SEARCH FOR NEW DRUGS

SUBSTITUTED AMIDES AND HYDRAZIDES OF DICARBOXYLIC ACIDS. PART 11.[1] SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF A SERIES OF PYRIDYLAMIDES OF DICARBOXYLIC ACIDS

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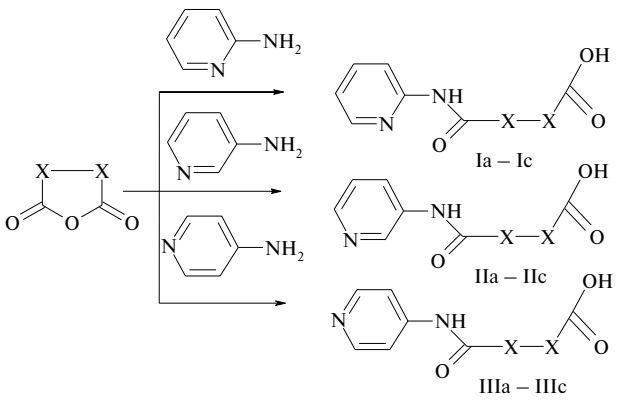
Previously [1, 2], we have found compounds producing a hypertensive effect in pyridylamides of some dicarboxylic acids. Below we report on the synthesis of a series of new pyridylamides of succinic (Ia – IIIa), maleic (Ib – IIIb), and phthalic (Ic – IIIc) acids and attempts at establishing a relationship between the hypertensive activity and structure of these compounds.

Amides I – III were obtained by acylating the corresponding 2-, 3-, and 4-aminopyridines with succinic, maleic, and phthalic acid anhydrides under mild conditions using the well-known procedure described previously [2].



I – III: (X – X) = CH_2–CH_2 (a); CH=CH (b); 1,2-C_6H_4 (c)

The proposed structures of the synthesized compounds were confirmed by the results of spectroscopic measurements (Table 1) and by comparison with the spectra of substituted dicarboxylic acid amides synthesized and studied previously [1 – 4].

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EXPERIMENTAL CHEMICAL PART

The ^{1}H NMR spectra were recorded on a RYa-2310 (60 MHz) instrument (Russia) using DMSO-d_6 as the solvent and HMDS as the internal standard. The course of reactions was monitored and the purity of the reaction products was checked by TLC on Silufol UV-254 plates (Czech Republic) eluted in an acetone – ethyl acetate – ether (1 : 1 : 1) system; the spots on the plates were detected by exposure to iodine vapor.

The yields, physicochemical characteristics, and parameters of the ^{1}H NMR spectra of the originally synthesized compounds are listed in Table 1. The data of elemental analysis coincide with the values obtained by analytical calculations according to the empirical formulas.

2-Pyridylamides of maleic and phthalic acids (IIb, IIc, IIIb, IIIc). To a solution of 0.94 g (10 mmole) of 3- or

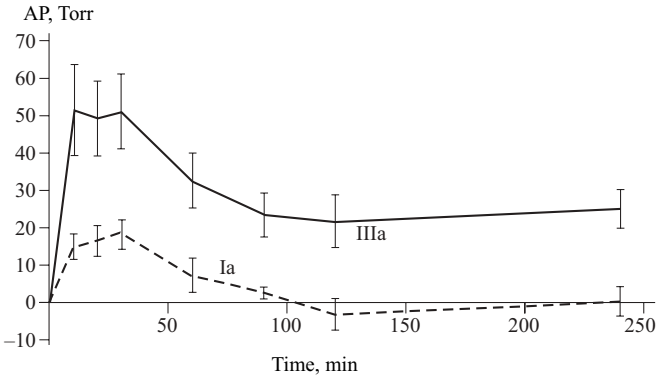

Fig. 1. Arterial pressure (AP) variation in narcotized cats treated with 2- and 4-pyridylamides of succinic acid (Ia, IIIa) in a dose of 5 mg/kg (i.v.).

