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Synthesis and Anti-Inflammatory Activity of New Nicotinoyl Amides

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Abstract

The article presents the results of a study of the amination reaction of nicotinic acid chlorohydride with amines morpholine, cytisine, and 1-aminoadamantane, which are often used in the search and creation of drugs for respiratory and circulatory stimulants. The study was conducted to search for new biologically active compounds with anti-inflammatory activity. The synthesis of new aminoamides was carried out by the interaction of nicotinic acid with molecules of morpholine, cytisine, and adamantane in anhydrous ethanol. As a result of the conducted studies, new amides of nicotinic acid with high yields (90.7–93.1%) were obtained. The structures of the new compounds were determined using NMR ^{1}H and ^{13}C spectroscopy methods, as well as data from two-dimensional spectra of COSY (^{1}H-^{1}H), HMQC (^{1}H-^{13}C), HMBC (^{1}H-^{13}C) and mass spectrometry. The results of an experimental study of the anti-inflammatory activity of synthesized new amides are presented. The anti-inflammatory effect of nicotinic acid N-adamantylamide was established, other new amides were ineffective compared with ibuprofen ($p_2 < 0.05$).

1. Introduction

The synthesis of new potentially biologically active compounds and the study of their activity is an urgent task in pharmaceutical chemistry. One of the promising and frequently used substrates in the search for new biologically active substances are substituted amides of pyridine carboxylic acid [1–3]. Based on amides nicotinic acid, there are a significant number of drugs used in medical practice to treat various diseases. Thus, some effective drugs for the treatment of cardiovascular diseases, cancer, AIDS, etc. have been synthesized based on 3-hydroxynicotinic acid amides [3–5]. For example, the drug “Cordiamine” (nicotinic acid diethylamide) is currently successfully used in medical practice for the treatment of cardiovascular diseases [3, 6–7].

In this work, to search for new biologically active compounds with anti-inflammatory and other types of activity, we studied the amination reaction of nicotinic acid chlorohydride (1) with amines of various structures (morpholine, the alkaloid cytisine and 1-aminoadamantane). Cytisine is a well-known natural alkaloid used in medical practice as a respiratory and circulatory stimulant [8]. Adamantane derivatives have found practical application as drugs with antiviral (for example, rimantadine, amantadine) and antiparkinsonian activity. Adamantane is the ancestor of a homological series of a family of hydrocarbons with a diamond-like structure - diamantane, triamantane, etc. Currently, one of the directions of modern organic chemistry, the chemistry of organic polyhedra, has emerged and is developing based on adamantane chemistry [9–15].Polymer materials and various compositions with improved performance properties, thermostable lubricants, etc. are also being developed based on adamantane

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[16–21]. The chemical transformation of the pyridine fragment of nicotinic acid using an amide bond with known heterocyclic molecules – morpholine, cytisine, and adamantane, can lead to the appearance of "building blocks" structures with new types of biological activity.

2. Experimental part

^{1}H and ^{13}C NMR spectra were recorded on a «JNM-ECA Jeol 400» spectrometer (frequency 399.78 and 100.53 MHz, respectively) using DMSO-d_6 and $CDCl_3$ solvents. Chemical shifts were measured relative to signals from residual protons or carbon atoms of the deuterated solvent. Melting points were determined on an «SMP10» device. To record mass spectra, and determine molecular weights and elemental composition, a high-resolution mass spectrometer was used "DFS Thermo Scientific" with an ionizing voltage of 70 eV (evaporator temperature 270–300 °C). IR spectra were recorded on the device Fourier spectrometer "Avatar 360esp" in tablets with KBr. TLC analysis was performed on «Silufol UV-254» plates and developed with iodine vapor.

2.1. Synthetic procedures

General procedure for obtaining nicotinic acid amides (2-4).

0.31 M nicotinoyl chloride was dissolved in 30 ml of ethanol and 0.78 M triethylamine and 0.26 M amine (morpholine, cytisine, and 1-aminoadamant) were added. The reaction mixture was stirred for 10–11 h at a temperature of 70–75 °C, then cooled, filtered and evaporated on a rotary evaporator. The resulting mass was purified by chromatography on a flash column with silica gel (eluent CH_3Cl, CH_3Cl - EtOH, 100:1→10:1). Individual substances have been isolated in an oily as well as a solid powdery state.

