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

R. N. Galeeva,[1] E. V. Rudometova,[1] M. Yu. Gavrilov,[1] V. É. Kolla,[1] M. E. Kon'shin,[1] and F. Ya. Nazmetdinov[1]

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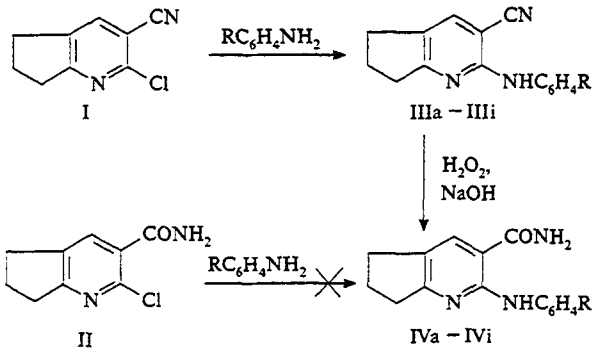
As reported, 2-arylamino-6-methyl- and 4,6-dimethylnicotinic acid amides exhibit high anticonvulsive activity [1, 2], while 2-arylamino-5,6,7,8-tetrahydroquinoline-3-carboxylic acid amides show analgesic and antiinflammatory activity [3]. It was therefore of interest to study the properties of previously unreported compounds with close structures, 2-arylamino-6,7-dihydro-5H-pyrindine-3-carboxylic acid amides.



R = H (IIIa, IVa), 2-CH_3 (IIIb, IVb), 3-CH_3 (IIIc, IVc), 4-CH_3 (IIId, IVd), 2-OCH_3 (IIIe, IVe), 4-OCH_3 (IIIf, IVf), 2-Br (IIIg, IVg), 4-Br (IIIh, IVh), 3-Cl (IIIi, IVi).

In order to solve this task, we have attempted to synthesize 2- arylamino-6,7-dihydro-5H-pyrindine-3-carboxylic acid amides on the basis of 2-chloro-6,7-dihydro-5H-pyrindine-3-carboxylic acid (II) [4] and the corresponding arylamines. However, it was found that the reaction does not proceed on boiling the initial reagents for 4 h in a 50% acetic acid or butanol, nor upon their melting (135°C, 8 h). Instead, the reaction mixture exhibited either separation of the initial compounds or gumming. It was only 2-(*p*-toluidino)-6,7-dihydro-5H-pyrindine-3-carboxylic acid amide (IVd) that was obtained with a 23% yield upon an 8-h boiling of amide II and *p*-toluidine hydrochloride in ethanol.

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

The increasing acidity of the reaction medium favors an increase in the mobility of chlorine in the initial compound. However, the yield of the final product was still insufficient and the reaction duration was very long. For this reason, we have attempted to use 2-chloro-3-cyano-6,7-dihydro-5H-pyrindine (I) as the initial compound [4].

Table 1 lists the characteristics of 2-arylamino-3-cyano-6,7- dihydro-5H-pyrindines (IIIa – IIIi) obtained at a yield of 21 – 70% by heating 2-chloro-3-cyano-6,7-dihydro-5H-pyrindine and arylamines for 3 h at 180°C. Nitriles IIIa – IIIi appear as colorless crystalline substances well soluble in the usual organic solvents and insoluble in water and diluted mineral acids. The IR spectra of these compounds show absorption bands at 3300 – 3350 cm^{-1} (NH) and 2200 – 2260 cm^{-1} (CN). The ^1H NMR spectra exhibit the following signals (ppm): 2.09 – 2.29 (m, 2H, 6-CH_2), 2.84 – 3.09 (m,

TABLE 1. Characteristics of Synthesized Compounds

Compound	Yield, %	M.p., °C	R_f	Empirical formula
IIIa	70	88 – 90	0.70	$C_{15}H_{13}N_3$
IIIb	35	57 – 59	0.67	$C_{16}H_{15}N_3$
IIIc	62	85 – 87	0.62	$C_{16}H_{15}N_3$
IIId	52	141 – 143	0.60	$C_{16}H_{15}N_3$
IIIe	21	114 – 116	0.93	$C_{16}H_{15}N_3O$
IIIf	43	118 – 120	0.39	$C_{16}H_{15}N_3O$
IIIg	31	129 – 131	0.89	$C_{15}H_{12}N_3Br$
IIIh	32	123 – 125	0.82	$C_{15}H_{12}N_3Br$
IIIi	47	92 – 94	0.69	$C_{15}H_{12}N_3Cl$
IVa	72	194 – 196	0.75	$C_{15}H_{15}N_3O$
IVb	55	128 – 130	0.73	$C_{16}H_{17}N_3O$
IVc	69	212 – 214	0.86	$C_{16}H_{17}N_3O$
IVd	33	207 – 209	0.85	$C_{16}H_{17}N_3O$
IVe	32	245 – 246	0.74	$C_{16}H_{17}N_3O_2$
IVf	63	130 – 132	0.72	$C_{16}H_{17}N_3O_2$
IVg	51	114 – 116	0.65	$C_{15}H_{14}N_3BrO$
IVh	58	194 – 196	0.91	$C_{15}H_{14}N_3BrO$
IVi	63	172 – 174	0.63	$C_{15}H_{14}N_3ClO$

TABLE 2. Analgesic and Antiinflammatory Activity of compounds IVa, IVc – IVh

Compound	Analgesic activity: defensive reflex, sec	Antiinflammatory activity: edema inhibition, % of control
IVa	17.0 ± 5.3	60.3 ± 1.1
IVc	16.2 ± 2.4	Inactive
IVd	18.8 ± 0.5*	61.5 ± 2.7
IVe	13.8 ± 1.6	Inactive
IVg	19.6 ± 2.8*	Inactive
IVh	24.2 ± 3.0*	65.0 ± 3.8
Ortophen	17.2 ± 3.6	59.3 ± 1.0
Control (2% starch mucilage)	12.5 ± 1.2	–

* $p < 0.05$ against control.

