STRUCTURE AND ANTIINFLAMMATORY ACTIVITY OF ISONICOTINIC AND NICOTINIC AMIDES

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It was suggested that butadion and indomethacin, the derivatives of anthranilic acid, are capable of competitively interacting with receptors or enzymatic systems involved in the synthesis, deposition, or release of histamine and serotonin from their depots in tissues. This conclusion was based on the fact that the distance between the carboxy or enolic group and the second reaction center (hydroxy or amino group) in molecules of these antiinflammatory drugs (having an acid character) falls within 0.455 – 0.480 nm for anthranilic acid and 0.584 – 0.667 nm for indomethacin, which corresponds to the distances between nitrogen atoms in the molecules of histamine (0.455 nm) and serotonin (0.580 nm) [1].

Recently, the class of registered antiinflammatory drugs was extended to include amizon or 1-methyl-4- (benzylaminocarbonyl)pyridinium iodide [2]. A significant antiinflammatory activity was also reported for some other arylamides of isonicotinic and nicotinic acids. The structure of the latter derivatives resembles that of serotonin. The nitrogen atom entering into the amide group of amizon may play the role of a weakly basic nitrogen atom of serotonin, while the nitrogen atom of the pyridine cycle of amizon may perform the function of a primary amino group.

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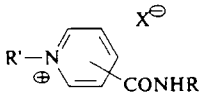
TABLE 1. Physicochemical Properties and Antiinflammatory Activity of Pyridinecarboxylic Amides



Compound	CONHR position	R	R'	X	M.p., °C	Dose, mg/kg	Edema inhibition, %
I (Amizon)	4	$PhCH_2$	CH_3	I	178 – 179 (A)	54.5	50.6 ± 3.4
II	3	$PhCH_2$	CH_3	I	162 – 163 (B)	44.0	34.2 ± 4.0
III	4	$PhCH_2$	C_2H_5	I	152 – 163 (B)	26.3	34.3 ± 3.5
IV	4	$PhCH_2$	$CH_2CH{=}CHC_6H_5$	Br	163 – 164 (B)	81.2	28.6 ± 1.3
V	4	$PhCH_2$	O	–	169 – 170 (C)	37.8	20.7 + 4.2
VI	3	$PhCH_2$	O	–	161 – 162 (C)	42.2	18.6 ± 3.7
VII	4	$PhCH_2$	–	–	83 – 85 (B)	31.3	38.1 ± 3.6
VIII	3	$PhCH_2$	–	–	73 – 74 (B)	51.5	30.9 ± 3.0
IX	4	Ph	H	Cl	223 – 225 (B)	98.0	18.5 ± 2.1
X	3	Ph	H	Cl	119 – 120 (B)	54.0	17.7 ± 4.4
XI	4	$CH_2CH{=}CH_2$	H	Cl	140 – 141 (B)	30.5	39.8 ± 5.5
XII	3	$CH_2CH{=}CH_2$	H	Cl	126 – 127 (B)	56.0	41.4 ± 3.6
XIII	4	$CH_2CH{=}CH_2$	CH_3	I	64 – 65 (B)	106.0	36.4 ± 2.7
XIV	4	$CH_2CH{=}CH_2$	O	–	36 – 37 (B)	83.0	28.6 ± 1.2
XV	4	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	Br	158 – 160 (D)	39.5	29.0 ± 4.2

Note. Solvents: (A) isopropyl alcohol; (B) ethanol – acetone; (C) acetone; (D) ethanol – benzene.

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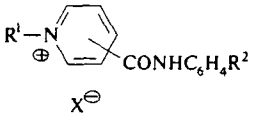
The distance between nitrogen atoms of the pyridine ring and amide group in isonicotinic amides amounts to 0.583 nm, which is precisely the distance between the corresponding nitrogen atoms in serotonin. In nicotinic acid amides, this distance (with an allowance for the possible rotation about the bond between carbon atoms of the carbonyl group and pyridine residue) varies within 0.437 – 0.505 nm. A comparison of the structures of pyridinecarboxylic arylamide derivatives and serotonin allows us to conclude that there is a qualitative relationship between the antiinflammatory activity of these compounds and their structure.

Arylamides of pyridinecarboxylic acids are synthesized by condensation of pyridinecarboxylic anhydride or N-oxide with the corresponding amines in the presence of triethylamine, which is achieved by prolonged heating in anhydrous benzene. Heating of the resulting pyridine bases with alkyl halides leads to the corresponding tertiary salts.

