SYNTHESIS BASED ON β-PHENYLETHYLAMINES. IV. SYNTHESIS AND ANTIARRHYTHMIC ACTIVITY OF SUBSTITUTED PHENYLALKYLAMINES AND N-BENZYLTETRAHYDROISOQUINOLINES

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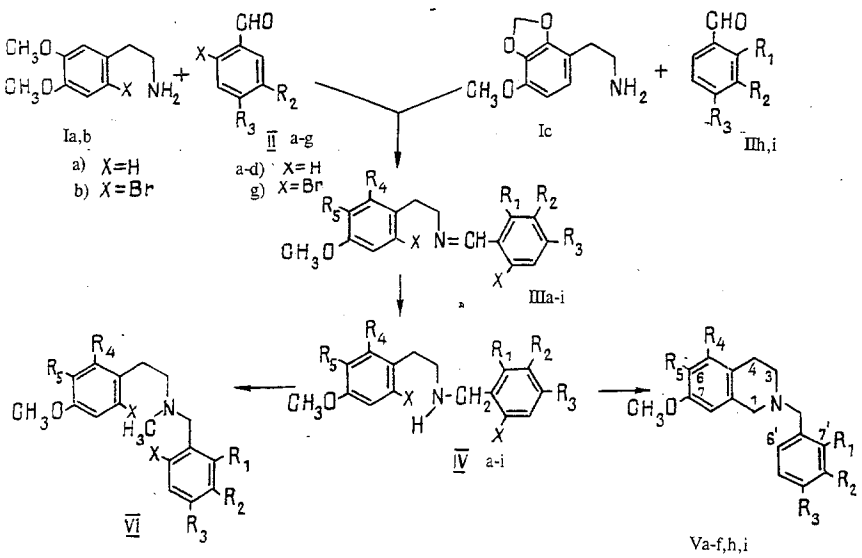
A number of N-benzyltetrahydroisoquinolines forming analogues of sendaverine have been synthesized. Results on the pharmacological activity of the compounds synthesized are presented.

The problem of creating new effective drugs for the treatment of cardiovascular diseases is not losing its topicality, and this is leading to an intensive search for active cardiotonics of low toxicity. The chemical structures of antiarrhythmic drugs are very diverse [1]. Among cardiotropic substances of nonsteroid structure there are a number of substituted phenylalkylamines [2], which has induced us to carry out the synthesis of a number of β-phenylethylamines that can be used as the starting materials for obtaining substituted N-benzyltetrahydroisoquinolines and to determine, with these compounds as examples, the relationship between chemical structure and pharmacological activity.

N-Benzyltetrahydroisoquinolines were synthesized by the interaction of homoveratrylamine (Ia) or 4-methoxy-2,3-methylenedioxyphenethylamine (Ic) with substituted benzaldehydes (IIa-i) to form the Schiff compounds (IIIa-i), which were reduced with sodium tetrahydroborate to the bases (IVa-i). The Mannich cyclization of the amines (IV) with formaldehyde in an acid medium gave the substituted N-benzyltetrahydroisoquinolines (Va-f, h, i).*

Methylation of the amines under the conditions given in [3] yielded the N-methyl derivatives in accordance with the scheme shown below.



*Compound (IVg) did not give a cyclization product, which is explained by the passivating influence of the bromine.

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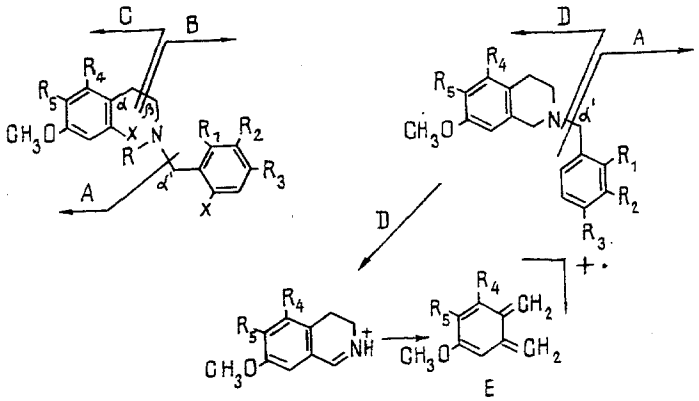
III — VI	R_1	R_2	R_3	R_4	R_5	X
a	H	H	OH	H	OCH_3	H
b	H	H	OCH_3	H	OCH_3	H
c	H	—OCH_2O—		H	OCH_3	H
d	H	OCH_2Ph	OCH_3	H	OCH_3	H
e	H	OH	OCH_3	H	OCH_3	H
f	H	OCH_3	OCH_3	H	OCH_3	H
g	H	—OCH_2O—		H	OCH_3	Br
h	OCH_3	H	H	—OCH_2O—		H
i	—OCH_2O—		OCH_3	—OCH_2O—		H

