ISOQUINOLINE DERIVATIVES

V.* SYNTHESIS OF SOME 1-SUBSTITUTED 6,7-DIMETHOXY-1,2,3,4-TETRAHYDROISOQUINOLINE-4-SPIROCYCLOPENTANES AND THEIR ANALOGS

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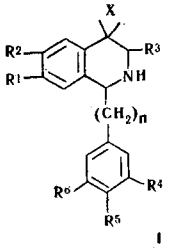
UDC 547.831.4'514.1.07

1-(3,4-Dimethoxyphenyl)-1-aminomethylcyclopentane (IV) was condensed with substituted phenylacetyl and benzoyl chlorides to synthesize 1-[R',R",R"'-phenylacet(benz)amidomethyl]-1-(3,4-dimethoxyphenyl)cyclopentanes (VI), which were converted to 1-[R',R",R"'-phenyl(benzyl)]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentanes (IX) by cyclization and subsequent reduction. Reduction of VI yielded the corresponding secondary amines (VII). The compounds obtained were subjected to chromatographic analysis. The IR spectra were investigated. Compounds VII and IX were subjected to pharmacological testing.

In an investigation of the effect of various substituents in general structure I on the pharmacological properties [1-3], we undertook the synthesis of 6,7-dimethoxy-1-aryltetrahydroisoquinoline derivatives with a spirocyclopentane ring in the 4-position.



I

One of the starting materials in our synthesis was 1-(3,4-dimethoxyphenyl)-1-aminomethylcyclopentane (IV), which was obtained from the corresponding nitrile (III) [4]. We could not reproduce the patent results in [4], so we changed the reaction conditions and the method used to isolate III and IV. Nitrile III was obtained from 3,4-dimethoxybenzyl cyanide (II) and dibromobutane in the presence of technical grade sodium amide in toluene. Compound III was freed from unchanged II by alkaline saponification. Nitrile III was converted to amine IV by reduction with lithium aluminum hydride (LAH).

The corresponding amides (VI, Table 1) were obtained by condensation of amine IV with substituted phenylacetyl or benzoyl chlorides (V).

Secondary amines VII (Table 2) were synthesized by reduction of amides VI with LAH.

The amides were converted to dihydroisoquinolines (VIII) by Bischler–Napieralski cyclization, and VIII were reduced with LAH in ether to the corresponding tetrahydroisoquinolines (IX), which were characterized as the hydrochlorides (Table 3).

*See [6] for communication IV.
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Institute of Precision Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 637-640, May, 1971. Original article submitted July 24, 1970.

TABLE 1. 1-[R',R",R"'-phenylacet(benz)amidomethyl]-1-(3,4-dimethoxyphenyl)cyclopentanes (VI)

R'	R"	R"'	n	mp	R_f*	Empirical formula	Found, %			Calc., %			Yield, %
							C	H	N	C	H	N	
H	H	H	1	124—125, oil	0,57 0,58	$C_{22}H_{27}NO_3$	74,9	7,8	3,8	74,7	7,7	3,9	29,5 60,0
H	CH_3O	H	1	96—97, oil	0,52 0,53	$C_{23}H_{29}NO_4$	72,0	7,7	3,4	72,0	7,6	3,6	18,0 80,2
CH_3O	CH_3O	H	1	oil	0,40	$C_{24}H_{31}NO_5$	69,8	7,7	3,4	69,7	7,6	3,3	95,2
H	H	H	0	126—127, oil	0,67 0,65	$C_{21}H_{25}NO_3$	74,4	7,2	4,1	74,3	7,4	4,1	30,6 61,9
CH_3O	CH_3O	H	0	70—71, oil	0,55 0,54	$C_{23}H_{29}NO_5$	69,3	7,5	3,3	69,1	7,4	3,5	77,2 19,8
CH_3O	CH_3O	CH_3O	0	120—121	0,61	$C_{24}H_{31}NO_6$	67,2	7,3	3,3	67,1	7,2	3,2	96,3

*By thin-layer chromatography with benzene–acetone (4 : 1) as the mobile phase.

TABLE 2. 1-[R',R",R"'-phenylethyl(benzyl)aminomethyl]-1-(3,4-dimethoxyphenyl)cyclopentane hydrochlorides (VII)

