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# SYNTHESES BASED ON β-PHENYLETHYLAMINES V. SYNTHESIS AND PRELIMINARY PHARMACOLOGICAL SCREENING OF SOME PHENYLALKYLAMINES AND N-BENZYLTETRAHYDROISOQUINOLINES

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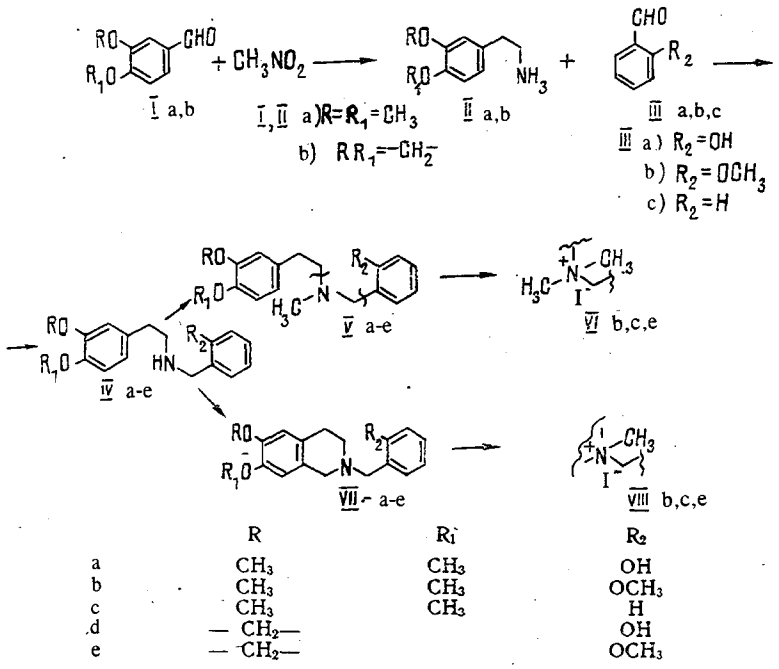
*The synthetic series of substituted N-benzyltetrahydroisoquinolines has been continued and the pharmacological activities of the compounds obtained have been investigated.*

Synthetic chemistry provides an approach to the the question of creating new drugs by modifying the molecular structures of biologically active compounds, which will permit the creation of more effective agents for treatment and prophylaxis combining high activity and low toxicity.

There is information in the literature on the synthesis of a series of N-benzyltetrahydroisoquinolines — analogues of the alkaloids sendaverine, corgoine, intebrimine — and on the detection of various types of activity in them [1-3]. In the present communication we report on the synthesis and a comparative study of the pharmacological activities of a series of substituted phenylalkylamines and also of N-benzyltetrahydroisoquinolines obtained from them and the methiodides of the latter.

As the initial β-phenylethylamines we used homoveratrylamine (IIa) and homopiperonylamine (IIb), which were synthesized by condensing veratraldehyde and piperonal, respectively, with nitromethane, followed by diisobutylaluminum hydride (DIBAH) reduction as in [4]. The tertiary amines were obtained by a scheme analogous to that described in the preceding communication [3]. The corresponding methiodides were synthesized by boiling some of the amines (VII, V) with methyl iodide in methanol. The structures of the substances obtained were confirmed by the results of mass and PMR spectroscopies.




| | R | $R_1$ | $R_2$ |
|---|---|---|---|
| a | $CH_3$ | $CH_3$ | OH |
| b | $CH_3$ | $CH_3$ | $OCH_3$ |
| c | $CH_3$ | $CH_3$ | H |
| d | $-CH_2-$ | | OH |
| e | $-CH_2-$ | | $OCH_3$ |

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The patterns of the resorptive action of the compounds (IV, V, VII) synthesized were similar, on the whole. After the intraperitoneal injection of the compounds in high doses (1/2 and 3/4 of $LD_{50}$), we first observed the phenomenon of total excitation to some degree or other, going as far as brief convulsions. Then a fall in motor activity and splaying of the extremities set in. Under the influence of the compounds respiration become rapid and superficial, while lethal doses caused shortness of respiration and, finally, its cessation. The $LD_{50}$ values of the hydrochlorides of (IV, V, and VII) ranged from 65 mg/kg for (IV) to 400 mg/kg for (VII) (see the Experimental part). As a rule, the toxicity of the compounds fell on passing from the secondary amines (IV) to the tertiary amines (V) and then to the cyclic N-benzyltetrahydroisoquinolines (VII). The variations in the $LD_{50}$ values for the methiodides (VI and VIII) were more considerable — from 30 mg/kg for (VIIIb) to 1200 mg/kg for (VIb).