N-Morpholinamide nicotinic acid (2) is isolated as a yellow thick oil, yield 93.1%. IR spectrum (KBr), ν, cm^{-1}: 1112, 1249 (C-O-C), 1522 (CH), 1609 (C=N), 1717 (-C=O), 2858 (-CH_2). NMR spectrum ^{1}H ($CDCl_3$), δ, ppm, (J, Hz): 3.35-3.78 (8H, m, H-2ax, 6ax, 2eq, 6eq, 3ax, 5ax, 3eq, 5eq), 7.21-7.24 (1H, m, H-13), 8.27-8.28 (1H, m, H-14), 8.55 (2H,s, H-12,10). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 42.67 (C-5), 47.78 (C-3), 64.53 (C-2), 66.75 (C-6), 123.59 (C-13), 131.20 (C-9), 135.18 (S-14), 147.90 (S-10), 150.88 (C-12), 167.74 (C-7). COSY NMR spectrum: H-13→H-14, H-13→H-12. HMQC NMR spectrum: H-13→C-13, H-14→C-14, H-12→C-12, H-10→C-10. NMR spectrum HMBC: H-3.5→C-2.6; H-13→C-9, C-12; H-14→C-10, C-12, C-7; H-10→C-13, C-9, C-14, C-12, C-7. Elemental analysis: Found, %: C 62.20; H 6.10; N 14.20. $C_{10}H_{12}N_2O_2$. Calculated, %: C 62.78; H 6.48; N 14.94. Mass spectrum, *m/z* (I, %): 192.21 (8.24), 108.2 (17.40), 94.1 (100.0), 75.0 (21.73), 44.3 (11.38). Found, *m/z*: 192.0 $[M]^+$. $C_{10}H_{12}N_2O_2$. Calculated, *m/z*: 192.2.

N-Cytisinamide nicotinic acid (3) is isolated in the form of a crystalline substance with a yellow tint, yield 91.4%, melting point 161–164 °C. IR spectrum (KBr), ν, cm^{-1}: 1525 (CH), 1610 (-C=N), 1715 (-C=O), 2856 (-CH_2). NMR spectrum ^{1}H ($CDCl_3$), δ, ppm, (J, Hz): 1.87-2.01 (3H, m, H-12ax, 12eq, 3), 2.25-2.29 (1H, m, H-2ax), 2.42-2.47 (1H, m, H-4ax), 2.97-3.07 (1H, m, H-11), 3.20-3.26 (1H, m, H-4eq), 3.55-4.15 (3H, m, H-2eq,13ax,13eq), 5.80-5.99 (1H, m, H-9), 6.42-6.44 (1H, m, H-7), 7.03-7.25 (3H, m, H-8,21,22), 8.01 (1H, br.s, H-20), 8.48 (1H, s, H-18). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 26.20 (C-12), 27.63 (C-3), 35.41 (C-11), 46.18 (C-2), 48.89 (C-13), 52.19 and 53.19 (C-4), 105.63 (C-9), 116.55 and 117.83 (C-7), 123.40 (C-21), 128.22 (C-17), 134.72 (C-22), 147.34 and 148.18 (C-10), 150.70 (C-20), 163.28 (C-6), 168.60 (C-14). COSY NMR spectrum: H-12ax,12eq→H-11, H-13ax-→H-13eq, H-9→H-8, H-7→H-8. HMQC NMR spectrum: H-13ax,13eq→C-13, H-11→C-11, H-9→C-9, H-7→C-7, H-8→C-8, H-18→C-18. HMBC NMR spectrum in C: H-12→C-3, C-11, C-13, C-10; H-2→C-17, C-22; H-9→C-11, C-10, C-7; H-7→C-9; H-8→C-10, C-6. Elemental analysis: Found, %: C 69.0; H 5.70; N 14.10. $C_{17}H_{17}N_3O_2$. Calculated, %: C 69.28; H 5.90; N 14.36. Mass spectrum, *m/z* (I, %): 295.34 (7.23), 148.14 (19.2), 102.13 (1.1), 96.15 (100.0), 77.11 (55.0). Found, *m/z*: 295.33 $[M]^+$. $C_{17}H_{17}N_3O_2$. Calculated, *m/z*: 295.34.