R'	R"	R"'	n	mp	Empirical formula	Found, %				Calc., %				Yield, %
						C	H	N	Cl	C	H	N	Cl	
H	H	H	1	137—138	$C_{22}H_{29}NO_2 \cdot HCl$	70,3	8,0	3,7	9,4	70,4	8,2	3,6	9,6	56,6
H	CH_3O	H	1	143—144	$C_{23}H_{31}NO_3 \cdot HCl$	68,0	7,9	3,4	8,7	67,9	7,8	3,3	8,6	61,5
CH_3O	CH_3O	H	1	130—131	$C_{24}H_{33}NO_4 \cdot HCl$	64,0	7,8	3,2	8,1	64,2	7,8	3,3	8,3	45,0
H	H	H	0	182—183	$C_{21}H_{27}NO_2 \cdot HCl$	69,4	7,7	3,8	9,7	69,5	7,6	3,7	9,8	52,1
CH_3O	CH_3O	H	0	178—179	$C_{23}H_{31}NO_4 \cdot HCl$	67,1	8,0	3,2	8,4	67,0	7,8	3,4	8,6	75,3
CH_3O	CH_3O	CH_3O	0	174—176	$C_{24}H_{33}NO_5 \cdot HCl$	63,9	7,5	2,9	7,7	63,8	7,6	3,0	7,8	52,7

As should have been expected, the cyclization of VI proceeds more readily and with higher yields than the cyclization of amides [1,2] which do not have methoxy substituents in the phenylethylamine fragment or have one methoxy group in the 4-position [5].

The purities of the synthesized compounds were confirmed by thin-layer, gas-liquid, or paper chromatography.

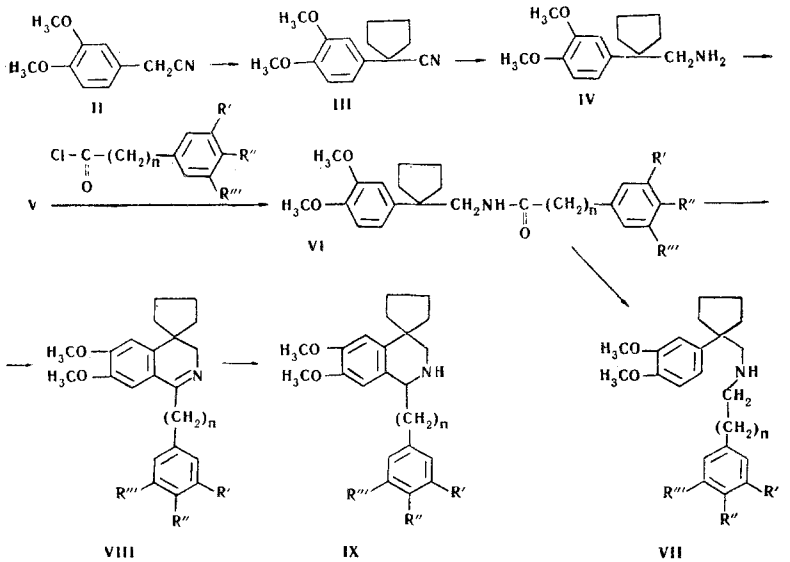

TABLE 3. 1-[R',R",R"'-Phenyl(benzyl)]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentane Hydrochlorides (IX)

R'	R"	R"'	n	mp	Empirical formula	Found, %				Calc., %				Yield, %
						C	H	N	Cl	C	H	N	Cl	
H	H	H	1	175—176	$C_{22}H_{27}NO_2 \cdot HCl$	70,7	7,4	3,8	9,5	70,6	7,5	3,7	9,5	80,0
H	CH_3O	H	1	158—159	$C_{23}H_{29}NO_3 \cdot HCl$	71,2	7,3	3,6	8,9	71,1	7,5	3,5	8,8	92,2
CH_3O	CH_3O	H	1	208—210	$C_{24}H_{31}NO_4 \cdot HCl$	66,6	7,5	3,4	8,1	66,4	7,4	3,2	8,2	90,0
H	H	H	0	190—191	$C_{21}H_{25}NO_2 \cdot HCl$	70,1	7,4	3,8	9,6	70,0	7,3	3,9	9,8	75,5
CH_3O	CH_3O	H	0	233	$C_{23}H_{29}NO_4 \cdot HCl$	65,9	7,1	3,4	8,5	65,8	7,2	3,3	8,4	80,2
CH_3O	CH_3O	CH_3O	0	237—238	$C_{24}H_{31}NO_5 \cdot HCl$	64,2	7,1	3,2	8,0	64,0	7,1	3,1	7,9	78,5

The IR spectra of the intermediate and final compounds have characteristic frequencies which correspond to their structures.

The hydrochlorides of the final VII and IX were subjected to pharmacological testing. Their action on the systemic arterial pressure and the coronary circulation was studied. All of the compounds have a short-term hypotensive effect. A decrease in the arterial pressure by 30-40 mm in 5-6 min is observed when they are introduced intravenously in concentrations of 1-3 mg/kg. No changes in the coronary circulation under the influence of hydrochlorides VII and IX in doses of 1, 3, and 5 mg/kg were observed for intravenous injection.

