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

V. É. Ashirova, S. M. Alekseev, R. P. Evstigneeva, I. K. Sarycheva, I. S. Morozov, A. S. Losev, and L. M. Shmuilovich

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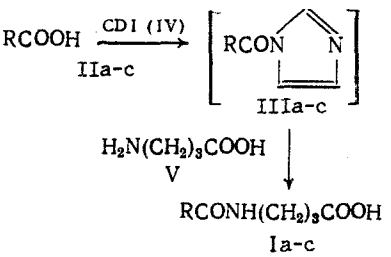
Currently several amino acids are regarded as neurotransmitters. For example, the role of γ-aminobutyric acid (GABA) as a mediator of physiological inhibition at the level of the central nervous system is demonstrated [3, 5, 6]. GABA is effective in treating cerebral deficiencies resulting in convulsions 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

M. V. Lomonosov Moscow Institute of Fine Chemical Technology. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 23, No. 7, pp. 817-819, July, 1989. Original article submitted May 10, 1988.

KU 2-8 in chloroform. The reaction products were purified using silica gel chromatography; Ib and c were chromatographed in system C and Ia in system D. The yield of the amides of lauric, linoleic, and linolenic acids were 62.1, 61.0, and 59.3%, respectively. The structure and individuality of compounds Ia-c were confirmed by infrared and proton magnetic resonance spectroscopy, as well as from elementary analysis data.

The IR spectra of compounds Ia-c showed absorption bands (ν, cm^{-1}) of CH_2 (2900) and CH_3 (2830), which are characteristic of fatty acid functional groups. The absorption of CO (1700) is shifted to 1680 due to the formation of an amide bond. In addition, there is a NH absorption band (3300) and amide bands of 1625 and 1540.

The PMR spectra show the signals of the α- and β-protons of fatty acids at δ 1.60-1.61 and δ 2.32-2.34 ppm, and those of the α- and β-proton of GABA at δ 1.78-1.88 and δ 2.18-2.19 ppm, as well as the protons of aliphatic radicals.

EXPERIMENTAL

In the experiment the following materials and reagents were used: lauric acid of "pure" grade (TU 6-09-613-76), linoleic acid of "pure" grade (TU 6-09-1920-78), linolenic acid of "pure grade" (TU 6-09-14-754-74), carbonyl diimidazole ("LOBA Feinchemie," FRG), γ-aminobutyric acid of "pure" grade (TU 6-09-05-74-72), and ion-exchange resin KU 2-8 in the H^+ form.

The TLC analysis was carried out on Silufol plates (Czechoslovakia) in the following mixtures of solvents: hexane–ethyl acetate, 2:1 (system A) and chloroform–methanol, 10:1 (system B). In order to detect the spots on the chromatograms, they were sprayed with a 10% solution of phosphomolybdic acid in ethanol and then heated at 120°C for 1-2 min.

The purification of the synthesized compounds was conducted using column chromatography on silica gel L 100/160 ("Chemapol," Czechoslovakia). The following were used as eluting agents: a 20:1 mixture of chloroform and ethanol for amides of linoleic and linolenic acids and a 20:1 mixture of chloroform and isopropanol for the amide of lauric acid.

The IR spectra were taken on a "Shimadzu IR435" (Japan) in Vaseline oil. The PMR spectra were recorded on the "Brucker WM 250" impulse NMR spectrometer (FRG) with an operating frequency of 250 MHz. Hexamethyldisiloxane was used as the internal standard.

The elementary analysis data is in agreement with the calculations.

γ-Carboxypropylamide of Lauric Acid (Ia). A suspension of 2.06 g (0.019 moles) γ-aminobutyric acid in 10 ml of chloroform was added over the course of 20 min to a solution of 4 g (0.019 moles) lauric acid and 4 g (0.025 moles) carbonyldiimidazole in 15 ml of chloroform after 20 min of stirring at 18-20°C. The reaction mixture was stirred for 2 h at 50°C, while the course of the synthesis is monitored using the TLC method in system B (R_f = 0.58). When the reaction was completed, the solvent was distilled off in vacuum (10-12 mm Hg), and the residue was purified by column chromatography in system D. The yield of Ia was 3.5 g (62.1%). The mp was 76-78°C. IR spectrum (vaseline oil), ν, cm^{-1}: 3284 (NH); 2900 (CH_2); 2850 (CH_3); 1680 (C=O); 1625 (amide I); 1540 (amide II). PMR-spectrum (deuteromethanol) δ, ppm: 0.90 (3H, t, CH_3, J = 7 Hz); 1.30 (20H, w.s., CH_2 chains); 1.60 (2H, m, CH_2–CH_2–CO–NH); 1.88 (2H, m, NH–CH_2–CH_2–CH_2–COOH); 2.19 (2H, t, NH–CH_2–CH_2–CH_2–COOH, J = 7.5 Hz); 2.32 (2H, t, CH_2–CH_2–CO–NH, J = 7.5 Hz); 3.22 (2H, t CO–NH–CH_2–CH_2, J = 7 Hz). $C_{16}H_{31}O_3N$.