The proposed structures of the synthesized compounds are confirmed by IR spectroscopic data, and their purity is verified by thin-layer chromatography on Silufol plates eluted with the mixtures *n*-butanol – 5% ammonia – acetic acid – water (6 : 1 : 1 : 2) or ethanol – 25% ammonia (10 : 1).

As is seen from the data presented in Tables 1 and 2, all the isonicotinic arylamides studied suppress the development of kaolin-induced edema to a greater extent as compared to the corresponding isomers (cf. I vs. II, V vs. VI, VII vs. VIII, IX vs. X). A significant role belongs to the basicity of both nitrogen atoms. Tertiary salts are more effective as compared to the initial pyridine bases (I vs. VII, II vs. X). Conversion of the pyridine bases into N-oxides markedly decreased the anti-

TABLE 2. Physicochemical Properties and Antiinflammatory Activity of Pyridinecarboxylic Arylamides



Compound	Pyridine position substituted	R^1	R^2	X	M.p., °C	Dose, mg / kg	Edema inhibition, %
XVI	4	H	2-OCH_3	Cl	210 – 212 (C)	72.0	22.6 ± 1.9
XVII	3	H	2-OCH_3	Cl	188 – 190 (E)	115.0	32.3 ± 1.9
XVIII	4	O	2-OCH_3	–	184 – 185 (F)	58.5	8.6 ± 2.5
XIX	3	O	2-OCH_3	–	140 – 142 (D)	105.8	32.3 ± 6.8
XX	4	H	3-OCH_3	Cl	232 – 234 (C)	44.0	30.8 ± 1.9
XXI	3	H	3-OCH_3	Cl	185 – 187 (E)	200	40.1 ± 5.2
XXII	4	O	3-OCH_3	–	238 – 239 (F)	54.5	8.0 ± 3.9
XXIII	3	O	3-OCH_3	–	155 – 157 (F)	53.0	26.9 ± 3.8
XXIV	4	H	4-OCH_3	Cl	244 – 245 (C)	51.0	33.8 ± 1.8
XXV	3	H	4-OCH_3	Cl	188 – 189 (D)	49.5	39.6 ± 5.2
XXVI	4	O	4-OCH_3	–	238 – 240 (F)	53.0	38.7 ± 6.2
XXVII	3	O	4-OCH_3	–	195 – 196 (F)	52.0	39.9 ± 5.1
XXVIII	4	H	2-$COOCH_3$	Cl	194 – 195 (E)	38.2	18.6 ± 4.3
XXIX	3	H	2-$COOCH_3$	Cl	168 – 169 (E)	69.5	4.3 ± 2.5
XXX	4	O	2-$COOCH_3$	–	181 – 183 (F)	65.0	37.2 ± 4.7
XXXI	3	O	2-$COOCH_3$	–	179 – 180 (F)	84.0	36.6 ± 1.8
XXXII	3	H	3-$COOCH_3$	Cl	243 – 245 (F)	76.0	27.2 ± 5.3
XXXIII	4	O	3-$COOCH_3$	–	205 – 206 (F)	200	21.8 ± 5.1
XXXIV	3	O	3-$COOCH_3$	–	220 – 221 (F)	98.0	35.0 ± 3.8
XXXV	4	H	4-$COOCH_3$	Cl	238 – 240 (F)	113	36.8 ± 3.3
XXXVI	3	H	4-$COOCH_3$	Cl	178 – 180 (G)	67.5	30.5 ± 2.9
XXXVII	4	H	4-$COOC_2H_5$	Cl	144 – 145 (F)	128	15.8 ± 6.5
XXXVIII	3	H	4-$COOC_2H_5$	Cl	110 – 112 (G)	160	33.3 ± 2.9
XXXIX	4	O	4-$COOCH_3$	–	249 – 250 (H)	200	32.0 ± 5.7
XL	3	O	4-$COOCH_3$	–	178 – 180 (E)	76.0	10.6 ± 5.0
XLI	4	O	4-$COOC_2H_5$	–	246 – 247 (C)	139.5	31.1 ± 2.6
XLII	3	O	4-$COOC_2H_5$	–	210 – 212 (I)	200	44.6 ± 2.2

Note. Solvents: (C) acetone; (D) ethanol – benzene; (E) ethanol; (F) water; (G) ethanol – water; (H) DMF; (I) chloroform.