A comparison of the toxicities of compounds having similar structures and differing only by the substituent in the benzyl part of the molecule showed that the toxicities of compounds containing an OH group were lower than those of the unsubstituted compounds and much lower than those of the corresponding compounds with a methoxy group in the second position. The replacement of two methoxy groups by a methylenedioxy group in the amines (IV, V, and VII) led to a fall in the toxicity of compounds "a" in comparison with "d" but to no such relationship in the analogous series "b" and "e".

In relatively small doses (1.3 mg/kg with intraperitoneal injection) most of the hydrochlorides of compounds (IV, V, VII) ((IV d) is an exception) lowered the arterial pressure with no appreciable change in respiration, and in a concentration of $1 \cdot 10^{-5}$-$3 \cdot 10^{-5}$ g/ml relaxed the smooth musculature of the isolated intestine. The effect of quaternizing the nitrogen in compounds (VIe) and (VIIIb and e) was expressed in the fact that, conversely, these compounds in the same doses injected intraperitoneally raised the pressure sharply (by 60-80 mm Hg).

Some of the compounds synthesized exhibited a weak local anesthetic action. Not one of the compounds investigated hd an influence on the course of experimental arrhythmia caused by aconitine.

## EXPERIMENTAL

**Methods of Investigation.** The investigation of the resorptive action of the compounds synthesized, with the determination of $LD_{50}$ (the dose causing the death of 50% of the animals) was conducted on white mice with intraperitoneal injection. The influence of the compounds on arterial pressure and respiration was investigated in acute experiments on anesthetized cats, while anesthetized rats were used to study the influence of the compounds on the course of aconitine-induced arrhythmia. The influence of the compounds on the tonus of the smooth musculature was investigated in experiments on isolated small intestine.

For general observations, see [3].

**3,4-Methylenedioxy- and 3,4-dimethoxyphenylethylamines were obtained by the method of [4] with reduction by DIBAH.**

**o-Methoxybenzaldehyde was synthesized as in [5].**

**Preparation of the Amines (IVa-e).** A mixture of a substituted phenylethylamine (II, 0.01 mole) and a benzaldehyde (III, 0.01 mole) in 50 ml of benzene was boiled with the azeotropic distillation of water. The benzene was distilled off, the imine residue was dissolved in 200 ml of methanol, and, with cooling and vigorous stirring, it was reduced with sodium tetrahydroborate (0.05 mole). After evaporation, the residue was dissolved in water and extracted with chloroform. The chloroform solution was washed with water and dried with sodium sulfate. The solvent was then distilled off, the technical amine was dissoved in acetone, and the solution was acidified with conc. HCl to pH 5. The hydrochloride of the amine (IV) that precipitated was filtered off.

**N-(2-Hydroxybenzyl)-3,4-dimethoxyphenethylamine (IVa).** mp of the hydrochloride 182-184°C. $C_{17}H_{21}O_3N$, yield 92%. Mass spectrum m/z: 287 ($M^{+\cdot}$), 152, 151, 136, 121, 107. PMR spectrum: 3.80 (3H, s, $OCH_3$), 3.81 (3H, s, $OCH_3$), 3.92 (2H, s, $-CH_2-$), 2.74 (4H, m, $-CH_2-$), 6.77, 6.87, 7.24 (Ar−H). $LD_{50}$, mouse, i/p. 190 mg/kg.

**N-(2-Methoxybenzyl)-3,4-dimethoxyphenethylamine (IVb).** mp of the hydrochloride 152-154°C. $C_{18}H_{23}O_3N$, yield 79%. Mass spectrum m/z: 301 ($M^{+\cdot}$), 121, 134, 135, 150, 164, 178. PMR spectrum: 2.7 (4H, s, $-CH_2-$), 3.58 (2H, s, $-CH_2-$), 3.70 (9H, s, 3-$OCH_3$), 6.65, 6.82, 7.17 (Ar−H). $LD_{50}$ mouse, i/p. 105 mg/kg.