N-Adamantilamide nicotinic acid (4) is isolated in the form of a yellow powder, yield 90.7%, melting point 275-277 °C. IR spectrum (KBr), ν, cm^{-1}: 1525 (CH), 1605 (-C=N), 1720 (-C=O), 2857 (-CH_2), 3365 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, (J, Hz): 1.48 (6H, s, H-1 1ax, 11eq, 15ax, 15eq, 16ax, 16eq), 1.73 (6H, s, H-13ax, 13eq, 18ax, 18eq, 19ax, 19eq), 1.96 (3H, s, H-12, 4.17), 3.65 (1H, br.s, H-9), 7.21 (1H, s, H-3), 8.02 (1H, s, H-4), 8.52 (1H, s, H-2), 8.84 (1H, s, H-6). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 28.73 (C-12,14,17), 35.66 (C-13,18,19), 45.64 (C-11,15,16), 51.37 (C-10), 121.12 (C-3), 131.50 (C-5), 136.02 (C-4), 147.04 (C-2), 150.05 (C-6), 168.04 (C-7). COSY NMR spectrum: H-13ax,13eq,18ax,18eq→H-12,14. HMQC NMR spectrum: H-12,14,17→C-12,14,17, H-11ax, 11eq, 15ax, 15eq, 16ax, 16eq→C-11,15,16. NMR spectrum HMBC: H-11ax, 11eq, 15ax, 15eq, 16ax, 16eq→C-12,14,17, C-13,18,19, C-10. Elemental analysis: Found, %: C 74.40; H 7.70; N 10.85. $C_{16}H_{20}N_2O$. Calculated, %: C 74.54; H 8.02; N 11.01. Mass spectrum, *m/z* (I, %): 256.34 (11.27), 158.12 (17.2), 100.11 (7.1), 84.11(100.0), 56.13 (53.0). Found, *m/z*: 256.33 $[M]^+$. $C_{16}H_{20}N_2O$. Calculated, *m/z*: 256.34.

2.2. Study of the anti-inflammatory activity of new compounds

The experimental model for the study of anti-inflammatory activity was chosen by the guidelines for the experimental (preclinical) study of new pharmacological substances by A.N. Mironova (Moscow, 2012). Laboratory animals have previously undergone the quarantine procedure. The maintenance of laboratory rats was carried out based on the KazNMU vivarium by GOST 33215-2014 "Guidelines for the maintenance and care of laboratory animals Rules for the equipment of premises and organization of procedures". The animals were kept in standard controlled vivarium conditions in specialized cages in compliance with all requirements. Before the start of the experiment, free constant access to food and water was provided, and the natural light regime was observed. The distribution of laboratory animals into groups and series was carried out by ranking by weight. Colored labels were used for marking.

The study of anti-inflammatory activity was carried out by the method of formalin paw edema in non-linear white rats. An acute inflammatory reaction was reproduced by subplantar (under the sole or plantar aponeurosis) injection of 0.1 ml of 2% formaldehyde solution into the right paw using a conventional insulin syringe. The process of inflammation development is accompanied by hyperemia and an increase in paw volume due to an exudative reaction. Paw volume was measured before and after formaldehyde injection, and the difference between these two volumes was used as an indicator of inflammation. The severity of the inflammatory reaction was assessed 30 min, 1, 2, and 3 hours after the onset of inflammation by changing the volume (ml) of the paw (oncometrically).

The test substances were injected into the stomach through a probe 1 h before the injection of formalin at a dose of 100 mg/kg in the form of a 2% aqueous alcohol solution. At the same time, the access of laboratory animals to food was limited to a few hours before oral administration. The anti-inflammatory effect of the studied compounds was assessed by reducing edema, expressed as a percentage of the control. A solvent of the tested compounds, a 35% aqueous alcohol solution, was used as a negative control, and ibuprofen at a dose of 100 mg/kg was used as a positive control [22–24].

Ibuprofen was chosen as a control drug because it is a clinically effective and safe anti-inflammatory drug in the form of an easy-to-dose oral suspension. The percentage of suppression of inflammatory edema in animals of the experimental and control groups was calculated using the formula described by Newbold [25]:

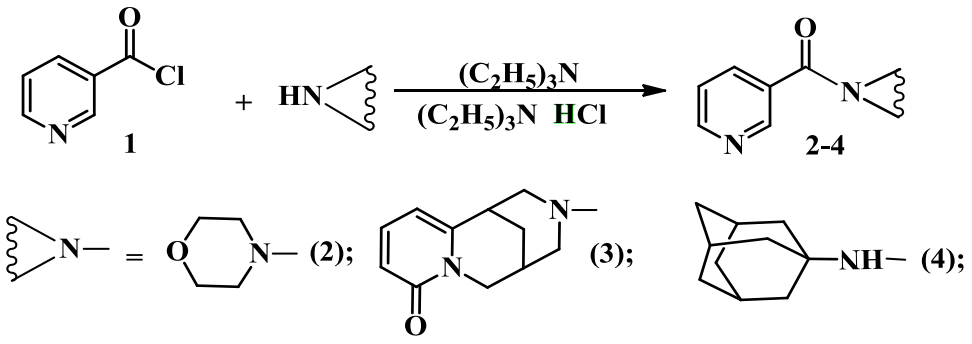
$$\text{Percent inhibition} = 100 \times \left(1 - \frac{a-x}{b-y}\right)$$

where a = the average volume of the hind paw of the test group – positive control of animals after injection of formalin, b = the average volume of the hind paw of animals of negative control after injection of formalin, x = the average volume of the hind paw of animals of the test group – positive control before injection of formalin, y – the average volume of the hind paw of animals of negative control before injection of formalin.

