

USE OF 2,4,6 - TRIBROMOPHENYL AMINOACID ESTERS

IN PEPTIDE SYNTHESIS

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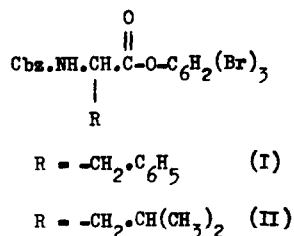
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(Received in UK 2 August 1967)

Activated esters of aminoacids, such as the p-nitrophenyl-, thiophenyl-, p-cyano-phenyl-, and others are in present use for the synthesis of peptides^{1,2}. We have made use of 2,4,6 - tribromophenol for the activation of aminoacids, and report in this note on the synthesis of two such esters and their use in peptide synthesis.

2,4,6 - Tribromophenyl ester of Carbobenzyloxy - L - phenylalanine (I) - To a solution of carbobenzyloxy - L - phenylalanine (329 mg., 1.1 m moles) and 2,4,6 - tribromophenol (407 mg., 1.26 m moles) in 3.0 ml. of ethyl acetate, was added N,N - dicyclohexylcarbodiimide (248 mg., 1.2 m moles) in 1.5 ml. of ethyl acetate. The reaction mixture was allowed to stand in ice for 20 minutes and thereafter for 2 hours at room temperature. Dicyclohexylurea (m.p. 224°, after recrystallisation from ethanol) was removed by filtration, and the clear filtrate taken to dryness under vacuo at 45°, giving a solid residue which was recrystallised from ethanol. The desired ester was obtained as fine needles, m.p., 134°. λ max (ethyl acetate) 260 m μ (ϵ , 600); 280 m μ (ϵ , 420.) (Found:- C, 45.16 ; H, 3.07 ; N, 2.53. C₂₃H₁₈N requires:- C, 45.10 ; H, 2.94 ; N, 2.29 %.)

2,4,6 - Tribromophenyl ester of Carbobenzyloxy - L - leucine (II) - This was prepared in identical manner to that described for the synthesis of the carbobenzyloxy - L - phenylalanine ester, and was obtained as a clear oil which could not be induced to crystallise (Found:- C, 42.53 ; H, 3.91 ; N, 2.65. C₂₀H₂₀N requires:- C, 41.55 ; H, 3.46 ; N, 2.42 %.)



Carbobenzyloxy - L - phenylalanyl - glycine ethyl ester. To a suspension of glycine ethyl ester HCl (46 mg., 0.326 m moles) in 1.0 ml of CHCl_3 was added triethylamine (0.05 ml., 0.65 m moles), followed by carbobenzyloxy - L - phenylalanine - 2,4,6 - tribromophenyl ester (200 mg., 0.33 m moles) in 1 ml. of CHCl_3 . The reaction mixture was left at room temperature for 24 hours, filtered, and the clear filtrate washed successively with distilled water, $\text{IN-NH}_4\text{OH}$, IN-HCl and water. The filtrate was then dried over sodium sulphate and taken to dryness to give a residue which was recrystallised from ethyl acetate and petroleum ether (40-60°) to give crystals with m.p., 110°. (Found:- C, 64.95 ; H, 6.42 ; N, 6.79 . $\text{C}_{21}\text{H}_{24}\text{N}_2$ requires:- C, 65.63 ; H, 6.25 ; N, 7.20 %.)

Carbobenzyloxy - L - leucyl - glycine ethyl ester. This was prepared from carbobenzyloxy - L - leucine - 2,4,6 - tribromophenyl ester and glycine ethyl ester. HCl as described above for the phenylalanine ester. Recrystallisation from ethyl acetate and petroleum ether (40 - 60°) gave crystalline material with m.p., 102°. (Found:- C, 60.92 ; H, 7.57 ; N, 8.04 . $\text{C}_{18}\text{H}_{26}\text{N}_2$ requires:- C, 61.70 ; H, 7.43 ; N, 8.00 %.)

References

1. M. Bodanszky and V. du Vigneaud, J.Am.Chem.Soc., 81, 5688 (1959).
2. J.P. Greenstein and M. Winitz, "Chemistry of the Amino Acids", Published by John Wiley & Sons, Inc., New York and London, Vol. 2, 1027 (1961).