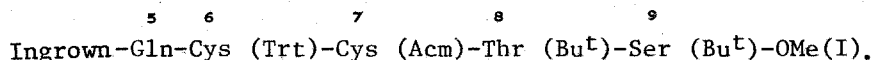


SYNTHESIS OF A PROTECTED FRAGMENT A⁵⁻⁹ OF HUMAN INSULIN

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In connection with the development of a new scheme for the block synthesis of the A chain of human insulin, we have carried out the synthesis of the protected pentapeptide (I) corresponding to fragment A⁵⁻⁹ of human insulin:



The pentapeptide (I) was synthesized by a 2 + 3 scheme, the initial substances begin the methyl ester of O-tert-butyl-L-serine (II), the pentafluorophenyl ester of N-benzyloxycarbonyl-O-tert-butyl-L-threonine (III), the pentafluorophenyl ester of S-carbamoylmethyl-N-biphenylylisopropoxycarbonyl-L-cysteine (IV), S-triphenylmethyl-L-cysteine (V), and the pentafluorophenyl ester of N^α-diphenylylisopropoxycarbonyl-L-glutamine (VI).

Intermediates were the methyl ester of N-benzyloxycarbonyl-O-tert-butyl-L-threonyl-O-tert-butyl-L-serine (VII), the methyl ester of S-carbamoylmethyl-N-biphenylylisopropoxycarbonyl-L-cysteinyl-O-tert-butyl-L-threonyl-O-tert-butyl-L-serine (VII), the methyl ester of S-carbamoylmethyl-L-cysteinyl-O-tert-butyl-L-threonyl-O-tert-butyl-L-serine (IX), N^α-biphenylylisopropoxycarbonyl-L-glutaminy-L-S-triphenylmethyl-L-cysteine (X), and the pentafluorophenyl ester of N^α-biphenylylisopropoxycarbonyl-L-glutaminy-L-S-triphenyl-L-cysteine (XI).

The biphenylylisopropoxycarbonyl derivatives were obtained by the method of Sieber and Iselin [1]. For the synthesis of the pentafluorophenyl esters of the N-protected amino acids and peptides we used a method suggested by Kisfaludy et al. [2].

To purify the intermediates and also to isolate and purify the protected pentapeptide (I) we used column chromatography on silica gel with the following solvent systems for elution: ethyl acetate-hexane (1:3), ethyl acetate-hexane (1:1), and chloroform-methanol (18:1).

The structure of the compound (I) obtained was determined unambiguously by the method of synthesis, and its individuality was shown chromatographically and confirmed by the results of analytical determinations.

Methyl Ester of N-Biphenylylisopropoxycarbonyl-L-glutamyl-S-triphenylmethyl-L-cysteinyl-S-carbamoylmethyl-L-cysteinyl-O-tert-butyl-L-threonyl-O-tert-butyl-L-serine (I). Yield 60%. TLC on "Silufol UV-254" plates: R_f 0.37 (benzene-ethanol (20:3)), [α]_D²² -22° (c 1.0; methanol). Found, %: C 64.13; H 6.97; N 8.05; S 5.10. C₆₅H₈₃N₇O₁₂S₂. Calculated, %: C 64.07; H 6.86; N 8.04; S 5.26.

LITERATURE CITED

1. P. Sieber and B. Iselin, *Helv. Chim. Acta*, **51**, 622 (1968).
2. L. Kisfaludy, M. Löw, O. Nyeki, T. Szirtes, and I. Schon, *Ann. Chem.*, 1421 (1973).

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