γ-Carboxypropylamide of Linoleic Acid (Ib). The synthesis was carried out under the conditions of the previous experiment. The initial reagents were 5 g (0.018 moles) linoleic acid and 3.3 g (0.02 moles) carbonyldiimidazole in 25 ml chloroform and 1.9 g (0.018 moles) GABA. The monitoring of the course of the synthesis was conducted using TLC in system C (R_f = 0.58). The target compound was purified via silica gel chromatography in system D. The yield of Ib was 3.98 g (61.0%). The mp was 54-55°C. IR spectrum (Vaseline oil), ν, cm^{-1}: 3292 (NH); 2900 (CH_2); 2840 (CH_3); 1685 (C=O); 1627 (amide I); 1540 (amide II). PMR spectrum (deuteromethanol), δ, ppm: 0.92 (m 3H, CH_3); 1.32 (s, CH_2 chains) 1.60 (m, 2H, $\underline{CH_2}$–$\underline{CH_2}$–NH); 1.73 (m, 2H, NH CH_2–$\underline{CH_2}$–CH_2–COOH); 2.10 (q, 2H, CH=CH–$\underline{CH_2}$–CH_2); 2.18 (t, 2H, CH_2–CH_2–COOH, J = 7.5 Hz); 2.30 (t, 2H, CH_2–$\underline{CH_2}$–CO–NH, J = 7.5 Hz), 2.82 (t, =$\underline{CH}$–$\underline{CH_2}$–CH=, J = 5.5 Hz); 3.22 (5, 2H, CO–NH–$\underline{CH_2}$–CH_2, J = 7 Hz); 5.35 (t, $\underline{CH}$ chains, J = 6 Hz,; $C_{22}H_{39}O_3N$.

γ-Carboxypropylamide of Linolenic Acid (Ic). The synthesis was carried out under the conditions of the previous experiment. The initial reagents were 3 g (0.01 mole) linoleic acid and 2.5 g (0.015 mole) carbonyldiimidazole in 18 ml chloroform and 1.1 g (0.01 mole) GABA. The monitoring of the course of the synthesis was conducted using the TLC in system C

($R_f = 0.58$). The reaction product was purified via silica gel chromatography in system D. The yield of Ic was 2.31 g (59.3%). The mp was 40-42°C. The IR spectrum (Vaseline oil), ν, cm^{-1}: 3294 (NH); 2900 (CH_2); 2840 (CH_3); 1685 (C=O); 1627 (amide I); 1540 (amide II). PMR spectrum (deuteromethanol) δ, ppm: 0.92 (3H, m, $\underline{CH_3}$); 1.32 (w.s., CH_2 chains); 1.61 (2H, m, $CH_2-\underline{CH_2}-CO-NH$); 1.78 (2H, m, $NH-CH_2-\underline{CH_2}-CH_2-COOH$); 2.10 (2H, q, $CH=CH-\underline{CH_2}-CH_2$, J = 7.5 Hz); 2.18 (2H, t, $CH_2-\underline{CH_2}-COOH$, J = 7.5 Hz); 2.34 (2H, t, $CH_2-\underline{CH_2}-CO-NH$, J = 7.5 Hz); 2.82 (2H, t, $=CH-\underline{CH_2}-CH=$, J = 5.5 Hz); 3.22 (2H, t, $CO-NH-\underline{CH_2}-CH_2$, J = 7 Hz); 5.35 (t, $\underline{CH}$ chains, J = 6 Hz), $C_{22}H_{37}O_3N$.

EXPERIMENTAL (PHARMACOLOGICAL)

The synthesis of γ-carboxypropylamide of palmitic acid is carried out according to the method described in [8]. We conducted an investigation of the influence of a one-time introduction of the following compounds on the rectal temperature of mice (tetrahybrids CBWA, males weighing 17-22 g) over the course of 4 h: GABA-palmitate (GPT), GABA-laurinate (GLA), and GABA-linoleate (GLI). The compounds were dissolved in Tween-80 and a 250 mg/kg dose was injected intraperitoneally; the control animals were injected with Tween-80. We assessed the dynamics of the temperature change in comparison with the initial temperature. The results of the measurement were analyzed statistically using the Student t-test.

