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SYNTHESIS OF METHIONINE-5-ENKEPHALIN

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There has recently been a report of the isolation from animal brain of a group of peptides having affinity for the opiate receptor [1]. One of these peptides, which has acquired the name of methionine-5-enkephalin, is a new pentapeptide of structure (I) (all the asymmetric amino acids have the L configuration):



Structure (I) was shown by a complete amino acid analysis, the cleavage of the natural peptide by the Edman method, and mass spectrometry [1], and has also been confirmed by synthesis [2, 3]. We have developed a new method for the total chemical synthesis of methionine-5-enkephalin (I) in solution. The synthesis is performed by a 4 + 1 scheme providing for the use as starting materials of the pentafluorophenyl ester of N-tert-butoxycarbonyl-O-benzyl-L-tyrosine (II), the pentafluorophenyl ester of N-tert-butoxycarbonylglycine (III), N-tert-butoxycarbonylglycine (IV), the p-nitrobenzyl ester of L-phenylalanine (V), and the sodium salt of L-methionine (VI).

The intermediate compounds in this synthesis are the previously unknown p-nitrobenzyl ester of N-tert-butoxycarbonylglycyl-L-phenylalanine (VII), the p-nitrobenzyl ester of glycyl-L-phenylalanine (VIII), the p-nitrobenzyl ester of N-tert-butoxycarbonylglycylglycyl-L-phenylalanine (IX), the p-nitrobenzyl ester of glycylglycyl-L-phenylalanine (X), the p-nitrobenzyl ester of N-tert-butoxycarbonyl-O-benzyl-L-tyrosylglycylglycyl-L-phenylalanine (XI), and the N-hydroxysuccinimide ester of N-tert-butoxycarbonyl-L-tyrosylglycylglycyl-L-phenylalanine (XII).

To eliminate the benzyl and o-nitrobenzyl protective groups from compound (XI) we used catalytic hydrogenation in the presence of palladium black. The last stage of the synthesis consisted in the elimination of the tert-butoxycarbonyl protective group from N-tert-butoxycarbonyl-L-tyrosylglycylglycyl-L-phenylalanyl-L-methionine (treatment with a 15% solution of HCl in dioxane for 40 min at 20°C).

Methionine-5-enkephalin (I). mp 190-194°C (decomp.), R_f 0.40 (butan-1-ol-acetic acid-water (4:1:1)), 0.32 (ethyl acetate-pyridine-acetic acid-water (60:20:6:11)) (TLC on silica gel, spots revealed with ninhydrin), [α]_D²⁰ +32.0° (c 1.0; methanol). Amino acid analysis: Tyr 1.06, Gly 2.00, Phe 1.10, Met 0.96.

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