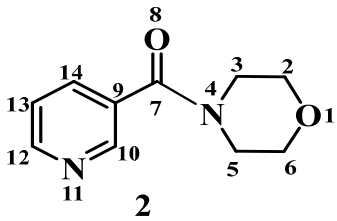
Statistical processing of experimental data was carried out using the SPSS 16.0 program using parametric statistics methods (Student's criterion) with the calculation of the arithmetic mean and standard error (M±m) [26–28]. The value of $p<0.05$ was considered statistically significant.

3. Results and discussion

Reactions for the synthesis of nicotinic acid amides were carried out in ethanol by stirring and heating the reaction mixture. The yields of products (2-4) were 90.7–93.1%.



The structure of the synthesized compounds (2-4) was confirmed by IR, ^{1}H, and ^{13}C NMR spectroscopy data, as well as data from two-dimensional spectra COSY (^{1}H - ^{1}H), HMQC (^{1}H-^{13}C) and HMBC (^{1}H-^{13}C). Thus, the ^{1}H NMR spectrum of compound (2) is characterized by the presence of an eight-proton multiplet signal of the protons of the morpholine ring H-2ax, 6ax, 2eq, 6eq, 3ax, 5ax, 3eq, 5eq at 3.35–3.78 ppm. Pyridine protons appeared as one-proton multiplets at 7.21-7.24 (H-13) and 8.27-8.28 (H-14) and a two-proton singlet at 8.55 (H-12, 10) ppm.



2

^{13}C NMR spectrum of compound (2), signals of carbon atoms of the morpholine ring appeared at 42.67 (C-5), 47.78 (C-3), 64.53 (C-2) and 66.75 (C-6) ppm. The carbon atoms of the pyridine fragment were recorded at 123.59 (C-13), 131.20 (C-9), 135.18 (C-14), 147.90 (C-10) and 150.88 (C-12) ppm. The C-7 carbonyl carbon atom was detected at 167.74 ppm.

The structure of compound (2) was also confirmed by the methods of two-dimensional NMR spectroscopy COSY (^{1}H-^{1}H), HMQC (^{1}H-^{13}C) and HMBC (^{1}H-^{13}C), which makes it possible to establish spin-spin interactions of homo- and heteronuclear nature. The observed NMR correlations of COSY (^{1}H-^{1}H, HMQC (^{1}H-^{13}C) and HMBC (^{1}H-^{13}C) in the molecule are presented in Fig. 1.

In the spectra ^{1}H-^{1}H COSY compounds, spin-spin correlations are observed through three bonds of protons of neighboring methine-methine groups H^{13}-H^{14} (7.26, 7.68 and 7.68, 7.26), H^{13}-H^{12} (7.26, 8.53 and 8.53, 7.26) ppm. Heteronuclear interactions of protons with carbon atoms through a single bond were established using ^{1}H-^{13}C spectroscopy HMQC for the following pairs present in the compound: H^{13}-C^{13} (7.24, 123.79), H^{14}-C^{14} (7.64, 135.31), H^{12}-C^{12} (8.54, 151.10), H^{10}-C^{10} (8.53, 147.75) ppm.

Heteronuclear interactions of protons with carbon atoms through two or more bonds were established using ^{1}H-^{13}C spectroscopy HMBC for the following pairs present in the compound: $H^{3.5}$-$C^{2.6}$ (3.77, 64.46); H^{13}-C^{9} (7.25, 131.25), H^{13}-C^{12} (7.25, 150.79); H^{14}-C^{10} (7.65, 147.94), H^{14}-C^{12} (7.65, 150.96), H^{14}-C^{7} (7.65, 168.08); H^{10}-C^{13} (8.55, 123.61), H^{10}-C^{9} (8.55, 131.25), H^{10}-C^{14} (8.55, 135.51), H^{10}-C^{12} (8.55, 150.96), H^{10}-C^{7} (8.55, 168.02) ppm.

Formalin-induced rat paw edema is a widely used laboratory model for determining the acute phase of inflammation, suitable for screening anti-inflammatory drugs. Experimental data showed (Table) that intraplantation administration of formalin into the right hind paw of rats triggered the vascular phase of inflammation, which caused an increase in permeability and an increase in paw volume, indicating edema, reaching a maximum after 2 h in the negative control group.

