

ISOQUINOLINE DERIVATIVES

III.* SYNTHESIS OF SEVERAL 1-(4-ALKOXYBENZYL)-7-ALKOXY-1,2,3,4-TETRAHYDROISOQUINOLINE-4-SPIROCYCLOPENTANES AND THEIR ANALOGS

A. L. Mndzhoyan, É. A. Markaryan,
and T. M. Martirosyan

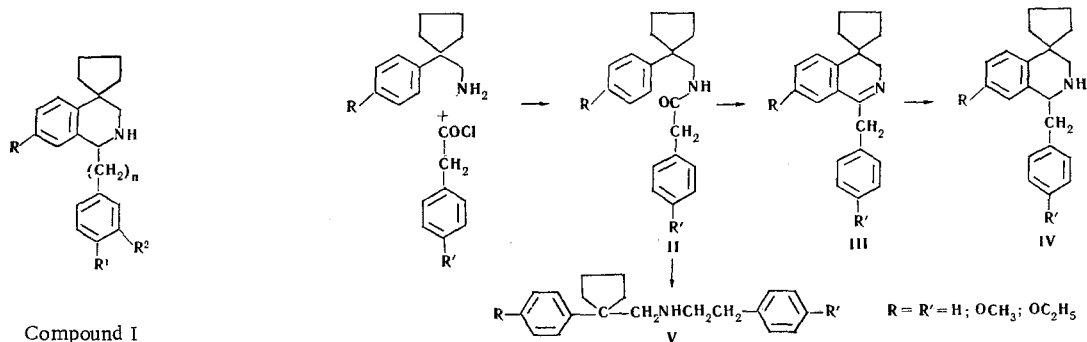
UDC 547.833.9.07:542.953

The corresponding amides were obtained by condensation of 1-(p-alkoxyphenyl)-1-aminomethylcyclopentanes with p-alkoxyphenylacetyl chlorides; the cyclization of the amides with subsequent reduction yielded 1-(4-alkoxybenzyl)-7-alkoxy-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentanes. The amides were converted to secondary amines by reduction. The IR and UV spectra of the intermediate and final compounds were studied. The purity of the compounds obtained was verified by chromatography.

We have previously reported [1, 2] the synthesis and pharmacological properties of tetrahydroisoquinolines (I) and their derivatives.

In continuing these investigations, we have synthesized tetrahydroisoquinolines of structure IV with various substituents, R and R', in order to study the change in the pharmacological properties under the influence of alkoxy groups. The synthesis was realized via a scheme similar to that described in [1].

Substituted amides II were obtained by condensation of 1-(p-alkoxyphenyl)-1-aminomethylcyclopentanes [3, 4] with p-alkoxyphenylacetyl chlorides in benzene. The IR spectra of the amides have HN absorption bands ($3310\text{--}3320\text{ cm}^{-1}$) and C=O absorption bands ($1650\text{--}1670\text{ cm}^{-1}$).



The corresponding dihydroisoquinolines (III), which are oily substances, were obtained by cyclization of II with phosphorus oxychloride. All of III was reduced without preliminary purification and isolation in pure form in ether solution with lithium aluminum hydride to 1-(4-alkoxybenzyl)-7-alkoxy-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentanes (IV) which were characterized in the form of their hydrochlorides. The latter are colorless crystals which are soluble in alcohols and water. The IR spectra of the hydro-

*For Communication II, see [2].

Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan. Translated from *Khimiya Geterotsiklicheskikh Soedinenii*, No. 10, pp. 1381-1383, October, 1970. Original article submitted January 15, 1969.

TABLE 1. 1-(4-R'-Phenylacetamidomethyl)-1-(4-R-phenyl)-cyclopentanes (II).

R	R'	mp	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
H	H	105	C ₂₀ H ₂₃ NO	81,72	7,63	4,69	81,87	7,83	4,77	83,8
H	OCH ₃	92—93	C ₂₁ H ₂₅ NO ₂	78,06	7,62	4,21	77,98	7,79	4,33	95,6
H	OC ₂ H ₅	88—89	C ₂₂ H ₂₇ NO ₂	78,34	7,95	4,40	78,30	8,06	4,15	88,7
OCH ₃	H	107	C ₂₁ H ₂₅ NO ₂	78,08	7,82	4,01	77,98	7,79	4,33	92,1
OCH ₃	OCH ₃	96—97	C ₂₂ H ₂₇ NO ₃	75,12	7,54	4,12	74,75	7,69	3,96	98,9
OCH ₃	OC ₂ H ₅	90—91	C ₂₃ H ₂₉ NO ₃	75,01	7,30	4,06	75,17	7,19	3,81	81,2
OC ₂ H ₅	H	84—85	C ₂₂ H ₂₇ NO ₂	78,29	8,37	4,59	78,30	8,06	4,15	87,6
OC ₂ H ₅	OCH ₃	95—96	C ₂₃ H ₂₉ NO ₃	74,81	7,10	4,13	75,17	7,19	3,81	90,9
OC ₂ H ₅	OC ₂ H ₅	105—106	C ₂₄ H ₃₁ NO ₃	75,36	8,22	4,19	75,55	8,11	3,67	78,2

