SUMMARY

1. A series of alkyl 2-morpholinoethyl methylphosphonothionates and alkyl 1-methyl-2-morpholinoethyl methylphosphonothionates have been synthesized and they have been shown to be reversible inhibitors of acetylcholinesterase and butyrylcholinesterase.

2. It has been shown that the alkyl 1-methyl-2-morpholinoethyl methylphosphonothionates exist in solution in the form of two optical isomers in a ratio of 1:3.

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SYNTHESIS OF ENKEPHALINS BY THE METHOD OF POLYMERIC ACTIVATED ESTERS BASED ON 4-HYDROXY-3-NITROBENZOPHENONE

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Leucine- and methionine-enkephalins have been synthesized by the successive growth of the peptide chain from the C-end by the method of polymeric activated esters based on 4-hydroxy-3-nitrobenzophenone with yields of 90 and 70%, respectively, calculated on the initial C-terminal amino acid. Polystyrene with 2% of divinylbenzene was used as the polymeric matrix. Using the synthesis of methionine-enkephalin as an example, the possibility has been shown of using polymeric activated esters for the synthesis of peptides with a free carboxy group.

In spite of the comparative simplicity of the chemical structure of the enkephalins, their synthesis give low yields of the desired products and require additional purifications of both the intermediate and the final substances, which, in our opinion, makes their economic efficiency problematical. In a review [1] giving some information on investigations in this field up to 1982, it was correctly observed that so far the syntheses of even short peptides "in their absolute majority is far from perfect." In actual fact, in classical methods of synthesizing the enkephalins in solution, variants of fragment condensation are most frequently used. However, in these cases the absence of a statement of the overall yield from the initial compounds and the fact that the yields given relate only to the stages of obtaining protected pentapeptides from two fragments and subsequent, frequently multistage, purification are indicative. Thus, the yields of leucine-enkephalin in the last stage have amounted to 40-70%, and those of methionine-enkephalin to 55-77% (see, for example, [2, 3]).

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TABLE 1. Preparation of Polymeric Activated Esters of N-Protected Amino Acids

Polymeric activated esters	Capacity for the protected amino acid added, mmole/g	
	dicyclohexylcarbodiimide method	symmetrical anhydride method
BOC-Phe-|P|*	0,20	0,40
BOC-Gly-Gly-|P|	0 19	0.30
Z-Tyr-(Bzl)-|P|	—	0,50
BOC-Tyr-|P|	0,17	—

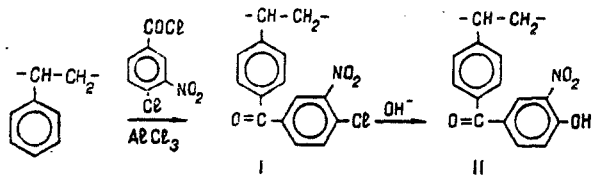
*\|P\| — 4-Hydroxy-3-nitrobenzophenone grafted onto a polystyrene matrix.

Such extremely low yields are not indicative of an efficiency of the scheme of synthesis as a whole. On the successive growth of the chain in classical syntheses in solution using trivial methods of condensation (the dicyclohexylcarbodiimide method, the p-nitrophenyl activated-ester method), the efficiency of the whole scheme can now be evaluated from the yields of the desired products calculated on the initial C-terminal amino acid, but these indices remain very low and, for example, for leucine-enkephalin do not exceed 15% [4]. In this field, the more modern method of synthesis in solution by the successive growth of the chain using N-hydroxy-5-norbornene-2,3-dicarboximide-activated esters in a two-phase system, where, for leucine-enkephalin, the yield amounted to 70% calculated on the initial amino acid [5], is favorably distinguished. As an example of the solid-phase (Merrifield) synthesis of enkephalins we can give the synthesis of leucine-enkephalin, which after careful purification enabled a product to be obtained with a yield of 55% calculated on the protected pentapeptide detached from the resin (i.e., the yield on the initial amino acid was still lower) [6], and other, analogous, investigations on solid-phase synthesis have proved to be no better. In this case, apparently, one must take into account the fact that some fundamental deficiencies of Merrifield synthesis are now discussed in detail in practically all handbooks on peptide synthesis.

