SYNTHESIS AND STUDY OF ANTIAGGREGATIVE AND HYPOTENSIVE ACTIVITY OF 3,3-DIALKYL- ISOQUINOLINE AZOMETHINES AND THEIR DERIVATIVES

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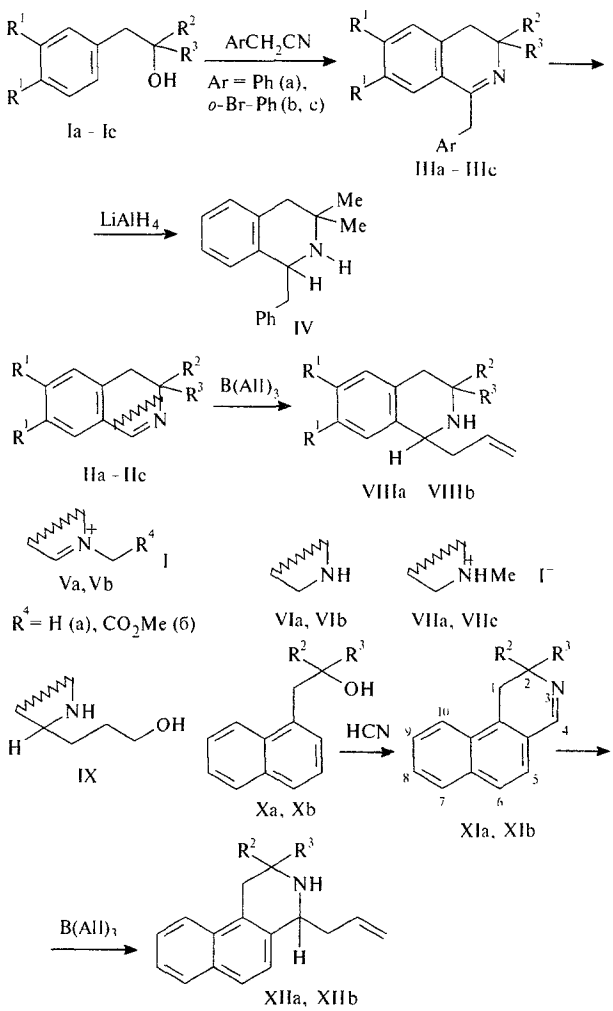
Some representatives of the class of isoquinoline derivatives were reported to exhibit antiaggregative activity [1 – 6]. In addition, a number of 1-substituted isoquinolines, such as 1-benzylisoquinolines, produce a hypotensive action [7, 8]. Allyl radical is close to the benzyl radical with respect to many chemical properties [9]. Therefore, it was of interest to compare the antiaggregative and hypotensive properties of some isoquinoline derivatives containing benzyl or allyl residues in position 1.

Reactions of carbinols Ia – Ie with the corresponding substituted benzyl cyanides lead to compounds IIIa – IIIc. Compound IIIa can be reduced by $LiAlH_4$ to tetrahydroisoquinoline IV. Interactions of carbinols Ia – Ie with HCN lead to azomethines IIa – IIe [10 – 12], which can be readily iodoalkylated to form salts Va, Vb and compounds VIa, VIb and VIIa, VIIb [12]. In order to obtain the 1-allyl derivatives of isoquinoline, we have carried out allylboriding of the above azomethines. Similarly to the processes studied previously for compounds IIa and IIb [13], the reactions of compounds IIc – IIe with triallylborane proceed under mild conditions (20°C) and lead to the corresponding 1-allyl-1,2,3,4-tetrahydroisoquinolines VIIIa – VIIIe. Alcohol IX was obtained using a hydroboriding-oxidation reaction described elsewhere [13].

Analogous syntheses were carried out using other carbinols (Xa and Xb) as the initial compounds. The subsequent allylboriding of the products of these reactions led to the corresponding benzo[f]isoquinoline derivatives (XIIa and XIIb).

