PSEUDOPEPTIDE ANALOGS OF THYROLIBERIN

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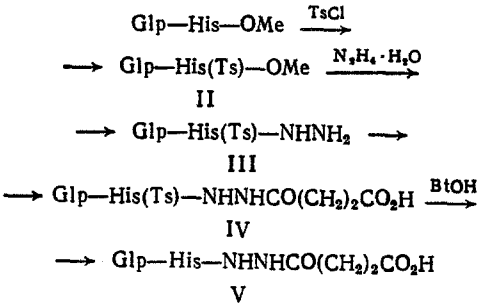
Substitutions of amino acid moieties in the molecule of thyroliberin (Glp-His-Pro-NH_2, TRH) by their natural analogs can substantially change the spectrum of its biological activity and even completely eliminate its hormonal TRH effect [10]. However, such modifications do not influence the stability of the peptides towards enzyme systems in the body. At the same time substitutions in the natural peptides with artificial moieties can increase their resistance to enzymic degradation and permeability through hematoencephalic barrier [1]. Since the metabolism of TRH involves simultaneous breaking of the pyroglutamyl-histidine and histidine-proline bonds [7], modifications of histidine and proline in the TRH molecule by substituents blocking the action of peptidases may increase the peptide stability.

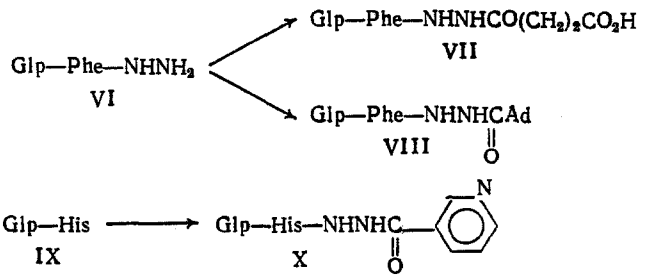
A group of pseudopeptides was prepared as TRH derivatives containing biologically active moieties. The prolinamide moiety of TRH was substituted with hydrazides of biologically active acids (nicotinic, succinic, and adamantanecarboxylic acids) and histidine moiety of TRH was substituted with phenylalanine, glutamine, and artificial analogs of glutamine.



Abbreviations: SuOH = N-hydroxysuccinimide, BtOH = N-hydroxybenztriazole, DCCI = N, N'-dicyclohexylcarbodiimide.

N-(Pyroglutamylhistidyl)-N-3-carboxypropionyl hydrazide (V) was prepared from methyl ester of pyroglutamylhistidine (I) [5] by acetylation of the hydrazide III with succinic anhydride. The imidazole cycle of histidine was blocked by treatment of peptide I with tosyl chloride. The detosylation of IV was achieved easily at room temperature in the presence of N-hydroxybenztriazole.

The succinoyl (VII) [2] and adamantanoyl (VIII) derivatives of the pyroglutamylphenylalanine hydrazide (VI) were prepared by treatment of VI with succinyl anhydride and adamantanecarbonyl chloride, respectively.



