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SYNTHESIS AND ANTIARRHYTHMIC ACTIVITY OF 1-BENZYL-3,3-DIALKYL-3,4-DIHYDROISOQUINOLINE CHLORIDES

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Cyclocondensation of dialkylbenzylcarbinols with benzylcyanides was used to synthesize 1-benzyl-3,3-dialkyl-3,4-dihydroisoquinolines. The hydrochlorides of the compounds synthesized here were tested for antiarrhythmic activity in a calcium chloride model. The maximum antiarrhythmic index (AI) was found with isoquinolines with cycloalkanone fragments such as cyclopentanone and cyclohexanone in position 3, which had AI values of 15.5 and 16.3, three times the corresponding value for lidocaine.

Keywords: cyclocondensation, dialkylbenzylcarbinones, benzylcyanides, 1-benzyl-3,3-dialkyl-3,4-dihydroisoquinoline chlorides, antiarrhythmic actions, calcium chloride model, lidocaine.

Isoquinoline derivatives have antiarrhythmic activity (AA). Recent examples of studies of this type of activity among isoquinolines include those reported in [1, 2]. In [3, 4] we presented the results of our studies of AA in a series of 3,3-dialkyl-3,4-dihydroisoquinoline derivatives. These results show that seeking agents in this area has potential. A positive property of the compounds of this series is that many of them combine the antiarrhythmic effect with antihypertensive and antiaggregant activity against platelets.

The aim of the present work was to synthesize 1-benzyl-3,3-dialkyl-3,4-dihydroisoquinoline derivatives and study the link between their antiarrhythmic actions and structure. It should be noted that the substances selected here are structurally close to alkaloids of the 1-benzylisoquinoline series, such as papaverine, laudanosine, and others, and also No-Shpa (drotaverine hydrochloride).

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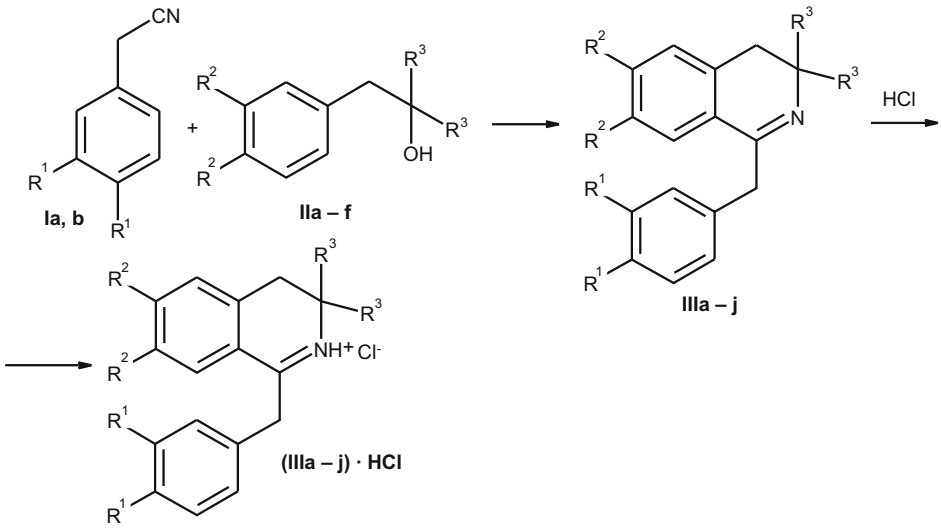

TABLE 1. Properties of Compounds Synthesized Here

Compound	R^2	$2R^3$	R^1	Atomic formula	T_m, °C	Yield, %
IIIa · HCl	H	$(CH_2)_5$	H	$C_{21}H_{23}N \cdot HCl$	159 – 160	65
IIIb · HCl	H	2CH3	OCH_3	$C_{20}H_{23}NO_2 \cdot HCl$	148 – 149	73
IIId · HCl	OCH_3	$2CH_3$	OCH_3	$C_{22}H_{27}NO_4 \cdot HCl$	153 – 155	72
IIIe · HCl	OCH_3	$2C_2H_5$	H	$C_{22}H_{27}NO_2 \cdot HCl$	212 – 213	70
IIIf · HCl	OCH_3	$2C_2H_5$	OCH_3	$C_{24}H_{31}NO_4 \cdot HCl$	183 – 185	66
IIIg · HCl	OCH_3	$(CH_2)_4$	H	$C_{22}H_{25}NO_2 \cdot HCl$	229 – 230	76
IIIh · HCl	OCH_3	$(CH_2)_4$	OCH_3	$C_{24}H_{29}NO_4 \cdot HCl$	212 – 213	74
IIIi · HCl	OCH_3	$(CH_2)_5$	H	$C_{23}H_{27}NO_2 \cdot HCl$	222 – 224	69
IIIj · HCl	OCH_3	$(CH_2)_5$	OCH_3	$C_{25}H_{31}NO_4 \cdot HCl$	162 – 164	77