Extremely promising in the synthesis of peptides is the use of polymeric activated esters (PAEs), which permits the use of readily removed excesses of reagents and the production fairly rapidly and with high yields of substances having a high degree of purity. The method is suitable technologically and includes a minimum of auxiliary operations. At the same time, the main defects of Merrifield synthesis are eliminated, since the peptide synthesized is always present in solution, and it is easy to check its homogeneity and, if necessary, to purify it at each stage. A review [7] has been devoted to questions of the use of PAEs in peptide synthesis. Thus, polymeric N-hydroxysuccinimide activated esters have been used for the synthesis of leucine-enkephalin [8]. However, these esters are not sufficiently reactive and the condensation stage lasts 12-14 h, which in this case considerably lowers the efficiency of the very PAE method. Furthermore, attention is attracted by the fact that in spite of the high, almost quantitative, yields of protective peptides, the product obtained after the elimination of the protective groups required extremely careful two-stage purification accompanied by an extremely low yield of desired product — 50% calculated on the protected pentapeptide.

In our opinion, the most successful are PAEs based on 4-hydroxy-3-nitrobenzophenone [9], which are distinguished by high reactivity, stability on storage, and simplicity of preparation. It is just these PAEs that we have used for the synthesis of enkephalins.

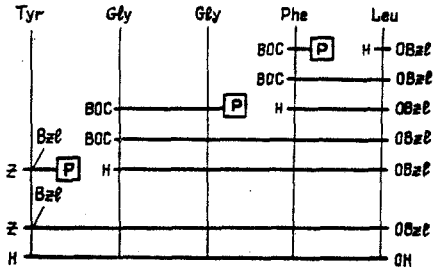
4-Hydroxy-3-nitrobenzophenone bound to a polymer was obtained by a scheme proposed by the author using as the polymeric matrix a copolymer of styrene with 2% of divinylbenzene:



I II

To characterize polymers I and II we used the results of elementary analysis for nitrogen and a determination of the amount of OH groups [9]. In the samples of polymer II obtained the amount of OH groups averaged 0.6-0.7 mmole/g. Polymeric activated esters of N-protected amino acids were obtained directly by two methods — the dicyclohexylcarbodiimide (DCHC) method and with the aid of symmetrical anhydrides [9]. The results are shown in Table 1. Here and below the abbreviations recommended by IUPAC for amino acids, peptides, and protective groups are used.

The synthesis of leucine-enkephalin was carried out by the following scheme:

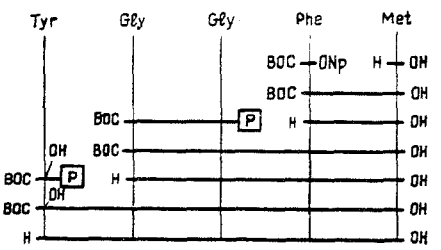


where $\overline{|P|}$ represents 4-hydroxy-3-nitrobenzophenone fixed to a polystyrene matrix (polymer II).

The proposed combination of protective groups permits their simultaneous elimination by catalytic hydrogenolysis in the last stage. The markers necessary for chromatographic and electrophoretic control — protected peptides — were obtained as the result of the synthesis of leucine-enkephalin by classical methods in solution using the same scheme, starting from the tosylate of leucine benzyl ester, and employing p-nitrophenyl activated esters and DCHC with the addition of N-hydroxybenzotriazole. The yield of leucine-enkephalin amounted to 22% calculated on the initial C-terminal amino acid.

The synthesis of leucine-enkephalin by the PAE method on the basis of 4-hydroxy-3-nitrobenzophenones was carried out in dimethylformamide (DMFA) or, in individual cases, in chloroform, with a 1.5-fold excess of activated esters. According to the results of thin-layer chromatography (TLC) and electrophoresis, the condensation reaction was complete after only 30-50 min. In each stage, chromatographically and electrophoretically pure substances were obtained which did not require additional purification. The yields amounted to 96-100%. The tert-butoxycarbonyl (BOC) protective group was removed by the action of trifluoroacetic acid (TFA) and final deblocking was effected by catalytic hydrolysis in a mixture of acetic acid and anisole. As a result of the synthesis, chromatographically and electrophoretically pure crystalline leucine-enkephalin requiring no additional purification was obtained with an overall yield of 90% calculated on the initial tosylate of leucine benzyl ester. The preparation had the correct amino acid analysis and its constants agreed completely with those given in the literature.