All the newly synthesized compounds (Table 1) were isolated and studied in the form of soluble salts. The substances obtained previously were tested in the form of hydroiodides (IIa, Va, Vb, VIIa, and VIIb) and hydrochlorides (otherwise).

The ^1H NMR spectra of the salts of 1-benzylisoquinolines IIIb and IIIc (Table 2) are analogous to the spectra of known compounds of this series [7, 12]. The proposed structures are confirmed by the presence of singlet signals at 3.85



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and 3.90 ppm in the ^{1}H NMR spectra of these salts, as well as the absorption bands at 1630 cm^{-1} in the IR spectra of their bases. The ^{1}H NMR spectrum of the reduction product IV containing a chiral center (1-C) markedly differs from the spectra of the initial azomethines. In particular, there is a diastereotopic splitting of the signals from protons of the CH_2 groups and a clear triplet due to the proton at 1-C (Table 2).

A more complicated pattern is observed in the ^{1}H NMR spectra of allylboriding products VIIIc – VIIIe, XIIa, and XIIb. These substances, as well as compound IV, are derivatives of 1,2,3,4-tetrahydroisoquinoline. In these compounds, in contrast to the initial azomethines, the protons of the two methyl groups in position 3 (IV and XIIa) are manifested as two singlets reflecting the loss of planar structure of the isoquinoline cycle as a result of hydriding or allylboriding. In addition to this, the spectra of the allylboriding products exhibit signals corresponding to the allyl residue (5.20 – 5.27 ppm, $H_2C=$; 5.97 – 6.10 ppm, –HC=) and the H_2C–C= group (Table 2). IR spectra of the bases of compounds IV, VIII, and XII display absorption bands due to the NH groups (3370 cm^{-1}) and a double bond of the allyl residue (1645 cm^{-1}).

TABLE 1. Physicochemical Properties of the Synthesized Compounds

Compound	Yield, %	M.p., °C	Empirical formula
IIIb	32	161 – 162	$C_{18}H_{18}BrN \cdot HCl$
IIIc	74	210 – 211	$C_{20}H_{22}BrNO_2 \cdot HCl$
IV	88	221 – 222	$C_{18}H_{21}N \cdot HCl$
VIIIc	82	168 – 170	$C_{17}H_{23}N \cdot HI$
VIIId	70	173 – 174	$C_{19}H_{27}NO_2 \cdot HCl$
VIIIe	77	175 – 176	$C_{18}H_{25}NO_2 \cdot HCl$
XIIa	87	197 – 198	$C_{18}H_{21}N \cdot HCl$
XIIb	68	181 – 183	$C_{20}H_{23}N \cdot HCl$

The clearest evidence for the proposed structures of the new allyl derivatives of isoquinoline (VIIIa – VIIIe, XIIa, and XIIb) is found in their ^{13}C NMR spectra (Table 3). As seen from these data, the spectra contain signals due to the $R^2 – R^3$ groups and the corresponding 1-C and 3-C atoms. In addition, there are signals from the allyl and benzyl CH_2 groups (34.9 – 37.7 ppm) and the carbon atoms linked by double bonds in the allyl group (118.6 – 119.4 ppm,

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds (chemical shifts δ, ppm)