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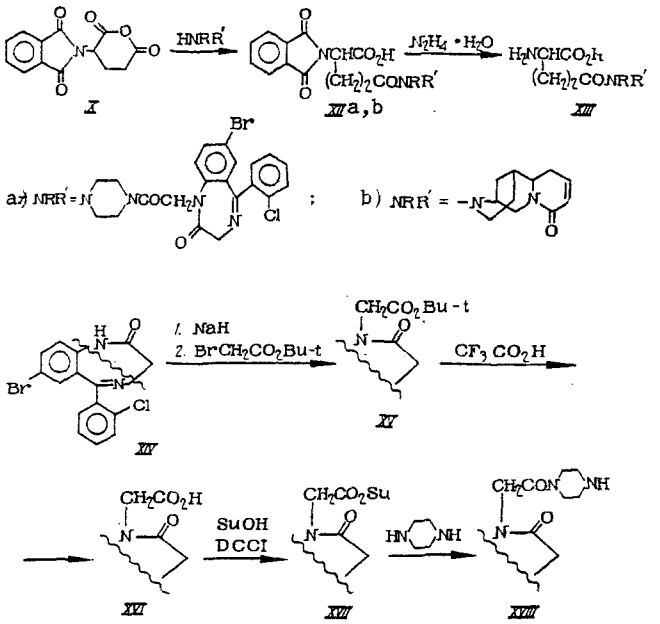
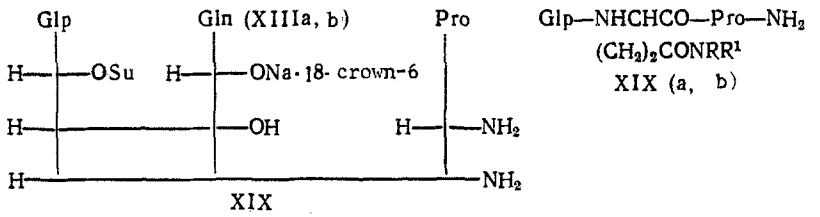
Unlike the hydrazides V, VII, and VIII, the N-(pyroglutamyhistidyl)-N'-nicotinic hydrazide (X) could not be prepared by the carbodiimide condensation of pyroglutamylhistidine hydrazide with nicotinic acid present in divalent dissociated form. Compound X [2] was prepared by treatment of pyroglutamylhistidine (IX) with nicotinoyl hydrazide. Glutamine analogs containing moieties of the tranquilizer phenazepam (XIV) [3] and of the alkaloid stimulant cytisine were prepared by reactions with phthalyl glutamyl anhydride which selectively forms gamma-amides [8]. Deprotection of the amino group in XII was performed by hydrazinolysis.



Alkylation of the benzodiazepine XIV with tert-butyl bromoacetate and subsequent acid hydrolysis of the ester XV by trifluoroacetic acid yielded 7-bromo-1-carboxymethyl-5-(2-chlorophenyl)-1,2-dihydro-3H-1,4-benzodiazepine-2-one (XVI). Mild activation of the carbonyl group in N-hydroxysuccinimide ester XVII in twofold excess of piperizine yielded asymmetrically actylated 7-bromo-1-[(piperazin-1-yl)carbonylmethyl]-5-(2-chlorophenyl)-1,2-dihydro-3H-1,4-benzodiazepin-2-one (XVIII).

The pseudopeptide analogs XIXa,b were prepared from activated esters by scheme 2 + 1. The carboxyl group was protected by salt formation in the presence of 18-crown-6 ether which allows peptide synthesis in homogeneous organic phase.



XIX

EXPERIMENTAL (CHEMICAL)

The infrared spectra were recorded on the spectrophotometer Specord IR in choroform and KBr tablets. Thin-layer chromatography was performed on Silufol plates (Kavalier, Czechoslovakia) and Kieselgel 60 (Merck, West Germany) using chromatographic conditions mentioned in the text below. High performance liquid chromatography was performed on the liquid chromatograph Series 8800 Gradient Liquid Chromatographic System (DuPont, USA) using Zorbax C8 and Zorbax ODS 4.6 mm × 25 cm columns (DuPont, USA). As a sorbent for adsorption chromatography Silasorb 300 (30 μm) (Chemapol, Czechoslavakia) was used. Specific rotation was determined on the spectropolarimeter Perkin-Elmer 241 MC. The amino acid analyses of acidic hydrolysates of peptides were performed on the automatic amino acid analyzer AAA-339 (Mikrotechna, Czechoslavakia). Peptides were hydrolyzed by the standard procedure (6 N HCl, 110°C, 24 h). Dimethylformamide used in the condensation reactions was distilled over ninhydrin. The results of amino acid and elemental analyses corresponded satisfactoriy to the composition of synthesized compounds. The amino acids and reagents used were from Reanal (Hungary), Merck (West Germany), and Fluka (Switzerland). In thin-layer chromatography the following solvent sys-

tems were used: (A) n-butanol–acetic acid–water (4:1:1), (B) aceticacid–benzene–acetone (1:100:50), (C) chloroform–methanol (1:1), (D) acetic acid–water–ethyl acetate–pyridine (1:3:5:5), (E) ethanol–25% ammonia (4:1) and (F) water–ethanol–25% ammonia (6:18:1).