Methionine-enkephalin was obtained by the following scheme:



Methionine was introduced with a free carboxy group, which had to be protected by salt formation in the course of condensation. The triethylammonium and triethylbenzylammonium salts of methionine are insoluble in DMFA, and although the sodium salt of methionine dissolves in aqueous dimethylformamide the polymeric activated ester hydrolyzes completely under these conditions with the liberation of the protected amino acid. We studied the de-

pendence of the degree of hydrolysis of the PAE on the time for the case of BOC-Tyr, using its absorption in the UV at 280 nm.

Hydrolysis in an aqueous organic medium in the presence of NaOH began during the very first few minutes and took place very rapidly, while in an organic medium in the presence of TEA the hydrolysis of the PAE took place considerably more slowly, since here water was present in only trace amounts. Under these conditions the condensation reaction was able to proceed practically to completion before the polymeric reagent had begun to hydrolyze to an appreciable degree. Furthermore, the degree of accumulation of the dipeptide under these conditions depended substantially on the nature of the side chain of the amino acid, and in the case of isoleucine the reaction took place more slowly. Another advantage of the use of the polymeric matrix in this case was the fact that in a real synthesis it is possible by using a readily removable excess of PAE, greatly to increase the rate of occurrence of the condensation mixture, reducing to a minimum the possibility of the formation of by-product as a consequence of the far slower hydrolysis stage.

Because of the poor solubility of the triethylammonium salt of methionine we did not succeed in obtaining the C-terminal peptide using the PAE. This dipeptide was obtained by the classical method in solution using p-nitrophenyl esters. The TEA salt of the protected dipeptide was now readily soluble in DMFA. After the removal of the BOC protection in this solvent, the synthesis of the tetrapeptide was again conducted with the aid of the PAE BOC-Gly-GLY-|P|, with a yield of 99%. In this way it was established that the condensation reaction using a PAE based on 4-hydroxy-3-nitrobenzophenone can take place successfully, even when the carboxy group of the amino component remains free, if protection by salt formation with an organic amine (TEA) and not with NaOH is used.

The subsequent stages of the preparation of the protected pentapeptide with the sequence of methionine-enkephalin by the PAE method took place with no complications and with high yields. The final product was purified with the aid of preparative TLC. As a result, a chromatographically and electrophoretically pure preparation with constants agreeing completely with those given in the literature and with the correct amino acid analysis was obtained with a yield of 70% calculated on the initial methionine.

EXPERIMENTAL

All the amino acids used, apart from the glycine, had the L-configuration. Solvents: N,N'-dimethylformamide (DMFA), chloroform, methylene chloride, and methanol, which were purified only by standard methods and were redistilled.

The purity of the substances obtained was checked with the aid of TLC and, where possible, electrophoresis. TLC was conducted on Silufol-254 plates, spots being revealed with chlorine and benzidine. Electrophoresis was conducted on Whatman Filter Paper paper in 2% acetic acid solution for 45-60 min at a voltage of 1400-1450 V; E_{Gly} and E_{His} are the mobilities relative to glycine and to histidine.

Melting points were determined on a Boëtius heated stage. Specific rotations were measured on a SM-2 polarimeter at 18-20°C. Elementary analysis was carried out on a Hewlett-Packard 185 B automatic analyzer, and amino acid analysis on a type AAA 339 automatic analyzer. Hydrolysis of the peptides for amino acid analysis was carried out by two methods:

a) a 1-1.5-mg sample of peptide was hydrolyzed with a mixture of 6 N HCl with the addition of phenol at 120°C for 20 h in a sealed tube;

b) a 1-1.5-mg sample of peptide was hydrolyzed with a mixture of 6 N HCl and trifluoroacetic acid (2:1) with the addition of 5% of thioglycolic acid in an evacuated tube at 166°C for 25 min.

All solvents were evaporated at a temperature not exceeding 40°C. UV spectra of the substances were taken on a SF-26 instrument in ethanol at a cell thickness of 1 cm.

Amino acid derivatives were obtained by standard procedures.

