SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF SUBSTITUTED AMIDES OF 2-CHLORO- AND 2-ARYLAMINO-5,6-TRI(TETRA)METHYLENEISONICOTINIC ACIDS

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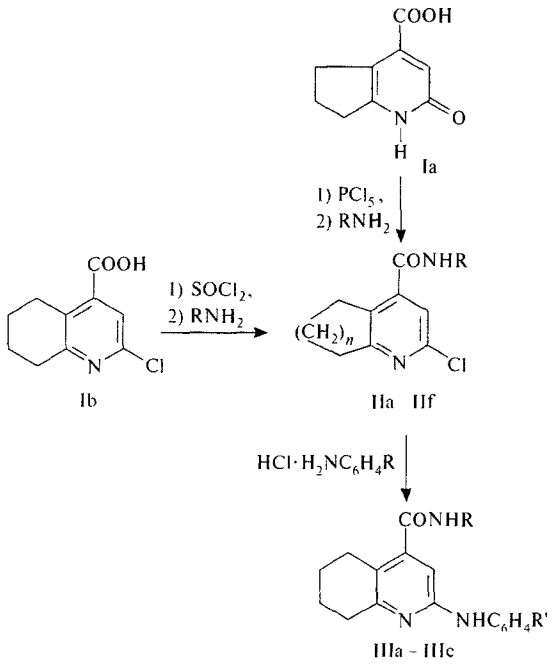
As was demonstrated, isopropylamides of 2-arylamino-5,6,7,8-tetrahydroquinoline-4-carboxylic acids possess several types of pharmacological activity [1]. In continuation of the previous investigation, we have synthesized a series of new alkyl- and arylamides of 2-chloro-5,6-trimethylene(5,6-tetramethylene)isonicotinic acids (IIa – IIf) and 2-arylamino-5,6-tetramethyleneisonicotinic acids (IIIa – IIIe) and studied their antiinflammatory, analgesic, and anticonvulsive properties.



II: $n = 1$ (IIa, IIb), 2 (IIc – IIf); R = n-C_4H_9 (IIa, IIc), $C_6H_5CH_2$ (IIb), $(C_2H_5)_2NC_2H_4$ (IId), p-$CH_3OC_6H_4$ (IIe), o-$CH_3OC_6H_4$ (IIf); III: R = n-C_4H_9 (IIIa), $(C_2H_5)_2NC_2H_4 \cdot HCl$ (IIIb – IIId), o-$CH_3OC_6H_4$ (IIIe); R' = H (IIIa, IIIb, IIIe), p-CH_3 (IIIc), p-CH_3O (IIId).

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Alkylamides IIa and IIb were obtained in 31 – 36% yield upon converting acid Ia [2] into 2-chloro-5,6-trimethyleneisonicotinic acid chloroanhydride. This compound was treated, without isolating from the reaction mixture, by alkylamines in the presence of triethylamine. Interaction of acid Ib [1] with excess thionyl chloride also results in the formation of a chloroanhydride, whose reaction with amines leads to a high yield of alkyl- and arylamides IIc – IIf (Table 1). Nucleophilic substitution of an arylamine group for the chlorine atom in position 2 of amides IIa – IIf is achieved by a 20-h boiling with the corresponding arylamine hydrochloride in isoamyl alcohol and leads to compounds IIIa – IIIe.

Compounds IIa – IIf have the form of white crystalline substances well soluble in alcohols. The IR spectra of these compounds contain absorption bands at 1650 – 1660 cm^{-1} (CO) and 3290 – 3320 cm^{-1} (NH). The IR spectra of compounds IIIa – IIIe display a band at 1670 – 1680 cm^{-1} (CO) and a pair of bands at 3170 – 3210 and 3340 – 3360 cm^{-1} (NH). The proposed structures of the synthesized compounds were also confirmed by the data of 1H NMR spectroscopy (see Table 2).