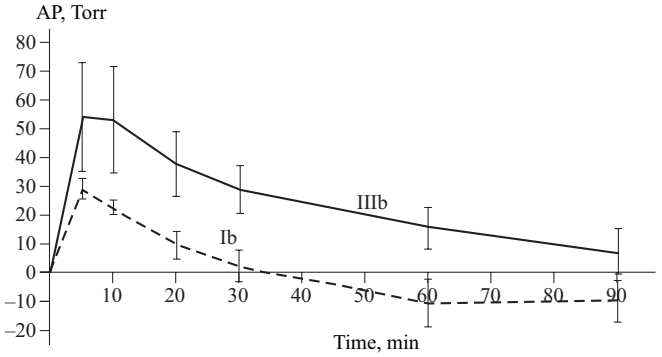

Fig. 2. Arterial pressure (AP) variation in narcotized cats treated with 2- and 4-pyridylamides of maleic acid (Ib, IIIb) in a dose of 5 mg/kg (i.v.).

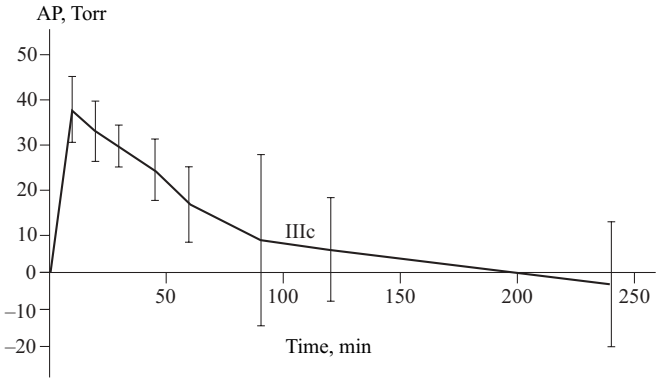

Fig. 3. Arterial pressure (AP) variation in narcotized cats treated with 4-pyridylamide of phthalic acid (IIIc) in a dose of 5 mg/kg (i.v.).

4-aminopyridine in 40 – 50 ml of ethyl acetate (for compound IIc), diethyl ether (for (IIb), or dioxane (IIIb, IIIc) was added with stirring a solution of maleic or phthalic anhydrides (10 mmole) in 50 – 60 ml of ethyl acetate (for compounds IIc and IIIc), diethyl ether (for (IIb), or dioxane (IIIb) and the mixture was allowed to stand at room temperature for 1 – 2 h. The precipitated product was separated by filtration and recrystallized from ethanol (for compound IIIb), water (IIb), ethanol – DMSO (1 : 1, IIc), or acetonitrile – water (5 : 1, IIIc) mixtures.

The synthesis, physicochemical properties, and spectroscopic characteristics of succinic acid pyridylamides (Ia, IIa, IIIa), maleic acid 2-pyridylamide (Ib), and phthalic acid pyridylamide (Ic) were reported previously [1 – 3].

EXPERIMENTAL BIOLOGICAL PART

The effect of the synthesized compounds on the systemic arterial pressure was studied in cats narcotized with phenobarbital sodium (400 mg/kg, i.p.). The arterial pressure was measured in the carotid artery by a direct method using a mercury manometer [5]. 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 the femoral vein. The reference hypertensive drug was midodrine hydrochloride (gutron, Nicomed, Austria) [6] administered intravenously in a dose of 2.5 mg/kg. Each compound was tested in a group of 5 – 7 animals.

In order to check for the role of antagonism between the most active hypertensive derivative (IIIa) [6] and NO in the hypertensive effect, we have compared the effects of sodium nitroprusside (10 μg/kg, i.v.) on the systemic arterial pressure in intact animals and 20 min after injection of compound IIIa (5 mg/kg). The results were averaged over six experiments in the test and control groups.

It was established that, among all the tested compounds, only 2- and 4-pyridylamides Ia, Ib, and IIIa – IIIc produced a significant hypertensive action (Table 2). Among the phthalic acid derivatives, only 4-pyridylamide IIIc was studied because the other compounds in this series were insoluble in water.

