to speed up the onset of corazole convulsions under the influence of compound (IX), and the capacity of diester (VIII) to considerably increase the locomotive activity and to improve the preservation of CRPA in rats. Further examination of the distinct antagonism of diester (XIII) to corazole is required, which makes it possible to assume that this compound has anticonvulsive properties, possibly as a result of antagonism to Glu. We may assume that the differences in the pharmacological properties of diesters (VIII-XIII) are connected with the different rate of generating Glu from them under influence of blood enzymes.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF AMIDES AND NITRILES OF 2-ARYLAMINO-5-CARBOXY(CARBETHOXY)-6-METHYLNICOTINIC ACIDS AND 1-ARYL-6-CARBETHOXY-7-METHYL-4-OXO-1,4-DIHYDROPYRIDO[2,3-d]PYRIMIDINES

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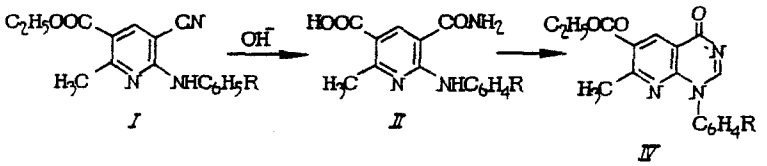
Amides and nitriles of 2-arylaminonicotinic acids have anticonvulsive properties [8] and are also used as starting compounds for the preparation of pyrido[2,3-d]pyrimidines [7]. With the aim of further search for biologically active compounds of this series we have carried out the synthesis of 2-arylamino-5-carbethoxy-6-methylnicotinonitriles (Ia-f, Table 1) and 2-arylamino-5-carboxy-6-methylnicotinamides (IIa-d).



R=2′-MeO (Ia, IIa, IIIa, IVa), 2′-Me (Ib, IIb, IIIb, IVb), 3′-Me (Ic, IIc, IIIc, IVc), 4′-Br (Id IId.IIId.IVd), 4′-Me (Ie), 3′-Br (If).

Nitriles Ia-d were prepared in high yields by heating 5-carbethoxy-6-methyl-2-chloronicotinonitrile with aryl amines in ethanol.

Investigation showed that both the ester group and the nitrile group in compounds Ia-d are easily saponified with an alcoholic potassium hydroxide solution under mild conditions and that in yields of 76-88% 2-arylamino-5-carboxy-6-methylnicotinamides IIa-d are formed. Reaction of amides IIa-d with sodium hydroxide yields the sodium salts of 2-arylamino-5-carboxy-6-methylnicotinamides (IIIa-d).

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TABLE 1. Characteristics of the Prepared Compounds

Compound	mp, °C	Yield, %	R_f	Empirical formula
Ia	181—182	66	0,77	$C_{17}H_{17}N_3O_3$
Ib	109—110	81	0,75	$C_{17}H_{17}N_3O_2$
Ic	126—127	86	0,73	$C_{17}H_{17}N_3O_2$
Id	174—175	78	0,72	$C_{16}H_{14}BrN_3O_2$
Ie	149—150	73	0,77	$C_{17}H_{17}N_3O_2$
If	193—194	83	0,70	$C_{16}H_{14}BrN_3O_2$
IIa	294—295	80	0,63	$C_{15}H_{15}N_3O_4$
IIb	248—250	88	0,61	$C_{15}H_{15}N_3O_3$
IIc	269—270	87	0,57	$C_{15}H_{15}N_3O_3$
IId	297—298	76	0,85	$C_{14}H_{12}BrN_3O_3$
IVa	188—189	56	0,88	$C_{18}H_{17}N_3O_4$
IVb	163—165	47	0,58	$C_{18}H_{17}N_3O_3$
IVc	252—253	45	0,73	$C_{18}H_{17}N_3O_3$
IVd	247—248	52	0,75	$C_{17}H_{14}BrN_3O_3$

Note. Solvent for compounds I benzene—chloroform—acetone 10:9:1, for compounds II and IV ethyl acetate.