TABLE 2. Hydrochlorides of 1-(4-R'-Benzyl)-7-R-1,2,3,4-tetrahydroquinoline-4-spirocyclopentanes (IV)

R	R'	mp	Empirical formula	Found, %				Calc., %				Yield, %
				C	H	N	Cl	C	H	N	Cl	
H	H	256—257	C ₂₀ H ₂₃ N · HCl	76,27	8,00	4,29	11,60	76,53	7,70	4,46	11,29	62,5
H	OCH ₃	136—137	C ₂₁ H ₂₅ NO · HCl	73,45	7,45	4,38	10,32	73,34	7,62	4,07	10,31	51,0
H	OC ₂ H ₅	168—169	C ₂₂ H ₂₇ NO · HCl	74,18	7,69	4,08	9,77	73,82	7,88	3,91	9,90	30,3
OCH ₃	H	262—263	C ₂₁ H ₂₅ NO · HCl	73,56	7,46	4,26	10,83	73,34	7,62	4,07	10,31	81,4
OCH ₃	OCH ₃	172—173	C ₂₂ H ₂₇ NO ₂ · HCl	70,82	7,13	3,99	9,02	70,66	7,54	3,74	9,48	90,6
OCH ₃	OC ₂ H ₅	191—192	C ₂₃ H ₂₉ NO ₂ · HCl	71,15	7,24	4,00	8,96	71,20	7,79	3,61	9,14	83,5
OC ₂ H ₅	H	175—176	C ₂₂ H ₂₇ NO · HCl	74,08	7,36	4,13	9,52	73,82	7,88	3,91	9,90	25,0
OC ₂ H ₅	OCH ₃	109—110	C ₂₃ H ₂₉ NO ₂ · HCl	71,25	7,25	3,65	9,64	71,20	7,79	3,61	9,14	61,2
OC ₂ H ₅	OC ₂ H ₅	132—133	C ₂₄ H ₃₁ NO ₂ · HCl	71,85	8,51	3,72	8,58	71,71	8,02	3,48	8,82	43,5

TABLE 3. Hydrochlorides of 1-(β-4-R'-Phenylethylaminomethyl)-1-(4-R-phenyl)cyclopentanes (V)

R	R'	mp	Empirical formula	Found, %				Calc., %				Yield, %
				C	H	N	Cl	C	H	N	Cl	
H	H	146—147	C ₂₀ H ₂₅ N · HCl	75,87	8,51	4,72	11,87	76,04	8,29	4,43	11,22	20,3
H	OCH ₃	156—157	C ₂₁ H ₂₇ NO · HCl	73,07	8,33	4,24	10,31	72,91	8,11	4,04	10,21	40,6
H	OC ₂ H ₅	157—158	C ₂₂ H ₂₉ NO · HCl	74,35	8,48	4,31	9,65	73,82	8,44	3,91	9,93	61,4
OCH ₃	H	137—138	C ₂₁ H ₂₇ NO · HCl	73,22	8,03	3,82	10,58	72,91	8,11	4,04	10,21	33,9
OCH ₃	OCH ₃	156—157	C ₂₂ H ₂₉ NO ₂ · HCl	70,35	8,35	4,09	9,72	70,28	8,04	3,72	9,43	41,5
OCH ₃	OC ₂ H ₅	125—126	C ₂₃ H ₃₁ NO ₂ · HCl	70,90	8,81	3,42	9,43	70,83	8,27	3,59	9,09	50,7
OC ₂ H ₅	H	190—191	C ₂₂ H ₂₉ NO · C ₂ H ₂ O ₄ *	69,59	7,13	3,22	—	69,88	7,33	3,39	—	35,0
OC ₂ H ₅	OCH ₃	145—146	C ₂₃ H ₃₁ NO ₂ · HCl	70,66	8,22	3,74	9,51	70,83	8,27	3,59	9,09	40,0
OC ₂ H ₅	OC ₂ H ₅	176—177	C ₂₄ H ₃₃ NO ₂ · HCl	71,72	8,15	3,65	8,22	71,35	8,48	3,46	8,77	21,2

*Oxalate.

chlorides of IV have characteristic absorption bands at 1520, 1590, and 1620 cm⁻¹ (isoquinoline) and 2600, 2640, 2720 cm⁻¹ (+NH₂). The UV spectra of the hydrochlorides of IV are also characteristic for this class of compounds [2, 5]: λ_{max} 262 ± 5 nm (log ε 2.70 ± 0.06), λ_{min} 243 ± 8 nm (log ε 2.48 ± 0.08). One spot was exposed by paper chromatography of IV and their hydrochlorides.

