ISOQUINOLINE DERIVATIVES

VI.* SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF 4,6,7-SUBSTITUTED 1(2)-ARYLALKYL-1,2,3,4-TETRAHYDROISOQUINOLINES AND THEIR ANALOGS

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The condensation of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (II) with diphenylacetyl and diphenylpropionyl chlorides gave the corresponding amides (III). Reduction of III with lithium aluminum hydride converted them to tertiary amines IV, which were characterized as their hydrochlorides. The condensation of equimolecular amounts of amines I with the acid chlorides of substituted phenylacetic and diphenylpropionic acids gave amides V. The reduction of amides V with lithium aluminum hydride gave secondary amines VI. The corresponding tetrahydroisoquinolines (VII) were obtained by the cyclization of amides V and subsequent reduction with lithium aluminum hydride. The condensation of 1-diphenylethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with formalin gave VIII. The IR spectra of the synthesized compounds were examined. The effect of these compounds on the arterial blood pressure and the coronary blood flow was studied.

Continuing our study of the biological functions of isoquinoline derivatives as a function of structure [1, 2], we planned the syntheses of tetrahydroisoquinoline derivatives and their analogs with arylalkyl substituents in the 1 and 2 positions of the isoquinoline ring, with or without a spirocyclohexane ring (IV, VI-VIII).

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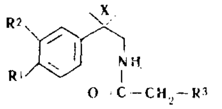
* See [1] for communication V.

† Deceased.

TABLE 1



R¹	R²	R³	X	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
						C	H	N	C	H	N	
H	H	C_6H_5	$-(CH_2)_5-$	90—91	$C_{21}H_{25}NO$	82,2	8,2	4,4	82,0	8,1	4,5	50
OCH_3	H	$C_6H_4OCH_3$	$-(CH_2)_5-$	89—90	$C_{23}H_{29}NO_3$	75,3	8,1	4,1	75,1	7,9	3,8	75
H	H	$C_6H_3(OCH_3)_2$	$-(CH_2)_5-$	97—98	$C_{23}H_{29}NO_3$	75,4	8,2	3,7	75,1	7,9	3,8	76
OCH_3	OCH_3	$CH(C_6H_5)_2$	H_2	118—119	$C_{25}H_{27}NO_3$	76,7	6,7	3,5	77,0	6,7	3,5	93

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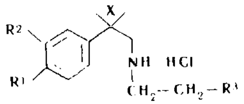
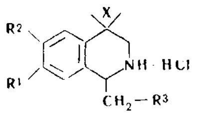
TABLE 2