4H, 5-CH_2 and 7-CH_2), 7.29 – 7.53 (m, aromatic protons), 8.05 – 8.09 (s, 1H, 4-H), and 8.29 – 9.08 (s, NH).

2-Arylamino-3-cyano-6,7-dihydro-5H-pyrindines (IIIa – IIIi) are readily hydrated under conditions of the Radziszewski reaction with the formation of amides IVa – IVi at a yield of 32 – 72%. Amides IVa – IVi appear as colorless crystalline substances soluble in alcohols, dimethylformamide, and diluted mineral acids, and insoluble in water. The IR absorption spectra of these compounds show bands of stretching vibrations of the amide carbonyl groups at 1670 – 1680 cm^{-1}, NH_2 groups at 3160 – 3210 cm^{-1} and amino groups of the arylamino radical at 3350 – 3380 cm^{-1}. The ^1H NMR spectra contain the following signals (ppm): 2.08 – 2.15 (m, 2H, 6-CH_2), 2.88 – 2.95 (m, 4H, 5-CH_2 and 7- CH_2), 7.02 – 8.22 (m, aromatic protons, amide NH_2, 4-H), and 11.60 – 11.63 (s, NH).

EXPERIMENTAL CHEMICAL PART

The IR absorption spectra were recorded on an UR-20 spectrophotometer using samples prepared as nujol mulls. The ^1H NMR spectra were measured on an RS-60 spectrometers using 5% solutions in DMSO-d_6 and CCl_4, with HMDS as the internal standard. TLC was performed on Silufol UV-254 plates eluted in a butanol – benzene (1 : 1) system. The data of elemental analyses for C, H, N, and halogen corresponded to the values calculated by empirical formulas.

2-Arylamino-3-cyano-6,7-dihydro-5H-pyrindines(IIIa – IIIi). A mixture of 1.79 g (0.01 mole) of 2-chloro-3-cyano-6,7-dihydro-5H- pyrindine and 0.01 mole of arylamine was heated at 180°C for 3 h. Then the reaction mass was cooled, dissolved in benzene, and passed through a column filled with alumina. Then benzene was distilled off and the residue crystallized from ethanol.

2-Arylamino-6,7-dihydro-5H-pyrindine-3-carboxylic acid amides (IVa – IVi). A solution of 0.01 mole of 2-arylamino-3-cyano-6,7-dihydro-5H-pyrindine (IIIa – IIIi) in 70 ml of ethanol containing 0.40 g (0.01 mole) of sodium hydroxide and 0.68 g (0.02 mole) of 30% H_2O_2 was boiled for 6 h and poured into 200 ml of water. The residue was filtered, dried, and crystallized from ethanol.

2-(4-Toluidino)-6,7-dihydro-5H-pyrindine-3-carboxylic acid amides (IVd). A mixture of 1.97 g (0.01 mole) of 2-chloro-6,7-dihydro-5H-pyrindine amide and 1.30 g (0.01 mole) of aniline hydrochloride in 50 ml butanol was boiled for 10 h. Then butanol was distilled off with vapor and 10% NaOH was added to the solution. The precipitate was filtered, dried, and crystallized from ethanol.

A mixture of this product with compound IVd obtained by the previous method showed no depression in the melting temperature.

EXPERIMENTAL BIOLOGICAL PART

Compounds IVa, IVc – IVh were studied with respect to analgesic, antiinflammatory, and anticonvulsive activity.

The analgesic activity was studied in a "hot plate" test [5] on white mice and evaluated as an increase in the latent period of response to the thermal irritation. The compounds tested were injected intraperitoneally at a dose of 50 mg / kg.

The antiinflammatory activity was studied on white mongrel rats weighing 130 – 180 g with a model of acute inflammatory edema induced by subplantar injections of 0.1 ml of a 1% carrageenan solution into the hind foot. The effect was evaluated by the degree of inhibition of the foot edema growth and expressed as percentage of the control. The foot volume was measured by oncometric techniques [6]. The compounds (50 mg / kg) and the reference drug (ortophen, 10 mg / kg) were intraperitoneally injected 1 h before the carrageenan introduction. The antiinflammatory effect was checked 4 h after the inflammation induction.

The anticonvulsive activity of the synthesized compounds was studied on white mice using the maximum electroshock method [7]. The compounds tested were introduced at a dose of 300 mg / kg. The behavior of animals was monitored during a 2-h period of time.

The results of tests on the analgesic activity showed the presence of a moderate protective action in compound IVh. At the stage of maximum effect (30 min), the compound increased the duration of defensive reflex to a greater extent than did ortophen (Table 2). Amides IVa and IVc – IVg exhibited no analgesic properties.

A comparatively high antiinflammatory activity was observed for compounds IVa, IVd, and IVh.

Amides IVa and IVc – IVh exhibited no anticonvulsive activity.

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