SEARCH FOR NEW DRUGS

SYNTHESIS AND STUDY OF ANTIARRHYTHMIC AND ANTIAGGREGATIVE ACTIVITY OF AMIDINO ACIDS OF THE 3,4-DIHYDROISOQUINOLINE SERIES

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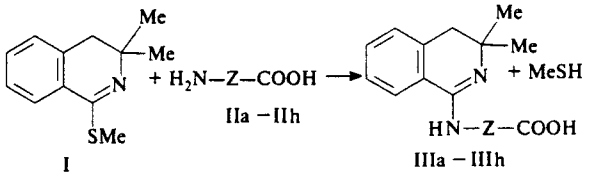
It was reported that compounds containing amidino groups exhibit antiarrhythmic activity [1 – 3]. According to other data [4 – 6], many of the 3,4-dihydroisoquinoline derivatives are also capable of producing the antiarrhythmic effect. Therefore, it was of interest to synthesize the derivatives of 3,4-dihydroisoquinoline with amidino groups and study their antiarrhythmic and antiaggregative activity.

The target compounds were obtained by the reaction between 1-methylthio-3,3-dimethyl-3,4-dihydroquinoline (I) and amino acids (IIa – IIh) containing primary amino groups.



Z = CH_2 (a); $(CH_2)_2$ (b); $(CH_2)_5$ (c); $CHCH_2CHMe_2$ (d); CHMe (e); $CHCH_2Ph$ (f); CHCH(Me)Et (g); $CH(CH_2)_2SMe$ (h)

Spectroscopic investigations confirmed the structures assigned to the synthesized compounds IIIa – IIIh (Table 1). For example, the ^1H NMR spectra (Table 2) displayed signals characteristic of the 3,3-dimethyl-3,4-dihydroquinoline fragments and the Z "bridges," with both positions and relative intensities corresponding to the suggested features. Because compounds IIId – IIIh contain asymmetric centers, the sig-

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TABLE 1. Yields, Physicochemical Characteristics, and Biological Activity of Amino Acids IIIa – IIh

Compound	Yield, %	M.p., °C	Empirical formula	Acute toxicity (LD_{50}), mg / kg	Inhibition of thrombocyte aggregation, %	Antiarrhythmic activity	
						ED_{50} (i.v.), mg / kg	AI (LD_{50} / ED_{50})
IIIa	26	125 – 155 (decomp.)	$C_{13}H_{16}N_2O_2$	1379.0 (1079 – 1763)	5.4 ($p > 0.05$)	101.2 (81.8 – 125.1)	13.6
IIIb	91	208 – 224	$C_{14}H_{18}N_2O_2$	399.3 (364.8 – 437.0)	12.9 ($p < 0.05$)	59.9 (45.5 – 78.9)	6.7
IIIc	53	210 – 215	$C_{17}H_{24}N_2O_2$	316.7 (286.0 – 350.7)	10.8 ($p < 0.05$)	36.7 (25.1 – 53.8)	8.6
IIId	48	182 – 183.5	$C_{17}H_{24}N_2O_2$	411.0 (365.5 – 462.2)	5.1 ($p > 0.05$)	22.8 (16.3 – 31.9)	20.3
IIIe	52	174 – 177	$C_{14}H_{18}N_2O_2$	751.8 (682.4 – 828.3)	0	45.5 (19.1 – 107.9)	15.0
IIIf	64	160 – 177	$C_{20}H_{22}N_2O_2$	392.1 (339.7 – 452.7)	0	65.7 (47.0 – 92.0)	6.0
IIIg	63	129 – 133	$C_{17}H_{24}N_2O_2$	282.0 (160.0 – 418.0)	0	0	0
IIIh	89	151 – 157	$C_{16}H_{22}N_2O_2S$	187.0 (52.5 – 382.6)	0	136.0 (124.6 – 151.5)	1.4

Note. Additional experiments showed that the broad m.p. intervals are caused by the formation ofintramolecular cyclization products of amidino acids in the course of melting.

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TABLE 2. Parameters of the ^1H NMR Spectra of Amino Acids IIIa – IIIh

Compound	Chemical shift, δ, ppm				Other protons
	3-$(CH_3)_2$ (6H)	4-H (2H)	NCH or NCH_2	H arom.	
IIIa	1.36 s	3.03 s	4.03 (s, 2H)	7.35 – 8.0 (m, 4H)	
IIIb	1.37 s	3.00 s	3.73 (t, 2H, $J_{\alpha\beta}$ 5.7 Hz)	7.35 – 7.95 (m, 4H)	2.55 (t, 2H, $J_{\alpha\beta}$ 5.7 Hz, CH_2COO)
IIIc	1.15 s	2.78 s	3.27	7.2 – 7.9 (m, 4H)	1.38 (m, $[(CH_2)_3]$), 2.01 (t, CH_2COO)
IIId	1.35 s 1.44 s	3.00, 3.09 (J_{AB} 16.5 Hz)	4.33 (q, 1H, J 14.5 Hz)	7.45 (d, 1H, J_{56} 7.6 Hz, 5-H), 7.54 (t, 1H, $J_{67} = J_{78}$, 7-H), 7.71 (t, 1H, $J_{56} = J_{67}$, 6-H), 8.04 (d, 1H, J_{78} 7.6 Hz, 8-H)	1.00 (d, 3H, J 10.5 Hz, γ-CH_3), 1.03 (d, 3H, J 10.5 Hz, γ-CH_3), 1.75 (m, 1H, γ-H), 1.95 (t, 2H, J 14.4 Hz, β-H)
IIIe	1.36 s	3.00 s	4.32 (q, J 6.4 Hz)	7.22 – 8.15 (m, 4H)	1.53 (d, 3H, J 6.4 Hz, β-H)
IIIf	1.24 s, 1.47 s	2.90, 3.07 (J_{AB} 15.8 Hz)	4.85 (dd, 1H, $J_{\alpha\beta}$ 9.8 Hz, $J_{\alpha\beta}$ 4.4 Hz)	7.45 (m, 6H, C_6H_5, 5-H), 7.56 (t, 1H, J_{67} 7.6 Hz, 7-H), 7.66 (t, 1H, $J_{67} = J_{56}$, 6-H), 8.06 (d, 1H, J_{78} 7.6 Hz, 8-H)	3.31 (dd, 1H, $J_{\beta\beta}$ 14.3 Hz, $J_{\beta\alpha}$ 9.8 Hz), 3.59 (dd, 1H, $J_{\beta\beta}$ 14.3 Hz, $J_{\beta\beta}$ 4.4 Hz)
IIIg	1.39 s	3.05 s	3.95 (d, J 8.6 Hz)	7.3 – 8.1 (m, 4H)	1.04 (m, 9H, CH_3, C_2H_5, β-H)
IIIh	1.39 s, 1.44 s	3.10 bs	4.54 (t, J 13 Hz)	7.5 – 8.4 (m, 4H)	2.17 (s, 3H, SCH_3), 2.40 (m, 2H, β-H), 2.62 (t, 2H, CH_2S)