The structures of the substances obtained were confirmed by their mass and PMR spectra. With respect to their structures, they can be divided into two groups: substituted phenylalkylamines (IV and VI) and N-benzyltetrahydroisoquinolines (V) — analogues of alkaloids of the types of sendaverine and corgoine [4].

Under the action of electron impact, the amines formed unstable molecular ions the characteristic direction of breakdown of which was, as a rule, the splitting out of the benzyl group (pathway A), possibly stabilized in the form of the tropylium ion [5]. Another direction of breakdown was the cleavage of the C_α—C_β bond, leading to the formation of intense peaks of the B^+ and C^+ ions.

In the spectra of (IV) and (VI) there were the peaks of ions resulting from the cleavage of the C_β—N bond, but they were weak. The presence of two bromine atoms in the amine VIg did not change the direction of breakdown, but an additional ion, $(M - Br)^+$, appeared.



The molecular ions of compounds (V) were more stable. The nature of the fragmentation of this group of bases is connected with the cleavage of the N—C'_α bond, with localization of the charge on the benzyl moiety (A^+) or on the nitrogen atom (D^+). The retrodiene decomposition of the dihydroisoquinoline ring of the D^+ ion leads to the formation of the intense ion E^+.

PHARMACOLOGY*

The resorptive actions of all the compounds investigated were qualitatively similar. After their intraperitoneal injection in toxic doses, mobility was severely limited, the extremities splayed out, tremor, and, in some animals, convulsions were observed. Respiration became rapid and superficial, or, in the case of lethal doses, rare and labored, with final cessation. The doses of the substances synthesized (IV)-(VIa-i) that caused the death of the animals (LD_{50}) ranged from 75 to 380 mg/kg, which gives grounds for considering them to have a relatively low toxicity.

All the compounds significantly suppressed the orienting reaction of mice and, in different degrees, potentiated the action of hypnotics. Thus, relatively small doses of the hydrochlorides of (IVa and h) and of (VIb and h) lengthened more than threefold the sleep induced by ethaminal sodium and by chloral hydrate. In small doses, the majority of the compounds lowered the arterial pressure to a moderate degree, while some caused brachycardia and exerted a well-defined antiarrhythmic action. Here, in the aconite model of arrhythmia the highest antiarrhythmic activity was shown by the hydrochlorides of compounds

*The pharmacological part was performed by U. Khaitov.

(IV)-(VIe), while compounds (VIc and f) were most effective on the model of arrhythmia caused by calcium chloride. The results of comparative experiments performed under analogous conditions showed that with respect to the spectrum of their antiarrhythmic action and the breadth of their specific antiarrhythmic activity — i.e., the ratio of LD_{50} to dose — these compounds are not inferior to such antiarrhythmic drugs as quinine, novocainamid, lidocaine, and fenoptin.

EXPERIMENTAL

Methods of Investigation. The resorptive action and toxicity of the compounds synthesized, together with the determination of LD_{50} values were studied on random-bred white mice. Influence on the central nervous system was judged from the change in the orienting reaction and the duration of sleep induced by ethaminal sodium and chloral hydrate. The action of the compounds on the course of experimental cardiac arrhythmia caused by aconitine and calcium chloride was investigated in acute experiments on narcotized rats. The influence of the compounds on arterial pressure was investigated in acute experiments on cats. Mass spectra were taken on a MKh-1310 instrument with a system for direct introduction into the ion source. PMR spectra were obtained on a TESLA BS-567A instrument (100 MHz, δ scale 0 — HMDS).

o-Methoxybenzaldehyde was obtained by the method of [6], **3-benzyloxy-4-methoxybenzaldehyde** by that of [7], and **4-methoxy-2,3-methylenedioxybenzaldehyde** and **4-methoxy-2,3-methylenedioxyphenylethylamine** by that of [8].