Methyl Ester of Pyroglutamyl-(N^{im}-tosyl)histidine (II). The solution of 1.545 g (5.5 mmole) pyroglutamylhistidine methyl ester (I) [4] in 25 ml methanol and 10 ml chloroform was mixed with 1.46 g anhydrous Na_2CO_3 and dropwise over 0.5 h with the solution of 1.31 g (6.9 mmole) tosyl chloride in 15 ml chloroform. The reaction mixture was mixed at room temperature and after 1 h acetic acid was added. The mixture was filtered and the filtrate was evaporated to dryness in vacuum. The residue was chromatographed on silica gel with successive solvent elution with hexane–chloroform (4.5:0.5; 2:3; 1:4), chloroform, chloroform–methanol (4:1; 1.5:3.5), and methanol. The yield was 1.34 g (56%) II, melting point 110°C (thawing), and Rf = 0.53 in the solvent system A. IR spectrum, KBr, ν_{max}, cm^{-1}: 3333, 1733, 1670, 1333, 1156, 660. $C_{19}H_{22}N_4O_6$.

Pyroglutamyl-(N^{im}-tosyl)histidine Hydrazide (III). The solution of 2.17 g (5 mmole) II in 8 ml methanol and 4 ml butanol was heated for 1 h at 70°C with 0.825 ml (15 mmole) of 94.5% solution of hydrazine hydrate. After 24 h the mixture was cooled and the white crystalline precipitate was filtered and washed with methanol and ether. The yield was 2.02 g (93%) III, melting point 180°C (thawing), and Rf 0.35 in the solvent system A. IR spectrum, KBr, ν_{max}, cm^{-1}; 3233, 1660, 1520, 1150, and 660. $C_{18}H_{22}N_6O_5$.

N-Pyroglutamyl-(N^{im}-tosyl)histidyl-N'-β-carboxypropionyl Hydrazide (IV). The solution of 782 mg (1.8 mmole) III in 7 ml glacial acetic acid was mixed with 180 mg (1.8 mmole) succinic anhydride and stirred for 20 min at room temperature. The precipitate was filtered, washed with ether, and recrystallized from methanol. The yield was 927 mg (96%) IV, melting point 165°C (decomposition), and Rf = 0.48 in the solvent system A. IR spectrum, KBr, ν_{max}, cm^{-1}: 3200, 1700, 1660, 1200, 1110, and 660. $C_{22}H_{26}N_6O_8$.

N-(Pyroglutamylhistidyl)-N'-β-carboxypropionyl Hydrazide (V). The solution of 534.5 mg (1 mmole) IV in 5 ml dimethylformamide was mixed with 150.7 mg (1.1 mmole) N-hydroxybenztriazole and stirred for 1 h. The solution was concentrated in vacuum at 40-50°C and the oily residue was mixed with anhydrous ether, filtered, and recrystallized from the mixture of methanol and ethyl acetate (3:2). The yield was 330.6 mg (87%), V, melting point 170°C (thawing), and Rf = 0.11 in the solvent system A. $C_{15}H_{20}N_6O_6$. Amino acid analysis indicated 1.00 Glu and 0.95 His.

N-(Pyroglutamylphenylalanyl)-N'-adamantoyl Hydrazide (VIII). The solution of 650 mg (2.4 mmole) pyroglutamylphenylalanine (VI) [2] was mixed with 690 mg (3.5 mmole) adamantoyl chloride [4] in 8 ml anhydrous pyridine at room temperature for 1.5-2 h. The reaction mixture was poured on ice and extracted with ethyl acetate. The organic layer was washed with water and dried over $MgSO_4$. Ehtyl acetate was evaporated and the white residue was recrystallized from anhydrous ethyl acetate. The yield was 770.5 mg (72%) VIII, melting point 153-155°C, and Rf = 0.86 in the solvent system A. IR spectrum, $CHCl_3$, ν_{max}, cm^{-1}: 3430, 3060, 2900, 2840, 1730, 1680, and 1640. Mass spectrum, m/e: 452. $[\alpha]_D^{20} = \pm 4.82°$ (c = 0.83 g/100 ml, dimethylformamide). $C_{25}H_{32}N_4O_4$. Amino acid analysis indicated 1.00 Glu and 0.97 Phe.