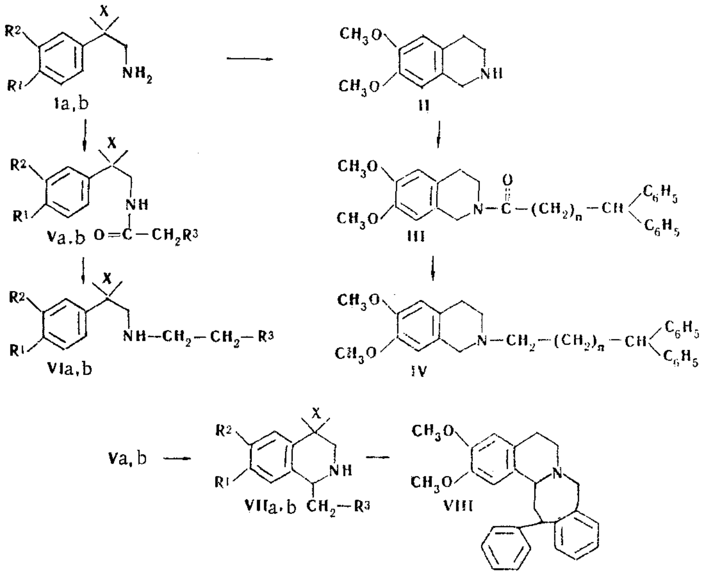


R^1	R^2	R^3	X	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
						C	H	N	Cl	C	H	N	Cl	
H	H	C_6H_5	$-(CH_2)_5-$	215—216	$C_{21}H_{27}N \cdot HCl$	76,2	8,8	4,4	10,4	76,4	8,5	4,2	10,7	72
OCH_3	H	$C_6H_4OCH_3$	$-(CH_2)_5-$	157—158	$C_{23}H_{31}NO_2 \cdot HCl$	70,5	8,5	3,4	9,3	70,8	8,2	3,5	9,0	81
H	H	$C_6H_3(OCH_3)_2$	$-(CH_2)_5-$	163—164	$C_{23}H_{31}NO_2 \cdot HCl$	71,0	8,5	3,4	9,2	70,8	8,2	3,5	9,0	66
OCH_3	OCH_3	$CH(C_6H_5)_2$	H_2	188—189	$C_{25}H_{29}NO_2 \cdot HCl$	72,7	7,4	3,3	8,4	72,8	7,3	3,4	8,6	95

TABLE 3



R^1	R^2	R^3	X	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
						C	H	N	Cl	C	H	N	Cl	
H	H	C_6H_5	$-(CH_2)_5-$	235—236	$C_{21}H_{25}N \cdot HCl$	76,6	8,2	4,5	10,9	76,9	7,9	4,2	10,8	44
OCH_3	H	$C_6H_4OCH_3$	$-(CH_2)_5-$	209—210	$C_{23}H_{29}NO_2 \cdot HCl$	74,4	7,9	3,9	9,2	74,2	8,1	3,7	9,5	46
H	H	$C_6H_3(OCH_3)_2$	$-(CH_2)_5-$	158—159	$C_{23}H_{29}NO_2 \cdot HCl$	74,4	8,4	3,5	9,2	74,2	8,1	3,7	9,5	78
OCH_3	OCH_3	$CH(C_6H_5)_2$	H_2	206—207	$C_{25}H_{27}NO_2 \cdot HCl$	73,0	7,1	3,6	8,9	73,2	6,8	3,4	8,6	47



I, V, VI, VII a $X = -(CH_2)_5-$; $R^1 = H, OCH_3$; $R^2 = H$; $R^3 = C_6H_5, CH_3OC_6H_4, (CH_3O)_2C_6H_3$.
b $X = H_2$; $R^1 = R^2 = OCH_3$; $R^3 = CH(C_6H_5)_2$. III, IV $n = 0, 1$

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (II) [3] was synthesized by the condensation of 3,4-dimethoxyphenylethylamine (Ib) with 20% formalin. The condensation of II with diphenylacetyl and diphenylpropionyl chlorides gave amides III, which were converted to tertiary amines IV by reduction with lithium aluminum hydride (LAH). The reaction of equimolecular amounts of Ia, b with the acid chlorides of substituted phenylacetic and diphenylpropionic acids in the presence of pyridine gave amides V (Table 1), which were converted to secondary amines VI (Table 2) by reduction with LAH. Bischler–Napieralski cyclization of V gave the dihydro derivatives, which, after separation from the unchanged amide, were reduced with LAH to the corresponding tetrahydroisoquinolines VII (Table 3).

The condensation of 1-diphenylethyl-6,7-dimethoxy- 1,2,3,4-tetrahydroisoquinoline (VIIb) with 36% formalin [4] yielded 2,3-dimethoxy-13-phenyl-5,6,8,13,14,14a-hexahydroisoquinolino[2,1-b][2]benzazepine (VIII). The purities of the intermediates and final products were checked by thin-layer chromatography (TLC) on aluminum oxide and on paper. The IR spectra displayed absorption bands characteristic for these compounds.

The action of the hydrochlorides of IV and VI-VIII on the arterial blood pressure and on the coronary circulation was investigated [5]. These compounds do not have a significant effect on the arterial blood pressure, but they do act differently on the coronary blood flow. Compounds VIII, VIb, and VIIa increase the coronary blood flow by 20-80% in doses of 0.5-3 mg/kg of animal weight. However, IV and VIa in the same doses reduce the outflow of blood from the coronary sinus by up to 50%.

