SYNTHESIS OF PROTECTED PEPTIDES CORRESPONDING TO FRAGMENT A^{13-16} OF HUMAN INSULIN

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In order to study new variants of the block synthesis of the A-chain of human insulin, we have performed the synthesis of the differently protected tetrapeptides (I) and (II) corresponding to the fragment A^{13-16} of human insulin:

$$\overset{13}{\text{Nps}}\text{-Leu-}\overset{14}{\text{Tyr}}(\text{Bu}^t)\text{-}\overset{15}{\text{Gln}}\text{-}\overset{16}{\text{Leu}}\text{-OMe} \quad \text{(I)}$$

$$\text{Bpoc-Leu-Tyr}(\text{Bu}^t)\text{-Gln-Leu-OMe} \quad \text{(II)}$$

Peptides (I) and (II) were obtained by stepwise synthesis in solution, the starting materials used being the methyl ester of L-leucine (III), the pentachlorophenyl ester of N^{α}-benzyloxycarbonyl-L-glutamine (IV), the pentafluorophenyl ester of N^{α}-benzyloxycarbonyl-L-glutamine (V), the pentachlorophenyl ester of N-benzyloxycarbonyl-O-tert-butyl-L-tyrosine (VI), the pentafluorophenyl ester of N-benzyloxycarbonyl-O-tert-butyl-L-tyrosine (VII), the pentachlorophenyl ester of N-(o-nitrophenylsulfenyl)-L-leucine (VIII), and the pentafluorophenyl ester of N-biphenylisopropoxycarbonyl-L-leucine (IX).

O-tert-butyl-L-tyrosine (VI), the pentafluorophenyl ester of N-benzyloxycarbonyl-O-tert-butyl-L-tyrosine (VII), the pentachlorophenyl ester of N-(o-nitrophenylsulfenyl)-L-leucine (VIII), and the pentafluorophenyl ester of N-biphenylylisopropoxycarbonyl-L-leucine (IX).

Intermediate compounds in the synthesis of the protected peptides (I) and (II) were the methyl ester of N^{α}-benzyloxycarbonyl-L-glutaminyl-L-leucine (X), the methyl ester of L-glutaminyl-L-leucine (XI), the methyl ester of n-benzyloxycarbonyl-O-tert-butyl-L-glutaminyl-L-leucine (XII), and the methyl ester of O-tert-butyl-L-tyrosyl-L-glutaminyl-L-leucine (XIII).

The structures of the protected peptides (I) and (II) obtained follow from the method of synthesis, and their individuality was confirmed by the results of analytical determination and chromatographic behavior.

Methyl Ester of N-(o-Nitrophenylsulfenyl)-L-leucyl-O-tert-butyl-L-tyrosyl-L-glutaminyl-L-leucine (I). Yield 66%, mp 189-190°C (decomp.), $[\alpha]_D^{26}$ −25.0° (c 0.4; dimethylformamide). TLC on Silufol UV-254 plates. R_f 0.37 (benzene–ethanol (9:2)) (system 1), 0.56 (chloroform–methanol–acetic acid (95:10:3)) (system 2).

Methyl Ester of N-Biphenylylisopropoxycarbonyl-L-leucyl-O-tert-butyl-L-tyrosyl-L-glutaminyl-L-leucine (II). Yield 71.5%, mp 154-156°C (decomp.), $[\alpha]_D^{22}$ −41.0° (c 1.0; methanol). R_f 0.54 (system 1), 0.75 (system 2).

The preparation of peptides (I) and (II) ensured the necessary conditions for realizing a new scheme for the block synthesis of the A-chain of human insulin using in the intermediate stages of the synthesis peptide derivatives with readily removable acid-labile protective groups.

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