6-Bromopiperonal. With stirring, at room temperature, 3.5 ml of bromine (in 10 ml of acetic acid) was added dropwise to a solution of piperonal (10 g; 0.07 mole) in 50 ml of acetic acid. The reaction mixture was stirred for another 2 h and was poured into 400 ml of ice water.

The precipitate that deposited was filtered off, giving 13.8 g of a crude product. After recrystallization from benzene, mp 130-131°C.

General Procedure for Obtaining the Amines (IIa-i). A solution of a substituted phenylethylamine (I) (0.021 mole) in 100 ml of benzene was treated with 0.02 mole of a substituted benzaldehyde (IIa-g), and the mixture was boiled with the azeotropic elimination of water. The imine (III) obtained after the benzene had been distilled off was dissolved in methanol (200-500 ml) and, with vigorous stirring at 0-5°C, was reduced with sodium tetrahydroborate (0.15 mole). After evaporation, the residue was dissolved in water and extracted with ether (or chloroform). The extracts were washed with water and dried with sodium sulfate. After the solvent had been distilled off the technical amine was obtained.

N-(Methoxybenzyl)-3,4-dimethoxyphenylethylamine (IVb). mp of the hydrochloride (HC) 225-227°C, $C_{18}H_{23}NO_3$, yield 87%. Mass spectrum, *m/z* (%): 301 (M^+), 164 (41), 121 (100). PMR spectrum: 3.76 (s, 6H), 3.72 (s, 3H), 3.34 (s, 2H), 2.58 (m, 4H).

N-(4-Hydroxybenzyl)-3,4-dimethoxyphenylethylamine (IVa). mp of the HC 120-125°C, $C_{17}H_{21}NO_3$, yield 74%. Mass spectrum, *m/z* (%): 287 (M^+), 164 (37), 107 (100).

N-(3,4-Methylenedioxybenzyl)-3,4-dimethoxyphenylethylamine (IVc). mp of the HC 193-195°C, $C_{18}H_{21}NO_4$, yield 79%. Mass spectrum, *m/z* (%): 315 (M^+), 178 (37), 164 (11), 135 (100). PMR spectrum: 5.75 (2H, OCH_2O), 372 (6H, $2OCH_3$), 3.59 (s, 2H), 2.72 (m, 4H).

N-(3-O-Benzyl-4-methoxybenzyl)-3,4-dimethoxyphenylethylamine (IVd). mp of the HC 150-152°C, $C_{25}H_{29}NO_4$, yield 89%. Mass spectrum, *m/z* (%): 407 (M^+), 270 (30), 227 (100). PMR spectrum: 4.98 (s, OCH_2Ar), 3.68 (6H), 3.65 (3H), 3.35 (s), 2.58 (m).

N-(3-Hydroxy-4-methoxybenzyl)-3,4-dimethoxyphenylethylamine (IVe). mp of the HC 145-148°C, $C_{18}H_{23}NO_4$, yield 64%. Mass spectrum, *m/z* (%): 317 (M^+, 0.3), 315 (3.2), 166 (16.3), 164 (10), 152 (26.9), 151 (11.3), 149 (6.3), 138 (10), 137 (100), 122 (6.3), 97 (6.3), 95 (5.6), 83 (5.0), 57 (6.9), 55 (6.9).

N-(3,4-Dimethoxybenzyl)-3,4-dimethoxyphenylethylamine (IVf). mp of the HC 140°C, $C_{19}H_{25}NO_4$, yield 74%. Mass spectrum, *m/z* (%): 331 (M^+, 1.4), 180 (9), 179 (9), 178 (9), 152 (19), 151 (100), 149 (6.5), 107 (7.8), 97 (9.6), 95 (9.6), 83 (7.8), 81 (9.6), 6.9 (9.6), 55 (9.6).

N-(2-Methoxybenzyl)-4-methoxy-2,3-methylenedioxyphenylethylamine (IVh). mp of the HC 106-107°C, $C_{18}H_{22}NO_4$, yield 64%. PMR spectrum: 5.93 (s, OCH_2O), 3.78 (s, 6H), 3.55 (2H), 2.70 (ArH).

N-(4-Methoxy-2,3-methylenedioxybenzyl)-4-methoxy-2,3-methylenedioxyphenylethylamine (IVi). mp of the HC 156-157°C, $C_{19}H_{21}NO_6$, yield 27%. PMR spectrum: 5.96, 5.90, 3.85, 3.78, 3.59 (2H), 2.68 (4H), 6.18 d, 6.78 d.

