SUBSTITUTED AMIDES AND HYDRAZIDES OF DICARBOXYLIC ACIDS. PART 9.[1] PHARMACOLOGICAL ACTIVITY OF THE PRODUCTS OF INTERACTION OF 2-AMINOPYRIDINES AND 2-AMINOPYRIMIDINE WITH DICARBOXYLIC ACID ANHYDRIDES

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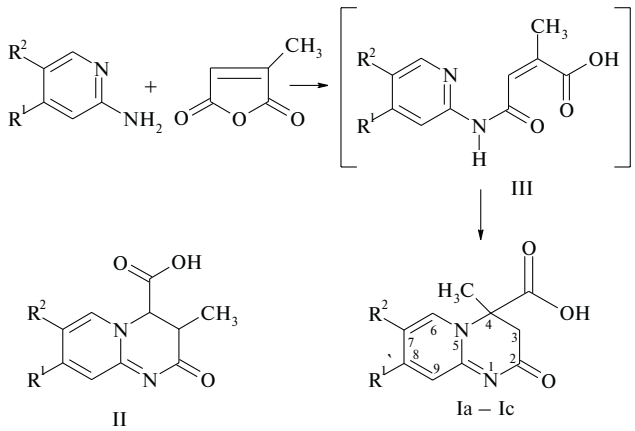
There is evidence that some heterylamides of maleic, citraconic, succinic, and phthalic acids, obtained by acylating certain heterocyclic amines with the corresponding acid anhydrides, possess hypo- and hypertensive, hypo- and hyperglycemic, analgesic, antiinflammatory, and antibacterial properties [1 – 10]. At the same time, the pharmacological activity of pyridyl- and pyrimidylamides of dicarboxylic acids was insufficiently studied.

It was reported almost half a century ago [11] that the interaction of 2-aminopyridine with citraconic acid anhydride yields the corresponding 2-pyridylamide, but this structure was not confirmed by spectroscopic data. Later [12 – 15], it was unambiguously established that 2-aminopyridines can be acylated by interaction with esters and chloroanhydrides of unsaturated carboxylic acids, leading to the formation of oxo derivatives of pyrido[1,2-a]pyrimidine. The reactions of 2-aminopyrimidine and its derivatives with electron-deficient alkenes (in particular, with dicarboxylic acid anhydrides) possessing two vicinal carbonyl groups were not studied in detail (only the aforementioned paper [11] is available, which presented insufficiently convincing data).

In this context, we studied the interaction of 2-aminopyridine, 2-amino-5-bromopyridine, and 2-amino-4-picoline with citraconic anhydride (see Scheme 1). The reaction proceeded in ethyl acetate at room temperature and was accompanied by instantaneous crystallization of the products (Ia – Ic). The structures of these compounds were established based on spectroscopic data.

Scheme 1



I – III: $R^1 = R^2 = H$ (a); $R^1 = H$, $R^2 = Br$ (b); $R^1 = CH_3$, $R^2 = H$ (c).

The ^1H NMR spectra of the reaction products contained a clear signal due to diastereotopic geminal protons of the 3-CH_2 methylene group, representing two doublets of the AB-system in the regions of 2.89 – 2.97 and 3.21 – 3.27 ppm (J_2 = 18.0 – 19.0 Hz). This fact, in the absence of a signal due to amide NH groups, was indicative of the formation of 4-methyl-2-oxo-3,4-dihydropyrido[1,2-a]pyrimidine-4-carboxylic acids (Ia – Ic) rather than pyridylamides of citraconic acid (which could be expected based on the data from [11]). Moreover, the presence of the characteristic signal due to the 3-CH_2 group allowed us to reject the possible isomer structure of 3-methyl-2-oxo-3,4-dihydropyrido[1,2-a]pyrimidine-4-carboxylic acids (II, Scheme 1).