TABLE 2. Acute Toxicity and Antiaggregatory Activity of Compounds IIIa-d

Compound	Acute toxicity, LD_{50}, mg/kg	Concentration of the compound, mg/ml	Inhibition of thrombocyte aggregation, %
IIIa	506 (465—550)	1,27	9,6
IIIb	550 (516—588)	1,38	26,3
IIIc	472 (415—537)	1,18	9,6
IIId	448 (377—532)	1,12	16,6
Papaverine hydrochloride	31 (26,3—36,6)	0,08	27,3

Note. In parentheses the limits of variation.

It is known that 2-arylaminonicotinamides by reaction with ethyl orthoformate are converted to 1-aryl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines, which are of interest as biologically active compounds [10]. We have carried out experiments to extend that reaction to compounds that contain a carboxyl group. It was found that on prolonged heating of amides IIa-d with an excess of ethyl orthoformate, in addition to the formation of the pyrimidine ring, esterification of the carboxyl group occurs and that 1-aryl-6-carbethoxy-7-methyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines (IVa-d) are formed.

The structures of the prepared compounds were confirmed by IR and PMR spectral data.

EXPERIMENTAL (CHEMICAL)

IR spectra were taken on a UR-20 spectrometer from dispersions in paraffin oil. PMR spectra were recorded on an RYa-2310 (60 MHz) spectrometer, internal standard HMDS, solvent DMSO-d_6. TLC was carried out on Silufol UV-254 plates. Data of elemental analyses were in agreement with calculated values.

2-Arylamino-5-carbethoxy-6-methylnicotinonitriles (Ia-f). A solution of 2.25 g (10 mmole) of 5-carbethoxy-6-methyl-2-chloronicotinonitrile and 15 mmole of aryl amine in 25 ml of ethanol is refluxed for 4-6 h. The precipitate formed after cooling is filtered off and crystallized from aqueous ethanol. IR spectra, ν_{max}, cm^{-1}: 1690-1710 (C=O, $COOC_2H_5$), 2230-2250 (CN), 3340-3400 (NH). PMR spectra, δ, ppm: 9.28-9.55 s (1H, NH), 8.18-8.42 s) (1H, C_4), 6.98-7.48 m (4H, arom. protons), 4.15-4.22 q (2H, CH_2 of $COOC_2H_5$), 2.42-2.65 s (3H, CH_3), 2.12-2.25 s (3H, CH_3 of R), 1.28-1.35 (3H, CH_3 of $COOC_2H_5$).

2-Arylamino-5-carboxy-6-methylnicotinamides (IIa-d). A solution of 10 mmole of Ia-d and 2.8 g (50 mmole) of KOH in 20 ml of ethanol is refluxed for 10 min and stored at room temperature for 20 h. The mixture is poured out in 50 ml of water and neutralized with 50% acetic acid. The precipitate is filtered off and crystallized from DMF—H_2O. IR spectra, ν_{max}, cm^{-1}: 3560-3580 (OH, in CCl_4), 3180-3220 and 3400-3420 (NH_2, $CONH_2$), 3340-3380 (NH), 1635-1650 (C=O, $CONH_2$), 1660-1675 (C=O, COOH). PMR spectra, δ, ppm: 10.05-11.32 s (1H, OH), 8.42-8.58 s (1H, NH), 7.85-8.32 s (1H, C_4), 7.38-7.78 br. s (2H, $CONH_2$), 6.93-7.15 m (4H, arom. protons), 2.52-2.59 s (3H, CH_3), 2.18-2.32 s (3H, CH_3 of R).

Sodium Salts of 2-Arylamino-5-carboxy-6-methylnicotinamides (IIIa-d). To a solution of 0.4 g (10 mmole) of NaOH in 20 ml of water is added the equivalent amount of amide IIa-d; the mixture is heated until a solution is obtained, filtered, and the water is evaporated.