Amides II were converted to secondary amines V by reduction with lithium aluminum hydride; the amines were also characterized in the form of their hydrochlorides, which were recrystallized from alcohol-ether.

The pharmacological properties of the hydrochlorides of IV and V will be published later.

EXPERIMENTAL

The IR spectra in mineral oil were obtained with a UR-10 spectrophotometer. The UV spectra in alcohol were obtained with an SF-4 spectrophotometer.

1-(4-R'-Phenylacetamidomethyl)-1-(4-R-phenyl)cyclopentanes (II, Table 1). A mixture of 0.1 mole of 1-(4-R-phenyl)-1-aminomethylcyclopentane and 0.15 mole of anhydrous pyridine in 80 ml of absolute benzene was added dropwise in 30 min to 0.1 mole of 4-R'-phenylacetylchloride in 100 ml of absolute benzene. The mixture was stirred for 1 h and refluxed for 6 h, filtered, and the precipitate was washed three times with benzene. The benzene filtrate was washed with 60 ml of 10% sodium carbonate, 50 ml of dilute hydrochloric acid (1:5), and 20-30 ml of water, and dried with sodium sulfate. The solvent was removed by distillation, and the residue was triturated with petroleum ether and crystallized from benzene-petroleum ether (1:1). Thin-layer chromatography was carried out on aluminum oxide of activity II. The mobile phase was benzene-ethyl acetate (5:1). The R_f values of the II ranged from 0.55 to 0.62.

1-(4-R'-Benzyl)-7-R-3,4-dihydroisoquinoline-4-spirocyclopentanes (III). Freshly distilled phosphorus oxychloride (0.5 mole) and 0.03 mole of P_2O_5 were added to a solution of 0.08 mole of II in 150 ml of absolute toluene in 6 h. The solvent was removed and the residual mass was triturated with 100 ml of ice water. A 20% solution of sodium carbonate was then gradually added until the pH was 10-11. The aqueous layer was extracted with ether (3×100 ml). The ether extract was dried over sodium sulfate, and the solvent was removed. The base obtained was converted into the hydrochloride by mixing ether solutions of III and hydrogen chloride cooled to 0° (pH 3). The precipitated hydrochloride of III was isolated and used in the next step without purification.

1-(4-R'-Benzyl)-7-R-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentanes (IV, Table 2). The hydrochloride of III was treated with 25% ammonium hydroxide, extracted with ether, and dried with sodium sulfate. Removal of the solvent yielded III in the form of an oily product. A solution of 0.03 mole of III and 100 ml of absolute ether was then added in 20 min to a solution of 0.08 mole of lithium aluminum hydride in 150 ml of absolute ether, and the mixture was stirred at room temperature for 30 min and refluxed for 8-10 h. Water (10-15 ml) was added with cooling, the mixture was filtered, and the precipitate was washed with 100 ml of ether. The ether solution was dried with sodium sulfate, filtered, and treated with an ether solution of HCl at $5-7^\circ$ until an acid reaction was obtained. The hydrochloride of IV obtained was crystallized from alcohol-ether. Chromatography was carried out on grade "S" paper from the Volodarskii factory. The average R_f values of the hydrochlorides of IV ranged from 0.74 to 0.78 when a butanol-benzene-water system (3:1:2) was used as the mobile phase.

1-(β -4-R'-Phenylethylaminomethyl)-1-(4-R-phenyl)cyclopentanes (V, Table 3). These compounds were obtained by reduction of II with lithium aluminum hydride in ether via the method described in [1]. The oily amines were isolated in the form of hydrochlorides.

LITERATURE CITED

1. A. L. Mndzhoyan, É. A. Markaryan, T. M. Martirosyan, and S. S. Vasilyan *Khim. Geterotsikl. Soed.*, 529 (1969).
2. A. L. Mndzhoyan, É. A. Markaryan, L. P. Solomina, and S. S. Vasilyan, *Khim. Geterotsikl. Soed.*, 827 (1969).
3. S. I. Sergievskaya, K. V. Levshina, A. I. Gavrilova, and A. K. Chizhov, *Zh. Obshch. Khim.*, 28, 1845 (1958).
4. A. L. Mndzhoyan and M. G. Tsinker, *Arm. Khim. Zh.*, 22, 314 (1969).