The antihypoxic properties of GABA amides of fatty acids were examined on a model of acute hypobaric hypoxia (AHBH) by "raising" mice moving at a speed of 50 m/sec to an "altitude" of 11,000 m and recording both the survival time of the animals (reserve time) and the fraction of highly resistant animals (the relative number of animals having survived more than 20 min at a given "altitude"). The results were compared with the control data. Varying doses of compounds in a solution of Tween-80 were injected intraperitoneally for 1 h until hypoxia was induced. Control animals were injected with Tween-80.

Within the first 30 min, the one-time introduction of the compounds being studied caused a clear decrease in the rectal temperature of the mice. The most significant decrease (over 5°C; $p < 0.001$) was for GLA; in the following 30 min the opposite effect occurred, which led to the restoration of the temperature for GLI ($p > 0.5$) and a slight drop for GLA and GPT ($p < 0.05$). Later, after 2 to 4 h, the effects of the compounds reversed. The temperature of the animals that were given GLI rose and was somewhat higher than that of the control animals (but not consistently), and the temperature of the animals given GPT began to decrease smoothly ($p < 0.05$). The rectal temperature of animals that were given GLA remained below that of the control, but higher than for GPT.

The results indicate a substantial influence of the structure of lipophilic radicals on the metabolic effects of GABA amides of fatty acids.

Table 1 shows the results of the study of the antihypoxic properties of GABA amides of fatty acids.

The data provide evidence of the fact that of the three compounds studied (GPT, GLI, and GLA) only GLA demonstrated antihypoxic properties at a dose of 10 mg/kg ($p < 0.05$). GPT showed little activity (within the range of doses under investigation), and GLI had a weak effect at doses of 50 to 100 mg/kg. Consequently, the hypothesis of Minard and Grant [9], which states that there must be a connection between the hypothermic and antihypoxic effect as demonstrated by the AHBH model, was not confirmed. It is apparent that the achievement

TABLE 1. Antihypoxic Effects (in min) of GABA Amides of Higher Fatty Acids on the AHBH Model

Dose, mg/kg	GLI	GPT	GLA
1	8,37±3,17	10,8±4,13	7,67±3,91
2,5	8,14±3,55	10,83±4,4	11,42±3,87
5	10,33±4,5	11,28±3,94	14,42±3,55
10	10,9±4,11	10,36±4,31	16,83±2,32
20	—	10,67±3,68	12,58±3,37
50	11,73±3,15	11,75±3,71	10,61±4,21
100	13,6±3,4	11,12±3,98	11,25±3,93
Control	10,6±1,32 min (100±12,45 %), $n = 40$		

of hypothermic and antihypoxic effects for this particular class of compounds has to do with the molecular mechanisms of action, which differ from those of aminazine, adenosine, and GABA. Thus, the modification of GABA by lipophilic radicals leads to a substantial change in the fundamental properties of the initial substance, and one can expect a wide spectrum of pharmacological activity from GABA amides.

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SYNTHESIS AND LOCAL ANESTHETIC ACTIVITY OF SUBSTITUTED ANILIDES OF 6-METHYLPIPECOLINIC ACID

R. G. Glushkov, O. S. Sizova, A. V. Azimov, T. K. Trubitsyna, A. V. Denisov, N. P. Solov'eva, M. D. Mashkovskii, and L. N. Yakhontov

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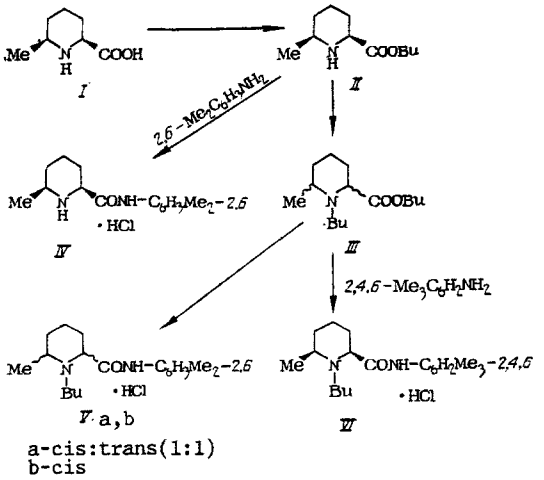
Extensive experience in the use of medical applications of local anesthetics of various chemical compound groups has demonstrated that with respect to pharmacotherapeutic characteristics, the greatest interest has been shown in preparations whose basic structure includes 2,6-xylidine, i.e., lidocaine, and particularly the long-acting preparation marcaine (bupivacaine) that induces all types of anesthesia [7, 8]. For the purpose of finding new improved local anesthetics of the 2,6-xylidine ring we synthesized and studied marcaine analogs, i.e., subtituted anilides of 6-methylpipecolinic acid.



S. Ordzhonikidze All-Union Scientific Pharmaceutical Chemistry Institute, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 23, No. 7, pp. 820-824, July, 1989. Original article submitted October 10, 1988.

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