As can be seen from Fig. 1, succinic acid 4-pyridylamide IIIa more significantly increases the arterial pressure than does 2-pyridylamide (Ia) of the same acid. Figure 2 shows that generally the same relationship is observed for the series of maleic acid derivatives studied, where 4-pyridylamide (IIIb) is more active than 2-pyridylamide (Ib). Figure 3 shows comparative data on the hypertensive activity of 4-pyridylamides, from which it is seen that the action of phthalic acid derivative (IIIc) is shorter than that of succinic acid 4-pyridylamide (IIIa), but longer than the effect of the analogous maleic acid derivative (IIIb).

The results of our investigation of the effect of pyridylamides of dicarboxylic acids show that these compounds are comparable in activity with midodrine, while some of the tested substances are even superior to the reference drug. Irrespective of the anhydride used for acylation, 4-pyridylamides (IIIa, IIIb) exhibit more pronounced and

TABLE 1. Yields and Physicochemical Characteristics of Pyridylamides of Some Dicarboxylic Acids

Compound	Yield, %	M.p., °C	Empirical formula	^{1}H NMR spectrum (DMSO-d_6): δ, ppm
IIb	91	183 – 185	$C_9H_8N_2O_3$	6.28, 6.58 (dd, 2 H, CH=CH), 7.15 – 9.25 (m, 4 H, C_5H_4N), 9.28 (s, 1, NH), 10.58 (bs, 1 H, NH)
IIc	86	222 – 223	$C_{13}H_{10}N_2O_3$	7.05 – 9.13 (m, 8 H, C_6H_4, C_5H_4N), 10.55 (s, 1 H, NH)
IIIb	99	203 – 204	$C_9H_8N_2O_3$	2.52 (s, 3H, CH_3), 2.58 (s, 4H, CH_2–CH_2), 7.42 – 8.05 (m, 4H, C_6H_4), 10.28 (bs, 1 H, NH), 13.32 (bs, 1 H, COOH)
IIIc	75	161 – 163	$C_{13}H_{10}N_2O_3$	6.45 – 8.58 (m, 8H, C_6H_4, C_5H_4N), 11.18 (bs, 1 H, NH)

TABLE 2. Hypertensive Activity of Pyridylamides of Some Dicarboxylic Acids*

Compound	Dose, mg/kg (i.v.)	Blood pressure increase, Torr	Hypertensive effect duration, min
Ia	5	21.2 ± 2.94^{1}	45
Ib	5	35.6 ± 4.45^{1}	15
IIIa	5	53.0 ± 9.96^{1}	240
IIIb	5	54.0 ± 18.91^{2}	30
IIIc	5	39.6 ± 7.10^{1}	45
Midodrine	2.5	26.4 ± 5.81^{3}	90

* Compounds IIa and IIb are inactive; compounds Ic and IIc are insoluble in water; differences from reference are reliable for

prolonged action as compared to that of 2-pyridylamides (Ia, Ib). With respect to duration of the effect, succinic acid derivatives (Ia, IIIa) are superior to their counterparts with unsaturated acid fragments (Ib, IIIb). This can be related to differences both in the pharmacokinetics of the compounds studied and in the degree of their binding to the corresponding structures.

Investigation of the effect of the most active derivative (IIIa) on the hypotensive activity of sodium nitroprusside showed that the former substance significantly (by 41.8%) reduced the vasodilatory action of the latter compound: the arterial pressure decreased by 40.7 ± 5.33 Torr in the intact control group and by 23.7 ± 2.03 Torr against the background of succinic acid 4-pyridylamide IIIa. This effect can be related to the well-known antagonism between the unsubstituted 4-pyridylamide and NO [7, 8] and is probably mediated by potential-dependent potassium channels [8].

Thus, the investigation showed that it would be expedient to continue the search for hypertensive agents among 2-and 4-pyridylamides of dicarboxylic acids. The mechanism of the hypertensive action of these compounds is apparently related to blocking the potential-dependent potassium channels in the smooth muscles of blood vessels.

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