SYNTHESIS AND STUDY OF ANTIMICROBIAL AND ANTIINFLAMMATORY ACTIVITY OF 2-SUBSTITUTED NICOTINIC ACID AMIDES

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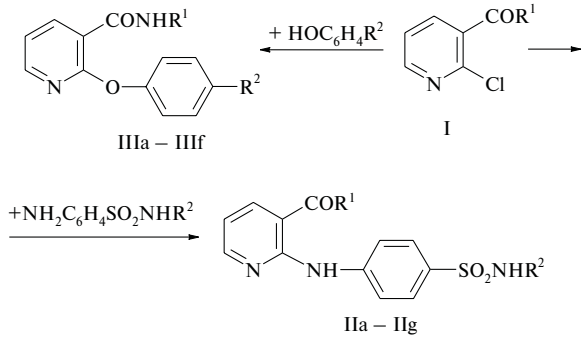
Previously, we have synthesized alkyl(aryl)amides of 2-chloro-, 2-amino-, and 2-arylaminonicotinic acids possessing anticonvulsant activity [1, 2]; 2-chloro-, 2-methoxy-, and 2-hydroxynicitinic acid amides, some of which exhibited antiinflammatory activity [3, 4]; and 2-arylhydroxynicotinonitriles and unsubstituted amides of 2-arylhydroxynicotinic acids producing antiinflammatory and hypoglycemic effects [5].

In the search for new antiinflammatory and antibacterial agents in the group of 2-substituted nicotinic acid amides, we have synthesized a series of nicotinamides containing pharmacophore 4-sulfamylanilino or aryloxy groups at C-2 atom of the pyridine ring.



IIa: R^1 = 3-$CH_3C_6H_4NH$, R^2 = H;
IIb: R^1 = morpholino, R^2 = 4,6-dimethylpyrimidinyl;
IIc: R^1 = *n*-C_4H_9NH, R^2 = 4,6-dimethylpyrimidinyl;
IId: R^1 = *cyclo*-$C_6H_{11}NH$, R^2 = 4,6-dimethylpyrimidinyl;
IIe: R^1 = 3-$CH_3C_6H_4NH$, R^2 = 4,6-dimethylpyrimidinyl;
IIf: R^1 = $C_6H_5CH_2NH$, R^2 = 4,6-dimethylpyrimidinyl;
IIg: R^1 = 4-$CH_3COC_6H_4NH$, R^2 = 4,6-dimethylpyrimidinyl;
IIIa: R^1 = *cyclo*-C_6H_{11}, R^2 = F;
IIIb: R^1 = $C_6H_5CH_2$, R^2 = OCH_3;
IIIc: R^1 = 4-$CH_3COC_6H_4$, R^2 = OCH_3;
IIId: R^1 = 2,4-$(CH_3)_2C_6H_3$; R^2 = OCH_3;
IIIe: R^1 = 4-$CH_3COC_6H_4$, R^2 = $NHCOCH_3$;
IIIf: R^1 = 4-antipyryl, R^2 = $NHCOCH_3$.

Compounds IIa – IIg were synthesized by heating 2-chloronicotinic acid amides with *p*-aminosulfanylamides in 50% acetic acid (this medium seems to simultaneously produce a catalytic action). The target 2-aryloxynicotinic acid amides (IIIa – IIIf) were obtained via interaction of 2-chloronicotinic acid amides with phenols in DMF in the presence of anhydrous potassium carbonate.

The final products IIa – IIf and IIIa – IIIf (Table 1) appear as colorless or slightly tinted crystalline substances well soluble in organic solvents and insoluble in water. The proposed structures were confirmed by the results of ^{1}H NMR measurements.

EXPERIMENTAL CHEMICAL PART

The ^{1}H NMR spectra were measured on an RYa-2310 spectrometer using DMSO-d_6 as the solvent and HMDS as the internal standard. The yields and some properties of the synthesized compounds are listed in Table 1. The data of elemental analyses agree with the results of analytical calculations using empirical formulas.

N-(4-Acetylphenyl)-2-chloronicotinamide (I, R^1 = 4-$MeCOC_6H_4NH$). To 1.57 g (0.01 mole) of 2-chloronicotinic acid was added 20 ml of thionyl chloride and the mixture was heated on a water bath for 3 h, after which the excess thionyl chloride was distilled off in vacuum. The residue was mixed with 20 ml of benzene, 1.31 g (0.01 mole) of *p*-aminoacetophenone, and 3 ml of triethylamine and the mixture was heated on a water bath for 1 h. The precipitated triethylamine hydrochloride was separated by filtration; volatile impurities (benzene, etc.) were distilled off with water vapor. The residue was treated with a 10% sodium hydrocar-

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bonate solution. The precipitated product was separated by filtration and recrystallized from ethanol; ^{1}H NMR spectrum (δ, ppm): 2.43 (s, 3H, CH_3), 7.00 – 8.13 (m, ArH), 9.93 (s, 1H, NH-amide).

The synthesis and the properties of other 2-chloronicotinamides (I) are described elsewhere [1 – 4].