Compound	R^2–R^3	CH_2–C_4(Ar), CH_2–C=	$2CH_3O$	CH–$C_{(1)}$ (bm)	H_2C=, –HC= (2m)	Ar	NH^+ $(NH)^+$
IIIb	1.23 s	2.63 s (CH_2–C_4), 3.85 s (CH_2–Ar)	–	–	–	7.15 – 7.80 m (8H)	11.80 s
IIIc	1.27 s	2.62 s (CH_2–C_4), 3.90 s (CH_2–Ar)	3.70 s, 3.72 s	–	–	6.50 s (H–C_5), 6.70 s (H–C_8), 7.10 – 7.40 m (4H)	11.90 s
IV	1.08 s, 1.18 s	*	–	4.30 t	–	6.67 – 7.47 m (9H)	5.33 bs
VIIIc	1.0 – 2.05 m ($5CH_2$)	2.65 – 3.40 m	–	4.63	5.27, 5.97	7.02 – 7.60 m (4H)	8.50 c, 8.80 s
VIIId	1.0 – 2.12 m ($5CH_2$)	2.82 – 3.20 m	3.71 s, 3.73 s	4.41	5.24, 6.08	6.80 s (H–C_5), 6.90 s (H–C_8)	9.27 s, 9.68 s
VIIIe	1.0 – 2.15 m ($4CH_2$)	2.50 – 3.25 m	3.71 s, 3.72 s	4.42	5.21, 6.03	6.72 s (H–C_5), 6.90 s (H–C_8)	9.30 s, 9.60 s
XIIa	1.03 s and 1.07 s ($2CH_3$)	3.45 m	–	4.50	5.25, 6.10	7.45 – 8.10 m (6H)	9.70 bm
XIIb	1.50 – 2.40 m (CH_2)$_5$	3.40 m, 3.50 m	–	4.76	5.20, 6.0	7.43 – 8.10 m (6H)	9.67 c, 10.15 s

* 4-CHAHB: δ_A = 2.40 ppm, δ_B = 2.90 ppm, $^2J_{AB}$ = 10.0 Hz; PhCHAHB: δ_A = 3.1 ppm, δ_B = 3.4 ppm, $^2J_{AB}$ = 6.0 Hz.

TABLE 3. ^{13}C NMR Spectra of Compounds VIIIc – VIIIe, XIIa, and XIIb (chemical shifts δ, ppm)

Compound	$R^2 – R^3$ signals	1-C and 3-C	4-C and CH_2–C=C	CH_2=CH	$2CH_3O$	Ar
VIIIc	20.8, 20.9, 24.7, 28.5, 33.1 ($5CH_2$)	51.2 and 57.3	35.1, 37.5	119.5, 133.2	–	126.7 and 131.4 (C-4a, 8a), 125.9, 126.7, 129.3, 130.9 (C-5,6,7,8)
VIIId	21.1 (2C), 24.9, 28.0, 32.5 ($5CH_2$)	50.9 and 57.0	34.9, 37.7	118.9, 134.4	55.5, 55.7	109.9, 112.2, 123.5 (2C) (C-4a, 5, 8, 8a), 147.4 and 148.1 (C-6.7)
VIIIe	23.2, 23.3, 31.9, 36.9 ($4CH_2$)	52.8 and 63.7	37.3, 37.7	118.6, 133.9	55.4, 55.7	109.9, 112.3, 123.9, 124.5, (C-4a, 5, 8, 8a), 147.5 and 148.0 (C-6.7)
XIIa	25.5 and 26.5 ($2CH_3$)	53.7 and 62.1	34.9, 37.5	119.4, 113.8	–	123.2, 123.6, 126.2, 126.8, 127.4 (2C), 128.3, 128.6, 131.1, 132.0
XIIb	23.5, 23.6, 32.6, 33.9 ($4CH_2$)	53.3 and 63.4	37.3, 37.6	119.4, 133.4	–	123.3, 123.8, 126.2, 126.8 (2C), 128.0, 128.3, 129.4, 131.2, 132.0

H_2C=; 133.2 – 134.4 ppm, –HC=) and the aromatic part of the molecule (Table 3).

EXPERIMENTAL CHEMICAL PART

The IR spectra were measured on an UR-20 spectrophotometer (Germany) using samples dissolved in $CHCl_3$. The ^1H NMR spectra of salts IIIb, IIIc, and IV were recorded on a 60-MHz RYa-2310 spectrometer (Russia). The ^1H and ^{13}C NMR spectra of salts VIIIc – VIIIe, XIIa, and XIIb were measured with 200-MHz Bruker AC-200 spectrometer (Germany). All the NMR measurements were performed using DMSO-d_6 as the solvent and HMDS as the internal standard.

