SYNTHESIS AND PSYCHOTROPIC ACTIVITY OF AMIDES OF 2-AMINONICOTINIC ACID

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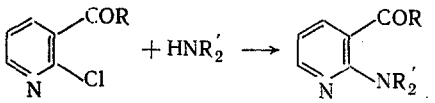
It is known that nicotinamide, which is an endogenous ligand of benzodiazepine receptors, causes effects similar to the effects of preparations of the benzodiazepine series and proves to have anticonvulsive, sedative, antiaggressive, and other forms of action [1, 2, 3, 5, 10-15].

In continuation of investigations on the search for neurotropic agents among the derivatives of nicotinic acid [6, 7], the synthesis has been carried out and the psychotropic activity has been studied of amides of 2-aminonicotinic acid (Ia-f) which have a particular electronic-structural similarity to tranquillizers of the benzodiazepine series [8].

In addition to amides (Ia-f) the amides (Ig-k), synthesized previously in [7], were subjected to a more detailed pharmacological study.

Compounds (Ia-f), mostly containing tertiary amino groups (TAG) in position 2 of the pyridine ring, were synthesized by heating amides of 2-chloronicotinic acid (IIa-c) at 100-160°C with an excess of the appropriate amine in dimethylformamide (DMF) or xylene or without solvent.



IIa-c Ia-f

(Ia-c, j, IIa) R = NH_2; (Id, IId) R = morpholino; Ie-g, IIc) R = 3-trifluoromethylanilino; (Ik) R = o-anisidino; (Ia, i) NR_2' = 4-2- hydroxyethylpiperazino; (Ic, e) NR_2' = 4-phenylpiperazino; (Ib, f) NR_2' = morpholino; (Id, g, j) NR_2' = benzylamino; (Ih, k) NR_2' = 2-hydroxyethylamino.

The structure of amides (Ia-f) was confirmed by data of elemental analysis and IR spectra. Thus, in the spectrum of compound (Ib) taken in a Nujol mull there were bands at 3290-3370 (νNH_2), 1656 (vamide I), 1609, 1584, and 1560 cm^{-1}. In the IR spectrum of (If) (mull) bands were detected at 3116 (νNH), 1678 (ν amide I), 1625, 1609, and 1546 cm^{-1}.

EXPERIMENTAL (CHEMICAL)

IR spectra were taken on a Perkin-Elmer 580 spectrophotometer.

2-Chloronicotinic Acid Morpholide (IIb). A mixture of 2-chloronicotinic acid (4.71 g, 0.03 mole) and thionyl chloride (30 ml) was boiled for 1 h, evaporated in vacuum, and the residue dissolved in anhydrous benzene (30 ml). Morpholine (5.2 g, 0.06 mole) in anhydrous benzene (5 ml) was added dropwise to the obtained solution after cooling with water, the reaction mixture was stirred for 1 h at 20°C, treated with sodium bicarbonate solution and with water, the resulting solid was filtered off, and after recrystallization from ethyl acetate amide (IIb) 4 g (59%) was obtained having mp 93-94°C. Found, %: Cl 15.21, N 11.88. $C_{10}H_{11}ClN_2O_2$. Calculated, %: Cl 15.64, N 12.36.

Amides of 2-Aminonicotinic Acid (Ia-f). A. A mixture of (IIb) (0.57 g, 2.5 mmole) and benzylamine (1.34 g, 12.5 mmole) was heated at 100°C for 13 h, the reaction mixture was treated with water, extracted with ether, the ether solution dried, evaporated, and (Id) base

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TABLE 1. Amides of 2-Aminonicotinic Acids Ia-f

