SYNTHESIS AND BIOLOGICAL ACTIVITY OF SUBSTITUTED AMIDES OF 2-AMINONICOTINIC ACID

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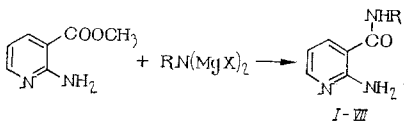
A number of amides of nicotinic acid are used as drugs (cordiamin, nicodine, phenatine [1]; nicofezone [2]); moreover, searches for biologically active compounds in this series are continuing [3]. We were interested in determining the influence of the introduction of an amino group into the pyridine ring of amides of nicotinic acid on the biological activity. For this purpose we synthesized a series of substituted esters of 2-aminonicotinic acid (I-VII; Table 1), based on the methyl ester of this acid and dimagnesylamines.



I-VII

The results of the experiments showed that this reaction proceeds readily, and compounds I-VII are obtained in satisfactory yields. The reaction between the methyl ester of 2-aminonicotinic acid and N-bromomagnesiumpiperidine proceeds with the formation of the piperidide of 2-aminonicotinic acid (VIII), yield 39%. Compounds I and VIII were isolated only in the form of the hydrochlorides.

Amides I-VIII are colorless crystalline substances, readily soluble in the usual organic solvents, and form water-soluble hydrochlorides. In the IR spectra of II-VII (IKS-14 instrument, 0.005 M in carbon tetrachloride, LiF and NaCl prisms), the following bands are observed: ν_{NH_2} 3510 ± 13; 3451 ± 12 cm^{-1}, ν_{NH} of secondary amide 3372 ± 6 cm^{-1}, ν_{CO} 1640 ± 14 cm^{-1}.

The antispasmodic and antitremor activity, the exciting and inhibiting effect on the central nervous system, as well as the soporific action and acute toxicity of the hydrochlorides I-VIII were studied.

Antispasmodic activity was determined on white mice according to the test of maximum electroshock [4] and the corazol test [5], while the antitremor activity was determined according to the nicotine and arecoline tests [6]. The exciting and inhibiting action was determined on mice visually after intraperitoneal

TABLE 1. Substituted Amides of 2-Aminonicotinic Acid

Compound	R	Yield, %	mp of base (deg)*	Found, N, %	Empirical formula	Calc., N, %	mp of hydrochloride (deg)
I	n-C_3H_7	20	—	19,69	$C_9H_{13}N_3O \cdot HCl$	19,95	255—7
II	n-C_4H_9	16	112—14	21,83	$C_{10}H_{15}N_3O$	21,75	268—70
III	cyclo-C_6H_{11}	25	180—2	19,3	$C_{12}H_{17}N_3O$	19,25	197—8
IV	$C_6H_5CH_2$	53	184—5	18,42	$C_{13}H_{13}N_3O$	18,49	229—30
V	C_6H_5	69	172—3	19,58	$C_{12}H_{11}N_3O$	19,71	208—10
VI	p-$CH_3C_6H_4$	50	200—2	18,28	$C_{13}H_{13}N_3O$	18,49	247—8
VII	p-$CH_3OC_6H_4$	54	201—3	17,26	$C_{13}H_{13}N_3O_2$	17,27	230—2

*Compounds I and II were crystallized from alcohol; III-VII were crystallized from benzene.

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TABLE 2. Antispasmodic Activity and Toxicity of Substituted Amides of 2-Aminonicotinic Acid in Comparison with Phenobarbital

Compound	Antispasmodic activity according to maximum electroshock		Toxicity	
	peak of action (min)	ED_{50} at the peak of action (mg/kg)	LD_{50} (mg/kg)	conditional therapeutic latitude (ratio of LD_{50} to ED_{50} accord. to max. electroshock)
III	—	300 (254,0—354,0)	—	—
IV	15	169 (132,2—216,0)	455 (382,0—541,4)	2,7
V	30	120 (103,0—139,0)	295 (224,0—389,0)	2,5
VI	15	121 (103,0—142,0)	116 (79,4—169,4)	1,0
VII	60	275 (271,0—279,0)	225 (170,4—297,0)	0,8
Phenobarbital	60	15,5 (12,8—18,8)	123 (94,0—161,0)	7,9

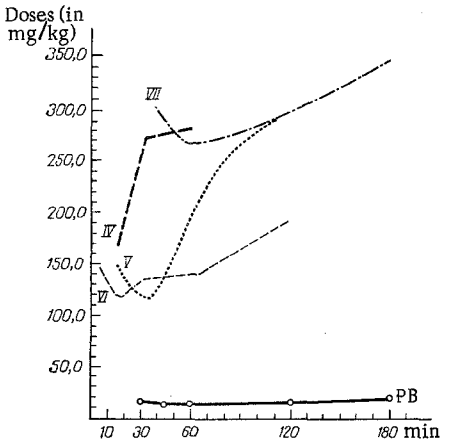

Fig. 1. Variation of the antispasmodic activity of compounds IV-VII in comparison with phenobarbital (PB) according to the test of maximum electroshock after intraperitoneal injection into white mice.

injection of the preparations in increasing doses all the way up to the lethal doses, while the soporific action was determined according to the test of a side position.