The structure of compounds Ia – Ic indicates that the acylation reaction (proceeding at the amino group of 2-aminopyridine) involves the lactone carbonyl group re-

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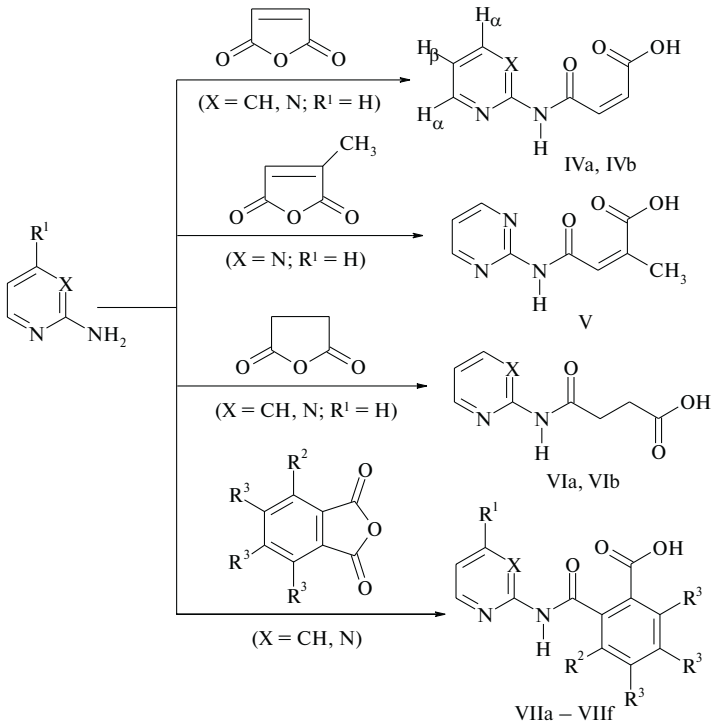
mote from the methyl substituent. The intermediate compound probably has a structure of the corresponding 2′-pyridylamide of (*Z*)-2-methyl-1,4-butenedioic acid (III). Indeed, the reaction of 2-amino-4-picoline with citraconic anhydride led initially to a mixture of cocrystallizing products: 4′-methyl-2′-pyridylamide of (*Z*)-2-methyl-1,4-butenedioic acid (IIIa: $R^1 = CH_3$, $R^2 = H$) with a relative content of 41% (the ^{1}H NMR spectrum contains a characteristic signal at 6.02 ppm due to a CH methine group of the citraconoyl fragment[4]) and 4,8-dimethyl-2-oxo-3,4-dihydropyrido[1,2-a]pyrimidine-4-carboxylic acid (Ic) with a relative content of 59% (the ^{1}H NMR spectrum contains two doublets of the AB-system at 2.97 and 3.24 ppm with $J_2 = 19.0$ Hz). Subsequent recrystallizations allowed us to isolate pure acid Ic from this mixture.

The IR spectra of pyrido[1,2-a]pyrimidines I exhibit a relatively high-frequency absorption band due to stretching vibrations of the carboxy group (1755 – 1760 cm^{-1}) and a band due to the C(2)=O carbonyl group (1650 – 1658 cm^{-1}). These signals are consistent with the proposed structure and agree with the published data [13].

In view of the unusual course of acylation of 2-aminopyridines by citraconic acid anhydride, it should be pointed out that the reactions of 2-aminopyridines with maleic, succinic, phthalic, 3-nitrophthalic, and tetrachlorophthalic anhydrides under mild conditions (ethyl acetate, room temperature) lead to the predicted 2-pyridylamides of the corresponding acids (IVa, VIa, and VIIa – VIId, Scheme 2). We have also established that, under analogous conditions, 2-aminopyrimidine is readily acylated by the above dicarboxylic acid anhydrides, as well as by citraconic acid anhydride, with the formation of monosubstituted 2-pyridylamides of the corresponding acids (IVb, V, VIb, VIIe, and VIIf, Scheme 2).

