SYNTHESIS OF IODINE-CONTAINING PEPTIDES OF GASTRIN

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It is known that the biological activity of the peptide hormone gastrin is connected with the C-terminal amino-acid sequence Trp-Met-Asp-Phe-NH_2 [1]. We have effected the synthesis of two peptides corresponding to this sequence containing p-iodobenzenesulfonic acid residues, $IC_6H_4SO_2$-β-Ala-Trp-Met-Asp-Phe-NH_2 (I) and $IC_6H_4SO_2$-β-Ala-Glu-Trp-Met-Asp-Phe-NH_2 (II). The presence of the "heavy atom" of iodine in the modified peptides creates the conditions for studying them by means of electron microscopy. Furthermore, when the ordinary iodine is replaced by radioactive iodine it is possible to use such materials for determining the amount of gastrin by the radioimmunochemical method [2].

We obtained the pentapeptide (I) by condensing the tetrapeptide ClH-Trp-Met-Asp-Phe-NH_2 (III) [3] with p-nitrophenyl p-iodobenzenesulfonyl-β-alanine (IV) in dimethylformamide in the presence of two equivalents of triethylamine. Yield 79%, mp 206-208°C. $C_{38}H_{44}IN_7O_9S_2 \cdot H_2O$. Because of the inadequate solubility of the pentapeptide (I) in ammoniacal water containing NaCl (the usual conditions for the introduction of the gastrin peptides into the organism), it was decided to include a glutamic acid residue in the N-terminal part of the iodine-containing peptide. The pentapeptide BOC-GLu(OBu^t)-Trp-Met-Asp-Phe-NH_2 (V) was obtained from the tetrapeptide (III) with the aid of the corresponding 2,4,5-trichlorophenyl ester [4]. Yield 91%, mp 201.5-202.5°C. $C_{43}H_{59}H_7O_{11}S \cdot H_2O$. The removal of the protective group of the pentapeptide (V) with a solution of HCl in acetic acid gave the hydrochloride of the free pentapeptide (yield 100%), which was condensed with the ester (IV). The yield of the hexapeptide (II) was 90%, mp 202-205°C, composition $C_{43}H_{51}IN_8O_{12}S_2 \cdot H_2O$. Readily soluble in ammoniacal water and not precipitated from aqueous solutions by sodium chloride.

The activated ester (IV) was prepared in two ways: from p-iodobenzenesulfonyl-β-alanine (mp 158-160°C, from chloroform) by the carbodiimide method, and by the acylation of the p-nitrophenyl ester of β-alanine (VI) with p-iodobenzenesulfonyl chloride, the second variant proving to be the more convenient. The hydrobromide of the ester (VI) was obtained by the action of a solution of HBr in acetic acid on Z-β-Ala-ONp [5]. Yield 92%, mp 195-197°C, composition $C_9H_{10}N_2O_4 \cdot HBr$. The reaction of the hydrobromide (VI) with p-iodobenzenesulfonyl chloride in chloroform in the presence of triethylamine gave an 86% yield of the ester (IV), mp 134-136°C (from a mixture of ethyl acetate and hexane), composition $C_{15}H_{13}IN_2O_6S$.

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