Salts VIIIc – VIIIe and XIIb were recrystallized from acetonitrile, and the other compounds, from isopropyl alcohol. The data of elemental analyses agree with the results of analytical calculations. Table 4 gives the pharmacological characteristics of the substances studied, of which compounds IIa and IIb were previously reported in [10]. Compound IIb was previously characterized in the form of hydroiodide [10]; we have also biologically tested a hydrochloride with m.p. = 189 – 190°C. The synthesis and properties of other compounds were previously described in [14] (compound IIIa), [12] (IIb – IIe, Va, Vb, XIa, XIb), [11] (VI, VIIa, VIIb), and [13] (VIIIa, VIIIb).

1-(*o*-Bromobenzyl)-6,7-(R^1)$_2$-3,4-dihydroisoquinolines (IIIb, IIIc). To 1.96 g (0.01 mole) of *o*-bromobenzyl cyanide in 30 ml benzene at a temperature not exceeding 5°C was added dropwise 4 ml of concentrated H_2SO_4 (for compound IIIb) or 2 ml glacial AcOH followed by 4 ml concentrated H_2SO_4 (for IIIc). Then 0.01 mole of the corresponding carbinol in 20 ml benzene was added and the reaction mixture was vigorously stirred at 60°C for 2 h (IIIb) or 30 min (IIIc), cooled, and poured into 100 ml of ice-cold water. The benzene layer was decanted and the aqueous phase neutralized with aqueous ammonia. The separated oily base was extracted with ether and dried over K_2CO_3. The ether solution was filtered and bubbled with gaseous HCl. The precipitate was filtrated, dried, and recrystallized to obtain the corresponding target compounds in the form of hydrochloride.

1-Benzyl-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (IV). To a solution of 0.19 g (0.005 mole) of $LiAlH_4$ in 50 ml

TABLE 4. Antiaggregative and Hypotensive Properties of the Synthesized Compounds

Compound	R^1	R^2-R^3	Inhibition of thrombocyte aggregation		Hypotensive effect		
			%	*p*	Maximum AP reduction, Torr	Duration, min	*p*
IIa	H	2Me	13.0 ± 0.2	< 0.05	15	1	< 0.05
IIb	MeO	2Me	12.5 ± 0.1	< 0.05	*	–	–
IIc	H	$(CH_2)_5$	13.4 ± 0.3	< 0.05	26	10	< 0.05
IId	MeO	$(CH_2)_5$	14.2 ± 0.3	< 0.05	17	10	< 0.05
IIe	MeO	$(CH_2)_4$	16.3 ± 0.4	< 0.05	30	10	< 0.05
IIIa	H	2Me	27.4 ± 0.2	< 0.05	–	–	–
IIIb	H	2Me	13.0 ± 0.1	< 0.05	23	10	< 0.05
IIIc	MeO	2Me	67.0 ± 0.02	< 0.04	54	10	< 0.001
IV	H	2Me	17.0 ± 0.2	< 0.05	71	60	< 0.001
Va	H	2Me	–	–	70	5	< 0.001
Vb	MeO	2Me	5.4 ± 0.4	< 0.05	42	7	< 0.05
VIa	H	2Me	7.9 ± 0.2	< 0.05	–	–	–
VIb	MeO	2Me	6.2 ± 0.3	< 0.05	*	–	–
VIIa	H	2Me	2.0 ± 0.1	< 0.05	18	10	< 0.05
VIIb	MeO	2Me	2.0 ± 0.2	< 0.05	–	–	–
VIIIa	H	2Me	–	–	48	20	< 0.05
VIIIb	MeO	2Me	2.1 ± 0.2	< 0.05	48	15	< 0.05
VIIIc	H	$(CH_2)_5$	4.0 ± 0.3	< 0.05	33	5	< 0.05
VIIId	MeO	$(CH_2)_5$	6.4 ± 0.4	< 0.05	39	10	< 0.05
VIIIe	MeO	$(CH_2)_4$	–	–	32	5	< 0.05
IX	MeO	2Me	9.2 ± 0.1	< 0.05	–	–	–
XIa	–	2Me	35.0 ± 0.3	< 0.01	25	10	< 0.05
XIb	–	$(CH_2)_4$	19.6 ± 0.2	< 0.05	26	10	< 0.05
XIIa	–	2Me	51.7 ± 0.1	< 0.01	50	5	< 0.05
XIIb	–	$(CH_2)_5$	48.4 ± 0.2	< 0.01	20	5	< 0.05
Papaverine			71.7 ± 0.0	< 0.01	25	2	< 0.05