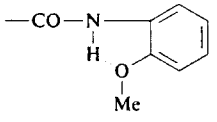
inflammatory activity (V vs. VII, VI vs. VIII). An increase in the size of substituent at the pyridine nitrogen atom in the tertiary salts also reduces the activity (I, III vs. IV). Substituting benzyl for the phenyl group leads to some increase in the electron density on the amide nitrogen atom, which may account for a significant increase in the protective action as compared to that of lower homologs (VII vs. IX, VIII vs. X).

The level of activity remains virtually unchanged on the passage from benzyl- to allylamides (VII and XI, VIII and XII). However, quaternized benzylamides exhibit a higher antiinflammatory activity (I vs. XIII, IV vs. XIV).

The introduction of polar substituents into the phenyl residue of pyridinecarboxylic arylamides noticeably complicates the structure – activity relationship.

In the series of methoxy derivatives, a higher activity is observed for the nicotinic amides. The change from pyridine bases to N-oxides leads to a decrease in activity of the *ortho* and *meta* derivatives, while not affecting the level of activity in the *para* isomers.

The series of methoxycarbonyl derivatives also exhibits a lower activity of the *ortho* isomers (XXVIII and XXIX) as compared to *meta* (XXXII) and *para* (XXXCVand XXXVI) derivatives. We may suggest that interaction with the receptor is weakened by the existence of an intramolecular hydrogen bond in the *ortho* derivatives. The formation of the intramolecular hydrogen bond can be judged by the IR spectra, where the absorption bands due to bending vibrations of NH groups in the *ortho* isomers is shifted by $10-15\ cm^{-1}$ toward longer wavelengths as compared to the corresponding bands in the IR spectra of the *meta* isomers.



However, this suggestion is not confirmed by the data for N- oxides (XXX vs. XXXI, XXXIII vs. XXXIV, XXXVII vs. XXXVIII).

Note that the level of activity of all the compounds studied is significantly lower compared to that of amizon (compound I) and only in a few cases approaches the activity of the pyridine base (compound VII).

EXPERIMENTAL CHEMICAL PART

The UV and IR spectra were recorded on the Specord and UR-20 spectrophotometers, respectively. The UV spectra exhibit the absorption bands at 266 – 280 and 206 – 220 nm. The IR spectra measured in KBr disks show the following peaks (ν_{max}, cm^{-1}): 1705 (CO stretching in carboalkoxy groups), 1670 – 1690 (amide I), 1540 – 1550 (NH bending). In the spectra of the *ortho* substituents, the latter band is displaced by $10-15\ cm^{-1}$ toward longer wavelengths. In addition, there is absorption at $3400-3500\ cm^{-1}$ attributed to intermolecular association due to the hydrogen bond formation.

Synthesis of arylamides of pyridinecarboxylic acids and their N-oxides. A mixture of 0.1 mole of a pyridinecarboxylic acid (or the corresponding N-oxide) and 30 ml thionyl chloride was boiled for 2 h, after which the excess thionyl chloride was distilled off in vacuum. The residue was triply purified by adding 10 ml anhydrous benzene and removing it by distillation in vacuum. Then the residue was mixed with 50 ml of anhydrous benzene and 20.2 g (0.2 mole) of triethylamine. To this suspension was added, with cooling to 5°C and stirring, 0.1 mole of the corresponding amine and the mixture was heated for 10 h. Finally, the reaction mixture was filtered, the filtrate evaporated, and the residue crystallized. Characteristics of the synthesized compounds are listed in Tables 1 and 2.

Synthesis of tertiary salts. A mixture of 0.01 mole pyridine base, 0.012 mole alkyl halide, and 100 ml anhydrous ether was boiled for 4 h and cooled on ice. The precipitate was filtered and crystallized. The properties of compounds are listed in Tables 1 and 2.

EXPERIMENTAL BIOLOGICAL PART

The antiinflammatory activity of the synthesized compounds was studied on mongrel rats with a model of edema induced by subplantar injections of 0.1 ml of a 10% kaolin suspension. Each compound was studied in a group of 7 animals injected intraperitoneally at a dose of 0.1 LD_{50} 30 min before kaolin introduction. The edema volume was determined plethysmometrically [3] in the peak of the inflammation reaction (4 h after kaolin injection). The antiinflammatory activity was characterized by the percentage edema inhibition [4]. The experimental data are presented in Tables 1 and 2.

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