TABLE 1. Yields and Characteristics of Synthesized Compounds

Compound	Yield, %	M.p., °C	Empirical formula
IIa	36	91 – 93	$C_{13}H_{17}ClN_2O$
IIb	31	125 – 127	$C_{16}H_{15}ClN_2O$
IIc	56	62 – 64	$C_{14}H_{19}ClN_2O$
IId	65	113 – 115	$C_{16}H_{24}ClN_3O$
IIe	56	147 – 149	$C_{17}H_{17}ClN_2O_2$
IIf	59	115 – 117	$C_{17}H_{17}ClN_2O_2$
IIIa	47	174 – 175	$C_{20}H_{25}N_3O$
IIIb	91	135 – 137	$C_{22}H_{30}N_4O \cdot HCl$
IIIc	60	89 – 90	$C_{23}H_{32}N_4O \cdot HCl$
IIId	75	96 – 98	$C_{23}H_{32}N_4O_2 \cdot HCl$
IIIe	21	157 – 159	$C_{23}H_{23}N_3O_2$

TABLE 2. Parameters of the ^{1}H NMR Spectra of Synthesized Compounds

Compound	Chemical shift, δ, ppm						
	CH_2 (m, C-5,8 or 5.7)	CH_2 (m, C-6,7 or 6.0)	CH_2 (m)	CH_3	CH pyrid. (s)	H arom. (m)	NH
IIa	2.76 – 3.21 (5.7)	1.92 – 2.36 (6)	1.26 – 1.70; 3.26 – 3.53	0.81 – 1.06 t	7.16	–	6.23
IIb	2.63 – 3.03 (5.7)	1.73 – 2.20 (6)	4.26 – 4.51	–	6.99	7.03 – 7.20	6.36
IId	2.60 – 2.86 (5.8)	1.53 – 1.86 (6.7)	2.26 – 2.53; 3.03 – 3.36	0.76 – 1.10, t	6.83	–	6.66
IIf	2.50 – 2.91 (5.8)	1.51 – 1.85 (6.7)	–	3.75	7.76	6.77 – 7.26	9.73
IIIa	2.57 – 2.98 (5.8)	1.60 – 1.98 (6.7)	1.20 – 1.43; 2.96 – 3.30	0.69 – 0.93, t	6.81	7.39 – 8.08	8.60, 9.33
IIIb	2.46 – 2.76 (5.8)	1.50 – 1.82 (6.7)	2.13 – 2.44; 3.13 – 3.46	0.70 – 1.03	6.53	6.96 – 7.23	6.76, 9.40
IIIc	2.48 – 2.90 (5.8)	1.62 – 1.93 (6.7)	2.96 – 3.36; 3.51 – 3.76	1.35, 1.13 – 1.50, t	7.31	6.86 – 7.10	8.96, 10.96
IIId	2.43 – 2.86 (5.8)	1.61 – 1.90 (6.7)	3.00 – 3.33; 3.51 – 3.82	1.10 – 1.43	6.70	7.05 – 7.33	9.0, 11.06
IIIe	2.60 – 2.88 (5.8)	1.60 – 1.95 (6.7)	–	3.91	6.91	7.26 – 8.08	9.33, 9.84

Compounds IIIb – IIId possess basic properties and form water-soluble hydrochlorides.

EXPERIMENTAL CHEMICAL PART

The ^{1}H NMR spectra were measured on an RS-60 spectrometer using samples prepared as 5% solutions in DMSO-d_6, with HMDS as the internal standard. The IR absorption spectra were recorded on UR-20 and Specord spectrophotometers using samples prepared as nujol mulls. The data of elemental analyses for C, H, N, and Cl agree with the values calculated by empirical formulas.

2-Chloro-5,6-trimethyleneisonicotinic acid alkylamides (IIa and IIb). To a mixture of 3.58 g (20 mmole) of acid Ia and 30 ml of phosphorus oxychloride was gradually added with stirring 8.36 g (40 mmole) of phosphorus pentachloride and the mixture was boiled until complete dissolution, after which excess $POCl_3$ was distilled off in vacuum (water-jet pump). The resulting 2-chloro-5,6-trimethyleneisonicotinic acid chloroanhydride was dissolved, without isolating from the mixture, in 30 ml of benzene. This solution was gradually added to a mixture of 23 mmole of alkylamine, 10 ml of benzene, and 4.5 ml of triethylamine and the mixture was heated for 1 h at 40 – 50°C. The precipitate of triethylamine hydrochloride was separated by filtration, after which the solvent and volatile impurities were distilled off from the filtrate. The residue was dissolved in benzene and passed through a column with aluminum oxide. Finally, the solvent (benzene) was distilled off and the product was crystallized from ethanol.