Compound	Yield, %	Preparative method	Mp, °C	Found, %				Empirical formula	Calculated, %			
				C	H	Cl	N		C	H	Cl	N
Ia	50—60	A, C	146—147 (with decomp.)	57,39	7,17	--	22,37	$C_{12}H_{14}N_4O_2$	57,58	7,24	—	22,38
Ib	82	A	132—134	57,93	6,37	--	20,29	$C_{10}H_{12}N_2O_2$	57,95	6,32		20,27
Ic·2HCl	85	B	232—233 (with decomp.)	54,21	5,63	19,59	15,94	$C_{16}H_{16}N_4O \cdot 2HCl$	54,08	5,67	19,96	15,77
Id·HCl	83,5	A	197—198	64,15	6,05	10,69	12,37	$C_{17}H_{16}N_2O_2 \cdot HCl$	61,16	6,03	10,62	12,58
Ie·2HCl	85	C	237—238 (with decomp.)	—	—	14,09	11,18	$C_{23}H_{21}F_3N_4O \cdot 2HCl$	—	—	14,20	11,22
If·HCl	93	B, C	175—176	—	—	8,80	10,82	$C_{17}H_{16}F_3N_2O_2 \cdot HCl$	—	—	9,14	10,83

Note. Substance (Ia) was recrystallized from a mixture of benzene and heptane, (Ib) from absolute alcohol, (Ic, e) from alcohol, (Id) from a mixture of absolute alcohol and ether, and (If) from ethyl acetate.

TABLE 2. Comparative Psychotropic Activity of Amides of 2-Aminonicotinic Acid

Compound	Motor activity		Orientation—investigation behavior		Antagonism to corazole		Potentiation of the effect of ethanol		Antihypoxic activity (prolongation of life)		Muscular weakening effect	
	dose, mg/kg	effect, %	dose, mg/kg	effect, %	dose, mg/kg	effect, %	dose, mg/kg	effect, %	dose, mg/kg	effect, %	dose, mg/kg	effect, %
Ia	50	57	200	66	200	0	100	134	200	40	200	0
Ib	50	74	100	0	200	16	100	192	200	158	200	0
Ic	100	130	100	0	100	33	100	149	100	700	100	0
Id	50	62	50	0	200	16	100	121	200	113	200	0
Ie	50	46	50	33	100	16	100	127	100	747	100	16
If	50	34	100	50	100	83	100	202	50	817	100	0
Ig	100	97	100	100	125	33	100	115	100	340	100	16
Ih	100	62	100	16	100	16	100	146	100	272	100	50
Ii	100	27	100	100	100	83	100	191	100	272	100	50
Ij	100	83	100	100	100	66	100	145	50	407	100	0
Ik	50	53	100	66	200	83	100	107	100	199	200	83
III	500	87	500	50	1250	50	500	157	100	230	1600	50

(0.7 g) was obtained. The hydrochloride of (Id) was obtained by dissolving the latter in absolute alcohol and adding an alcohol solution of hydrogen chloride.

B. A solution of (IIa) (1.57 g, 10 mmole) and N-phenylpiperazine (3.4 g, 21 mmole) in DMF (10 ml) was heated at 100°C for 7 h, the precipitated solid was filtered off, (Ic) base (2.3 g) was obtained, and was converted into (Ic) dihydrochloride by a method similar to A.

C. A solution of the 3-trifluoromethylanilide of 2-chloronicotinic acid (IIc) (1.5 g, 5 mmole) and N-phenylpiperazine (1.62 g, 10 mmole) in absolute xylene (20 ml) was heated at 160°C for 14 h, filtered, an ether solution of hydrogen chloride was added to the filtrate, and (Ie) dihydrochloride obtained.

The characteristics of compounds (Ia-f) are given in Table 1.

EXPERIMENTAL (PHARMACOLOGICAL)

The psychotropic activity of the amides of 2-aminonicotinic acid (Ia-k) was studied in experiments on male white mice of weight 18-22 g and male rats of weight 220-250 g according to the following tests: spontaneous motor activity on a Ugo-Bazile (Italy) actometer, orientation–investigation behavior in the laying on a grid test, antihypoxic activity of compounds on the life span of animals under conditions of hypobaric hypoxia in a pressure chamber, the anticonvulsive action on the antagonism of corazole and thiosemicarbazide, and the muscular weakening effect in the rotarod test. Simultaneously the ability of the test substances to influence acute alcohol intoxication on administration of a narcotic dose of ethanol has been clarified (the effect was assessed on the duration of the side position of mice). A detailed description of the procedures was given in [1, 2, 4, 9]. Compounds (Ia-k) were introduced intramuscularly 30-40 min before the experiment in the dose range 50-200 mg/kg. Nicotinamide (III) at doses of 500-1500 mg/kg served as reference preparation.