N-(Gamma-phthalylglutamyl)-N'-[7-bromo-5-(2-chlorophenyl)-1,2-dihydro-3H-1,4-benzodiazepine-2-on-1-ylacetyl]piperizine (XIIa). The solution of 0.99 g (2.1 mmole) XVIII in 15 ml dioxane was mixed with 0.54 g (2.1 mmole) phthalyl glutamyl anhydride. The reaction mixture was heated at 60°C for 2 h and evaporated in vacuum. The residue was dissolved in water and filtered. The yield was 1.2 g (93%) XIIa, melting point 200-203°C, and Rf = 0.33 in solvent system B. $C_{34}H_{29}BrClN_5O_7$.

1-(Gamma-phthalylglutamyl)cytisine (XIIb). This derivative was prepared analogically by cooling of the reaction mixture to room temperature and by separation and washing of the precipitate with dioxane and ether. The yield was 99%, melting point 256°C, Rf = 0.67 in the solvent system B. $C_{24}H_{25}N_3O_6$.

N-(Gamma-glutamyl)-N'-[7-bromo-5-(2-chlorophenyl)-1,2-dihydro-3H-1,4-benzodiazepine-2-on-1-ylacetyl]piperazine (XIIIa). The solution of 2.78 g (3.8 mmole) XIIa in 10 ml 0.42 M Na_2CO_3 was mixed with 0.2 ml 94.5% hydrazine hydrate. The mixture was kept at room temperature for 3 days, acidified to pH 3.0 with concentrated HCl, and chilled. The precipitate was separated by filtration and washed with water. The filtrate was mixed with Na_2CO_3 to pH 4 and kept in a refrigerator for 2 h. The new precipitate was again separated by filtration and washed with water. The yield was 1.5 g (65.8%) XIIIa, melting point 209-210°C, and Rf = 0.29 in the solvent system A. IR spectrum, $CHCl_8$, ν_{max}, cm^{-1}: 3010, 1650, 1540, 1300, and 1130. $C_{26}H_{27}BrClN_5O_5$.

1-(Gamma-glutamyl)cytisine (XIIIb). This hygroscopic derivative was prepared analogously and separated on cation exchanger KU-23. The yield was 71.2%, R_f = 0.40 in the solvent system D. $C_{16}H_{23}N_3O_4$.

7-Bromo-1-tert-butyloxycarbonylmethyl-5-(2-chlorophenyl)-1,2-dihydro-3H-1,4-benzodiazepin-2-one (XV). The solution of 1 g (2.90 mmole) 7-bromo-5-(2-chlorophenyl)-1,2-dihydro-3H-1,4-benzodiazepine-2-one (XIV) [6] in 15 ml dimethylformamide was mixed with 82 mg (3.4 mmole) sodium hydride. The reaction mixture was added. The mixture was further stirred for 7 h at room temperature and then poured on ice. It was extracted with ethyl acetate (2 × 30 ml) and the organic phase was washed with water and dried over $MgSO_4$. The solvent was evaporated and the residue was dissolved in hexane. The yield was 1.2 g (90%) XV, melting point 144-145°C, and R_f = 0.60 in the solvent system B. IR spectrum, CCl_4, ν_{max}, cm^{-1}: 3030, 1730, 1650, 1115, 735, and 570. $C_{21}H_{20}BrClN_2O_3$.

