A NEW SYNTHESIS OF TETRAGASTRIN

Yu. P. Shvachkin and L. A. Kolomeitseva

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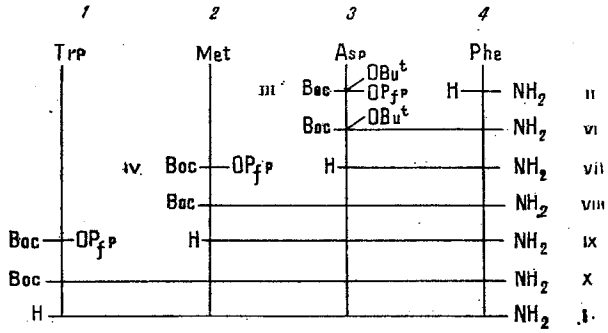
In connection with a study of the laws of the structural-functional organization of peptide hormones and their fragments, we have performed a new synthesis of tetragastrin (synonyms: fragment 14-17 of gastrin, C-terminal tetrapeptide of gastrin, trymapham, fragment 30-33 of cholecystokinin, the C-terminal tetrapeptide of cholecystokinin, and CCK-4) [1-3], which consists of the tetrapeptide of structure (I) (all amino acid residues belong to the steric L series):

$$\overset{1}{H}-\overset{2}{Trp}-\overset{3}{Met}-\overset{4}{Asp}-Phe-NH_2 \quad (I)$$

The synthesis of tetragastrin (I) was performed by a scheme providing for the stepwise formation of the peptide chain in solution with the use as amino components of amides of the C-terminal amino acids and intermediate peptides, and as activated carboxy components the pentafluorophenyl esters of the corresponding protected amino acids [4]



As can be seen from the scheme, the initial substances were L-phenylalanine (II), α-pentafluorophenyl N-tert-butoxycarbonyl-β-O-tert-butyl-L-aspartate (III), pentafluorophenyl ester of N-tert-butoxycarbonyl-L-methionine (IV), and the pentafluorophenyl ester of N$^{\alpha}$-tert-butoxycarbonyl-L-tryptophan (V). The intermediate compounds were the protected and partially deblocked peptides (VI-X).

To eliminate the tert-butoxycarbonyl protective groups from compounds (VI) and (VIII) we used treatment with trifluoroacetic acid. The demasking of the protected tetrapeptide (X) was effected by the action of a 1 N solution of hydrogen chloride in acetic acid.

The structures of all the compounds obtained followed unambiguously from the method of synthesis, and their individualities were checked by the results of analytical determinations.

Tetragastrin I (Monohydrate-monohydrochloride). mp 162-163°C (decomp.); $[\alpha]_D^{25}$ −31.5° (c 1.0; dimethylformamide); R_f 0.7 (BuOH−AcOH−water (4:1:1), TLC on Silufol-UV 254 plates. Found, %; C 52.94; H 6.12; N 12.54, $C_{29}H_{36}N_6O_8S \cdot H_2O \cdot HCl$. Calculated, %: C 53.49; H 6.4; N 12.91. Amino acid analysis: Trp 0.92 (1), Met 0.99 (1), Asp 1.00 (1), Phe 0.91 (1).

The new method of synthesis provides for the production of tetragastrin (I) in preparative amounts.

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