**N-Benzyl-3,4-dimethoxyphenethylamine (IVc).** mp of the hydrochloride 200-203°C, $C_{17}H_{21}O_2N$, yield 98%. Mass spectrum m/z: 271 ($M^{+\cdot}$), 152, 151. PMR spectrum: 2.65 (4H, m, $-CH_2-$), 3.43 (2H, s, $-CH_2-$), 3.74 (6H, s, $OCH_3$), 6.62 (3H, Ar−H), 7.20 (5H, Ar−H). $LD_{50}$ mouse, i/p. 165 mg/kg.

**N-(2-Hydroxybenzyl)-3,4-methylenedioxyphenethylamine (IVd).** mp of the hydrochloride 119-122°C, $C_{16}H_{17}O_3N$, yield 91%. Mass spectrum m/z: 271 ($M^{+\cdot}$), 136, 135, 121, 107. PMR spectrum: 2.52 (4H, m, $-CH_2-$), 3.43 (2H, s, $-CH_2-$), 5.73 (2H, s, $-OCH_2O-$). $LD_{50}$ mouse, i/p. 185 mg/kg.

**N-(2-Methoxybenzyl)-3,4-methylenedioxyphenethylamine (IVe).** mp of the hydrochloride 148-150°C, $C_{16}H_{19}O_3N$, yield 80%. Mass spectrum m/z (%): 285 ($M^{+\cdot}$). $LD_{50}$ i/p 65 mg/kg.

**Preparation of the Amines (V).** A mixture of an amine (IV) (0.01 mole), methanol (50 ml) and formalin (30%, 20 ml) was boiled under reflux for 1 h. With stirring, the cooled mixture was subjected to sodium tetrahydroborate reduction. After elimination of the methanol in vacuum, the residue was diluted with water and extracted with ether. The ethereal solution was washed with water and dried with sodium sulfate. The solvent was distilled off, the residue was dissolved in acetone, and the solution was acidified with conc. HCl to pH 3-4. The precipitate of the amine (V) hydrochloride that deposited was filtered off.

**N-Methyl-N-(2-hydroxybenzyl)-3,4-dimethoxyphenethylamine (Va).** mp of the hydrochloride 135-137°C, $C_{18}H_{23}NO_3$, yield 71%. Mass spectrum m/z: 301 ($M^{+\cdot}$), 283, 282, 194, 165, 164, 152, 151, 150(100), 137, 135, 107(%). $LD_{50}$ i/p 210 mg/kg.

**N-Methyl-N-(2-methoxybenzyl)-3,4-dimethoxyphenethylamine (Vb) was obtained by the method of [5].** mp of the hydrochloride 192-194°C, $C_{19}H_{25}NO_3$, yield 87%. Mass spectrum m/z (%): 315 ($M^{+\cdot}$). $LD_{50}$ i/p. 80 mg/kg.

**N-Methyl-N-benzyl-3,4-dimethoxyphenethylamine (Vc).** mp of the hydrochloride 175°C. $C_{18}H_{23}NO_2$, yield 73%. Mass spectrum m/z: (%): 285 ($M^{+\cdot}$, 3), 135 (23), 134 (100), 91 (98). PMR spectrum: 2.18 (3H, s, $-CH_3$), 2.61 (4H, m, $CH_2$), 3.43 (2H, s, $-CH_2-$), 3.74 (6H, s, $OCH_3$), 6.58 (2H, Ar−H), 6.63 (1H, Ar−H), 7.20 (5H, s, Ar−H). $LD_{50}$ i/p. 125 mg/kg.

**N-Methyl-N-(2-hydroxybenzyl)-3,4-methylenedioxyphenethylamine (Vd).** mp of the hydrochloride 122-124°C, $C_{17}H_{19}O_3N$, yield 67%. Mass spectrum m/z: 285 ($M_1^{+\cdot}$). $LD_{50}$ i/p. 350 mg/kg.

**N-Methyl-N-(2-methoxybenzyl)-3,4-methylenedioxyphenethylamine (Ve).** Obtained by the method of [5]. mp of the hydrochloride 179-181°C, $C_{18}H_{21}O_3N$, yield 64%. Mass spectrum m/z: 299 ($M^{+\cdot}$). PMR spectrum: 2.17 (3H, s, $-CH_3$), 2.65 (4H, m, $-CH_2$), 3.25 (2H, s, $CH_2$), 3.38 (3H, s, $OCH_3$), 5.58 (2H, s, $OCH_2O$), 6.38; 6.46; 7.20 (Ar−H). $LD_{50}$ i/p. 150 mg/kg.