EXPERIMENTAL

Nitrile of 1-(3,4-dimethoxyphenyl)-1-cyclopentanecarboxylic Acid (III). Pulverized sodium amide [15.6 g (0.4 mole)] was added to 35.4 g (0.2 mole) of nitrile II in 40 ml of toluene, the mixture was heated to 35°, and 43.2 g (0.2 mole) of dibromobutane was added dropwise with stirring. Stirring was continued for 6 h at 65-70°, after which 120 ml of dichloroethane was added, and the mixture was filtered. The filtrate was washed with water, the solvent was removed, and the residue was heated with stirring on a water bath for 4 h with 100 ml of 10% sodium hydroxide. Unsaponified nitrile III was extracted with dichloroethane, washed with water, and dried with anhydrous calcium chloride. The solvent was removed, and the resulting oil was crystallized from absolute ether to give 23.5 g (51%) of a product with mp 100-102° (from benzene). Found %: C 72.4; H 7.4; N 6.2. $C_{14}H_{17}NO_2$. Calculated %: C 72.6; H 7.4; N 6.0. Thin-layer chromatography (TLC) with a benzene–acetone (4 : 1) mobile phase gave R_f 0.61. Gas-liquid chromatography with 15% silicone oil "301" on Chromosorb G as the stationary phase and helium as the gas carrier at 60 ml/min and 220° gave a retention time of 4 min.

1-(3,4-Dimethoxyphenyl)-1-aminomethylcyclopentane (IV). A solution of 46.2 g (0.2 mole) of nitrile III in 200 ml of tetrahydrofuran was added dropwise with stirring in the course of 20 min to a solution of 15.2 g (0.4 mole) of LAH in 520 ml of absolute ether. The mixture was refluxed on a water bath for 12 h and decomposed, with ice-water cooling, with 50 ml of water. The mixture was filtered, and the residue on the filter was washed with 300 ml of ether and dried with anhydrous sodium sulfate. The residue after removal of the solvent was vacuum distilled to give 27.2 g (58%) of a product with bp 148-150° (0.5 mm), n_D^{20} 1.5498, d_4^{20} 1.0847. Found %: N 6.1; MR_D 68.09. $C_{14}H_{21}NO_2$. Calculated %: N 5.9; MR_D 67.75. The hydrochloride melted at 198-200° (alcohol–ether). Paper chromatography gave R_f 0.71.

1-[R',R",R"'-Phenylacet(benz)amidomethyl]-1-(3,4-dimethoxyphenyl)cyclopentanes (VI) (Table 1). A mixture of 0.1 mole of amine IV and 0.11 mole of anhydrous pyridine was added dropwise with stirring in the course of 20 min to 0.1 mole of acid chloride V in 150 ml of absolute benzene. Stirring was continued for 30 min, and the mixture was then refluxed on a water bath for 6 h. At the end of the reaction, the mixture was treated with 5% hydrochloric acid, water, and 5% sodium carbonate and dried with sodium sulfate. The solvent was removed, and the residue was crystallized from benzene–petroleum ether (1 : 1) to give an oil, crystals, and a mixture of them [2]. IR spectrum, cm^{-1}: 3260 (NH); 1640 (C=O).

1-[R',R",R"'-Phenylethyl(benzyl)aminomethyl]-1-(3,4-dimethoxyphenyl)cyclopentanes (VII) (Table 2). Amines VII were obtained by reduction of amides VI with LAH in ether as in [1]. IR spectrum: 2720 cm^{-1} (NH_2^+). Thin-layer chromatography with chloroform–ether (1 : 1) as the mobile phase gave R_f values from 0.65 to 0.75.

1-[R',R",R"'-Phenyl(benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentanes (IX) (Table 3). A total of 0.12 mole of freshly distilled phosphorus oxychloride was added to a solution of 0.03 mole of VI in 100 ml of anhydrous toluene, and the mixture was refluxed for 6 h. The solvent was removed, and the residue was decomposed with ammonium hydroxide, extracted with ether (3 × 100 ml), and dried with sodium sulfate. After removal of the solvent, the residue [0.022 mole (81%)] was dissolved in absolute ether and treated with an ether solution of hydrogen chloride up to pH 3. The precipitated dihydroisoquinoline hydrochloride (VIII) was decomposed with ammonium hydroxide to isolate the base, which was reduced with LAH, as in [2]. IR spectrum, cm^{-1}: 1600, 1520 (tetrahydroisoquinoline). The R_f values obtained by paper chromatography ranged from 0.7 to 0.85.

The IR spectra of mineral oil suspensions were obtained with a UR-10 spectrometer. Thin-layer chromatography was accomplished on activity II aluminum oxide. Ascending paper chromatography on grade "S" paper from the Leningrad Factory was accomplished with butanol–acetic acid–water (10:1:3). Gas-liquid chromatography was accomplished with a "Tsvet-64" chromatograph.

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