ISOQUINOLINE DERIVATIVES

II. Synthesis and Pharmacological Study of Some 7-Alkoxy-1-(3', 4'-dimethoxybenzyl)-4-spirocyclopentane-1, 2, 3, 4-tetrahydroisoquinolines*

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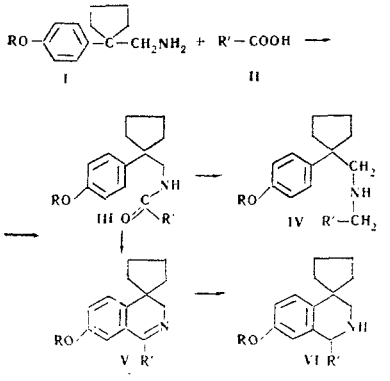
The condensation of 1-(p-alkoxyphenyl)-1-aminomethylcyclopentanes with dimethoxyphenylacetic acid has given the corresponding amides (III) which were isolated in the form of two isomers. The Bischler-Napieralski cyclization of the amides XIII converted them into 7-alkoxy-1-(3', 4'-dimethoxybenzyl)-4-spirocyclopentane-3, 4-dihydroisoquinolines (V), and reduction with the aid of lithium aluminum hydride into the amines IV. The reduction of the dihydroisoquinolines V gave the tetrahydro derivatives VI.

In a preceding communication we have described 7-alkoxy-1-(p-alkoxyphenyl)-4-spirocyclopentane-1, 2, 3, 4-tetrahydroisoquinolines and their noncyclized analogs, which proved to be pharmacologically active substances. Continuing our investigations, we have obtained 7-alkoxy-1-(3', 4'-dimethoxybenzyl)-4-spirocyclopentane-1, 2, 3, 4-tetrahydroisoquinolines (VI) and their analogs IV.

The high-temperature condensation [2] of dimethoxyphenylacetic acid (II) [3] with 1-(p-alkoxyphenyl)-1-aminomethylcyclopentane [4, 5] gave the corresponding 1-(4'-alkoxyphenyl)-1-(3", 4"-dimethoxyphenylacetamidomethyl)cyclopentanes III (Table 1).



R = 3,4-dimethoxybenzyl

Almost all the amides were isolated in the form of two isomers—a liquid and a crystalline one. It was to be expected that the isomerism was due either to the presence of different structural forms of the amides [6, 7] or to the existence of cis-trans isomers [8, 9].

In the subsequent reactions involved in the elimination of the amide group, the individual isomers gave identical products. In particular, the cyclization and reduction of the isomeric amides III (R = CH_3, C_2H_5, C_3H_7) gave identical substances VI and IV. The IR spectra of the amides synthesized confirmed their structure completely. In the 3340–3300 cm^{-1} region, the spectra has absorption bands of an NH group, and at 1640–1650 cm^{-1} those of an amide C=O group. The IR spectra of the isomeric amides confirm their identity. However, the individual isomers differ somewhat in the nature of the curve in the region of the band of the amide NH. Thus, while one of the isomers has a sharp peak, the other has a small shoulder in addition to the main peak. At the same time, the main peaks are displaced by about 10 cm^{-1}, which is obviously explained by the existence of cis-trans isomerism in the amides [8, 9]. No more detailed study of the amide isomerism was carried out within the framework of the present investigation.

The reduction of the amides III with lithium aluminum hydride gave the secondary amines IV, which were characterized in the form of their salts (Table 4). The Bischler-Napieralski cyclization of the amides gave the dihydroisoquinolines V, some of which could be characterized in the form of their hydrochlorides (Table 2). Some of the dihydroisoquinolines V (R = C_2H_5, C_3H_7) were used in the following stage without isolation. Reduction of the dihydro derivatives with lithium aluminum hydride in ethereal solution gave the 7-alkoxy-1-(3', 4'-dimethoxybenzyl)-4-spiropentane-1, 2, 3, 4-tetrahydroisoquinolines VI, which were characterized in the form of their hydrochlorides (Table 3). The IR spectra of the tetrahydroisoquinolines showed the absorption bands characteristic for tetrahydroisoquinoline in the 1600, 1520 cm^{-1} regions. There are two weak peaks in the 2675 and 2720 cm^{-1} regions which are characteristic for the $>NH_2^+$ group.

All the compounds IV–VI synthesized were subjected to pharmacological tests in the form of their salts. The substances relieved the contraction of the isolated intestine caused by barium chloride in concentrations of 1×10^{-6} and 1×10^{-7} by from 10 to 100% and in concentrations of only 1–2 mg/kg bodyweight of an animal they briefly lowered the arterial pressure.