**Preparation of the Amines (VI).** 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 (pH 2-3) was boiled under reflux for 2-4 h. The course of the reaction was monitored by TLC. After the solvent had been distilled off, the residue was made alkaline with conc. $NH_4OH$ to pH 9-10 and was extracte4d with chloroform. The organic extract was washed with water, dried with sodium sulfate, and evaporated; the residue was dissolved in acetone, and the solution was acidified with conc. HCl to pH 3-4. The precipiate of the amine (VI) hydrochloride that precipitated was filtered off.

**N-(2-Hydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIa).** mp of the hydrochloride 132-125°C, $C_{18}H_{21}O_3N$, yield 67%. Mass spectrum m/z (%): 299 ($M^{+\cdot}$ 57), 284 (33), 192 (57), 191 (15), 176 (16), 164 (100), 149 (15), 3.77 (3H, s, $OCH_3$), 3.80 (3H, s, $OCH_3$), 6.52; 6.61; 6.92; 7.26 (Ar−H). $LD_{50}$ i/p/ 290 mg/kg.

**N-(2-Methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIb).** mp of the hydrochloride 198-200°C, $C_{19}H_{23}O_3N$, yield 58%. Mass spectrum m/z: 313 ($M^{+\cdot}$)

**N-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIc).** mp of the hydrochloride 227-230°C, $C_{18}H_{21}O_2N$, yield 91%. Mass spectrum m/z (%): 283 ($M^{+\cdot}$ 100), 164 (81), 91 (63). PMR spectrum: 2.62 (4H, m, 2H-3, 2H-4), 3.39 (2H, s, H-1), 3.62 (2H, s, H-α), 3.71 (3H, s, $OCH_3$), 3.73 (3H, s, $OCH_3$), 6.36; 6.47; 7.22 (Ar−H). $LD_{50}$ i/p. 260 mg/kg.

**N-(2-Hydroxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (VIId).** mp of the hydrochloride 152-155°C, $C_{17}H_{17}O_3N$, yield 82%. Mass spectrum m/z: 283 ($M^{+\cdot}$), 190, 176, 161, 162, 148, 107. PMR spectrum: 2.77 (4H, m, 2H-3, 2H-4), 3.58 (2H, s, H-1), 3.78 (2H, s, H-α), 5.85 (2H, s, $OCH_2O$), 6.42 (1H, s, Ar−H), 6.54 (1H, s, Ar−H), 6.85 (5H, Ar−H).

**N-(2-Methoxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (VIIe) was obtained by the method of [5].** mp of the hydrochloride 195-197°C, $C_{18}H_{19}O_3N$, yield 88%. Mass spectrum m/z (%): 297 ($M^{+\cdot}$). PMR spectrum: 2.80 (4H, m, 2H-3, 2H-4), 3.55 (2H, s, H-1), 3.65 (2H, s, H-α), 6.45 (1H, s, Ar−H), 6.58 (1H, s, Ar−H), 6.94 (5H, Ar−H). $LD_{50}$ i/p. 140 mg/kg.

**Preparation of the methiodides (VI, VII).** A solution of a (V) (3.5 mmole) in 14 ml of methyl alcohol was treated with 3 ml (48 mmole) of methyl iodide, and the mixture was boiled for 2.5 h. After the end of the reaction, it was cooled and the crystals of the corresponding methiodide (VI) were filtered off.

**(VIb).** mp >350°C, yield 99%. $LD_{50}$ i/p. 1200 mg/kg.
**(VIc).** mp 185°C, yield 82%.
**(VId).** mp 204-206°C, yield 50%. $LD_{50}$ i/p. 350 mg/kg.
**(VIe).** mp 232-233°C, yield 89%. $LD_{50}$ i/p. 40 mg/kg.
**(VIIIb).** mp 243°C, yield 70%. $LD_{50}$ i/p. 30 mg/kg
**(VIIIc).** mp 220-222°C, yield 74%. Sparingly soluble in water.
**(VIIId).** mp 201-203°C, yield 73%.
**(VIIIe).** mp 233-234°C, yield 43%. $LD_{50}$ i/p. 250 mg/kg.

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