7-Bromo-1-carboxymethyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one (XVI). The solution of 1.2 g (2.6 mmole) XV in 10 ml trifluoroacetic acid was prepared at room temperature. After 10 min 50 ml chloroform and 100 ml water were mixed in. The organic phase was washed with 50 ml water and the precipitate was separated from the chloroform solution by filtration. The yield was 0.8 g (76%) XVI, melting point 245°C (thawing), and R_f = 0.46 in the solvent system B. IR spectrum, mujol oil, ν_{max}, cm^{-1}: 1720, 1670, 1200, 735, and 570. $C_{17}H_{12}BrClN_2O_3$.

N-[7-Bromo-5-(2-chlorophenyl)-1,2-dihydro-3H-1,4-benzodiazepin-2-on-1-ylacetyl]piperazine (XVIII). The solution of 1 g (2.5 mmole) XVI in 10 ml dimethylformamide was mixed with 0.3 g (2.7 mmole) N-hydroxysuccinimide and 0.55 g (2.7 mmole) dicyclohexylcarbodiimide. The reaction mixture was left overnight and then filtered. The filtrate was mixed with the solution of 0.42 g (4.9 mmole) piperazine in 5 ml dimethylformamide and left for 24 h. The mixture was then evaporated to dryness and the residue was partitioned between chloroform and water. The chloroform layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was dissolved in ether. The yield was 1 g (83%) XVIII, melting point 239-240°C, and R_f = 0.33 in the solvent system A. IR spectrum, CCl_4, ν_{max}, cm^{-1}: 3020, 1660, 1640, 730, and 670. $C_{21}H_{20}BrClN_4O_2$.

Pyroglutamyl-[gamma-[1-[7-bromo-5-(2-chlorophenyl)-1,2-dihydro-3H-1,4-benzodiazepine-2-on-1-ylacetyl]piperazinyl]]glutamylprolinamide (XIXa). The solution of 6.0 g (10 mmole) XIIIa with 5 ml 2N NaOH, 2.2 g (10 mmole) 15-crown-5-ether, and 50 ml dimethylformamide was prepared. Water was evaporated at 50°C in vacuum. This mixture was further mixed with the solution of 1.29 g (10 mmole) pyroglutamic acid, 1.26 g (11 mmole) N-hydroxysuccinimide, and 2.2 g (11 mmole) dicyclohexylcarbodiimide in 20 ml dimethylformamide. The reaction mixture was stirred for 24 h, acidified with 10 ml 1N HCl, and filtered. The precipitate was washed with 5 ml dimethylformamide. The fitrate was evaporated to dryness in vacuum and the residue was chromatographed on silica gel with successive elutions with methanol—chloroform mixtures 1:1, 3:2, and 4:1. The yield was 5.54 g (78%) pyroglutamyl-[gamma[1-[7-bromo-5-(2-chlorophenyl)-1,2-dihydro-3H-1,4-benzodiazepin-2-on-1-ylacetyl]piperazinyl]glutamine. The solution of 1.35 g of this intermediate in 5 ml dimethylformamide was mixed with 222 mg (1.9 mmole) prolinamide, 246 mg (2.1 mmole) N-hydroxysuccinimide, and 441 mg (2.1 mmole) dicyclohexylcarbodiimide. The reaction mixture was stirred for 20 h and filtered and the precipitate was washed with 3 ml dimethylformamide. The filtrate was evaporated in vacuum at 50°C. The residue was chromatographed on silica gel with successive elutions with methanol—chloroform mixtures 2:3 and 1:1. The yield was 890 mg (58%) XIXa.

Pyroglutamyl-(gamma-cytis-1-yl)glutamylprolinamide (XIXb). This derivative was prepared analogically as an oil with R_f = 0.30 in the solvent system E. $[\alpha]_D^{20}$ = −81.8° (c = 1.1 g/100 ml in methanol).

EXPERIMENTAL (PHARMACOLOGICAL)

The pharmacological study of peptide properties was performed in 1180 white male mice of 16-23 g body weight. The psychotropic activity was evaluated by the antidepressant, anticonvulsant, sedative, myorelaxant, and motor behavior effects (Table 1).