The structures of newly synthesized compounds (IV – VII) were confirmed by spectroscopic data (Table 1) in comparison with the known dicarboxylic acid heterylamides [1]. The ^{1}H NMR spectra of amides IV – VII contain a group of signals due to protons of the corresponding heterocyclic azine fragments in the region of 6.72 – 11.30 ppm. The signal from two methine protons in the spectra of maleamides IVa and IVb appears as a singlet at 6.14 and 6.25 ppm, respectively. The protons of two methylene groups in compounds VIa and VIb also give singlet signals observed at 2.35 and 2.42 ppm, respectively.

Scheme 2



Compound	X	R^1	R^2	R^3
IVa	CH	–	–	–
IVb	N	–	–	–
VIa	CH	–	–	–
VIb	N	–	–	–
VIIa	CH	H	H	H
VIIb	CH	CH_3	H	H
VIIc	CH	H	NO_2	H
VIId	CH	H	Cl	Cl
VIIe	N	H	H	H
VIIf	N	H	NO_2	H

EXPERIMENTAL CHEMICAL PART

The IR absorption spectra of the synthesized compounds were measured on UR-20 and Specord M-80 spectrophotometers (Germany) using samples prepared as nujol mulls. The ^{1}H NMR spectra were recorded with RYa-2310 (60 MHz) (Russia) and Bruker AS-300 (300.13 MHz) (Germany) instruments using DMSO-d_6 as the solvent and HMDS or TMS as the internal standard. The mass spectra were obtained with an MS-30 mass spectrometer (Kratos, Great Britain) using direct sample introduction into the ion source (emission current, 1000 mA; electron-impact ionization energy, 70 eV; evaporator temperature, 100 – 150°C).

The course of reactions was monitored and purity of the reaction products was checked by TLC on Silufol UV-254 plates (Czech Republic) eluted in an acetone – ethyl ace-

[4] According to the results of our ^{1}H NMR measurements, a relatively high-field signal of the methine proton in the spectra of citraconic acid heterylamides (in DMSO-d_6) occurs in the region of 5.88 – 6.15 ppm.

tate – ether (1 : 1 : 1) system; the spots on the plates were detected by exposure to iodine vapor. The yields, physicochemical characteristics, and spectral parameters of pyrido[1,2-a]pyrimidines (Ia – Ic) and amide IVa are presented with comments in the description of synthesis below. The data for compounds IV – VII are summarized in Table 1. The data of elemental analysis coincide with the values obtained by analytical calculations according to the empirical formulas.

4-Methyl-2-oxo-3,4-dihydropyrido[1,2-a]pyrimidine-4-carboxylic acids (Ia – Ic). To a solution of 10 mmole of 2-aminopyridine, 2-amino-5-bromopyridine, or 2-amino-4-picoline in 40 – 50 ml of ethyl acetate was added with stirring a solution of citraconic anhydride (1.12 g, 10 mmole) in 30 ml of ethyl acetate and the mixture was allowed to stand at room temperature for 2 – 3 h. The precipitated product was separated by filtration and multiply recrystallized (until reaching the desired purity) from a 70% (compound Ia) or 96% (Ib and Ic) aqueous ethanol solution.

Compound Ia. Yield, 1.80 g (82%); m.p., 233 – 234°C (with decomp.); IR spectrum (ν_{max}, cm^{-1}): 1758 (COOH), 1650 (C^2=O); ^{1}H NMR spectrum in DMSO-d_6 (δ, ppm): 1.40 (s, 3H, CH_3), 2.92, 3.21 (dd, 2H, AB-system J_2 18.0 Hz, CH_2), 6.81 (t, 1H, C^7H, for notations see Scheme 1), 7.07 (d, 1H, C^9H), 7.75 (t, 1H, C^8H), 8.32 (d, 1H, C^6H); mass spectrum *m/z* (I_{rel}, %; only peaks with $I_{rel} > 5\%$ are listed): 206(40) $[M]^+$, 189(5) $[M–OH]^+$, 188 $[M–H_2O]^+$, 162(16) $[M–CO_2]^+$, 161(100) $[M–CO_2–H]^+$, 160(28) $[M–CO_2–2H]^+$, 133(6) $[M–CO_2–H–CO]^+$, 132(23) $[M–CO_2–2H–CO]^+$, 131(21), 121(57), 120(27), 94(31) $[C_5H_4N–NH_2]^+$, 92(12), 79(8), 78(54), 69(9), 68(15), 67(18); $C_{10}H_{10}N_2O_3$; m.w., 206.20.