Compounds IIIa-j were synthesized by the cyclocondensation reaction of benzylcyanides Ia-j with carbinols IIa-f [3 – 5]. Pharmacological studies were performed using the hydrochlorides of isoquinolines IIIa-j prepared by passage of gaseous HCl through ether solutions of the corresponding bases. The resulting hydrochlorides (IIIa-j) · HCl were yellow crystalline substances soluble in water. The properties of the substances synthesized here are presented in Table 1. Compound IIIc (R^1 = H, R^2 = MeO, R^3 = Me) has been described in [5].

The structures of the compounds synthesized here were confirmed by their PMR spectra (Table 2). The spectra of the hydrochlorides contained a singlet from benzyl CH_2 group protons (4.56 – 4.71 ppm) and multiplets from aromatic protons in the isoquinoline ring and benzyl residue, with an overall integral intensity corresponding to the number of atoms in the isoquinoline ring and benzyl residue. The NH^+ group corresponded to a proton singlet at 13.62 – 14.50 ppm. Spectra also contained signals from protons in substituents at R^3, OCH_3, and methylene groups in position 4.

The IR spectra of bases of the study compounds contained absorption bands from the C=N group at 1630 – 1640 cm^{-1}.

EXPERIMENTAL CHEMICAL SECTION

IR spectra were recorded on a Specord M-80 instrument in chloroform at a concentration of 0.01 M; PMR spectra were recorded on a Bruker AMX 300 instrument (4300 MHz) in DMSO-d_6 solution with HMDS as internal standard (0.05 ppm relative to TMS).

Substances were recrystallized from propan-2-ol. Elemental analysis data (C, H, N, and Cl) were consistent with calculated values. Product purity was monitored by TLC using a system consisting of chloroform and acetone (9:1) and detection with iodine vapor. Bases for collection of IR spectra were prepared by treatment of the corresponding hydrochlorides with 25% ammonia solution.

1-[3,4-$(R^1)_2$-Benzyl]-6,7-$(R^2)_2$-3,3-$(R^3)_2$-3,4-dihydroisoquinoline chlorides (IIIa-j). A solution containing 0.03 mol of corresponding nitrile Ia, b and 0.03 mol of carbinol IIa-f

TABLE 2. PMR Spectra of Hydrochlorides of Compounds Synthesized here, δ, ppm, J, Hz

Compound	$2R^3$	OCH_3	4-CH_2, s	1-CH_2, s	Aromatic protons, m	Ring NH^+, s
IIIa · HCl	1.55 (broad s, 10H, $5CH_2$)	3.67 (c,3H) 3.72 (c,3H)	3.08	4.58	6.81 – 8.10 (m, 9H)	14.38
IIIb · HCl	1.48 (s, 6H, $2CH_3$)	3.65 (c, 3H) 3.70 (c, 3H)	3.09	4.56	6.74 – 8.12 (m, 7H)	14.50
IIId · HCl	1.46 (s, 6H, $2CH_3$)	3.68 (c, 6H) 3.83 (c, 6H)	3.07	4.64	6.75 – 7.48 (m, 5H)	13.70
IIIe · HCl	0.92 (t, 6H, $2\underline{CH_3}CH_2$) 1.83 (q, 4H, $2CH_3\underline{CH_2}$), J = 7.2	3.73(c,3H) 3.82 (c, 3H)	2.99	4.72	7.00 – 7.47 (m, 7H)	13.63
IIIf · HCl	0.94 (t, 6H, $2\underline{CH_3}CH_2$) 1.76 (q, 4H, $CH_3\underline{CH_2}$), J = 7.2	3.80 (c, 6H) 3.67 (c, 6H)	3.12	4.62	6.77 – 7.56 (m, 5H)	13.62
IIIg · HCl	1.61 (broad s, 8H, $4CH_2$)	3.76 (c, 3H) 3.94 (c, 3H)	3.03	4.66	6.97 – 7.39 (m, 7H)	13.90
IIIh · HCl	1.35 (broad s, 8H, $4CH_2$)	3.45 (c, 6H) 3.75 (c, 6H)	3.02	4.55	6.76 – 7.49 (m, 5H)	13.85
IIIi · HCl	1.34 (broad s, 10H, $5CH_2$)	3.73 (c, 3H) 3.88 (c, 3H)	3.16	4.71	7.09 – 7.49 (m, 5H)	13.68

