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SYNTHESIS OF A CYCLIC TRIPEPTIDE MODELLING THE "ACTIVE" CONFORMATION OF OXYTOCIN

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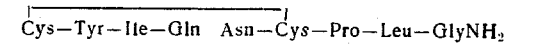
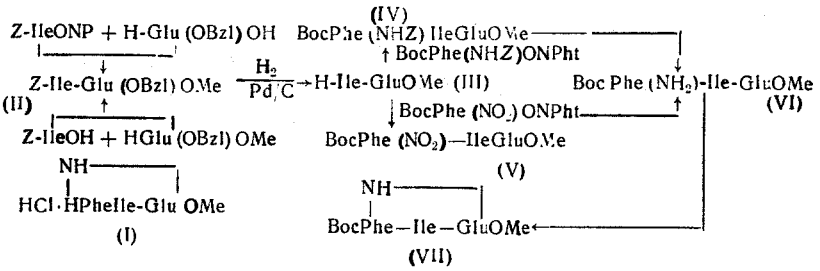
UDC 547.466.1+547.583.4

The opinion exists that in the stimulation of biological activity, the tyrosine residue leaves its original localization in the receptor, forming a "pseudobicyclic" structure through the formation of hydrogen bonds between its phenolic hydroxyl and the amide grouping of asperagine [1]:



Oxytocin

It appeared of interest to synthesize a cyclic tripeptide modelling the "pseudo-ring" of the active conformation of the hormone molecule and to study its biological activity. With this aim, we have synthesized the cyclic tripeptide (I), which proved to be inactive on testing on the rat uterus in vitro at concentrations of up to 1.0 mg/ml. The peptide (I) was synthesized in the following way:



The intermediate dipeptide (II) was obtained by the p-nitrophenyl ester method followed by treatment with diazomethane (yield 54%) and by the carbodiimide method starting from the diester of glutamic acid (yield 65%). The melting point of compound (II) was 123–124°C, $[\alpha]_D^{20}$ −16.0° (c 1.0; methanol). The initial tripeptide for cyclization (VI) was also obtained by two methods: by the hydrogenation of compounds (V) and (IV). Compounds (IV) and (V) were obtained from compound (III) and the hydroxyphthalimide esters of the corresponding substituted amino acids [tripeptide (IV) – yield 55%, mp 151–152°C, $[\alpha]_D^{20}$ −21.0° (c 1.0; methanol); tripeptide (V) – yield 73%, mp 145–147°C, $[\alpha]_D^{20}$ −26.0° (c 1.0; methanol)]. Both active esters were synthesized by the carbodiimide method: Boc-Phe(NHZ)-ONPht, mp 160–161°C, $[\alpha]_D^{20}$ −44.0° (c 1.0; ethyl acetate). Compound (VI) was subjected to cyclization immediately after its preparation.

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The cyclization reaction was performed in methylene chloride (c 10^{-3} M) at room temperature for four days, using equivalent amounts of carbodiimide and N-hydroxysuccinimide. After the solvent had been driven off, the unchanged polar components were eliminated on a column of IRA-410 (OH^-) anion-exchange resin and Dowex 50 × 12 (H^+) cation exchange resin. On subsequent gel chromatography on a column containing Sephadex LH-20 (methanol) calibrated with respect to the initial tripeptide (VI), a peak was separated which corresponded to the desired monomer (VII). Yield 12%, mp 165-166°C. Product (I) obtained after the treatment of compound (VII) with HCl in acetic acid differed chromatographically and electrophoretically from the starting materials and had negaitve reactions for an aromatic amino group at a COOH group.

In the process of synthesis, the purity of all the substances obtained was checked by thin-layer chromatography on silica gel and by high-voltage electrophoresis on paper. The elementary analyses of the substances corresponded to the calculated figures.

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SYNTHESIS OF NUCLEOTIDYL- AND OLIGONUCLEOTIDYL-(P → N)-LYSINES AND THEIR IMMOBILIZATION ON SEPHAROSE

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UDC 576.1

Immobilized nucleotides, oligonucleotides, and nucleic acids are widely used for the isolation of proteins [1] and nucleic acids [2]. Various methods have been proposed for the covalent fixing of nucleotides to a polymeric matrix: through a heterocyclic base [3] or a sugar [3, 4], and more rarely through a phosphoric acid residue [4-6]. The immobilization of oligonucleotides through the internucleotide phosphorus has not been described. Immobilized oligonucleotides in which the terminal groups and bases are accessible may have a high affinity for enzymes of the nucleic acid metabolism.

In this communication we consider the synthesis of α- and ε-lysine phosphoramides of nucleotides and dinucleoside phosphates, and also the immobilization of the latter compounds on Sepharose through the lysine residue.

The ethyl esters of thymidylyl-(5' → N^{α})-DL-lysine (I), thymidylyl-(5' → N^{ε})-DL-lysine (II), adenylyl-(5' → N^{α})-DL-lysine (III), and adenylyl-(5' → N^{ε})-DL-lysine (IV) were synthesized by the pyrophosphate (PP) [7] and the dicyclohexylcarbodiimide (DCC) [8] methods and through the mixed anhydrides with mesitylenecarboxylic acid [9]. In all cases, the α- and ε-amino groups of the lysine took part in the reaction with the nucleotide. On using the PP and DCC methods, the predominant product was the derivative at the α-amino group of the lysine. The yields of the ethyl esters of the nucleotidyl-(5' → N^{α})-DL-lysines were 70-80%, and of their ε-analogs 5-10%. By the mixed anhydride method, varying the pH of the medium, it was possible to obtain the ε-lysine derivatives as the main products. By this method, using a buffer with pH 9.5, we synthesized adenylyl-(5' → N^{α})-DL-lysine (V) and adenylyl-(5' → N^{ε})-DL-lysine (VI) with yields of 25 and 60%, respectively. The reaction mixtures were separated successively by chromatography and electrophoresis on paper.

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