It was established by the biological investigations that all the test compounds possessed sedative properties. They caused overall quietening of animals, reduced the spontaneous motor activity, and disturbed orientation–investigation behavior (Table 2).

The marked antihypoxic effect of the amides of 2-aminonicotinic acid was the leading component in their pharmacological action spectrum. The majority of the studied compounds increased the life span of animals in a pressure chamber and the most active were compounds containing TAG in position 2 (compound Ia was an exception).

An important direction of the activity of amides (Ia-k) was their anticonvulsive action. All the test compounds (with the exception of Ia) antagonized the effect of corazole, protecting animals from death by 16-83%. Compounds (Ia-c, j) displayed antagonism to thiosemicarbazide, reducing convulsive attacks in animals by 16-20% on average. The latter may be regarded as an influence on the GABAergic system. The series of compounds caused a muscular weakening effect. This action was not observed as a rule for compounds containing TAG in the 2 position. A special feature of amides (Ia-k) was the detected ability to increase the duration of the side position of animals on acute alcohol intoxication.

Consequently, all the studied compounds were similar to nicotinamide in their spectrum of action but surpassed it in absolute activity by more than 2-5 times. The role of substituents, particularly of TAG in the 2 position of the pyridine ring, for the development of the psychotropic effect has been established. It was shown that the introduction of this substituent led to a strengthening of the antihypoxic, sedative, and anticonvulsive activity.

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 3-MERCAPTOINDOLE DERIVATIVES

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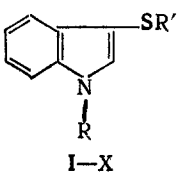
Derivatives of 3-mercaptoindoles (I) [4] are being studied for possible use as various medicinal preparations, including antimicrobial agents [5, 6]. The present work is a study of the antimicrobial properties of previously described alkyl and vinyl derivatives I-II-IX [2, 3] and a recently synthesized trisulfide derivative (X).

The latter was produced by the β-addition of EtSH to both vinyl groups of VI through the action of a radical initiator:



I—X

I: $R = R' = H$; II: $R = H$, $R' = Et$; III: $R = Et$, $R' = H$;
IV: $R = R' = Et$; V: $R = H$, $R' = Br$; VI: $R = R' = CH{=}CH_2$;
VII: $R = H$, $R' = CH{=}CH_2$; VIII: $R = Et$, $R' = CH{=}CH_2$;
IX: $R = CH{=}CH_2$, $R' = Et$; X: $R = R' = (CH_2)_2SEt$.

Trisulfide X is an oily liquid which can be purified by column chromatography.

The thiolation of compound VI in a thermostatic cell of an infrared spectrometer demonstrated that the addition of mercaptan first takes place in the vinyl group on the nitrogen atom. This conclusion was made on the basis of the intensity change in the absorption band of the vinyl groups in various heteroatoms, i.e., 1590 ($SCH{=}CH_2$) and 1640 cm^{-1} ($NCH{=}CH_2$).

The infrared spectrum of compound X is completely devoid of absorption bands that characterize vinyl group fluctuations, but do exhibit bands at 1380 and 2870-2970 cm^{-1} that are associated with the stretching vibrations of the methyl and methylene groups. Two triplets of methyl groups (δ 1.09, 1.13 ppm) are observed in the PMR spectrum of this compound. The protons of the methylene group bonded to the nitrogen atom are represented by a triplet (δ 4.20 ppm). The methylene protons bonded to the sulfur atom resonate in the stronger field (δ 2.33-2.76 ppm).

EXPERIMENTAL (CHEMICAL)

The infrared spectrum was recorded on a UR-20 (GDR) apparatus in a microlayer. The PMR spectrum was recorded on a BS-4878 spectrometer in $CHCl_3$. HMDS was the internal standard. Product purity was controlled by TLC on Al_2O_3. Solvents were ether and $CHCl_3$. Spots were detected on the chromatogram in iodine vapor.

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