Compound Ib. Yield, 2.10 g (74%); m.p., 199 – 200°C (with decomp.); IR spectrum (ν_{max}, cm^{-1}): 1760 (COOH), 1658 (C^2=O); ^{1}H NMR spectrum in DMSO-d_6 (δ, ppm): 1.45 (s, 3H, CH_3), 2.89, 3.27 (dd, 2H, AB-system J_2 18.0 Hz, CH_2), 7.02 (d, 1H, C^9H, for notations see Scheme 1), 7.81 (d, 1H, C^8H), 8.70 (s, 1H, C^6H); $C_{10}H_9BrN_2O_3$; m.w., 285.10.

Compound Ic. The first crystallization yields 2.0 g of a mixture of IIIa (III: R^1 = CH_3, R^2 = H) and Ic: m.p., 206 – 207°C (with decomp.); IR spectrum (ν_{max}, cm^{-1}): 3328 (COOH), 3142 (NH), 1678 (COOH, C=C), 1637 (CO_{amide}). Compound IIIa probably occurs in a 2-imide form, as evidenced by the relatively low frequency of the NH (amidine group) stretching vibrations in the IR spectrum and by the absence of a signal due to the amide proton in the region above 8 ppm. We failed to isolate product IIIa in pure form because repeated crystallization is accompanied by heterocyclization with the formation of pyridopyrimidine Ic.

^{1}H NMR spectrum of IIIa + Ic in DMSO-d_6 (δ, ppm): 1.42 (s, 3H, C^4-CH_3, Ic, 59%), 1.89 (s, 3H, –CH=C–CH_3, IIIa, 41%), 2.25 (s, 3H, 4′-CH_3, IIIa), 2.38 (s, 3H, C^8–CH_3, Ic), 2.97, 3.24 (dd, 2H, CH_2, AB-system J_2 19.0 Hz, Ic), 6.02 (s, 1H, CH, IIIa), 6.56, 6.58, 6.80, 6.83, 7.00, 7.79, 8.33 (group of signals, 7H, $2C_5H_3N$, NH, Ic + IIIa).

Triple recrystallization (repeated synthesis) yields pure Ic: yield, 1.75 g (80%); m.p., 211 – 212°C (with decomp.); IR spectrum (ν_{max}, cm^{-1}): 1755 (COOH), 1652 (C^2=O); ^{1}H NMR spectrum in DMSO-d_6 (δ, ppm): 1.42 (s, 3H, C^4-CH_3), 2.38 (s, 3H, C^8-CH_3), 2.97, 3.24 (dd, 2H, AB-system, J_2 19.0 Hz, CH_2), 6.83 (d, 1H, C^7H, for notations see Scheme 1), 7.00 (t, 1H, C^9H), 8.33 (d, 1H, C^6H); mass spectrum *m/z* (I_{rel}, %; only peaks with $I_{rel} > 5\%$ are listed): 220(24) $[M]^+$, 203(5) $[M–OH]^+$, 202(32) $[M–H_2O]^+$, 176(19) $[M–CO_2]^+$, 175(97) $[M–CO_2–H]^+$, 174(23) $[M–CO_2–2H]^+$, 161(10) $[M–CO_2–CH_3]^+$, 160(5) $[M–CO_2–H–CH_3]^+$, 147(10) $[M–CO_2–H–CO]^+$, 146(28) $[M–CO_2–2H–CO]^+$, 145(17), 135(62), 134(29), 131(11), 120(5), 119(6), 108(12),