N-(6-Bromo-3,4-methylenedioxybenzyl)-6-bromo-3,4-methylenedioxyphenylethylamine (IVg). mp of the HC 189-190°C, $C_{19}H_{21}NO_4Br_2$, yield 55%. Mass spectrum, *m/z* (%): 475/473/471 (M^+, 0.3), 392/394 (26), 242/244 (33), 213/215 (100), 135 (20). PMR spectrum: 6.87 (ArH), 6.81 (ArH), 5.75 (OCH_2O), 4.15 (2H), 3.76 (3H), 3.75 (3H), 3.12 (4H).

Preparation of the Amines (V). A mixture of the hydrochloride of an amine (IV) (0.02 mole), methanol (50 ml), formalin (30%, 20 ml), and a few drops of conc. HCl (to pH 2) was boiled under reflux for 4 h. After the solvent had been distilled off, the residue was diluted with water, made alkaline with NH_4OH, and extracted with chloroform. The extracts were washed with water and dried with sodium sulfate. After the solvent had been distilled off, the residue was dissolved in acetone, and conc. HCl was added, to pH 3. The precipitate of the hydrochloride of the amine (V) that deposited was filtered off.

N-(4-Methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (Vb). mp 190-193°C, $C_{19}H_{23}NO_3$, yield 82%. Mass spectrum, *m/z* (%): 313 (M^+, 34), 312 (38), 192 (21), 164 (48), 121 (100).

N-(4-Hydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (Va). mp of the HC 227-230°C, $C_{18}H_{21}NO_3$, yield 73%. Mass spectrum, *m/z* (%): 299 (M^+, 32), 298 (37), 192 (53), 164 (100), 107 (30).

N-(3,4-Methylenedioxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (Vc). mp of the HC 223-225°C, yield 76%. Mass spectrum, *m/z* (%): 327 (M^+, 3), 326 (3), 192 (88), 164 (71), 135 (100).

N-(3-O-Benzyl-4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (Vd). mp of the HC 205-208°C, yield 77%. Mass spectrum, *m/z* (%): 419 (M^+, 8.6), 418 (12), 328 (51), 227 (51), 192 (100), 164 (48), 137 (55), 91 (50). PMR spectrum: 7.22 (m), 6.92, 6.77 (s, 2H), 6.49 (s), 6.36 (s), singlets 3.76, 3.72, 3.70 (OCH_3), 5.04 (OCH_2Ar), 3.38 (s), 3.46 (s), 2.64 (m).

N-(3-Hydroxy-4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (Ve). mp of the HC 188°C, yield 73%. $C_{19}H_{23}NO_4$. Mass spectrum, *m/z* (%): 329 (M^+, 13.5), 328 (18.9), 193 (15), 193 (100), 164 (50), 149 (27), 138 (22), 137 (55), 123 (15), 111 (14), 97 (20.3), 95 (17.6), 85 (14.9), 83 (19), 57 (27), 55 (21.6).

N-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (Vf). mp of the HC 172°C, $C_{20}H_{25}NO_4$, yield 81%. Mass spectrum, *m/z* (%): 343 (M^+, 4), 342 (5), 202 (8), 200 (7), 194 (7.6), 193 (7), 192 (52), 165 (7), 163 (24), 152 (30), 151 (100), 149 (13), 140 (16), 137 (8), 121 (11), 109 (8), 107 (9), 97 (9), 95 (7), 83 (9), 81 (10), 69 (12), 57 (10), 55 (9). PMR spectrum: 2.65 (4H, m, 2H-3,2H-4), 3.45 (2H, s, H-α), 3.51 (2H, s, 2H-1), 3.72 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.76 (6H, s, $2OCH_3$), 6.38 (1H, s, H*-5), 6.48 (1H, s, H*-8), 6.72 (1H, s, H-2), 6.81 (2H, d, H-5′, H-6′).

N-(2-Methoxybenzyl)-5,6-methylenedioxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (Vh). mp of the HC 194-196°C, $C_{19}H_{22}NO_4$, yield 81%. Mass spectrum, *m/z* (%): 327 (M^+, 60), 326 (73), 206 (46), 178 (100), 121 (16). PMR spectrum: 6.95, 6.19, 5.93 (OCH_2O), 3.78 (2 OCH_3), 3.67, 3.55, 2.70.