* Hypertensive effects: compound IIb (AP increased by 28 Torr for 5 min); compound VIb (AP increased by 30 Torr within 30 min).

of absolute ether was added dropwise with stirring (20°C) a solution of 2.49 g (0.01 mole) of base IIIa in 30 ml of ether. The reaction mixture was heated to boiling for 1 h and cooled. Then 10 ml was added dropwise and the ether layer was decanted. The deposit of $Al(OH)_3$ was washed with ether (3 × 20 ml). The ether extracts were combined and treated as described above for salts IIIb and IIIc.

1-Allyl-3-R^2-3-R^3-6,7-(R^1)$_2$-1,2,3,4-tetrahydroisoquinolines (VIIIc – VIIIe) and 4-allyl-2-R^2-2-R^3-tetrahydrobenzo[f]isoquinolines (XIIa, XIIb). All operations with organoboron compounds are performed in a dry argon atmosphere. To a solution of 1.47 g (0.011 mole) triallylborane in 5 ml of ether was added with stirring a solution of 0.01 mole of the corresponding azomethine IIc – IIe in 30 ml ether and the mixture was heated to boiling for 1 h and cooled to 20°C. To this mixture were sequentially added 1 ml of methanol and 2.9 ml of a 5 M NaOH solution and the reaction mass was stirred for 30 min. Then the ether layer was decanted and the aqueous layer was extracted with ether (3 × 10 ml). The ether extracts were combined, washed with water and saturated NaCl solution, and dried over K_2CO_3. Then the solvent was evaporated until the solution volume was reduced to 10 ml. To this ether solution was carefully added 1.40 ml of a 50% HI solution. The precipitated crystalline hydroiodide IIIc was filtrated, dried, and recrystallized. Hydrochlorides of the other compounds were obtained similarly to compounds IIIc and IIId.

EXPERIMENTAL PHARMACOLOGICAL PART

The antiaggregative activity of the synthesized compounds was studied photometrically using the Born method and evaluated by the percentage decrease in the optical density of samples [15]. The thrombocyte aggregation was stimulated by ADP (0.05 mg per ml dog blood plasma). All the synthesized compounds were tested at a concentration of 0.2 mg/ml plasma.

The hypotensive activity of the compounds studied (5 mg/kg, i.v.) was determined in hexenal-narcotized (100 mg/kg) cats weighing 2.5 – 3.5 kg. Each compound was studied in a group of 7 animals.

The experimental data were processed using the Student t-criterion, the results being considered as reliable for $p < 0.05$.

As seen from the experimental data presented in Table 4, most of the synthesized compounds produce a weak antiaggregative effect. The most active compounds – the *o*-bromobenzene derivative IIIc and benzo[f]isoquinolines XIIa and XIIb containing the allyl residue in position 4 – are comparable in activity with the reference drug papaverine.

As for the effect of the synthesized compounds upon arterial pressure, the most pronounced hypotensive action (exceeding that of papaverine) was observed for compounds IV and Va. Note that the structurally similar compounds IIb and VIb produce a hypertensive effect.

Thus, the results of our tests agree with the previous data showing that the antiaggregative activity with respect to thrombocytes is inherent in isoquinolines containing methoxy groups in positions 6 and 7 and a benzyl residue in position 1 [1, 3, 7]. The presence of an alkyl residues in position 1 decreases the antiaggregative activity in the isoquinoline derivatives but increases this activity in the benzo[f]isoquinoline derivatives.

Data on the hypotensive activity of the compounds studied call for further investigation into the class of 1-benzylisoquinoline derivatives.

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