TABLE 1. Physicochemical Characteristics of 2-Pyridylamides and 2-Pyrimidylamides of Dicarboxylic Acids (IV – VII)

Compound	Yield, %	M.p., °C (with decomp.)	Empirical formula	^{1}H NMR spectrum (DMSO-d_6): δ, ppm*
IVa	83	132 – 133	$C_9H_8N_2O_3$	6.14 (s, 2H, CH=CH), 6.58 – 8.05 (m, 4H, C_5H_4N), 8.82 (bs, 1H, NH)
IVb	93	161 – 162	$C_8H_7N_3O_3$	6.25 (s, 2H, CH=CH), 6.59 (t, 1H, H_β in $C_4H_3N_2$), 8.25 (d, 2H, H_α), 8.30 (s, 1H, NH)
V	88	122 – 123	$C_9H_9N_3O_3$	1.98 (s, 3H, CH_3), 5.88 (s, 1H, CH=), 6.55 (t, 1H, H_β in $C_4H_3N_2$), 8.28 (d, 2H, H_α), 9.28 (bs, 1H, NH)
VIa*	80	142 – 143	$C_9H_{10}N_2O_3$	2.35 (s, 4H, CH_2–CH_2), 6.25 – 8.45 (m, 4H, C_5H_4N), 10.52 (bs, 1H, NH)
VIb	62	148 – 149	$C_8H_9N_3O_3$	2.42 (s, 4H, CH_2–CH_2), 6.53 (t, 1H, H_β in $C_4H_3N_2$), 8.30 (d, 2H, H_α), 8.45 (bs, 1H, NH)
VIIa	70	226 – 227	$C_{13}H_{10}N_2O_3$	6.55 – 8.88 (m, 8H, C_6H_4, C_5H_4N), 10.88 (bs, 1H, NH)
VIIb	65	132 – 133	$C_{14}H_{12}N_2O_3$	2.08 (s, 3H, CH_3), 6.08 – 8.55 (m, 7H, C_6H_4, C_5H_3N), 10.85 (bs, 1H, NH)
VIIc	84	161 – 162	$C_{13}H_9N_3O_5$	6.68 – 8.95 (m, 8H, C_6H_3, C_5H_4N, NH)
VIId	82	172 – 173	$C_{13}H_6Cl_4N_2O_3$	6.48 – 9.00 (m, 4H, C_5H_4N), 11.30 (bs, 1H, NH)
VIIe	86	125 – 126	$C_{12}H_9N_3O_3$	6.58 (t, 1H, H_β in $C_4H_3N_2$), 6.72 – 8.05 (m, 4H, C_6H_4), 8.23 (d, 2H, H_α), 8.42 (bs, 1H, NH)
VIIf	91	177 – 178	$C_{12}H_8N_4O_5$	6.68 (t, 1H, H_β in $C_4H_3N_2$), 8.28 (d, 2H, H_α), 7.78 – 8.62 (m, 3H, C_6H_3), 9.05 (bs, 1H, NH), 12.18 (bs, 1H, COOH)

* See Scheme 2 for H_α and H_β proton localization.

107(100) $[C_5H_3(CH_3)–NH]^+$, 106(7), 105(6), 93(15), 92(45), 91(9), 81(20), 80(39), 79(6); $C_{11}H_{12}N_2O_3$; m.w., 220.22.

Dicarboxylic acid 2-pyridylamides (IVa, VIa, VIIa – VIId). To a solution of 10 mmole of 2-aminopyridine or 2-amino-4-picoline in 40 – 50 ml of ethyl acetate was added with stirring a solution of maleic, succinic, phthalic, 3-nitrophthalic, or tetrachlorophthalic anhydrides (10 mmole) in 50 – 60 ml of ethyl acetate or dioxane and the mixture was allowed to stand at room temperature for 3 – 4 h. The precipitated product was separated by filtration and recrystallized from ethanol (for compounds IVa, VIa, VIIc), ethyl acetate – dioxane (1 : 1) mixture (compound VIIb), or ethanol – DMSO (4 : 1) mixture (compounds VIIa and VIId).

