SYNTHESIS PROPERTIES AND BIOLOGICAL ACTIVITY OF 2-AMINO (ALKYLAMINO)-5-CARBETHOXY-6-METHYLNICOTINONITRILES

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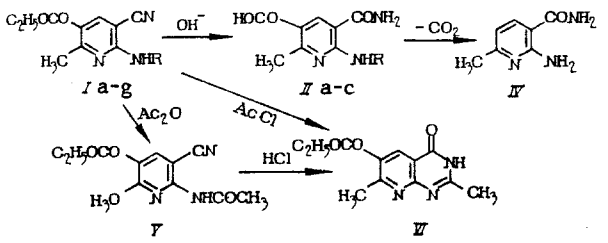
It was shown in the previously published papers that 2-aryl-aminonicotinic acids exhibit anti-inflammatory and analgetic activity [9], while amides and nitriles of these acids have anti-convulsant activity [7]. It was of interest to clarify whether these types of activity are characteristic for amides and nitriles of 2-amino and 2- alkylaminonicotinic acids containing a carboxylic and carbethoxy group in the pyridine ring. For this purpose, we carried out a synthesis of 2-amino- and 2-alkylamino-5-carbethoxy-6-methylnicotinonitriles (Ia-g, Table 1).



R=H (Ia, IIa, IIIa), $C_6H_5CH_2$(Ib, IIb, IIIb), CH_3(Ic, IIc), tert C_4H_9(Id), iso-C_5H_{11}(Ie), $HOCH_2CH_2$(If), cyclo-C_6H_{11} (Ig)

The investigations showed that because of the electron-acceptor properties of the nitrogen atom in the pyridine ring, the carbethoxy and nitrile groups, the chlorine atom in 5-carbethoxy-6-methyl-2-chloronicotinonitrile has a high mobility and is readily substituted by amino and alkylamino groups. Thus compounds Ia-g are formed in good yields.

In the reactions of compounds Ia-c with an alcoholic solution of potassium hydroxide, saponification of both the ester and the nitrile groups takes place, and 2-amino (alkylamino)-5-carboxy-6-methylnicotinamides (IIa-c) are formed, which by the action of an aqueous solution of sodium hydroxide are converted into the sodium salts of the corresponding acids (IIIa, b).

Boiling of nitrile in an excess of acetic anhydride gives 2-acetamido-5-carbethoxy-6-methylnicotinonitrile (V), which by the action of hydrogen chloride undergoes cyclization into 6-carbethoxy-2,7-dimethyl-3,4-dihydro-4-oxopyrido[2,3-d]-dipyrimidine (VI). The same compound is obtained by boiling nitrile in an excess of acetyl chloride.

Using acid IIa as an example, the possibility was shown of obtaining amide IV by its thermal decarboxylation. The structure of the obtained compounds was confirmed by the IR and PMR spectroscopy data.

EXPERIMENTAL (CHEMICAL)

The IR spectra were recorded on a UR-20 spectrophotometer in mineral oil mulls, the PMR spectra were obtained on a RYa-2310 spectrometer (60 MHz) using HMDS as internal standard and DMSO-D_6 as solvent. The TLC was carried out on Silufol UV-254 plates in a benzene—chloroform—acetone, 10:9:1, system for compounds I, V, and in ethyl acetate for compounds II, IV, VI. The absorption parameters of the OH group in the IR spectra of compounds If, IIa-c were obtained for their solutions in CCl_4. The electronic analysis data correspond to the calculated values.

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	Mp, °C	Yield, %	R_f	Empirical formula
Ia	195—196	64	0,20	$C_{10}H_{11}N_3O_2$
Ib	133—134	50	0,67	$C_{17}H_{17}N_3O_2$
Ic	122—123	67	0,54	$C_{11}H_{13}N_3O_2$
Id	113—114	68	0,81	$C_{14}H_{19}N_3O_2$
Ie	89—90	59	0,71	$C_{15}H_{21}N_3O_2$
If	120—121	52	0,19	$C_{12}H_{15}N_3O_3$
Ig	111—112	83	0,72	$C_{16}H_{21}N_3O_2$
IIa	224—246	67	0,75	$C_8H_9N_3O_3$
IIb	256—257	58	0,55	$C_{15}H_{15}N_3O_3$
IIc	265—267	70	0,73	$C_9H_{11}N_3O_3$
IV	198—201	22	0,17	$C_7H_9N_3O$
V	121—122	61*	0,72	$C_{12}H_{13}N_3O_3$
VI	305—307	24*	0,55	$C_{12}H_{13}N_3O_3$

*Yields are given for compounds V, VI obtained by method A.