1-Aryl-6-carbethoxy-7-methyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines (IVa-d). A solution of 10 mmole of IIa-d in 75 ml of ethyl orthoformate is refluxed for 36 h. After 12, 20, and 28 h 10-15 ml of the solvent is distilled off and the same amount of ethyl orthoformate is added. Then the volatile material is distilled off until there remains 20-25 ml of solution and the mixture is cooled. The precipitate is filtered off, dried, and crystallized from aqueous ethanol. IR spectra, ν_{max}, cm^{-1}: 1660-1680 (C=O, C_4), 1690-1710 (C=O, $COOC_2H_5$). PMR spectra, δ, ppm: 8.72-9.25 s (1H, C_2), 7.95-8.68 s (1H, C_5), 7.05-7.52 m (4H,

arom. protons), 4.22-4.32 q (2H, CH_2 of $COOC_2H_5$), 2.62-2.82 s (3H, CH_3), 2.02-2.48 s (3H, CH_3 of R), 1.32-1.38 t (3H, CH_3 of $COOC_2H_5$).

EXPERIMENTAL (PHARMACOLOGICAL)

Compounds Ia-f were tested for anti-inflammatory and anticonvulsive, and compound Ib also for analgesic activities. The biological activity of compounds IIIa-d were determined by data of acute toxicity and antiaggregatory activity with respect to thrombocytes. These compounds were also tested for anticonvulsive activity. The anticonvulsive activity was determined with the test of maximum electroschock [5] with white mice of both sexes weighing 22-25 g. The anti-inflammatory activity was studied in white rats weighing 160-220 g with the model of inflammatory edema evoked by subplantar administration of 0.1 ml of a 1% aqueous carrageenan solution in the hind paw of the rats. The volume of the inflamed foot was measured oncometrically 4 h after administration of the phlogogenic agent [6].

The analgesic activity was studied in mice weighing 22-24 g with the "hot plate" test [9]. The effect was measured by the latent time of the defensive effect. As reference for the anti-inflammatory activity we used ortofen and for the analgesic activity amidopyrine. All the compounds under investigation were administered intraperitoneally at a dose of 50 mg/kg, ortofen at 10 mg/kg. and amidopyrine at 100 mg/kg 30 min before determining the analgesic activity, and in the inflammation experiment 1 h before administering carrageenan. The control animals were given the same volume of 2% starch gel.

The acute toxicity was determined in white mice of both sexes weighing 16-20 g by intravenous administration [1]. The antiaggregatory activity was studied with Born's photometric method [4] with respect to thrombocytes of the plasm of dog's blood and expressed on a percentage basis of the decrease in optical density. Aggregation of thrombocytes was brought about by ADP at a dose of 0.05 mg per ml of plasm. As reference we used a known medicinal preparation having antiaggregatory activity, papaverine hydrochloride [3]. All the compounds were tested at concentrations that, calculated on the weight of the animals, were 1/10 LD_{50}.

As a result of the investigation it has been found that at a dose of 300 mg/kg compounds Ia-f and IIIa-d do not have anticonvulsive activity. Proved anti-inflammatory activity was found only for compound Ib, which at a dose of 50 mg/kg decreased the edema of the inflamed foot by 34.1%, but its activity is inferior to that of ortofen. Compound Ib did not have analgesic activity.

Determination of the acute toxicity showed that the average lethal dose (LD_{50}) of compounds IIIa-d varies within narrow limits, from 448 (IIId) to 550 mg/kg (IIIc), that is these compounds are of low toxicity [2]. Investigation of the influence of the compounds on the aggregatory properties of thrombocytes revealed that all of them have antiaggregatory activity and lower the aggregation by 10-26% (Table 2). The most active compound in this respect is IIIc, which inhibits aggregation to the same degree as papaverine hydrochloride, but is less toxic.

Thus, the results of the investigations show promise for the search for inhibitors of thrombocyte aggregation among derivatives of sodium salts of 2-arylamino-5-carboxynicotinamides.

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