Compound IVa. Yield, 1.59 g (83%); m.p., 132 – 133°C (with decomp.); IR spectrum (ν_{max}, cm^{-1}): 3316 (CO<u>OH</u>), 3240 (<u>NH</u>CO), 1710 (<u>CO</u>OH), 1684 (C=C), 1636 (<u>CO</u>NH); mass spectrum, m/z (I_{rel}, %; only peaks with $I_{rel} > 5\%$ are listed): molecular ion signal is missing, 99(5) $[M–2NH–C_5H_4N]^+$, 94(100) $[2NH_2–C_5H_4N]^+$, 91(10), 72(25) $[CH_2=CH–COOH]^+$, 67(65), 55(10) $[CH_2=CH–C\equiv O]^+$, 54(8), 50(15), 41(18); $C_9H_8N_2O_3$; m.w., 192.18.

Dicarboxylic acid 2-pyrimidylamides (IVb, V, VIb, VIIe, VIIf). To a solution of 0.95 g (10 mmole) of 2-aminopyridine in 30 ml of ethyl acetate was added with stirring a solution of maleic, citraconic, succinic, phthalic, or 3-nitrophthalic anhydride (10 mmole) in 50 – 60 ml of ethyl acetate. The solvent was evaporated and the residue was crystallized from ethanol.

TABLE 2. Bacteriostatic Activity of the Synthesized Compounds

Compound	MIC, μg/ml	
	Escherichia coli M_{17}	*Staphylococcus aureus* P-209
Ia	3.9	7.8
Ib	> 1000	> 1000
Ic	1000	1000
IVa	> 1000	1000
IVb	1000	1000
V	1000	1000
VIa	1000	1000
VIIa	1000	1000
VIIb	> 1000	1000
VIIc	1000	1000
VIId	500	500
VIIe	500	500
Ethacridine lactate	2000	500
Oxolinic acid	0.5 – 16*	12.5 – > 256*
Nalidixic acid	0.5 – 8*	12.5 – > 256*
Flumequine	0.5 – 16*	12.5 – > 256*

* MIC interval [20, 21].

EXPERIMENTAL BIOLOGICAL PART

The antimicrobial activity of the synthesized compounds with respect to the standard strains of *Escherichia coli* M_{17} and *Staphylococcus aureus* P-209 was determined by a conventional method of double serial dilutions in a beef-infusion broth for a bacterial load from 2.50×10^5 to 5×10^6 microbial cells per ml solution [16]. The active dose was characterized by the minimum inhibiting concentration (MIC) of each compound, that is, by the maximum dilution ensuring complete suppression of bacterial test culture growth. The bacteriostatic effect of the compounds studied was compared to that of several reference compounds including ethacridine lactate [17] and three modern antibacterial drugs representing the group of 4-oxoquinoline-3-carboxylic acids (oxolinic and nalidixic acids and flumequine) [18, 19 (Table 2)].

The hypoglycemic activity was studied on intact white mongrel rats weighing 220 – 250 g. The compounds studied and the reference drugs (glipizide and glibenclamide) were intraperitoneally injected in a dose of 5 or 50 mg/kg. The blood glucose level was determined by the glucose oxidase technique. The analyses were taken before and after (3 and 5 h) injections; animals in the control groups received an equivalent volume of pure 1% starch jelly. The animals were deprived of food 14 h before and during the experiment, while receiving water *ad libitum* [20].

The effect of the synthesized compounds on the systemic arterial pressure was studied in cats narcotized with medinal (400 mg/kg). Each compound to be tested was dissolved in 3 ml of an isotonic sodium chloride solution and infused in a dose of 5 mg/kg over 2 min into a femoral vein. The arterial pressure was measured in a carotid artery by a direct method using a mercury manometer.

