SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 2-ARYLAMINO-6,7-DIHYDRO-5H-PYRINDINE-3-CARBOXYLIC ACID ACYLHYDRAZIDES

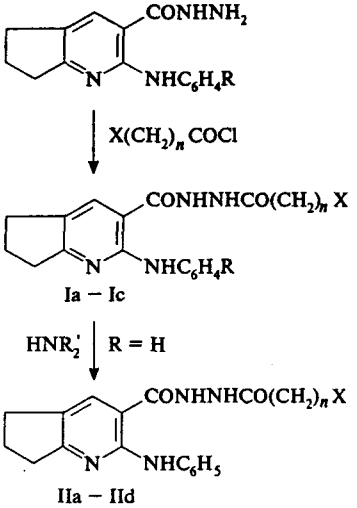
R. N. Galeeva,[1] Redduan Atmani,[1] M. Yu. Gavrilov,[1] F. Ya. Nazmetdinov,[1] L. P. Drovosekova,[1] V. É. Kolla,[1] and M. E. Kon'shin[1]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 32, No. 11, pp. 15 – 16, November, 1998.

Original article submitted December 8, 1997.

There are data on the antidepressant, antiinflammatory, and analgesic activity of 2-arylamino-5,6,7,8-tetrahydroquinoline-3-carboxylic acid β-dialkylaminoacetylhydrazides [1]. In the search for new antidepressants and antiinflammatory agents, we have synthesized a series of 2-arylamino-6,7-dihydro-5H-pyrindine-3-carboxylic acid acylhydrazides (Ia – Ic, IIa – IId)

Interaction of the initial hydrazides [2] with chloroacetyl chloride and 3-bromopropionyl chloride in glacial acetic acid in the presence of anhydrous sodium acetate leads to β-(chloroacetyl)hydrazides (Ia, Ib) and β-(3-bromopropionyl)hydrazide (Ic) with yields of 57 – 62%. The products are crystalline substances soluble in toluene, ethanol, and acetic acid. The IR spectra of compounds Ia – Ic contain absorption bands at 1660 – 1690 cm^{-1} (CO) and 3190 – 3390 cm^{-1} (NH).



Ia, Ib: $n = 1$, X = Cl, R = H (a), *m*-CH_3 (b); Ic: $n = 2$, X = Br, R = H; IIa: $n = 1$, N_2R' = morpholino;
IIb: $n = 2$, R' = C_2H_5; IIc: $n = 2$, N_2R' = morpholino; IId: $n = 2$, N_2R' = piperidino.

[1] Perm State Pharmaceutical Academy, Perm, Russia.

Heating compounds Ia, Ic with dialkylamines in benzene or ethanol leads to the formation of 2-anilino-6,7-dihydro-5H-pyrindine-3-carboxylic acid β-(dialkylaminoacyl)hydrazides (IIa – IId) with yields of 28 – 32%. Compounds IIa – IId appear as colorless crystalline substances soluble in ethanol and acetic acid. Their IR spectra display absorption bands at 1620 – 1670 cm^{-1} (CO) and 3210 – 3480 cm^{-1} (NH).

The proposed structures of the synthesized compounds were confirmed by the parameters of ^1H NMR spectra (Table 2).

EXPERIMENTAL CHEMICAL PART

The IR absorption spectra were recorded on a Specord M 80 spectrophotometer (Germany) using samples prepared as Nujol mulls. The ^1H NMR spectra were measured at 20°C on an RS-60 (60 MHz) spectrometer (Russia) using samples prepared as 5% solutions in DMSO-d_6, with HMDS as the internal standard. The TLC patterns were obtained on Silufol UV-254 plates eluted in a butanol – benzene (1 : 1) solvent system. The data of elemental analyses correspond to the values calculated by empirical formulas.

2-Arylamino-6,7-dihydro-5H-pyrindine-3-carboxylic acid β-(chloroacetyl)- and β-(3-bromopropionyl)hydrazides (Ia – Ic). To a solution of 0.01 mole of 2-arylamino-6,7-dihydro-5H-pyrindine-3-carboxylic acid hydrazide and 0.82 g (0.01 mole) of anhydrous sodium acetate in 20 ml gla-

TABLE 1. Yields and Characteristics of the Synthesized Compounds

Compound	Yield, %	M.p., °C	R_f	Empirical formula
Ia	61	205 – 206	0.76	$C_{17}H_{17}ClN_4O_2$
Ib	57	197 – 198	0.79	$C_{18}H_{19}ClN_4O_2$
Ic	62	198 – 199	0.74	$C_{18}H_{19}BrN_4O_2$
IIa	31	196 – 198	0.30	$C_{21}H_{25}N_5O_3$
IIb	32	174 – 176	0.77	$C_{22}H_{29}N_5O_2$
IIc	30	228 – 230	0.60	$C_{22}H_{27}N_5O_3$
IId	28	198 – 201	–	$C_{23}H_{29}N_5O_2$