Chromatographic systems (ratios of the solvents in volume units): 1) benzene–acetone (3:1); 2) hexane–ethyl acetate (4:1); 3) benzene–acetone (8:1); 4) benzene–acetone (1:3); 5) hexane–ethyl acetate (1:2); 6) chloroform–methanol–ethyl acetate–acetic acid (10:5:10:1);

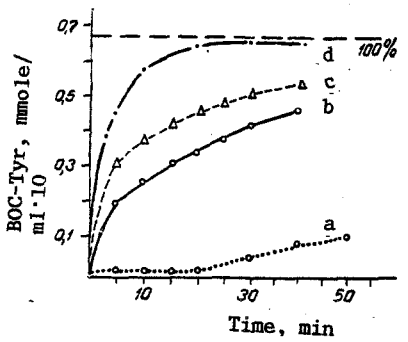


Fig. 1. Time dependence of the degree of hydrolysis of polymeric activated esters based on 4-hydroxy-3-nitrobenzophenone (0.5 g of the PAE in 5 ml of solvent, room temperature). The concentration of BOC-Tyr (ε = 1500) was determined from a measurement of the optical density at 280 nm of corresponding aliquots on dilution with ethanol: a) hydrolysis of BOC-Tyr-[P] in DMFA in the presence of triethylamine (TEA, 1 equiv.), trace amounts of water; b) hydrolysis of BOC-Tyr-[P] in DMFA–1 N NaOH solution (1:1); c) accumulation of BOC-Tyr-Ile-OMe on interaction of equivalent amounts of BOC-Tyr-[P] and HCl·H-Ile-OMe in the presence of 1 equiv. of TEA; d) accumulation of BOC-Tyr-Gly-OMe in a reaction mixture containing equivalent amounts of BOC-Tyr-[P], HCl·H-Gly-OMe, and TEA.

7) chloroform–methanol (3:1); 8) chloroform–methanol–32% acetic acid (12:9:4); 9) butan-1-ol–acetic acid–water (3:1:1); and 10) butan-1-ol–acetic acid–ethyl acetate–water (1:1:1:1).

The preparation of the 4-hydroxy-3-nitrobenzophenone grafted to a polymeric matrix ([P]) and polymeric activated esters of N-tert-butoxycarbonyl amino acids (BOC-Phe-[P] and others) based on it were carried out by the methods described in [9]. The polymeric matrix used was a macroporous copolymer of styrene with 2% of divinylbenzene having a particle size of 50-100 μm.

Benzyl Ester of N-tert-Butoxycarbonylphenylalanylleucine (I). A solution of 114 mg (0.29 mmole) of the tosylate of leucine benzyl ester in 10 ml of $CHCl_3$ was treated with a 5% solution of $NaHCO_3$ (3 × 20*). The organic layer was separated off, and 1.2 g of the PAE Boc-Phe-[P] containing 0.4 mmole of BOC-Phe per 1 g of polymer was added to it. The mixture was stirred with a magnetic stirrer. According to TLC and electrophoresis, the reaction was complete after 30 min. The polymer was filtered off and was washed with $CHCl_3$ and with ethyl acetate (EA). The filtrate was evaporated, the residue was dissolved in 50 ml of EA, and this solution was washed with 5% $NaHCO_3$ solution (2 × 20), 10 ml of water, 0.5 N H_2SO_4 (3 × 30), and 50 ml of water. Then it was dried over Na_2SO_4, the solvent was evaporated off, and the product was dried in vacuum. This gave 136 mg (100%) of product. mp 82-84°C, $[\alpha]_D^{20}$ +8.0° (c, 1.00; methanol). Rf 0.72 (system 1), 0.32 (system 2), 0.55 (system 3). After treatment with trifluoroacetic acid (TFA): E_{Gly} 1.21; E_{His} 0.55. Found, %: C 69.44; H 7.59; N 5.81. $C_{27}H_{36}N_2O_5$. Calculated, %: C 69.21; H 7.76; N 5.98.

Benzyl Ester of N-tert-Butoxycarbonylglycylglycylphenylalanylleucine (II). Peptide (I) (135.7 mg; 0.29 mmole) was treated with TFA (2 ml) for 30 min. The excess of TFA was distilled off and the residue was re-evaporated with benzene (3 × 15) and absolute ether (2 × 10). The residue was dried in vacuum over alkali. The trifluoroacetate so obtained was dissolved in 15 ml of DMFA, and 0.06 ml (0.45 mmole) of triethylamine (TEA) was added. After this, 1.5 g of the PAE BOC-Gly-Gly-[P], with a capacity of 0.3 mmole/g was added, and the mixture was stirred. According to the results of TLC and electrophoresis, the reaction was complete after 40 min. The polymer was filtered off and was washed with

*In the Russian original no units are given here and in similar contexts below. Presumably, ml – Translator.