2-Chloro-5,6-tetramethyleneisonicotinic acid alkyl- and arylamides (IIc, IIe, IIf). To a mixture of 2.1 g (10 mmole) of acid Ib and 30 ml of dry benzene was gradually added 1.8 g (15 mmole) of thionyl chloride and the mixture was boiled until complete dissolution. The excess thionyl chloride and benzene were distilled off at a reduced pressure (water-jet pump). The resulting 2-chloro-5,6-tetramethyleneisonicotinic acid chloroanhydride was dissolved in 20 ml of anhydrous benzene and added to a solution of 10 mmole alkyl- or arylamine in 5 ml benzene and 2.5 ml triethylamine. The mixture was heated to 50°C for 1 h, and then treated as described above.

2-Chloro-5,6-tetramethyleneisonicotinic acid diethylaminoethylamide (IId). To the chloroanhydride of acid Ib obtained as described above and dissolved in 20 ml of anhydrous benzene was added a solution of 1.16 g (10 mmole) of diethylaminoethylamine in 20 ml benzene and the mixture was heated for 1 h. Then the solution was decanted and the solvent (benzene) was evaporated. The residue was dissolved in water, filtered, and neutralized with a sodium hydrocarbonate solution. The precipitate was crystallized from hexane.

2-Arylamino-5,6-tetramethyleneisonicotinic acid alkyl- and arylamides (IIIa – IIIe). To a solution 10 mmole of amides IIa – IIf in 20 ml of isoamyl alcohol was added 10 mmole of the corresponding arylamine and the mixture was boiled for 20 h. Then the solvent and volatile impurities were distilled off with water vapor and the aqueous solution was decanted and cooled and alkalized by adding a few drops of a 10% sodium hydroxide solution. The resulting precipitate was filtered, dried, dissolved in benzene, and passed through a column with aluminum oxide. Finally, the solvent (benzene) was distilled off and the product was crystallized from ethanol. Compounds IIIb – IIId were isolated in the form of hydrochlorides obtained by bubbling dry hydrogen chloride through the solutions of bases in anhydrous ether.

TABLE 3. Analgesic Activity of Compounds IIb and IIIa in the Hot-Plate Test

Compound	Latent period of response, sec	
	before injection	60 min after injection
IIb	12.0	17.2*
IIIa	11.8	18.6*
Orthophen	10.3	17.1*

* $p < 0.05$ relative to the initial level.

EXPERIMENTAL PHARMACOLOGICAL PART

The analgesic activity was studied on a group of male and female mice weighing 16 – 20 g using the "hot plate" test [3]. The effect was evaluated as an increase in the latent period of response to the thermal irritation. The test was performed 30, 60, 120, and 180 min after intraperitoneal injection of the test compounds at a dose of 50 mg/kg or a reference drug (orthophen, 10 mg/kg).

The antiinflammatory activity was studied on white mongrel rats weighing 140 – 220 g using a model of acute inflammatory edema induced by subplantar injections of 0.1 ml of a 1% carrageenan solution into the hind foot. The activity, evaluated by the degree of inhibition of foot edema growth relative to that in the control group, was assumed to be reliably established for an inhibition effect of not less than 30%. The foot volume was measured by oncometric techniques; the reference drug was orthophen. The test compounds (50 mg/kg) or orthophen (10 mg/kg) were intraperitoneally injected 1 h before introducing carrageenan, and the antiinflammatory effect was assessed 4 h after edema model induction.

The anticonvulsive activity of the synthesized compounds was studied on white mice using the maximum electroshock method [4]. The compounds tested were intraperitoneally injected at a dose of 300 mg/kg.

It was found that, among the series of substances studied, only compounds IIb and IIIa exhibited analgesic activity (Table 3). Not one of the synthesized compounds showed evidence of anticonvulsive or antiinflammatory action.

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