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds

Compound	Chemical shift, δ, ppm							
	CH_2(6), m	CH_2(5.7), m	CH_3	N(CH_2), m	CH_2, m	H_{arom}, m	3NH, bs	H_γ, pyrid, s
Ia	1.73–2.10	2.53–2.93	–	–	4.23	7.13–7.83	6.90, 9.96, 10.53	8.16
Ib	1.85–2.23	2.56–2.93	3.26, s	–	4.18	6.90–7.72	6.71, 9.90, 10.46	8.01
Ic	1.83–2.26	2.63–2.96	–	–	3.30	7.06–7.80	6.83, 9.93, 10.46	8.00
IIa	1.76–2.16	2.61–3.03	–	3.46–3.70	3.26	7.03–7.76	6.90, 9.85, 10.50	7.96
IIb	1.73–2.02	2.60–2.93	1.13, t	3.70–3.96	3.13	7.11–7.71	6.90, 9.13, 10.46	8.05
IIc	1.76–2.01	2.70–2.96	–	3.13–3.46	3.13–3.46	6.90–7.76	6.80, 9.53, 10.51	7.96

TABLE 3. Antidepressant and Antiinflammatory Activity of Compounds Ia–Ic and IIa–IIc

Compound	Swim test		Carrageenan edema	
	Immobilization time, sec	Reliability parameters	Inhibition relative to control, %	Reliability parameters
Ia	164.0	$p_1 < 0.05$ $p_2 < 0.5$	...	...
Ib	156.5	$p_1 < 0.05$ $p_2 < 0.5$	26.5	$p_1 < 0.25$ $p_2 < 0.5$
Ic	144.0	$p_1 < 0.002$ $p_2 < 0.5$	12.8	$p_1 < 0.25$ $p_2 < 0.02$
IIa	163.1	$p_1 < 0.05$ $p_2 < 0.5$	31.8	$p_1 < 0.05$ $p_2 < 0.5$
IIb	149.0	$p_1 < 0.01$ $p_2 < 0.5$	38.8	$p_1 < 0.05$ $p_2 < 0.5$
IIc	139.4	$p_1 < 0.002$ $p_2 < 0.5$	32.6	$p_1 < 0.01$ $p_2 < 0.1$
Amitriptyline	137.4	$p_1 < 0.05$	...	...
Orthophen	...	...	59.3	$p_1 < 0.05$
Control	207.3	...	...	...

Note. p_1 and p_2 indicate the confidence levels with respect to control and reference (orthophen, amitriptyline), respectively.

cial acetic acid was gradually added 1.1 g (0.01 mole) chloroacetyl chloride [or 1.7 g (0.01 mole) 3-bromopropionyl chloride], the mixture was treated at 40–50°C for 2 h and allowed to stand overnight. Then the reaction mixture was diluted with water and neutralized with a sodium bicarbonate solution. The precipitate of compound I was filtered and recrystallized from dioxane.

2-Anilino-6,7-dihydro-5H-pyrindine-3-carboxylic acid β-(dialkylaminoacyl)hydrazides (IIa–IId). To a solution of 0.01 mole of compound Ia (or Ic) in 20 ml dioxane was added 0.03 mole of dialkylamine and the mixture was treated for 4 h at 100°C, cooled, poured into a sodium bicarbonate solution (pH 8.5). The volatile impurities were distilled off with water vapor. The residue was filtered and recrystallized from ethanol.

EXPERIMENTAL PHARMACOLOGICAL PART

The antidepressant activity of the synthesized compounds was assessed using a conventional forced swim test [3]. The experiments were performed on white mongrel male mice weighing 15–23 g kept in individual boxes for 2 h before testing. The synthesized compounds and the reference drug amitriptyline were intraperitoneally injected 30 min before the test at a dose of 10 mg/kg in the form of suspensions in a 2% starch jelly. The animals had to swim in a glass vessel (25 × 25 × 12 cm; water depth 15 cm; water temperature 22–25°C). The antidepressant activity was assessed as a decrease in the immobilization time of test mice during the first 6 min of forced swimming monitored by the number of immobilized animals and the duration of immobilization period.

The antiinflammatory activity was studied on white mongrel rats weighing 150–320 g using a model of acute inflammatory edema induced by subplantar injections of 0.1 ml of a 1% carrageenan solution into a hind foot. The foot volume was determined by the oncometric technique [4]. The synthesized compounds (50 mg/kg) and the reference drug orthophen (50 mg/kg) were intraperitoneally injected 1 h before carrageenan introduction. The antiinflammatory effect (not less than 30% inhibition of the exudation as compared to control) was checked 4 h after injecting carrageenan.

The acute toxicity (LD_{50}) of compounds Ia, IIa, and IIc was determined by single intraperitoneal injections with a 2% starch jelly to white mice weighing 16–20 g.

The results of testing showed that all the synthesized compounds reduce, albeit to different extents, the immobilization time of test mice, the antidepressant effect being most pronounced for compounds Ia, IIb, and IIc (Table 3).

Compounds IIa–IIc also exhibited antiinflammatory action, but the effect was less pronounced than that of orthophen.

The compounds studied for acute toxicity have proved to belong to the class of low toxicity ($LD_{50} > 500$ mg/kg).

REFERENCES

1. S. V. Ukhov, M. Yu. Gavrilov, S. N. Nikulina, et al., *Khim.-Farm. Zh.*, **25**(2), 20–21 (1991).
2. R. N. Galeeva, G. N. Novoselova, M. Yu. Gavrilov, and M. E. Konshin, *Khim.-Farm. Zh.*, **31**(6), 38–39 (1997).
3. D. Yu. Rusanov and A. V. Val'dman, *Farmakol. Toksokol.*, No. 5, 107–111 (1983).
4. L. S. Salyamon, *Drug Regulation of the Inflammatory Process* [in Russian], Leningrad (1958), pp. 11–43.