EXPERIMENTAL

The starting phenyl- and (p-methoxyphenyl)aminomethylcyclohexanes (Ia) and homoveratrylamine (Ib) were synthesized from the corresponding nitriles by the methods in [2, 6].

1-Phenylcyclohexane-1-carboxylic Acid Nitrile. This compound, which is described in [7], was obtained by a somewhat modified method. A 20-g (0.17 mole) sample of phenylacetonitrile was condensed with 39 g (0.17 mole) of 1,5-dibromopentane in toluene in the presence of 13.8 g (0.34 mole) of powdered sodium hydroxide. The mixture was heated for 10-12 h, cooled, and diluted with 50 ml of water. The upper layer was separated, and the aqueous layer was extracted with three 30-ml portions of toluene. The extract was washed with three 30-ml portions of water and dried over sodium sulfate. The toluene was removed, and the residue was vacuum-distilled to give 14.2 g (46.0%) of a product with bp 118-120° (1 mm) and n_D^{20} 1.5298. Found: N 7.3%. $C_{13}H_{15}N$. Calculated: N 7.5%. In [7], 58% of a product with bp 125-127° (3 mm) and n_D^{20} 1.5330 was obtained.

1-(p-Methoxyphenyl)cyclohexane-1-carboxylic Acid Nitrile. This compound was obtained in 53% yield by the method described above and had bp 138-141° (0.4 mm), d_4^{20} 1.0778, and n_D^{20} 1.5381. Found: C 78.3; H 7.2; N 6.2%. MR_D 62.490. $C_{14}H_{17}NO$. Calculated: C 78.1; H 7.4; N 6.4%. MR_D 62.494.

Amines Ia were obtained by the reduction of the corresponding nitriles with LAH by the method in [6].

1-Phenylaminomethylcyclohexane. This compound was obtained in 86% yield and had bp 123-125° (2 mm) and n_D^{20} 1.5440. Found: C 82.3; H 10.4; N 7.1%. $C_{13}H_{19}N$. Calculated: C 82.5; H 10.1; N 7.4%. In [6], 91% of a product with bp 129-131° (4 mm) and n_D^{20} 1.5462 was obtained.

1-p-Methoxyphenylaminomethylcyclohexane. This compound was obtained in 69% yield and had bp 148-150° (2 mm), d_4^{20} 1.0618, and n_D^{20} 1.5545. Found: C 76.8; H 9.3; N 6.2%. MR_D 66.095. $C_{14}H_{21}NO$. Calculated: C 76.6; H 9.6; N 6.3%. MR_D 66.116.

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (II). This compound was obtained in 74% yield by the condensation of 1 mole of homoveratrylamine with 1.1 mole of 20% formalin and had bp 150-153° (3 mm) and mp 80-81°. The hydrochloride had mp 253-254° [alcohol–water (1 : 1) [3]. Paper chromatography exposed one spot with R_f 0.64. IR spectrum: 3305 cm⁻¹ (NH).

N-(2-Diphenylacetamido)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (III, n = 0). This compound was synthesized in 99% yield via the method in [2] from equimolecular amounts of diphenylacetyl chloride and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and had mp 133-134° [benzene–petroleum ether (1 : 1)] and R_f 0.57 (TLC, system A). Found: C 77.1; H 6.7; N 3.8%. $C_{25}H_{25}NO_3$. Calculated: C 77.4; H 6.5; N 3.6%. IR spectrum: 1620 cm⁻¹ (amide CO).

N-(2-Diphenylpropionylamino)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (III, n = 1). This compound was similarly obtained in 98% yield and had mp 145-146° and R_f 0.52 (TLC, system A). Found: C 77.4; H 7.0; N 3.7%. $C_{26}H_{27}NO_3$. Calculated C 77.7; H 6.7; N 3.4%. IR spectrum: 1620 cm⁻¹ (amide CO).

N-(β-diphenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (IV, n = 0). This compound was obtained by the reduction of amide III with LAH [2] and was isolated in 58% yield as the hydrochloride with mp 173-174° [alcohol–ether (1 : 1)] and R_f 0.73 (TLC, system B). Found: C 73.5; H 7.1; N 3.5; Cl 8.8%. $C_{25}H_{27}NO_2 \cdot HCl$. Calculated: C 73.2; H 6.8; N 3.4; Cl 8.6%. IR spectrum: 1370 cm⁻¹ (CN).