The degree of inhibition of compound (3) had low values and ranged from 4.55% to 13.51%, paw swelling decreased slightly or persisted by the 3 h. As can be seen, a significant change with the greatest increase in paw volume occurred in compound (2) with a peak occurring in the 2 h of the experiment. In groups of compounds (2) and (3), the peak increase in paw volume occurred in the 3 h of the experiment.

Based on the data obtained, the following can be noted:

- an anti-inflammatory effect was noted in compound (4), where the inhibitory effect was 37.5%;
- a negative effect was observed in compound (2) (-138.10%), which indicates stimulation of the inflammation process;
- no effect on inflammation was found for compound (3).

Thus, compared with ibuprofen at a dosage of 100 mg/kg, these compounds were ineffective (p_2<0.05), with the exception of compound (4), which had some anti-inflammatory effect 3 h after administration. It was found that sample 2 complicated the symptoms of inflammation, an increase in edema was noted by the 3 h of the experiment and its percentage of inhibition was equal to negative values.

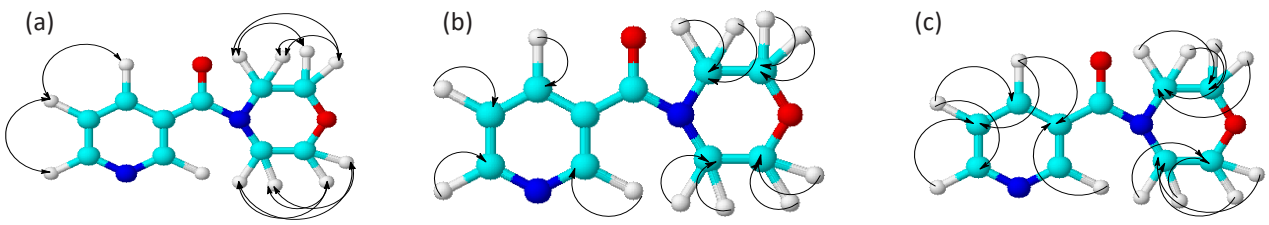


Fig. 1. Scheme of correlations in the spectra of COSY (a) and HMQC (b) and HMBC (c) of compound (2).

Table. Change in the volume of the hind paws of rats in the experimental and control groups

Test comp.	Dosage, mg/kg	Changes in the average paw volume of rats in experimental and control groups					Increase in foot volume relative to the initial value		Inhibit. percent. (%)
		Before injection	30 min	1 h	2 h	3 h	ml	%	
Negative control (solvent)	-	1.00±0.03	1.35±0.12	1.37±0.12	1.38±0.21	1.37±0.05	0.37	37.00	-
Positive control (ibuprofen)	100	1.1±0.03	1.38±0.9 p_1>0.05	1.37±0.01 p_1>0.05	1.40±0.06 p_1>0.05	1.31±0.03 p_1<0.05	0.21	19.09	43.24
2	100	1.02±0.06	1.36±0.11 p_1>0.05 p_2>0.05	1.45±0.08 p_1<0.05 p_2<0.05	1.38±0.07 p_1>0.05 p_2<0.05	1.52±0.17 p_1<0.05 p_2>0.05	0.5	49.02	-138.10
3	100	1.09±0.08	1.25±0.06 p_1>0.05 p_2>0.05	1.11±0.05 p_1<0.05 p_2<0.05	1.23±0.1 p_1>0.05 p_2>0.05	1.41±0.07 p_1>0.05 p_2>0.05	0.32	29.36	13.51
4	100	1.01±0.05	1.20±0.1 p_1>0.05 p_2>0.05	1.33±0.11 p_1>0.05 p_2>0.05	1.30±0.1 p_1>0.05 p_2>0.05	1.21±0.1 p_1<0.05 p_2>0.05	0.2	19.80	37.50

Note: P_1 – correlation coefficient compared with negative control; P_2 – correlation coefficient compared with positive control.

3. Conclusions

Thus, the reactions of amination of the nicotinic acid chloride with amines morpholine, cytisine, and 1-aminoadamantane, which are important synthons of many drugs, are considered. As a result of the conducted studies, new amides of nicotinic acid with high yields (90.7–93.1%) were obtained. The results of an experimental study of the anti-inflammatory activity of synthesized amides are presented. The anti-inflammatory effect of nicotinic acid N-adamantylamide was established, and other new amides, compared with ibuprofen at a dosage of 100 mg/kg, proved ineffective (p_2<0.05). The obtained compounds are of interest for further study of their biological properties.

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