N-(4-Methoxy-2,3-methylenedioxybenzyl)-7-methoxy-5,6-methylenedioxy-1,2,3,4-tetrahydroisoquinoline(Vi).mp of the HC 205-207°C, $C_{20}H_{21}NO_6$, yield 63%. Mass spectrum, *m/z* (%): 371 (M^+, 17), 372 (17), 206 (96), 178 (98), 165 (100). PMR spectrum: 6.78, 6.18, 5.98 (OCH_2O), 3.86 (OCH_3), 3.79 (OCH_3), 3.58, 3.53, 2.69.

Preparation of the Amines (VI). A mixture of an amine (IV) (0.012 mole), methanol (50 ml), and formalin (30%, 25 ml) was boiled under reflux for 2 h. After cooling, the vigorously stirred mixture was reduced with sodium tetrahydroborate. the residue after evaporation of the solvent was diluted with water and extracted with chloroform. The solvent was distilled off, and the hydrochloride was obtained by dissolving the residue in acetone and adding conc. HCl, to pH 3-4. The precipitate that deposited was filtered off.

N-(4-Methoxybenzyl)-N-methyl-3,4-dimethoxyphenylethylamine (VIb). mp of the HC 170-172°C, $C_{19}H_{25}NO_3$, yield 71%. Mass spectrum, *m/z* (%): 315 (M^+, 1.6), 164 (38), 121 (100). PMR spectrum: 3.76 (2 OCH_3), 3.74 (OCH_3), 2.17 ($N—CH_3$).

N-Methyl-N-(3,4-Methylenedioxybenzyl)-3,4-dimethoxyphenylethylamine (VIc). mp of the HC 172-176°C, $C_{19}H_{23}NO_4$, yield 59%. Mass spectrum, *m/z* (%): 329 (M^+, 1.5), 178 (44), 135 (100). PMR spectrum: 6.70 (d, J = 8 Hz), 6.63 (d, J = 8 Hz), 6.62 (s), 5.78 (s, OCH_2O), 3.74 (OCH_3), 3.72 (OCH_3), 2.17 ($N—CH_3$).

N-(3-Hydroxy-4-methoxybenzyl)-N-methyl-3,4-dimethoxyphenylethylamine (VIe). mp of the HC 153-156°C, $C_{26}H_{31}NO_4$. Mass spectrum, *m/z* (%): 421 (M^+, 0.5), 270 (32), 227 (100), 91 (16). PMR spectrum: 7.20 m, 6.48 (, J = 8 Hz), 6.70 (s), 6.59 (s), 4.92 (OCH_2Ar), 3.68 (OCH_3), 3.65 (OCH_3), 2.15 ($N—CH_3$).

N-(3,4-Dimethoxybenzyl)-N-methyl-3,4-dimethoxyphenylethylamine (VIf). mp of the HC 183-185°C, $C_{20}H_{27}NO_4$, yield 67%. Mass spectrum, *m/z* (%): 345 (M^+, 0.7), 343 (1), 194 (22), 152 (12), 151 (100), 149 (8), 139 (7), 109 (6), 107 (7), 97 (7), 95 (7), 81 (7), 69 (6), 60 (6), 57 (7), 55 (9).

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*The assignments of these signals may be interchanged.

N-(2-Methoxybenzyl)-N-methyl-4-methoxy-2,3-methylenedioxyphenylethylamine (VIh). mp of the HC 108-110°C, $C_{19}H_{24}NO_4$, yield 57%.

N-(4-Methoxy-2,3-methylenedioxybenzyl)-N-methyl-4-methoxy-2,3-methylenedioxyphenylethylamine (VIi). mp of the HC 157-159°C, yield 52%, $C_{20}H_{23}NO_6$.

N-(6-Bromo-3,4-methylenedioxybenzyl)-N-methyl-6-bromo-3,4-dimethoxyphenylethylamine (VIg). mp of the HC 93-95°C (99°C), $C_{19}H_{21}NO_4Br_2$, yield 80%. Mass spectrum, *m/z* (%): 485/487/489 (M^+, 1.3), 284/286 (14), 256/258 (56), 213/215 (100), 176/178 (10), 135 (7). PMR spectrum: 2.25 (s, N—CH_3), 250-2.75 (4H, CH_2), 3.50 (2H, s, N—CH_2), 3.75 (6H, s, 2-OCH_3), 5.82 (s, OCH_2O), 6.52-7.25 (4H, ArH).

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