The acute toxicity of IV-VII was studied on white mice according to the method of [7]. The results of the determination of the physiological action and toxicity were treated statistically according to the method of Litchfield and Wilcoxon [8] and are presented in Table 2.

Compounds III-IV exhibit antispasmodic activity according to the test of maximum electroshock, which depends on the nature of the radical at the amide group, decreasing in the series V > VI > IV > VII > III, and correspondingly 7.7, 7.7, 11, 17.7, and 19.3 times less than for phenobarbital. Compounds I, II, and VIII do not exhibit antispasmodic activity in doses of 600 mg/kg. The antispasmodic activity of compounds V and VI is the greatest and equal; for IV it is reduced 1.4 (1.1-1.9)-fold, for VII it is reduced 1.6 (1.3-2.1)-fold in comparison with VI and 2.3 (2-2.7)-fold in comparison with V at $P=0.05$, while a further decrease is observed for III.

The antispasmodic activity of IV-VII according to the test of maximum electroshock was studied in the dynamics of development with time. The results are presented in Fig. 1 in comparison with phenobarbital. From the figure it is evident that for compounds IV and VI the antispasmodic activity reaches a maximum after 15 min and decreases rapidly for IV and slowly for VI. The maximum antispasmodic activity of compound V develops after 30 min, while for VII after 1 h, i.e., as for phenobarbital. The antispasmodic activity of compound V is 1.7 (1.2-2.2) times lower 1 h after injection than at the peak of action, 2.5 (1.9-3.3) times lower after 2 h, while for compound VI it is 1.5 (1.3-2.2) times lower 2 h after injection than at the peak of action at $P=0.05$, etc.

The most rapid decrease in the antispasmodic activity is observed in compound IV, the slowest for VII; for it 3 h after the injection, the antispasmodic activity is only 1.03 (1.02-1.06) times lower than at the peak of action, with $P=0.05$. For compounds IV-VII, the antispasmodic activity decreases more rapidly than for phenobarbital.

Compounds IV-VII weaken (but do not entirely remove) the nicotine and arecoline tremors; i.e., they possess weak N- and M-cholinolytic activity. All compounds do not exhibit soporific and exciting effects on the central nervous system.

The acute toxicity decreases in the series VI > VII > V > IV. The toxicity of VI is equal to the toxicity of phenobarbital; VII, V, and IV are 1.8, 2.4, and 3.7 times less toxic than phenobarbital, respectively. The ratio of LD_{50} to ED_{50} according to the test of maximum electroshock – the conditional therapeutic latitude – was calculated and was 3-8 times lower than for phenobarbital.

The presence of substantial antispasmodic activity among the compounds investigated gives a basis for considering further searches for antispasmodic agents among substituted amides of 2-aminonicotinic acid extremely promising.

EXPERIMENTAL

Substituted Amides of 2-Aminonicotinic Acid (I-VII). To 0.1 mole dimagnesylamine, produced from 0.1 mole of the amine and 0.2 mole ethyl magnesium bromide, we added 0.05 mole of the methyl ester of 2-aminonicotinic acid in ether. The mixture was heated for 1.5-2 h, then decomposed with a saturated solution of ammonium chloride. The ether layer was removed, and the solvent and volatile impurities steam-distilled off. The residue was crystallized. Hydrochlorides of I-VII were produced by passing dry hydrogen chloride into alcohol solutions of the bases.

Hydrochloride of the Piperidide of 2-Aminonicotinic Acid (VIII). A solution of 0.05 mole of the methyl ester of 2-aminonicotinic acid in 50-70 ml dry ether was added to 0.2 mole N-bromomagnesiumpiperidine, heated for 2 h, and then treated as in the preceding experiment. The base of VIII was obtained, which was dissolved in alcohol, saturated with hydrogen chloride, and the hydrochloride of VIII isolated. Yield 39%, mp 250-252°. Found %: N 17.4. $C_{11}H_{15}N_3O \cdot HCl$. Calculated %: N 17.38.

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