SYNTHESIS AND ANTICONVULSANT PROPERTIES OF POLYFLUORINATED ALIPHATIC ACID AMIDES

V. A. Frolovskii,[1] T. L. Garibova,[1] T. A. Voronina,[1] Yu. N. Studnev,[1] and G. G. Rozantsev[1]

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The class of fluorine-containing organic compounds contains a large number of effective drugs representing various pharmacological groups (neuroleptics, antidepressants, cerebrovascular and antianginal agents, effective antiinflammatory fluorosteroids, antibacterial, antifungal, and antitumor agents, and some other) [1 – 7]. Pharmacologically active substances are especially frequently found among the fluorine-substituted cyclic and aromatic compounds with molecules containing a small number of fluorine atoms; examples are phenazepam, ftoracizine (fluoracizine), fluoxetine, foridon, etc. [3]. Although aliphatic mono- and (especially) poly- and perfluorinated derivatives are pharmacologically characterized to a smaller extent, these groups contain unique substances such as the blood substitute perftoran [8] and highly effective inhalation anesthetics (ftorotan, methoxyflurane, etc.) [3].

In searching for new pharmacologically active substances among fluoroorganic compounds, we synthesized a series of N-polyfluoroacyl derivatives of some amines and α-, β-, and γ-aminocarboxylic acids known to specifically influence CNS function. The synthesis was performed using the following schemes:

$$\underset{\text{I, II, V – X}}{HCF_2CF_2CH_2OCH_2C(O)Cl + RNH_2 \rightarrow HCF_2CF_2CH_2OCH_2C(O)NHR} \quad (1)$$

$$\underset{\text{III, IV}}{HCF_2CF_2CH_2OCH_2C(O)Cl + R^2NH \rightarrow HCF_2CF_2CH_2OCH_2C(O)NR^2} \quad (2)$$

$$\underset{\text{XI – XVIII}}{RFC(O)OMe + RNH_2 \rightarrow RFC(O)NHR} \quad (3)$$

The general procedure used for the synthesis of compounds according to scheme (3) was described in [9]. The same scheme was employed to obtain compounds V, VIII, and IX with a yield of 56.5, 38.7, and 60.4% [proceeding from (2,2,3,3-tetrafluoropropoxy)acetic acid methyl ester] or 78, 17, and 16.7% [proceeding from (2,2,3,3-tetrafluoropropoxy)acetic acid 2,2,3,3-tetrafluoropyl ester], respectively.

This paper reports on the results of testing some of the synthesized compounds for their anticonvulsant activity with respect to corazole-induced convulsion model.

EXPERIMENTAL CHEMICAL PART

The ^{1}H NMR spectra were measured on a Bruker Model 250 spectrometer using DMSO-d_6 as the solvent and TMS as the internal standard. The spectra of compounds I – X contain the following signals from protons of the polyfluoroacyl fragments (δ, ppm): 4.02 – 4.16 (t, 2H, J_{HF} 13.4 – 14.6 Hz, CH_2CF_2), 4.02 – 4.35 (s, 2H, OCH_2), 6.61 (tt, 1H, J_{HF} 52.0 – 52.2 Hz, J_{HF} 5.4 – 5.9 Hz, HCF_2). The spectra of compounds I, II, V, VI, and XI – XIII display a signal due to the amide proton in the region of δ = 9.58 – 7.87 ppm (t, J_{HH} 5.7 – 5.9 Hz), while compound IX exhibits two signals in this range. The signals of amide protons in the spectra of compounds VII and VIII are observed at δ = 8.17 ppm (d, J_{HH} 7.7 Hz), while the same signal for compound X is observed at δ = 10.16 ppm (s). The other signals in the ^{1}H NMR spectra d compounds I – XVIII correspond to the data published for analogous compounds. The ^{19}F NMR spectra and the spin – spin coupling constants for compounds I – XVIII virtually coincide with those reported in [10, 11].