TABLE 3. Effect of Some 2-Pyridylamides and 2-Pyrimidylamides of Dicarboxylic Acids (IV – VII) on Blood Glucose Level in Intact Rats*

Compound	Dose, mg/kg (i.p.)	Blood glucose level		
		initial, mM	after 3 h, % of initial	after 5 h, % of initial
IVb	50	5.1 ± 0.2	– 10.4 ± 3.0	– 12.5 ± 2.9
V	"	3.7 ± 0.2	– 6.6 ± 2.7	– 13.2 ± 2.8
VIa [1]	"	4.7 ± 0.1	+ 9.4 ± 2.2**	+ 0.6 ± 3.6**
VIIa	"	5.0 ± 0.2	– 8.0 ± 3.1	– 24.0 ± 4.0**
VIIb	5	5.2 ± 0.2	– 11.5 ± 3.1	– 9.6 ± 2.2
VIIc	50	5.2 ± 0.2	– 15.4 ± 3.4**	– 9.6 ± 1.9
VIId	"	4.5 ± 0.1	– 17.8 ± 6.0**	– 28.9 ± 5.4**
Glipizide	"	5.4 ± 0.2	– 28.5 ± 5.6**	– 31.9 ± 6.4**
Glibenclamide	5	4.5 ± 0.3	– 43.7 ± 0.8**	– 28.6 ± 6.7**
Control	–	4.7 ± 0.2	– 4.2 ± 1.2	– 8.9 ± 2.8

* Number of experimental animals in all tests $n = 6$.
** Differences from control are reliable for $p < 0.05$.

TABLE 4. Effect of Some 2-Pyridylamides and 2-Pyrimidylamides of Dicarboxylic Acids (IV – VII) on Systemic Arterial Pressure in Narcotized Cats

Compound	Arterial pressure, Torr								
	Initial	1 min	2 min	5 min	10 min	15 min	30 min	45 min	60 min
VIa (n = 5)	136.4	148.8 ± 2.1*	157.6 ± 2.9*	152.0 ± 3.3*	151.6 ± 3.3*	150.0 ± 4.1*	154.8 ± 3.8*	148.8 ± 2.0*	143.6 ± 4.8
VIIc (n = 6)	124.7	146.7 ± 4.3*	162.2 ± 9.9*	161.3 ± 12.7*	153.3 ± 10.6*	147.3 ± 9.0*	143.7 ± 6.4*	136.0 ± 6.0	131.7 ± 6.2

* Differences from the initial level are reliable for $p < 0.05$.

It was established that most of the tested compounds (I, IV – VII) exhibit a weakly pronounced antimicrobial activity with MIC = 500 – 1000 μg/ml (Table 2). A significant bacteriostatic effect was observed for 4-methyl-2-oxo-3,4-dihydropyrido[1,2-a]pyrimidine-4-carboxylic acid Ia, which effectively inhibited the growth of both *E. coli* (MIC = 3.9 μg/ml) and *St. aureus* (MIC = 7.8 μg/ml), being comparable in activity with the reference antibacterial drugs.

Some of the phthalic acid 2-pyridylamides (VIIa, VIIc, VIId) exhibited hypoglycemic activity (Table 3). Note that succinic acid 2-pyridylamide (VIa), which is structurally close to compounds VII but contains no benzene ring, exhibited the opposite effect – increased blood glucose level [1].

In the series of substituted dicarboxylic acid amides studied, 2-pyridylamides of succinic acid (VIa) and 3-nitrophthalic acid (VIIc) produced a hypertensive action in a dose of 5 mg/kg (Table 4). A very weak hypertensive effect was observed for phthalic acid 2-pyridylamide VIIa and acid Ia. Compound VIId was not studied because of poor solubility in water.

Thus, dicarboxylic acid heterylamides may be of interest in the search for preparations possessing bacteriostatic, hypoglycemic, and hypertensive activity.

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