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THE PREPARATION OF ALKYLOXYCARBONYL AMINO ACIDS AND THEIR N-HYDROXYSUCCINIMIDE ESTERS

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The t-butyloxycarbonyl (t-BOC) moeity became since its introduction as an amino protecting group in peptide synthesis second in use only to the benzyloxycarbonyl group (1). Owing to the instability of the t-butylchloroformate, the t-butyloxycarbonyl derivatives of amino acids have to be obtained by reaction of the corresponding isocyanate with t-butanol (2) or by the action of the amino acids with either t-butyl-p-nitrophenyl carbonate (3), t-butylazidoformate (4) or t-butylcyanoformate (5). The above methods suffer from various disadvantages, e.g., the vigorous conditions required for the synthesis of isocyanate from amino acid esters, the elaborate purification from p-nitrophenol of the t-butyloxycarbonyl amino acids, the reaction conditions employed with the t-butylazidoformate (45-50° for 18-24 hours).

We wish to report a new, rapid and tidy method for

the preparation of t-butyloxycarbonyl derivatives of amino acids. Aminolysis of t-butyloxycarbonyl N-hydroxysuccinimide ester by the sodium salt of various amino acids yields the corresponding t-butyloxycarbonyl amino acids in good yield; the N-hydroxysuccinimide formed being water soluble is easily separable from the t-butyloxycarbonyl amino acids. The aminolysis is carried out at 90° for 1½-2 hours; the reaction does not suffer from any of the disadvantages of the other methods.

t-Butyloxycarbonyl N-hydroxysuccinimide ester (m.p. 98-100° *, $C_9H_{13}N_1O_5$: Calcd. C, 50.23; H, 6.09; N, 6.51. Found: C, 49.98; H, 5.91; N, 6.70.), obtained by reacting N-hydroxysuccinimide in presence of pyridine with t-butyloxycarbonyl chloride, prepared in situ at -74° (6), gave t-butyloxycarbonyl amino acids in 70-80% yield; t-butyloxycarbonyl glycine (m.p. 80°, 78% yield), t-butyloxycarbonyl-L-tryptophane (m.p. 139-41°, 81% yield), t-butyloxycarbonyl-L-leucine.H_2O (m.p. 74°, 78% yield), t-butyloxycarbonyl-L-isoleucine.½H_2O (m.p. 59°, 83% yield).

Other alkyloxycarbonyl derivatives of amino acids were prepared, employing the corresponding alkyloxycarbonyl N-hydroxysuccinimide esters. Aminolysis of benzyloxycarbonyl N-hydroxysuccinimide ester (m.p. 78-80°

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* All melting points are uncorrected; m.ps. of the various amino acid derivatives are in good agreement with those reported in the literature and mixed m.ps. with the respective authentic compounds gave no depression.

$C_{12}H_{11}N_1O_5$: Calcd. C, 57.82; H, 4.45; N, 5.62. Found: C, 57.82; H, 4.55; N, 5.69), obtained by reacting N-hydroxysuccinimide with benzylchloroformate, gave benzyloxycarbonyl amino acids in over 90% yield; benzyloxycarbonyl glycine (m.p. 115°, 98% yield), benzyloxycarbonyl-L-alanine (m.p. 81-2°, 97% yield), benzyloxycarbonyl-L-glutamic acid (m.p. 116-7°, 98% yield), benzyloxycarbonyl-L-glutamine (m.p. 128-9°, 91% yield).

The reaction mixtures contain after completion of the amination, alkyloxycarbonyl amino acids and free N-hydroxy succinimide. After adjusting the pH to about pH 2 by addition of hydrochloric acid, followed by an equivalent of dicyclohexylcarbodiimide we found that the alkyloxycarbonyl amino acids N-hydroxysuccinimide esters were formed in 55-75% yield based on the free amino acid. Thus the following derivatives were prepared: benzyloxycarbonyl-glycine N-hydroxysuccinimide ester (m.p. 112°, 72% yield), benzyloxycarbonyl-L-alanine N-hydroxysuccinimide ester (m.p. 117-9°, 75% yield), t-butyloxycarbonyl-L-leucine N-hydroxysuccinimide ester (m.p. 111-3°, 57% yield). These compounds which are obtained in good yield employing a simple reaction procedure are valuable intermediates in peptide synthesis (7).

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