N-(γ-Diphenylpropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride. This compound was similarly obtained in 21% yield and had mp 179-180° and R_f 0.72 (TLC, system B). Found: C 73.9; H 7.3; N 3.4; Cl 8.1%. $C_{26}H_{29}NO_2 \cdot HCl$. Calculated: C 73.6; H 7.1; N 3.3; Cl 8.3%.

1-(R^3-Acetamidomethyl)-1-(R^1,R^2-phenyl)cyclohexane (Va) and 3,4-Dimethoxyphenylethylamide of Diphenylpropionic Acid (Vb) (Table 1). These compounds were obtained as in [2] from the acid chlorides of substituted phenylacetic and diphenylpropionic acids and amines I. The amides were recrystallized from benzene–petroleum ether (1 : 1). Thin-layer chromatography (system A): R_f 0.70 ± 0.03. IR spectrum: 3350 ± 5 (NH), 1650 ± 5 cm⁻¹ (CO).

Hydrochlorides of 1-(R^3-Ethylaminomethyl)-1-(R^1,R^2-phenyl)cyclohexanes (VIa) and N-(γ-Diphenylpropyl)-N-3,4-dimethoxyphenylethylamine (VIb) (Table 2). These compounds were obtained by the reduction of amides Va,b with LAH [2]. They were isolated as the hydrochlorides and recrystallized from alcohol–ether (1 : 1). Thin-layer chromatography (system B): R_f 0.70 ± 0.05. IR spectrum: 3310 cm⁻¹ (NH).

Hydrochlorides of 1-(R^3-Methyl)-R^1,R^2-1,2,3,4-tetrahydroisoquinoline-4-spirocyclohexanes (VIIa) and 1-Diphenylethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIb) (Table 3). These compounds were synthesized by the method described in [2] by refluxing 0.15 mole of amides Va,b in toluene in the presence of 40 g of phosphorus oxychloride and 3 g of phosphorus pentoxide. The resulting dihydro derivatives were reduced with LAH to tetrahydroisoquinolines VII, which were characterized as hydrochlorides, recrystallized from alcohol–ether (1 : 1). Paper chromatography revealed one spot with R_f 0.80 ± 0.05. IR spectrum: 3300 ± 20 cm⁻¹ (NH) and 1570 ± 5, 1600 ± 10 cm⁻¹ (isoquinoline).

2,3-Dimethoxy-13-phenyl-5,6,8,13,14,14a-hexahydroisoquinolino[2,1-b][2]benzazepine. A total of 0.6 ml of 36% formalin was added to a solution of 1 g of 1-diphenylethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline in 4 ml of methanol. The mixture was allowed to stand at room temperature for 3 days and was then refluxed for 0.5 h in the presence of 40.2 ml of dilute hydrochloric acid (1 : 1). The resulting hydrochloride was decomposed with 40% alkali solution to give 70% of a product with mp 183-184° (alcohol) and R_f 0.9 (paper chromatography). Found: N 3.8%. $C_{26}H_{27}NO_2$. Calculated: N 3.6%. IR spectrum: 1260, 1503, 1580, 1640, and 2845 cm⁻¹. The absence of an absorption band at 3200-3400 cm⁻¹ indicates that VIII was obtained. The hydrochloride had mp 214-215° [alcohol–ether (1 : 1)].

The IR spectra of mineral-oil suspensions and chloroform solutions (VIII) were recorded with a UR-10 spectrophotometer by L. V. Khazhakyan.

The thin-layer chromatography was performed on activity II aluminum oxide using system A [benzene–ethyl acetate (5 : 1)] for III and Va,b and system B [chloroform–ether (1 : 1)] for IV and VIa,b. The spots were developed with iodine vapors. Ascending chromatography was accomplished on grade S paper from the Leningrad Factory in a butanol–acetic acid–water system (10 : 1 : 3).

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