2-(4-Sulfamylanilino)nicotinic acid amides (IIa – IIg). A solution of 0.01 mole of 2-chloronicotinic acid amide and 0.01 mole of the corresponding sulfanylamide in 10 ml of 50% acetic acid was boiled for 6 h, cooled, neutralized with a 10% sodium hydrocarbonate solution, and diluted with water. The precipitate was separated by filtration and recrystallized from isopropanol; ^{1}H NMR spectrum (δ, ppm): 10.77 – 11.30 (bs, 1H, $SO_2\underline{NH}$), 8.32 – 9.43 (bs, 1H, NH-arylamide), 6.41 – 6.52 (d, 1H, NH-alkylamide), 6.01 – 6.46 (s, 1H, NH), 6.36 – 8.80 (m, ArH).

2-Aryloxynicotinic acid amides (IIIa – IIIf). A mixture of 0.01 mole of the corresponding 2-chloronicotinic acid amide, 0.01 mole of the corresponding phenol, and 1.4 g of anhydrous potassium carbonate in 10 ml of DMF was boiled for 6 h, cooled, and diluted with water. The precipitate was separated by filtration and recrystallized from isopropanol; ^{1}H NMR spectrum (δ, ppm): 8.87 – 10.73 (s, 1H, NH-amide), 6.80 – 8.23 (m, ArH).

EXPERIMENTAL PHARMACOLOGICAL PART

The antimicrobial activity of the synthesized compounds was determined by the conventional method of double serial dilutions in a meat-infusion broth (pH 7.2 – 7.4) with respect to the standard strains of *Escherichia coli* M-17 and *Staphylococcus aureus* P-209. The bacterial load was 250×10^3 cells/ml [6, 7]. The acting dose was taken equal to the minimum inhibiting concentration (MIC).

TABLE 1. Yields and Physicochemical Characteristics of the Synthesized Compounds

Compound	Yield, %	M.p., °C	Empirical formula
If	85	112 – 113	$C_{14}H_{11}ClN_2O_2$
IIa	79	221 – 223	$C_{18}H_{18}N_4SO_3$
IIb	84	99 – 100	$C_{22}H_{25}N_6SO_4$
IIc	77	192 – 194	$C_{22}H_{26}N_6SO_3$
IId	82	125 – 127	$C_{24}H_{28}N_6SO_3$
IIe	84	171 – 173	$C_{25}H_{24}N_6SO_3$
IIf	75	58 – 59	$C_{25}H_{24}N_6SO_3$
IIg	78	217 – 219	$C_{26}H_{24}N_6SO_4$
IIIa	83	85 – 86	$C_{18}H_{19}FN_2O_2$
IIIb	80	101 – 103	$C_{20}H_{18}N_2O_3$
IIIc	85	135 – 137	$C_{21}H_{18}N_2O_4$
IIId	82	123 – 125	$C_{21}H_{20}N_2O_3$
IIIe	89	215 – 217	$C_{22}H_{19}N_3O_4$
IIIf	81	238 – 239	$C_{25}H_{23}N_5O_3$

The antiinflammatory activity of the synthesized compounds was studied on white mongrel rats weighing 180 – 220 g, bearing a foot edema model induced by subplantar injections of 0.1 ml of a 1% carrageenan solution into the hind paws of the test animals. The compounds to be tested (in a dose of 50 mg/kg) and the reference drug ortophen (10 mg/kg) were intraperitoneally injected with a 2% starch jelly 1 h before carrageenan injection. The degree of edema development was evaluated oncometrically by measuring the inflamed foot volume 4 h after carrageenan injection [8], and expressed as the percentage edema growth inhibition relative to control.

The experimental data were statistically processed in terms of the Student *t*-criterion [9].

The maximum antiinflammatory activity in the series of 2-sulfamylanilinonicotinic acids studied (IIa – IIg) was observed for compounds IIa and IId; among 2-aryloxynicotinic acid amides, the maximum activity was observed for compound IIIc (Table 2). The antiinflammatory effect of these compounds was only slightly lower compared to that of ortophen. Compound IIa – IIg also exhibited a weak antimicrobial effect (Table 2). The results of our experiments show good prospects in searching for new antiinflammatory agents among 2-substituted nicotinic acid amides.

TABLE 2. Antiinflammatory and Antimicrobial Activity of the Synthesized Compounds

Compound	Dose, mg/kg	Edema growth inhibition (after 4 h) in rats, % of control	MIC, μg/ml	
			St. aureus	*E. coli*
IIa	50	51.6 ± 2.7*	500	500
IIb	50	33.0 ± 0.3*	125	125
IIc	…	…	125	125
IId	50	48.4 ± 1.9*	…	…
IIe	50	38.0 ± 1.3*	250	500
IIf	…	…	1000	1000
IIg	…	…	500	1000
IIIa	50	38.0 ± 2.5*	…	…
IIIc	50	52.0 ± 3.1*	…	…
IIIe	50	35.8 ± 2.7*	…	…
Ortophen	10	61.3**	…	…
Nalidixic acid***			12.5 – 256	0.5 – 8
Oxolinic acid***			12.5 – 256	0.5 – 16
Flumequine***			12.5 – 256	0.5 – 16
Ethacridine lactate			500	2000

* $p < 0.05$.
** $p < 0.001$ relative to control.
*** Published data [10, 11].

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