The IR absorption spectra were recorded with a Perkin-Elmer Model 580B spectrophotometer using samples prepared as KBr disks, except for compound VII measured as a thin film between NaCl crystal plates. The characteristic absorption bands were as follows (cm^{-1}): 3390 – 3320 (NH), 2960 – 2900 (OH), 1750 – 1680 (OC=O), and 1660 – 1600 (NC=O).

[1] Institute of Pharmacology, Russian Academy of Medical Sciences, Moscow, Russia.

The data of elemental analyses (C H, N, F) for compounds I – XVIII agree with the results of analytical calculations using the proposed empirical formulas.

(2,2,3,3-Tetrafluoropropoxy)acetic acid and its chloroanhydride. To a solution o 54.2 ml (0.603 mole) of 2, 2, 3, 3-tetrafluoropropanol and 57.0 g (0.603 mole) of monochloroacetic acid in 50 ml water was added (at a temperature not exceeding 42°C) 48.24 g of sodium hydroxide in 250 ml water. The mixture was kept at room temperature for 14 h, acidified with concentrated hydrochloric acid, and extracted with ether (3 × 50 ml). The combined extracts were dried over $MgSO_4$, the solvent was evaporated, and the residue was distilled to obtain 61.0 g (53.0%) of (2,2,3,3-tetrafluoropropoxy)acetic acid (TFPAA); b.p., 225 – 226°C; n_D^{14}, 1.376.

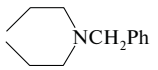
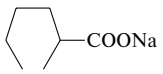
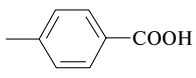
To a mixture of 32.6 g (0.172 mole) TFPAA, 80 ml benzene, and a few drops of DMF was slowly added 17 ml (0.209 mole) of thionyl chloride. The mixture was boiled for 3 h and distilled to collect a fraction with b.p. = 162 – 164°C, which yields 28.6 g (80%) of TFPAA chloroanhydride.

Methyl and 2,2,3,3-tetrafluoropyl esters of 2,2,3,3-tetrafluoropropoxy)acetic acid. To 50 ml of the corresponding alcohol was added at room temperature 30 g (0.144 mole) of TFPAA chloroanhydride. The reaction mixture was boiled for 0.5 h and distilled at atmospheric pressure. Yield of TFPAA methyl ester, 28 g (95.3%); b.p., 179 – 180.5°C; $n_D^{21.5}$, 1.3652. Yield of TFPAA 2,2,3,3-tetrafluoropyl ester, 37.9 g (86.2%); b.p., 214 – 216°C; n_D^{20}, 1.3532.

Synthesis of compounds I – X. To a solution of 33.5 mmole of the corresponding amine in 8.4 ml of 4 N aqueous NaOH solution at a temperature of 0 – 5°C were simultaneously added 20 mmole of TFPAA chloroanhydride and 5 ml of 4 N aqueous NaOH solution. The mixture was kept for 1 h at the indicated temperature and then for 30 min at room temperature. Then 5 ml of concentrated hydrochloric acid was added and the product was extracted with ethyl acetate (2 × 35 ml). The extract was dried over $MgSO_4$ and evaporated in vacuum. The residue was washed with an ether – heptane (2 : 1) mixture.

Synthesis of compounds V, VIII, and IX from TFPAA esters. To a solution of 48 mmole of the corresponding amine in 12 ml of 4 N aqueous NaOH solution at a temperature of 2 – 5°C was added 48 mmole of methyl or 2,2,3,3-tetrafluoropyl TFPAA esters. The mixture was kept for 1 h at the indicated temperature, then for 2 h at 30°C, and allowed to stand at room temperature overnight. Then 8 ml of concentrated hydrochloric acid was added and the product was extracted with ethyl acetate (2 × 50 ml). The extract was dried over $MgSO_4$ and evaporated in vacuum. The residue was washed with an ether – heptane (2 : 1) mixture.

