SYNTHESIS AND PHYSIOLOGICAL ACTIVITY OF FLUORO DERIVATIVES OF AMIDES OF NICOTINIC AND ISONICOTINIC ACIDS

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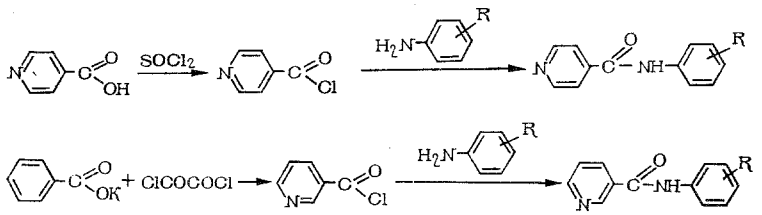
The synthesis of amides of nicotinic and isonicotinic acids was described in the literature [1-3]. To study the physiological activity of the given class of compounds, we have first obtained amides of nicotinic and isonicotinic acids with fluoro-containing substituents and their hydrochlorides (Tables 1 and 2). The synthesis was realized according to the scheme



The amides of nicotinic and isonicotinic acids represent crystalline substances, readily soluble in alcohol, crystallized from aqueous alcohol.

The hydrochlorides of amides of nicotinic and isonicotinic acids are crystalline substances, most of them soluble in water and alcohol. Hydrochlorides IV, V, VI, and XI are sparingly soluble in water.

We studied the toxicity, antiphlogistic, and antipyretic activity of hydrochlorides of amides of nicotinic and isonicotinic acids.

A sharp toxicity was studied on white mice under intraabdominal introduction of the tested compounds. The study of antiphlogistic action of substances was carried out on models of edema in the rat rear paw, caused by the subplantar introduction of 0.1 ml of 2% formalin solution. The compounds under study were introduced intraabdominally in a dose of 10% LD_{50} 30 min prior to the introduction of substances causing the infection. The volume of the paw was measured plethysmometrically hourly for 5 h.

The antipyretic activity of the preparations was studied in experiments on rats during milk fever. The milk was introduced intramuscularly by calculating 1 ml per 100 g of weight. The studied preparations in a dose of 10% LD_{50} were introduced at the peak of the fever. Antipyretic action was determined for 3 h.

Pharmacological studies of the hydrochlorides of the amides of nicotinic and isonicotinic acids showed that all of them possessed low toxicity, their LD_{50} deviated within the range of 360-740 mg/kg (see Table 2). The toxic properties depend to a certain extent on the structure. For compounds containing 3-CHF_2O and 2,3-$(CH_3)_2$ groups as substituents in the arylamide residue, the toxicity somewhat increased in the transition from nicotinic acid derivatives to isonicotinic acid derivatives. For compounds containing two methyl groups in the 3,4-positions, a reverse relationship was observed.

The effect of the structure on the toxicity of substances containing the 3-CHF_2O group was especially pronounced. Thus, in the transition from compound IX to compound III, the toxicity increased approximately twofold.

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TABLE 1. Amides of Isonicotinic and Nicotinic Acids

Compound	R	Yield, %	mp, deg	Found N, %	Empirical formula	Calc. N, %
I	3,4-$(CH_3)_2$	68	131—3	11,7 11,8	$C_{14}H_{14}N_2O$	11,1
II	2,3-$(CH_3)_2$57	57	203—4	11,3 11,5	$C_{14}H_{14}N_2O$	11,1
III	3-CHF_2O	52	89—91	10,1 10,0	$C_{13}H_{10}F_2N_2O_2$	10,6
IV	3-CF_3	23	191—5	10,0 10,2	$C_{13}H_9F_3N_2O$	10,5
V	3,5-$(CF_3)_2$	17	208—9	8,2	$C_{14}H_8F_6N_2O$	8,4
VI	4SO_2CHF_2	20	217—9	8,7 9,0	$C_{13}H_{10}F_2N_2O_3S$	8,9
VII	2,3-$(CH_3)_2$	47	133—6	11,7 11,9	$C_{14}H_{14}N_2O$	12,3
VIII	4-CHF_2	36	139—3	9,3 9,5	$C_{13}H_{10}F_2N_2O$	9,9
IX	3-CHF_2O	42	93—5	10,4 10,3	$C_{13}H_{10}F_2N_2O_2$	10,5
X	3,4-$(CH_3)_2$	49	93—7	12,36 12,1	$C_{14}H_{14}N_2O$	12,3
XI	3,5-$(CF_3)_2$	56	135—140	8,6 8,8	$C_{14}H_8F_6N_2O$	8,8
XII	3-CF_3	56	179—180	10,0 10,2	$C_{13}H_9F_3N_2O$	10,5

TABLE 2. Hydrochlorides of Amides of Isonicotinic and Nicotinic Acids and Their Toxicity, Antiphlogistic, and Antipyretic Activity