DMFA, EA, and ether. The filtrate was evaporated, the residue was dissolved in EA, and this solution was washed with 5% $NaHCO_3$ (2 × 20), water (20 ml), and 0.5 N H_2SO_4 (3 × 30), and water again and was then dried over Na_2SO_4. The solvent was distilled off and the product was dried in vacuum. This gave 160 mg (95%): mp 75-78°C, $[\alpha]_D^{20}$ +4.0° (c 1.00; methanol). Rf 0.86 (system 4), 0.78 (system 6). After treatment with TFA: E_{Gly} 1.10; E_{His} 0.55. Found, %: C 61.92; H 7.16; N 9.56. $C_{31}H_{44}N_4O_3$. Calculated, %: C 61.97; H 7.40; N 9.33.

Benzyl Ester of N-Benzyloxycarbonyl-O-benzyltyrosylglycylglycylphenylalanylleucine (III). Peptide (II) (160 mg; 0.27 mmole) was treated with TFA (3 ml) for 30 min. The excess of TFA was distilled off and the residue was re-evaporated with benzene (3 × 20) and with absolute ether (2 × 10). The residue was dried in vacuum over alkali. The trifluoroacetate so obtained was dissolved in 15 ml of DMFA, and the solution was treated with 0.08 ml (0.6 mmole) of triethylamine. After this, 822 mg of the PAE Z-Tyr(Bzl)-[P] (with a capacity of 0.5 mmole/g) was added and the mixture was stirred. According to TLC, the reaction was completed after 50 min. The polymer was filtered off and was washed with DMFA and with EA. The filtrate was evaporated, the residue was dissolved in EA (50 ml), and the solution was washed with 5% $NaHCO_3$ solution (2 × 30), with water, with 1 N HCl (3 × 20), and with water again and was dried over Na_2SO_4. The solvent was distilled off and the product was dried in vacuum, giving 237 mg (99%) of product. mp 121-123°C, $[\alpha]_D^{20}$ −15° (c 1.00; methanol). Rf 0.63 (system 6); 0.68 (system 7). Found, %: C 68.57; H 6.27; N 7.57. $C_{50}H_{55}N_5O_9 \cdot 1/2\ H_2O$. Calculated, %: C 68.24; H 6.31; N 7.96.

Tyrosylglycylglycylphenylalanylleucine – Leucine-enkephalin (IV). Palladium-on-carbon catalyst was added to a solution of 237 mg (0.27 mmole) of peptide (III) in 18 ml of acetic acid–anisole (5:1), and hydrogen was passed through the mixture for 6 h. Then the catalyst was filtered off and was washed with acetic acid, and the filtrate was evaporated in vacuum. The residue was dissolved in 15 ml of butan-1-ol–acetic acid–water (3:1:1) and the solution was treated with a small portion of activated carbon for an hour. The carbon was filtered off and was washed with the initial mixture. The solvent was evaporated off and the residue was treated with benzene which was evaporated off again. The product was dried in vacuum. This gave 145 mg (96%) of crystalline product. mp 151-152°C. $[\alpha]_D^{20}$ +25° (c 1.00; methanol). Rf 0.46 (system 8); 0.53 (system 9); 0.60 (system 10). E_{Gly} 0.79; E_{His} 0.45. Amino acid analysis: Gly 2.04 (2), Leu 1.00 (1), Tyr 0.98 (1), Phe 1.05 (1). The overall yield of leucine-enkephalin calculated on the initial tosylate of leucine benzyl ester was 90%.