TABLE 1. The Yields and Physicochemical Characteristics of the Synthesized Polyfluorinated Aliphatic Acid Amides

Compound	R_F	R(R_2)	Empirical formula (yield, %)	M.p., °C (n_D^{23})
I	–	CH_2Ph	$C_{12}H_{13}F_4NO_2$ (89.4)	57 – 58.5
II	–	$(CH_2)_2Ph$	$C_{13}H_{15}F_4NO_2$ (90.3)	oil (1.4672)
III	–		$C_{16}H_{20}F_4N_2O_2$ (78.8)	136 – 138
IV	–		$C_{10}H_{12}F_4NO_4Na$ (51)	98 – 99 (with decomp.)
V	–	CH_2COOH	$C_7H_9F_4NO_4$ (59)	73 – 74.5
VI	–	$(CH_2)_3COOH$	$C_9H_{13}F_4NO_4$ (66.5)	101 – 102.5
VII	–	$CH(COOH)(CH_2)_2COOH$	$C_{10}H_{13}F_4NO_6$ (70.1)	oil (1.4435)
VIII	–	$CH(COOH)(CH_2)_2C(O)NH_2$	$C_{10}H_{14}F_4N_2O_5$ (69.5)	93.5 – 95
IX	–	$CH_2C(O)NHCH_2C(O)OEt$	$C_{11}H_{16}F_4N_2O_5$ (75.7)	106 – 107
X	–		$C_{12}H_{11}F_4NO_4$ (85.3)	192 – 193
XI	$ClCF_2CF_2$	CH_2Ph	$C_{10}H_8F_4ClNO$ (84.5)	56 – 57
XII	(n-C_3F_7O)$CF(CF_3)$	CH_2COOH	$C_8H_4F_{11}NO_4$ (63.5)	67 – 69
XIII	$ClCF_2CF_2$	$(CH_2)_2COOH$	$C_6H_6F_4ClNO_3$ (91)	98 – 99
XIV	$ClCF_2CF_2$	$(CH_2)_3COOH$	$C_7H_8F_4ClNO_3$ (87)	78 – 79
XV	HCF_2CF_2	$(CH_2)_3COOH$	$C_7H_9F_4NO_3$ (85)	62 – 63
XVI	(n-C_3F_7O)$CF(CF_3)$	$(CH_2)_3COOH$	$C_{10}H_8F_{11}NO_4$ (60)	62 – 64
XVII	CF_3	$(CH_2)_3COOH$	$C_6H_8F_3NO_3$ (86)	77 – 78
XVIII	CF_3CF_2	$(CH_2)_3COOH$	$C_7H_8F_5NO_3$ (90)	88 – 89

The yields and physicochemical characteristics of the synthesized polyfluorinated aliphatic acid amides are summarized in Table 1.

EXPERIMENTAL PHARMACOLOGICAL PART

The anticonvulsant activity was evaluated by antagonism with respect to the corazole-induced convulsion model [12]. The tests were performed on male white mongrel mice weighing 18 – 23 g. The convulsant (corazole) subcutaneously injected in a dose of 130 mg/kg leads to tonic extension and a 95% loss of the control mice. The synthesized compounds were intraperitoneally injected (30 min before corazole) in a dose of 100 – 300 mg/kg with a Tween-80 suspension. The drug effect was assessed by determining the latent period before the onset of clonic convulsions, tonic extension, and the loss of test animals. The single dose effect was studied in a group of 10 – 12 mice. The experimental data were statistically processed using the Student and Fisher methods.

The reference drug was the well-known anticonvulsant chloracon, containing an amide fragment and a halogen substituent in the aliphatic chain [13]. The results of the pharmacological tests are summarized in Table 2.

It was found that substituting fluorine for hydrogen in the acyl fragment of chloracon decreases the anticonvulsant activity (compound XI). This is manifested by a twice shorter delay before the onset of tonic convulsions and by a greater proportion of lost animals. On the other hand, there is some increase in the latent period before the onset of clonic convulsions (table 2). At the same time, substituting a 2-(2,2,3,3-tetrafluoropropoxy)acyl (TFA) fragment for the acyl fragment of chloracon (compound I) preserves the protective effect (percentage survival), although the latent period before the onset of convulsions becomes shorter. Introduction of a methyl unit into the alkyl radical at the nitrogen atom of compound I (on passage to compound II) leads to an increase in the anticonvulsant activity (manifested by a 32% survival). These results are consistent with the published data [13]; note, however, that the latent period before the onset of convulsions for compound II is somewhat shorter than for I.