EXPERIMENTAL

1-(4'-Alkoxyphenyl)-1-(3", 4"-dimethoxyphenylacetamidomethyl)-cyclopentanes (III) (see Table 1). A mixture of equimolecular amounts of 3, 4-dimethoxyphenylacetic acid and 1-aminomethyl-1-(4'-alkoxyphenyl)cyclopentane was heated in an open flask to 185–200° C. The mixture was stirred at this temperature for 30–40 min, by which time the evolution of water vapor had ceased completely. After cooling, a sixfold volume of benzene was added and the resulting solution was washed successively with 5% hydrochloric acid, water, and 10% sodium carbonate solution. Then it was dried with sodium sulfate and the benzene was distilled off. The residue was crystallized from a mixture of

*For part I, see [1].

Table 1

1-(4-Alkoxyphenyl)-1-(3″, 4″-dimethoxyphenylacetamidomethyl)cyclopentanes (III)

R	Mp, °C	R_f	Empirical formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
CH_3	90—91	0.55	$C_{23}H_{29}NO_4$	71.95	7.76	3.50	72.03	7.62	3.65	48
	Oil	0.54		72.23	7.80	3.21				47
C_2H_5	103—104	0.60	$C_{24}H_{31}NO_4$	72.36	8.00	3.40	72.51	7.85	3.52	66.8
	91—92	0.64		72.63	7.89	3.55				8.8
n-C_3H_7	121—122	0.54	$C_{25}H_{33}NO_4$	72.72	8.68	3.72	72.98	8.80	3.40	2.8
	73—75	0.66		72.74	8.75	3.33				72.7
i-C_3H_7	98—99	0.58	$C_{25}H_{35}NO_4$	73.03	8.92	3.71	72.98	8.80	3.40	2
	Oil	0.58		73.01	8.86	3.70				92
n-C_4H_9	86—87	0.74	$C_{26}H_{35}NO_4$	73.50	8.20	3.20	73.37	8.29	3.28	50.6
	Oil	0.76		73.16	8.42	3.42				39.4
i-C_4H_9	Oil	0.74	$C_{26}H_{35}NO_4$	73.63	8.51	3.20	73.37	8.29	3.28	95

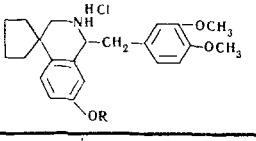
Table 2

Hydrochlorides of 7-alkoxy-1-(3′, 4′-dimethoxybenzyl)-4-spirocyclopentane-3, 4-dihydroisoquinolines (V)

R	Mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
			C	H	N	Cl	C	H	N	Cl	
CH_3	104—105	$C_{23}H_{27}NO_3 \cdot HCl$	68.71	7.15	3.72	8.25	68.73	7.02	3.48	8.82	32.7
i-C_3H_7	93—95	$C_{25}H_{31}NO_3 \cdot HCl$	69.84	7.58	3.40	8.06	69.83	7.50	3.25	8.24	36.1
n-C_4H_9	95—96	$C_{26}H_{33}NO_3 \cdot HCl$	70.21	7.50	3.21	8.26	70.33	7.72	3.15	7.98	45.1
i-C_4H_9	99—100	$C_{26}H_{33}NO_3 \cdot HCl$	70.51	7.85	2.80	8.18	70.33	7.72	3.15	7.98	72.5

Table 3

Salts of the 7-Alkoxy-1-(3′, 4′-dimethoxybenzyl)-4-spirocyclopentane-1, 2, 3, 4-tetrahydroisoquinolines (VI)



R	Mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
			C	H	N	Cl	C	H	N	Cl	
CH_3	109—110	$C_{23}H_{29}NO_3 \cdot HCl$	68.26	7.50	3.67	9.02	68.38	7.48	3.46	8.77	70
C_2H_5	74—75	$C_{24}H_{31}NO_3 \cdot HCl$	—	—	3.20	8.75	—	—	3.35	8.48	50
	184—185	$C_{24}H_{31}NO_3 \cdot C_2H_2O_4$*	66.58	6.70	2.67	—	66.22	7.05	2.97	—	38
n-C_3H_7	108—112	$C_{25}H_{33}NO_3 \cdot HCl$	69.29	7.96	3.01	7.82	69.50	7.93	3.24	8.26	60
i-C_3H_7	106—107	$C_{25}H_{33}NO_3 \cdot HCl$	69.57	7.92	3.14	8.12	69.50	7.93	3.24	8.26	70
n-C_4H_9	99—100	$C_{26}H_{35}NO_3 \cdot HCl$	70.23	8.04	3.17	8.37	70.01	8.13	3.14	7.94	60
i-C_4H_9	129—130	$C_{26}H_{35}NO_3 \cdot HCl$	70.08	8.28	3.38	7.83	70.01	8.13	3.14	7.94	60

*Oxalate.