TABLE 2. Acute Toxicity and Anti-Aggregation Activity of Compounds IIIa, b

Compound	Acute toxicity (LD_{50}, mg/kg)	Concentration of compound, mg/ml	Inhibition of aggregation of thrombocytes, %
IIIa	1675 (1319—2136)	4,19	18,3
III	648 (615—683)	1,62	17,1
Papaverine hydrochloride	31 (26,3—36,6)	0,08	27,3

Note. In brackets – fluctuation limits.

2-Amino- and 2-Alkylamino-5-carbethoxy-6-methylnicotinonitriles (Ia-g). A solution of 2.25 g (10 mmoles) of 5-carbethoxy-6-methyl-2-chloronicotinonitrile and 15 mmoles of alkylamine (in the case of ammonia – a fivefold excess) was boiled in 25 ml of ethanol for 4-6 h. The precipitate that separated out after cooling was filtered off and crystallized from a benzene–hexane mixture (compounds If, g) or from ethanol (the remaining compounds).

Amides of 2-Amino- and 2-Alkylamino-5-carboxy-6-methylnicotinic acid (IIa-c). A solution of 10 mmoles of compound Ia-c and 2.8 g (50 mmoles) of KOH in 20 ml of ethanol was boiled for 5-10 min, and allowed to stand for 15 h at room temperature. The mixture was poured into 100 ml of water, neutralized with 50% acetic acid, and the precipitate was filtered. The product was crystallized from butanol (IIa), a DMFA–H_2O mixture (IIb), and dioxane (IIc).

Sodium salts of amides of 2-amino- and 2-alkylamino-5-carboxy-6-methylnicotinic acids (IIIa, b) were obtained by dissolving 10 mmoles of the corresponding acid in 20 ml of an aqueous solution of 0.4 g (10 mmoles) of NaOH. The solution was filtered and evaporated.

2-Acetamide-5-carbethoxy-6-methylnicotinonitrile (V). A. A solution of 2.05 g (10 mmoles) of compound Ia was boiled for 5 h in an excess of acetic anhydride, then poured into 50 ml of water and neutralized with a 20% solution of NaOH. The oil that separated out was dissolved in benzene and passed through a column of Al_2O_3. The benzene was evaporated and the residue was crystallized from a benzene–hexane (1:4) mixture.

B. A 2.25 g portion (10 mmoles) of 5-carbethoxy-6-methyl-2-chloronicotinonitrile was heated at 120-140°C for 2 h with 0.59 g (10 mmoles) of acetamide. Then, 50 ml of water was added, and the mixture was neutralized with $NaHCO_3$. The precipitate was filtered, dried, and crystallized. Yield, 1.2 g (48%), mp 120-122°C. A mixed sample with the compound obtained in the preceding experiment did not give a depression of the melting point.

6-Carbethoxy-2,7-dimethyl-3,4-dihydro-4-oxopyrido[2,3-d]pyrimidine (V). A. Dry gaseous HCl was passed for 1.5 h through a solution of 2.46 g (10 mmoles) of compound V in dry

benzene. The benzene was evaporated, and the residue was treated with a 10% solution of sodium acetate, filtered, and crystallized from ethanol.

B. A solution of 2.05 g (10 mmoles) of compound Ia was boiled in excess of acetyl chloride for 8 h. It was then poured into 50 ml of water and neutralized with a 20% NaOH solution. The precipitate was filtered off and crystallized. Yield, 0.52 g (21%), mp 305-307°. A mixed sample with the compound obtained in the preceding experiment did not give a depression of the melting point.

2-Amino-6-methylnicotinamide (IV). A 1.95 g portion (10 mmoles) of compound IIa was heated for 10 min at about 260°C. The product was extracted with xylene and crystallized from a xylene hexane (2:1) mixture.

EXPERIMENTAL (PHARMACOLOGICAL)

Compounds Ia-g were tested for anticonvulsant, anti-inflammatory activity, and compound If also for analgetic activity. The biological action of compounds IIIa, b was evaluated from the data on the investigation of the acute toxicity and anti-aggregation activity with respect to thrombocytes. These compounds were also tested for the anticonvulsant activity. The anticonvulsant activity was determined from the maximal electrical shock test [5] on white mice. The anti-inflammatory action was studied on white rats on the model of an acute inflammatory edema induced by the introduction of a carrageenin solution into a posterior paw of a rat. The volume of the inflammed paw was measured oncometrically 4 h after the administration of the phlogogenic agent [6].

The analgetic activity was studied on mice according to the "hot plate" test [8].