The increase in lipophilicity (apparently due to the fluorination) in compounds I, II, and XI as compared to chloracon leads to increasing positive charge on the carbon atom of the carbonyl group, which may account for the low anticonvulsant activity of the former fluorine-substituted compounds.

Since TFA does not significantly change the anticorazole effect of chloracon, it was expedient to study the influence of this fragment upon the anticonvulsant properties of amino acids (proline, glycine, GABA, glutamine) N-acylated by 2-(2,2,3,3-tetrafluoropropoxy)acetic acid. As is known, the N-acylation of these amino acids by fluorine-free carboxylic acids does not always impart to them the desired pharmacological activity. We have synthesized the TFA-substituted compounds IV, V, VI, and VIII according to scheme (1). The results of the pharmacological tests showed that compounds IV and VI did not prevent the loss of animals from corazole convulsions, although compound IV in a dose of 300 mg/kg increased the latent period before the onset of tonic convulsions with lethal outcome. Compounds V and VIII produced a significant anticonvulsant effect (Table 2). The former compound was characterized by a markedly longer latent period before the onset of tonic extension and the loss of test animals as compared to the value for compound VIII. On the other hand, the percentage survival in the group of mice treated with compound V was lower as compared to that for compound VIII (Table 2).

The absence of anticonvulsant properties in N-[2-(2,2,3,3-tetrafluoropropoxy)acyl]-γ-aminobutyric acid (compound VI) can be related to insufficient basicity of the amino group in this compound as compared to the basicity of NH_2 group in GABA. However, additional fluorine saturation of the acyl fragment in compound VI (on passage to compound XVI) or shortening of the carbon chain (compound XV) affected neither the latent period before the onset of convulsions nor the degree of loss prevention. Apparently, the absence of the desired physiological activity in compounds VI, XV, and XVI is not related to the acidity of the acylating carboxylic acid.

TABLE 2. Anticonvulsant Properties of Some Polyfluorinated Aliphatic Acid Amides (Convulsant: Corazole, 130 mg/kg)*

Compound	Dose, mg/kg	Latent period before onset of convulsions, sec		Percentage survival **
		clonic convulsions	tonic expansion and loss	
Control (physiological solution)	–	128.0 ± 24.3	450 ± 71.2 467 ± 68.4	5
I	100	100 ± 16	419 ± 114	16
II	100	118 ± 39	353 ± 79	32
III	100	212 ± 62	421 ± 79	20
IV	100	76 ± 14	274 ± 53	0
	300	262 ± 35	1657 ± 309***	0
V	100	148 ± 65	1339 ± 237***	20
VI	100	172 ± 16	496 ± 190	0
VIII	150	206 ± 82	232 ± 86	32
XI	100	269 ± 37***	776 ± 96***	0
XV	100	207 ± 89	446 ± 49	0
XVI	100	144 ± 36	398 ± 53	0
Chloracon	100	201 ± 46	1502 ± 411***	16

* Experiments performed with participation of S. L. Rozenkevich.

** Data processed by the Fisher method revealed no reliable difference in percentage survival between test and control groups.

*** $p < 0.05$ (Student's method).

It should be noted that some lipophilic N-acylated GABA derivatives exhibit the properties of GABA-mimetics [14]. Therefore, an important role in the manifestation of anticonvulsant properties by compounds IV, V, VI, VIII, XV, and XVI belongs to their localization in the CNS and the degree of enzymatic conversion. The rate of biomodification probably strongly depends on the ratio and mutual arrangement of F, H, O, and C atoms in the acyl fragment.

Thus, we have synthesized a series of polyfluorinated aliphatic acid amides and studied some of these compounds with respect to anticonvulsant activity on the corazole-induced convulsion model. Some of the tested compounds possess pronounced anticonvulsant properties. The possibility of controlling the anticonvulsant activity of compounds by varying the ratio of F, H, O, and C atoms in the structure makes this direction of search rather promising.

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