TABLE 3. Acute Toxicity and Antiarrhythmic Activity of Compounds Synthesized here

Compound	LD_{50}, mg/kg	ED_{50}, mg/kg	Antiarrhythmic index (AI)	Relative activity
IIIa · HCl	32.5 (26.0 – 40.0)	2.1 (1.7 – 2.5)	15.5	3.0
IIIb · HCl	65.0 (53.0 – 80.0)	15.0 (12.0 – 17.0)	4.3	0.8
IIIc · HCl	16.3 (13.0 – 20.0)	5.5 (4.0 – 7.5)	2.9	0.6
IIId · HCl	69.0 (50.0 – 95.0)	8.7 (6.3 – 12.0)	7.9	1.5
IIIe · HCl	30.0 (24.0 – 38.0)	4.5 (3.9 – 5.0)	6.8	1.3
IIIf · HCl	70.8 (59.0 – 84.0)	–	–	–
IIIg · HCl	35.5 (31.0 – 40.0)	2.2 (1.6 – 3.0)	16.1	3.2
IIIh · HCl	32.5 (28.0 – 38.0)	4.5 (3.7 – 5.9)	7.2	1.4
IIIi · HCl	30.0 (24.0 – 38.0)	8.9 (7.8 – 10.2)	3.4	0.7
IIIj · HCl	18.4 (13.0 – 25.0)	2.7 (2.0 – 3.8)	6.8	1.3
Lidocaine	32.5 (34.2 – 44.5)	7.7 (5.9 – 9.4)	5.1	1.0

was supplemented with 6 ml of glacial acetic acid with thorough mixing, followed by dropwise addition of 12 ml of concentrated sulfuric acid. Acetic acid was not added in the cases of inactivated carbinols IIa, b. Reactions were mixed intensely at a temperature of 20°C for 2 h (compounds IIIb, d, f, h, j) or 1 h at 60 – 70°C (all others), after which they were poured into 150 ml of iced water and the benzene layer was removed. The aqueous phase was neutralized with ammonia solution. The resulting oil was extracted with ether and dried over NaOH; ether was removed by evaporation to a volume of about 200 ml, and dry HCl was bubbled through to yield the hydrochloride, which was collected by filtration, dried, and recrystallized.

EXPERIMENTAL PHARMACOLOGICAL SECTION

The acute toxicity of the compounds was determined by i.v. administration [6]. AA was studied in a model of arrhythmia induced by i.v. administration of 3% calcium chloride solution at a dose of 280 mg/kg [7]. Experiments were performed on white mice weighing 18 – 24 g. Test compounds were given 2 min before induction of arrhythmia and activity was evaluated in terms of the ability to prevent lethal heart rhythm impairments.

Mean lethal and effective antiarrhythmic doses were determined by an express method [6].

As shown by the results (Table 3), the most toxic compounds were the hydrochlorides IIIc and IIIj. I.v. administration of these compounds gave LD_{50} values of 16.3 and 18.4 mg/kg respectively, i.e., they were more toxic than lidocaine. The reference substance was 2% lidocaine hydrochloride for injection from OAO Biokhimik (Saransk, Russia). The hydrochlorides of isoquinolines IIIa, e,g-i also had relatively high toxicity, with LD_{50} values in the range 30.0 – 35.5 mg/kg, which is comparable with the toxicity of lidocaine. The smallest mean toxic doses were obtained with the salts of compounds IIIb, f,d, with LD50 65.0 – 70.8 mg.

Most of the test compounds had antiarrhythmic activity.

The exception was compound IIIf. HCl, for which no effective dose could be determined as it had no antiarrhythmic effect. The most active compounds were IIIa, g. The effective antiarrhythmic doses of these substances were 2.1 and 2.2 mg/kg respectively. Given that the toxic doses of these compounds were 32.5 and 35.5 mg/kg, they had significant therapeutic width, with antiarrhythmic indexes of 15.5 and 16.1.

Thus, antiarrhythmic activity was three times greater than that of reference compound lidocaine (AI = 5.1).

Analysis of the relationship between activity and structure showed that the greatest AI values were seen with isoquinolines containing *spiro*-cycloalkanones in position 3. The presence of a methoxy group in the isoquinoline ring or in the benzyl fragment played no significant role.

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