Table 4

Salts of 1-(4'-Alkoxyphenyl)-1-{[β-(3", 4"-dimethoxyphenyl)ethyl]-aminomethyl}-cyclopentanes (IV)

R	Mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
			C	H	N	Cl	C	H	N	Cl	
CH_3	115—116	$C_{23}H_{31}NO_3 \cdot HCl$[a]	68.18	7.51	3,30	8.31	68.07	7.94	3.44	8.74	74
C_2H_5	150—151	$C_{24}H_{33}NO_3 \cdot C_2H_2O_4$[b]	66.05	7.71	3,10	—	65.94	7.45	2.95	—	71
n-C_3H_7	55—56	$C_{25}H_{35}NO_3 \cdot C_4H_6O_6$[c]	63.96	7.63	2,37	—	63.60	7.54	2.55	—	30
i-C_3H_7	160—161	$C_{25}H_{35}NO_3 \cdot C_2H_2O_4$[b]	66.49	7.50	2,45	—	66.50	7.65	2.83	—	63
n-C_4H_9	64—65	$C_{26}H_{37}NO_3 \cdot C_4H_6O_6$[c]	64.20	7.80	2,75	—	64.15	7.71	2.49	—	60
i-C_4H_9	60—62	$C_{26}H_{37}NO_3 \cdot HCl$[a]	69.83	8.21	3,00	8.04	69.70	8.54	3.12	7.91	41

[a]Hydrochloride. [b]Oxalate. [c]Tartrate.

acetone and ether (1 : 1), and the noncrystallizing part was purified on a column of alumina of activity II. The substances were deposited on the column with benzene and eluted with a mixture of benzene and acetone (3 : 1), 50-ml fractions being collected. The fractions were monitored by thin-layer chromatography on alumina (activity II), with benzene—ethyl acetate (1 : 1) as the mobile phase. The crystals isolated after chromatography were recrystallized from a mixture of acetone and ether (1 : 1). IR spectra, cm^{-1}: NH) 3300, 3340; C=O in amides) 1640, 1650 cm^{-1}.

7-Alkoxy-1-(3', 4'-dimethoxybenzyl)-4-spirocyclopentane-3, 4-dihydroisoquinolines (V) (Table 2). A solution of 0.03 mole of III in 80 ml of anhydrous toluene was treated with 0.1 mole of freshly-distilled phosphorus oxychloride and 0.03 mole of phosphorus pentoxide. The mixture was boiled for 10–12 hr. After the solvent had been distilled off, the residue was decomposed with 25% aqueous ammonia solution, extracted with ether or benzene (3–4 × 50 ml), and dried with anhydrous sodium sulfate. After the solvent had been distilled off the residue was dissolved in absolute ether and treated with an ethereal solution of hydrogen chloride. The hydrochloride that deposited was purified by reprecipitation from a mixture of ethanol and ether or was used in the following stage directly without purification.

7-Alkoxy-1-(3', 4'-dimethoxybenzyl)-4-spirocyclopentane-1, 2, 3, 4-tetrahydroisoquinolines (VI) (Table 3). The hydrochloride of a dihydroisoquinoline V obtained in the preceding experiment was treated with 25% aqueous ammonia and extracted with ether, and the extract was dried with anhydrous sodium sulfate and the solvent was distilled off. Then 0.01 mole of the base V so obtained in 20 ml of anhydrous ether was added over 20 min to a solution of 0.02 mole of lithium aluminum hydride in 30–50 ml of absolute ether. The mixture was stirred at room temperature for 30 min, boiled in the water bath for 5–6 hr, and decomposed with 5 ml of water. The precipitate was filtered off and washed with 30 ml of ether, and the ethereal solution was dried with anhydrous sodium sulfate. Then it was filtered and the solvent was distilled off to give a resinous base. The latter was converted into the hydrochloride which was purified by reprecipitation. IR spectra, cm^{-1}: 1600–1610, 1510–1520, 2675, 2720.

Salts of 1-(4'-Alkoxyphenyl)-1-{[β-(3", 4"-dimethoxyphenyl)-ethyl]aminomethyl}cyclopentanes (IV) (Table 4). The amines were obtained by the reduction of the amides III with lithium aluminum hydride in ethereal solution as described previously [1]. The oily amines were isolated in the form of salts by mixing ethereal solutions of the amines and acids.

The IR spectra were recorded on a UR-10 instrument in paraffin oil by L. V. Khazhakyan and I. A. Gyul'baryan.

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