To evaluate the antidepressant effects of the derivatives, their interactions with 5-hydroxytryptophan, phenamine, and reserpine were compared [3]. In addition, the antidepressant activity was studied using the swimming test according to Persolt [9] where the time of active swimming and immobilization of animals was measured during 10 min. For the measurement of antiamnestic effects the animals were trained in conditioned passive avoidance reflex

TABLE 1. Psychotropic Activity of TRH Analogs

Compound	Dose, mg/kg	Antidepressant activity: swimming test, time of immobilization, min	Antidepressant activity: interaction with 5-hydroxytryptophan	Antidepressant activity: interaction with phenamine	Antiamnestic activity: electroshock latency, sec	Motor activity	Sedative effects
Control	—	1,0	1,0	1,0	21,8±14,84	1,0	0
	1,0	0,5±0,08*	—	—	—	—	—
	5,0	0,53±0,09*	—	—	NE	1,46*	NE
III	1,0	NE	—	—	—	—	—
	5,0	» »	—	—	NE	NE	NE
V	1,0	» »	—	—	—	—	—
	5,0	» »	—	—	68,5*±15,94	NE	NE
VII	1,0	» »	—	—	—	—	—
	5,0	0,73±0,02*	—	—	—	NE	NE
VIII	1,0	—	1,83*	0,58±0,08	—	—	—
	5,0	—	—	—	—	0,60*	50 %
X	1,0	—	2,69**±0,19	NE	—	—	—
	5,0	—	—	—	—	0,53*	50 %
XIXa	1,0	NE	0,81±0,2	NE	—	—	—
	5,0	» »	1,12±0,18	0,41±0,04	—	NE	NE
XIXb	1,0	» »	—	—	—	» »	—
	5,0	» »	—	—	NE	3,65	NE
Imipramine	5,0	0,61*±0,09	1,1±0,19	1,4±0,1	—	—	—
Piracetam	300	—	—	—	80,0**±13,2	—	—

Notes: * = $p < 0.05$, ** = $p < 0.01$, NE = no effect.

with the subsequent use of maximal electroshocks as the amnesia-inducing factor [1]. The anticonvulsant effects were measured by interactions with corazole [3] and registration of convulsions and animal survival. The effects on motor behavior were studied in an actometer (Ugo Bazile, Italy) and in open field [3]. The suppression of the orientation (sedation) was evaluated by the screen-crawling test and the myorelaxant effects by the rotarod test [3].

RESULTS AND DISCUSSION

The substitution of the prolinamide moiety in the molecule of TRH by adamantoyl or nicotinoyl hydrazides inverted its effects on the central nervous system. The respective compounds VIII and X showed sedative effects and decreased the motor activity. On the other hand, the substitution with succinyl hydrazide (compounds V and VII) increased the motor activity and produced an antiamnestic activity. The blockage of the imidazole cycle (compound III) caused a loss of psychotropic activity. Cytisine derivative XIXb had no antidepressant effect but exceeded TRH in the stimulation of motor behavior. The pseudopeptide XIXa had no sedative or myorelaxant effects characteristic for benzodiazepines, but produced anticonvulsant (5 mg/kg) and antidepressant effects.

The antidepressant activity of the compound VII determined in the swimming test was comparable to that of equal doses of the antidepressant chlorimipramine, while the compound XIXa had at least the same antagonistic effect on 5-hydroxytryptophan activity as imipramine did. The peptides studied had no antireserpine activity.

There was a noteworthy 60-fold decrease in the effective dose of the compound V which was showing antiamnestic activity comparable to that of piracetam.

Thus, modifications of the molecule of TRH by artificial biologically active compounds allows to change the spectrum of its activity.

LITERATURE CITED

1. T. L. Garibova, V. V. Rozhanets, I. Kh. Rakhmankulova, et al., Med. Biol. Inform., No. 4, 8 (1985).
2. A. A. Mazurov, S. A. Andronati, T. I. Korotenko, et al., Khim.-farm. Zh., No. 11, 1310-1313 (1987).
3. A. V. Bogatskii, S. A. Andronati, L. N. Yakubovskaya, et al., Phenazepam [in Russian], Kiev (1982).
4. L. N. Yakhontov and R. G. Glushkov, Synthetic Drugs [in Russian], Moscow (1983).
5. J. Boler, J.-K. Chang, F. Enzmann, and K. Folkers, J. Med. Chem., 14, No. 6, 475-476 (1971).