Compound	R	Yield, %	mp (deg)	Found Cl, %	Empirical formula	Calc. Cl, %	LD_{50}, mg/kg	Decrease during formalin edema (4th hour), %	Drop in temp., deg, during milk fever (1 h)
I	3,4-$(CH_3)_2$	85	268—270	12,9	$C_{14}H_{14}N_2O \cdot HCl$	13,5	510 (485,7—535,5)	18,8±7,0	2,3±0,29
II	2,3-$(CH_3)_2$	80	255	13,3 13,5	$C_{14}H_{14}N_2O \cdot HCl$	13,5	663 (634,4—692,8)	36,6±4,9	1,5±0,16
III	3-CHF_2O	89	197—200	11,0 11,2	$C_{13}H_{10}F_2N_2O_2 \cdot HCl$	11,2	360 (344,4—376,2)	27,7±3,0	0,9±0,27
IV	3-CF_3	87	195	11,5 11,6	$C_{13}H_9F_3N_2O \cdot HCl$	11,7	—	—	—
V	3,5-$(CF_3)_2$	90	235	9,9 10,0	$C_{14}H_8F_6N_2O \cdot HCl$	9,58	—	—	—
VI	4-SO_2CHF_2	89	238	9,8 10,0	$C_{13}H_{10}F_2N_2O \cdot HCl$	10,2			
VII	2,3-$(CH_3)_2$	69	207	13,3 13,4	$C_{14}H_{14}N_2O \cdot HCl$	13,5	(672,7—814,0)	45,5±4,8	1,0±0,25
VIII	4-CHF_2	97	140	11,3 11,2	$C_{13}H_{10}F_2N_2O \cdot HCl$	11,2	580 (487,4—690,2)	41,1±2,5	1,1±0,28
IX	3-CHF_2O	84	174	11,5 11,6	$C_{13}H_{10}F_2O_2 \cdot HCl$	11,8	690 (600,0—793,5)	21,4±8,0	0,7±0,29

All studied preparations exerted antiphlogistic action. In the transition from amides of nicotinic and isonicotinic acids, containing 3,4-$(CH_3)_2$ groups, to amides with 2,3-$(CH_3)_2$ groups, antiphlogistic activity sharply increased. The introduction of the 4-CHF_2O group into the phenyl residue of the molecule also leads to a sharp increase in the antiphlogistic effect. The hydrochlorides of amides containing fluorinated substituents in the metaposition exerted a less expressed antiphlogistic action.

The studied compounds exerted antipyretic action – all of them decreased the rectal temperature in the body of rats during milk fever by 1-2°. The derivatives of nicotinic and isonicotinic acids with the m-CHF_2O group displayed the smallest effect; and the derivatives containing 3,4-$(CH_3)_2$ and 3-CF_3 groups, the largest effect (2°). It was of interest that antipyretic activity was higher in derivatives of isonicotinic acid.

EXPERIMENTAL*

M-Difluoromethoxyphenylamide of Nicotinic Acid (IX). To 7.5 g of finely pulverized potassium salt of nicotinic acid in 30 ml of dry benzene with stirring and cooling (0°) was added 6 g of oxalyl chloride in 15 ml of dry benzene. The mixture was boiled for 30 min and the precipitate filtered off. To the benzene solution of nicotinyl chloride with cooling was added a solution of 5.6 g of m-difluoromethoxyaniline in 5 ml of absolute benzene and 3.2 g of dry pyridine. The mixture was heated for 5 h at 50-60° and then poured into

*With the collaboration of laboratory worker I. I. Muravov.

water. The amide was extracted with ether, the ether extracts dried over sodium sulfate and then evaporated. The amide was crystallized from aqueous alcohol. A colorless crystalline substance was isolated.

Amide IX was dissolved in ethyl acetate and treated with dry hydrogen chloride. The hydrochloride was obtained as a colorless crystalline substance.

Compounds VII, VIII, X-XII, and their hydrochlorides were prepared in a similar way.

m-Difluoromethoxyphenylamide of Isonicotinic Acid (III). To 10 g of isonicotinic acid was added 20 ml of thionyl chloride. The mixture was heated on a water bath for 1 h, the excess of thionyl chloride distilled off on a water bath, and the hydrochloride of isonicotinyl chloride isolated.

The hydrochloride of isonicotinyl chloride (5.54 g) was dissolved in 60 ml of pyridine, and the solution of m-difluoromethoxyaniline in 15 ml of pyridine was added; the mixture warmed up. The amide was extracted with ether. The ether was then distilled off and the residue distilled in vacuo, bp 230° (7 mm). The amide was crystallized from aqueous alcohol with carbon to yield a colorless crystalline substance.

Amide II was dissolved in ethyl acetate and treated with dry hydrogen chloride; the hydrochloride was obtained as a colorless crystalline substance.

Compounds I, II, IV-VI, and their hydrochlorides were prepared in a similar manner.

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