nals due to CH_2 and CH_3 groups of the isoquinoline fragment are split into components. Compounds IIIf – IIIh were synthesized proceeding from *L*-amino acids; the corresponding optical activity was also observed in the reaction products.

The IR spectra of compounds IIIa – IIIh, measured as vaseline oil suspensions, exhibited absorption bands in the region of 1600 – 1585 cm^{-1} (attributed to the vibrations of the benzene ring conjugated with an unsaturated group), 1625 – 1605 cm^{-1} (carboxyl group), 1700 – 1660 and 2800 – 2400 cm^{-1} (iminium group), and 3425 – 3400 (free NH groups).

EXPERIMENTAL CHEMICAL PART

The IR absorption spectra were measured on UR-20 and Specord-M80 spectrophotometers. The ^1H NMR spectra were recorded with RYa-2310 (60 MHz) and Tesla BS 587A (80 MHz) spectrometers using D_2O as the solvent for compound IIIc, methanol-d_4 in all other cases, and HMDS as the internal standard. The melting temperatures were determined by capillary techniques using a heating device of the PTP type. The course of reactions was monitored by TLC on Silufol UV-254 plates, eluted with an ethyl acetate – methanol (3 : 1) mixture and developed with a ninhydrin solution. The $[\alpha]_D$ values of compounds IIIf – IIIh, measured with an SM-2 instrument, were – 42° (22°C; *c* 4.2, ethanol), + 22° (25°C; *c* 3.4, ethanol), and – 22° (25°C; *c* 3.4, ethanol), respectively. The data of elemental analyses corresponded to the structures proposed. The yields and physicochemical characteristics are listed in Table 1.

Synthesis of N-(3,3-dimethyl-3,4-dihydro-1-quinoline)amino acids (IIIa – IIIh). A mixture of 0.02 mole of the corresponding amino acid and 0.02 mole of compound I [7] in 25 ml of ethyl alcohol was boiled for 12 h (IIIa), 4 h (IIIb), 8 h (IIIc), or 16 h (IIId – IIIh). On cooling, the precipitate of the unreacted initial amino acid was separated by filtering, the filtrate evaporated in vacuum, and the residue washed with hexane and recrystallized from ethanol (IIIb, IIIc), acetonitrile (IIId – IIIh), or 2-propanol (IIIa).

EXPERIMENTAL BIOLOGICAL PART

The acute toxicity was studied by intravenous injections to a group of both male and female white mice weighing 26 – 20 g [8].

The antiaggregative activity was studied by the spectrophotometric technique proposed by Born [9], using thrombocytes from the blood plasma of dogs, and evaluated by the percentage decrease in the optical density of samples. The thrombocyte aggregation was initiated by ADP (0.05 mg / ml). All compounds were tested at the same concentration (0.2 mg / ml).

The antiarrhythmic activity was studied on a model of arrhythmia in white mice, induced by intravenous injections of calcium chloride at a dose of 280 mg / kg [10].

RESULTS AND DISCUSSION

The acute toxicity evaluation showed that LD_{50} in most cases exceeded 300 mg / ml, the lower values observed only for compounds IIIg and IIIh (282.0 and 187 mg / kg, respectively; see Table 1). The minimum toxicity was observed for compound IIIa having LD_{50} = 1379 mg / kg.

Of the total of eight compounds studied, four exhibited a weak antiaggregative activity and seven showed an antiarrhythmic action with the maximum effect observed for compound IIId having an antiarrhythmic index (AI) of 20.3. With respect to the arrhythmia model studied, this markedly exceeded the values for the known antiarrhythmic prepaparations such as novocainamide with ED_{50} 52.0 (40.0 – 67.5) mg / kg and AI = 2.1, verapamil [ED_{50} 2.5 (1.0 – 3.5) mg / kg; AI = 4.2], aet-

mozin [ED_{50} 8.0 (6.7 – 9.5) mg / kg; AI = 4.5], and lidocaine [ED_{50} 7.7 (5.9 – 9.4) mg / kg; AI = 5.1].

Thus, the amidino acids of the 3,4-dihydroisoquinoline series studied in this work belong to the class of low-toxic compounds. Most of the compounds exhibit a moderate antiarrhythmic activity, and some of them produce a weak antiaggregative effect.

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