6. J. Bures, O. Buresova, and W. T. Bondanecky, Animal Behavior and Drug Action, Boston (1964), pp. 134-143.
7. M. Hichens, Drug Metab. Rev., 14, No. 1, 77-98 (1983).
8. F. E. King and D. A. A. Kidd, J. Chem. Soc., 3315-3319 (1949).
9. R. D. Persolt, A. Bertin, and M. Jalfre, Arch. Int. Pharmacodyn, 229, 327-336 (1977).
10. T. Szirtes, L. Kisfaludy, E. Palosi, and I. Szporny, J. Med. Chem., 27, 741-745 (1984).
11. D. F. Weber and R. M. Freidinger, Trends Neurosci., 8, 392-396 (1985).

SYNTHESIS AND PHARMACOLOGICAL STUDY OF γ-CARBOXYPROPYLAMIDES OF HIGHER FATTY ACIDS

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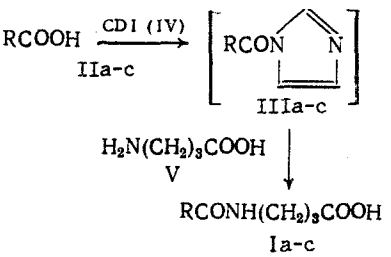
Currently several amino acids are regarded as neurotransmitters. For example, the role of γ-aminobutyric acid (GABA) as a mediator of physiological inhibition at the level of the central nervous system is demonstrated [3, 5, 6]. GABA is effective in treating cerebral deficiencies resulting in convulsions and is used in treating epilepsy, Parkinson's disease, and schizophrenia. It possesses cataleptic properties and plays an important role in brain function. At the same time, a major disadvantage of GABA is that it does not readily cross the blood–brain barrier (BBB). In order to introduce GABA into the brain, the use of large doses has been proposed, as well as experiments to synthesize derivatives of GABA [2, 4] capable of crossing the BBB. One approach to synthesizing derivatives entails the bonding of the amino group of GABA to several biologically active lipopholic compounds, which carry out the function of transporting GABA across the BBB and allow the synthesis of compounds with new, valuable pharmacological properties [7]. The role of molecules that transport GABA across the membranes of the brain's capillaries can be fulfilled by higher fatty acids. The synthesis of N-acetyl derivatives of higher fatty acids using previously prepared mixture of higher fatty acid anhydrides [8] is described.

This article describes a convenient method of experimentally synthesizing amides of higher fatty acids using GABA. Our previous method of producing derivatives of higher fatty acids using imidazolides of higher fatty acids formed the basis of our synthesis [1]. The synthesis of γ-carboxypropylamides of target higher fatty acids (Ia-c) was carried out according to the following scheme:



R = $(CH_2)_{10}CH_3$ (Ia, IIa, IIIa);
$(CH_2)_7(CH{=}CHCH_2)_2(CH_2)_3CH_3$ (Ib, IIb, IIIb);
$(CH_2)_7(CH{=}CHCH_2)_3CH_3$ (Ic, IIc, IIIc)

Lauric (IIa), linoleic (IIb), and linolenic (IIc) acids were chosen as the initial acids. The production of imidazolides of higher fatty acids (IIIa-c) was carried out in chloroform at room temperature with the aid of carbonyl diimidazole (IV) and was monitored using thin-layer chromatography (TLC) in system A. The reaction went to completion in 35-40 min. The conversion of imidazolides IIIa-c into target compounds Ia-c was carried out without isolating the imidazoles. A suspension of GABA (V) in chloroform was added at 50°C for 2 h. The process was monitored via the TLC method in system B. The imidazole formed during the course of the reaction was removed from the reaction mixture using the ion-exchange resin

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