely used to obtain bradykinin analogs [3, 4]. It also proved convenient for the compounds Tos-X-Arg-OH and we used it in the present work. On the following page, we give the characteristics of the compounds synthesized (their individuality was shown by TLC on silica gel, paper electrophoresis at pH 6.5, and the results of elementary analysis).

Tosylphenylalanyl- (or Tosylvalyl)arginine (I, II). A mixture of 5.7 mmole of the N-hydroxysuccinimide ester of the appropriate tosylamino acid in 7.5 ml of dioxane and 6 mmole of arginine in 4.5 ml of water was stirred at room temperature for 12-16 h. The precipitate that deposited was filtered off, washed with water, ethyl acetate, and dioxane, and recrystallized from n-butanol or isopropanol.


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