The acute toxicity was determined on white mice with an intravenous method of administration [1]. The anti-aggregation activity was studied by the Born photometric method [4] with respect to the plasma thrombocytes of dogs, and was evaluated as percentage of decrease in the optical density. The aggregation of the thrombocytes was induced by ADP (0.05 mg per 1 ml of plasma). The known drug, papaverine hydrochloride having anti-aggregation activity, was used as standard [3]. All the compounds were tested in concentrations, which when calculated per weight of the animal, comprised $^1/_{10}$ LD_{50}.

As a result of the investigations it was found that compounds Ia-g and IIIa, b in a dose of 300 mg/kg do not have anticonvulsant activity. A significant anti-inflammatory activity was found only in compound If, which in a dose of 50 mg/kg, decreases the edema of an inflammed paw by 38.4%, but is inferior in intensity of action to the standard of the anti-inflammatory activity – orthophen. Analgetic activity was not detected in this compound.

Examination of the acute toxicity showed that the mean lethal doses (LD_{50}) of compounds IIIa, b differ quite strongly – from 648 (IIIb) to 1675 mg/kg (IIIa), but both of these compounds are recognized as slightly toxic [2]. In the study of the aggregation properties of thrombocytes it was found that they both exhibit anti-aggregation activity, suppressing the aggregation by 17-18% (Table 2). Considering that these compounds have a much lower toxicity than papaverine hydrochloride, a further search for the aggregation inhibitors among the derivatives of the sodium salts of 2-alkylamino-5-carboxynicotinamides may be promising.

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SYNTHESIS OF ACYLTHIO DERIVATIVES OF PENTA-O-ACETYLGLYCYRRHIZIC ACID. ANTIFLAMMATORY AND ANTIULCEROUS PROPERTIES

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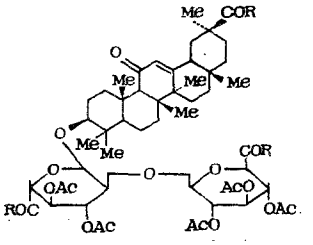
In continuation of our work on the transformation of the triterpene glycoside glycyrrhizic acid (GA) [1, 2, 5, 6] we have carried out conversions of the trichloride of penta-O-acetylglycyrrhizic acid (I) [6] with the purpose of synthesizing acylthioureas (III) and acetylthiosemicarbazides (IV), which are of interest as novel antiinflammatory agents and also as polydentate ligands for preparing complexes with bioactive metals.

As starting compound for the synthesis we used the triacylisothiocyanate of penta-O-acetylglycyrrhizic acid (II), which was obtained in a yield of 65% by refluxing trichloride I with freshly melted KSCN in acetonitrile for 1 h.

Reactions of triacylisothiocyanate II with primary amines and aniline proceed in dry chloroform in the presence of an excess of amine at room temperature with formation of corresponding triacylthioureas III in yields of 40-55%.

Compounds II react with suitable hydrazines V (equivalent amount or a slight excess) on refluxing in dichloromethane. The yields of substituted acylthiosemicarbazides IV were 45-71%.



I, II, III a-d, *IV* a-f

R=Cl(I), NCS(II), $NHCSNH(CH_2)_5CH_3$(IIIa),

$NHCSNHC_6H_{11}$-cyclo (IIIb), $NHCSNHC_6H_5$ (IIIc),

$NHCSNHCH_2C_6H_5$ (IIId), $NHCSNHNH_2$ (IVa),

$NHCSNHNHC_6H_5$ (IVb), $NHCSNHNHC_6H_4CH_3$-*o* (IVc),

$NHCSNHNHSO_2C_6H_4Me$-p (IVd), $NHCSNHNHCH_2C_6H_5$ (IVe),

$NHCSNHNHC_6H_3(NO_2)_2$-3,5 (IVf).

The structures of the prepared acylthio derivatives were confirmed by IR and UV spectra, and also by elemental analyses. Thus, IR spectra of compounds III and IV do not contain an absorption maximum of the CNS group (2050-1950 cm^{-1}), which is characteristic of starting acylisothiocyanate II, and have bands that are characteristic of NH and CONH groups (3400-3200 and 1570-1510 cm^{-1}). Intensive absorption maxima of the aglycon carbonyl group and the acetyl groups ($\nu_{C=O}$; 1660 and 1760–1750 cm^{-1}) are retained in the spectra of compounds III and IV. IR spectra of acylthioureas IIIc, d and semicarbazides IVb-e have characteristic absorption maxima of the aromatic groups (1620-1600 cm^{-1}).

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