N-tert-Butoxycarboxyphenylalanylmethionine (V). A solution of methionine (0.38 g; 2.6 mmole) in 2.6 ml of 1 N NaOH was treated with a solution of the p-nitrophenyl ester of N-tert-butoxycarbonylphenylalanine in 6 ml of dioxane. The mixture was stirred at room temperature for a day. The dioxane was evaporated off, water was added to the residue, the mixture was extracted with ether, and the aqueous layer was acidified with 0.5 N H_2SO_4. The product was extracted in ethyl acetate, and the extract washed with water and dried over Na_2SO_4. [The solvent was evaporated off and the residue]* was crystallized from ethyl acetate–hexane. Yield 0.85 g (85%). mp 139-140°C. Rf 0.65 (system 6), 0.63 (system 5).

N-tert-Butoxycarbonylglycylglycylphenylalanylmethionine (VI). Peptide (V) (238 mg; 0.6 mmole) was treated with a 2 N solution of HCl in acetic acid for 20 min. The product was precipitated with absolute ether, filtered off, and washed with absolute ether. The hydrochloride so obtained was dissolved in 15 ml of DMFA and this solution was treated with 0.17 ml (1.2 mmole) of triethylamine. After this, 6 g of the PAE Boc-Gly-Gly-[P] with a capacity of 0.2 mmole/g was added, and the mixture was stirred. After 20 min, the polymer was filtered off and was washed with DMFA. The filtrate was evaporated, the residue was dissolved in ethyl acetate, and the solution was washed with 0.5 N H_2SO_4 (2 × 20) and with saturated Na_2SO_4 solution (2 × 20). The solvent was evaporated off and the product was dried in vacuum. Yield 306 mg (99%). mp 113-114°C. Rf 0.38 (system 6), 0.68 (system 7). After treatment with TFA: E_{Gly} 0.35; E_{His} 0.18.

N-tert-Butoxycarbonyltyrosylglycylglycylphenylalanylmethionine (VII). Peptide (VI) (190 mg; 0.37 mmole) was treated with 2 N solution of HCl in acetic acid for 30 min. The product was precipitated with absolute ether, filtered off, and washed with absolute ether. The hydrochloride so obtained was dissolved in 15 ml of DMFA and the solution was treated with 0.11 ml (0.75 mmole) of triethylamine. Then 2.5 g of the PAE BOC-Tyr-[P] with a capacity

*Presumed omission from the Russian original – Translator.

of 0.3 mmole/g was added and the mixture was stirred. After 30 min the polymer was filtered off and washed with DMFA. The filtrate was evaporated, the residue was dissolved in 50 ml of ethyl acetate, and this solution was washed with 0.5 N H_2SO_4 (2 × 20) and with a saturated solution of Na_2SO_4 (2 × 20) and was dried over Na_2SO_4. The solvent was evaporated off and the product was dried in vacuum. Yield 250 mg (99%). mp 120-122°C. Rf 0.76 (system 7); 0.35 (system 6). After treatment with TFA: E_{Gly} 0.36; E_{His} 0.19.

Tyrosylglycylglycylphenylalanylmethionine – Methionine-enkephalin (VIII). Peptide (VII) (70 mg; 0.10 mmole) was treated with 2 N solution of HCl in acetic acid for 30 min. The hydrochloride was precipitated with absolute ether and, after filtration, was washed with absolute ether. Then the product was dissolved in 10 ml of methanol and the solution was treated with Dowex 1×4 resin in the acetate form. The resin was filtered off, the filtrate was evaporated, and the product was precipitated with absolute ether. This gave 56 mg (97%) of a substance showing on TLC the presence of trace amounts of impurities with Rf 0.50 (system 8), 0.30 (system 9). The product was purified on a plate coated with silica gel L 40/100 in system 9. This gave 47 mg (85%) of a substance homogeneous in TLC. mp 145-147°C. $[\alpha]_D^{20}$ +34° (c 1.00; methanol). Rf 0.72 (system 8), 0.65 (system 9), 0.80 (system 10). E_{Gly} 0.96; E_{His} 0.49. Amino acid analysis: Gly 1.98 (2), Met 1.00 (1), Tyr 1.07 (1), Phe 1.00 (1). The overall yield of methionine-enkephalin calculated on the initial methionine was 70%.

SUMMARY

1. The synthesis of leucine- and methionine-enkephalins has been performed with the use of polymeric activated esters based on 4-hydroxy-3-nitrobenzophenone, with yields on the initial amino acid of 90 and 70%, respectively.

2. It has been shown that these polymeric activated esters can be used successfully for the synthesis of peptides with a free carbon group.

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