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

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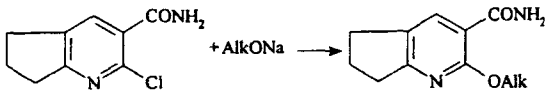
As is known [1], 2-alkoxy-5,6,7,8-tetrahydroquinoline-3-carboxylic acid amides exhibit anticonvulsive, antiinflammatory, and analgesic activity. In continuation of that work, we have synthesized related amides of 2-alkoxy-6,7-dihydro-5H-pyrindine-3-carboxylic acids (I – VI) and studied their pharmacological properties.



I: Alk = CH_3,
II: C_2H_5 (II),
III: *n*-C_3H_7,
IV: *iso*-C_3H_7,
V: C_4H_9,
VI: *iso*-C_4H_9.

Amides I – VI were obtained by interaction of 2-chloro-6,7-dihydro-5H-pyrindine-3-carboxylic acid with sodium alcoholates in the corresponding alcohol media. The products are colorless crystalline substances soluble in hexane, benzene, and ethanol. The proposed structures were confirmed by IR (see Table 1) and ^1H NMR data.

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TABLE 1. Yields and Analytical Characteristics of Synthesized Compounds

Compound	Yield, %	M.p., °C	R_f*	Empirical formula	IR spectrum, ν_{max}, cm^{-1}		
					Amide II	Amide I	NH_2
I	60	172 – 174	0.55	$C_{10}H_{12}N_2O_2$	1605	1680	3165, 3430
II	63	162 – 163	0.48	$C_{11}H_{14}N_2O_2$	1625	1680	3180, 3455
III	48	145 – 146	0.59	$C_{12}H_{16}N_2O_2$	1600	1680	3155, 3440
IV	38	147 – 148	0.42	$C_{12}H_{16}N_2O_2$	1605	1685	3170, 3460
V	32	52 – 54	0.62	$C_{13}H_{18}N_2O_2$	1605	1685	3175, 3465
VI	41	129 – 131	0.60	$C_{13}H_{18}N_2O_2$	1615	1680	3170, 3470

* Solvent: butanol – benzene (1 : 1).

The ^1H NMR spectrum of amide VI shows two singlets at 0.88 and 1.00 ppm (6H, $2CH_3$), a multiplet at 2.45 ppm (2H, CH_2 in position 6 of pyrindine), a broadened signal from methine group at 2.45 ppm, a multiplet at 2.58 – 3.00 ppm (4H, $2CH_2$ in positions 5 and 7 of pyrindine), a doublet at 4.13 ppm (CH_2 of isobutyl fragment), a broadened signal at 7.53 ppm (NH_2 of amide residue), and a singlet at 8 ppm (1H, H in position 4 of pyrindine). The ^1H NMR spectra of other compounds agree with the assigned structures.

EXPERIMENTAL CHEMICAL PART

The IR spectra of compounds I – IV were recorded on an UR-20 and Specord spectrophotometers using samples prepared as nujol mulls. The ^1H NMR spectra of were obtained on a RYa-2310 spectrometer using DMSO-d_6 as the solvent and HMDS as the internal standard. The elemental analysis data agree with the results of analytical calculations according to the empirical formulas.

Amides of 2-alkoxy-6,7-dihydro-5H-pyrindine-3-carboxylic acids (I – VI). To a solution of sodium alcoholate obtained from 0.72 g (0.03 mole) sodium and 25 ml of the corresponding alcohol was added 4.2 g (0.02 mole) of 2-chloro-6,7-dihydro-5H-pyrindine-3-carboxylic acid amide, and the reaction mixture was heated on a water bath for 14 – 20 h. Then alcohol was distilled off and the residue was washed with water, dried, and crystallized from ethanol. In the case of compounds V and VI, the dry residue was dissolved in dichloroethane, passed through a column filled with Al_2O_3, and crystallized from hexane.

EXPERIMENTAL BIOLOGICAL PART

The anticonvulsive activity of the synthesized compounds was studied on white mice weighing 16 – 22 g using the maximum electroshock test [2]. The compounds were intraperitoneally injected to animals

at a dose of up to 300 mg/kg. The effective dose (ED_{50}, mg/kg) was determined using a rapid method based on the protective action with respect to the tonic-extensor phase of convulsive attack [3]. Hexamidine was used as the reference drug.

The analgesic activity was assessed by the hot-plate method in experiments on white male and female mice weighing 16 – 22 g [4]. The test compounds and a reference drug (amidopyrine) were injected intraperitoneally at a dose of 50 mg/kg. The analgesic activity was evaluated by an increase in the latent period of the defensive response to thermal irritation. The test was carried out 30, 60, 120, and 180 min after the drug injection. The antiinflammatory activity was studied on white mongrel mice weighing 120 – 160 g, using a model of acute inflammatory edema induced by subplantar 0.1 ml injections of a 1% carrageenan solution into hind paws. The foot volume was determined by oncometric techniques [5]. The test compounds (50 mg/kg) and a reference drug (ortophen, 10 mg/kg) were injected intraperitoneally 1 h before the carrageenan introduction. The antiinflammatory action was assessed 4 h after the edema induction. The positive effect was judged by at least 30% inhibition of the edema growth as compared to the control.

The acute toxicity (LD_{50}) was determined by single intraperitoneal injection of the drugs with a 2% starch mucus suspension to white mice weighing 20 – 24 g [6].

The experimental results showed that only two of the six compounds studied in this work exhibited significant anticonvulsive activity. The ED_{50} of compound III was 250 mg/kg against 90.6 mg/kg for hexamidine, while the LD_{50} values are 410 and 340 mg/kg, respectively. Thus, the effective breadth of the "therapeutic" action of compound III is smaller than that of hexamidine. Compound II injected at a dose of 300 mg/kg exhibited a protective action only in 20% of the animals. Other compounds showed no anticonvulsive activity at all.

Analgesic activity (comparable to that of amidopyrine) was found only in compound III.

Compound IV produced an antiinflammatory effect and decreased the carrageenan-induced edema by 32.2%. The magnitude of the effect was inferior to that of ortophen, which inhibited the edema growth by 48.2% at a dose of 10 mg/kg.

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