ISOQUINOLINE DERIVATIVES

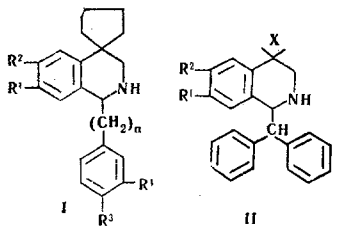
IV.* SYNTHESIS OF 1-DIPHENYLMETHYL-4,6,7-SUBSTITUTED 1,2,3,4-TETRAHYDROISOQUINOLINES AND THEIR ANALOGS

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

UDC 547.833.3:547.233.2

Amides IV, which are converted to 1-diphenylmethyl-4,6,7-substituted 1,2,3,4-tetrahydroisoquinolines (II) by cyclization and subsequent reduction with lithium aluminum hydride, were obtained by condensation of diphenylacetyl chloride with the corresponding substituted phenylethylamines (III). Amines VI, the open analogs of the tetrahydroisoquinolines, were synthesized by reduction of IV.

In order to study the pharmacological properties of several isoquinoline derivatives we previously obtained 1,4,6,7-substituted tetrahydroquinolines of the general structure I, where R^1-R^4 are H and AlkO and n is 0 and 1 [1-3].



I II

The goal of this research was to investigate the effect of an additional phenol group in the 1-benzyltetrahydroisoquinoline derivatives on the pharmacological activity. In particular, a study of the coronary-dilating and hypotensive properties is proposed for compounds with the II structure [1,2,6].

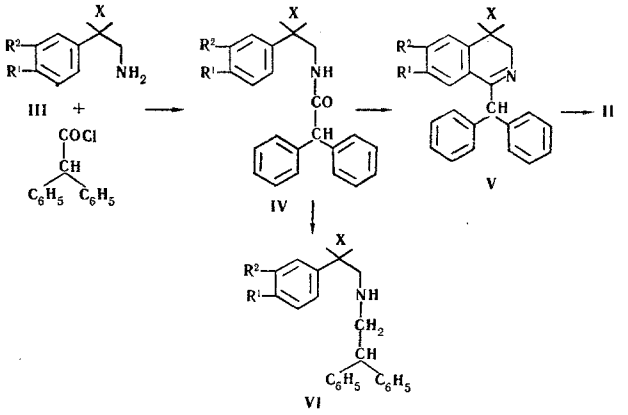
The starting alkoxyphenylaminomethylcyclopentanes [III, R^1 = OAlk, R^2 = H, and X = $(-CH_2-)_4$ were synthesized by the methods in [1-3]. Dialkoxyphenylethylamines III (R^1 and R^2 = OAlk and X = H_2) were obtained from the corresponding nitriles [4] by reduction with hydrazine hydrate.

Amides IV (Table 1) were obtained by the condensation of equimolecular amounts of the amine and diphenylacetyl chloride in the presence of pyridine.

Compounds IV with X = $(CH_2)_4$ (Table 1), which were isolated only in the form of crystals, have a strong narrow ν (N−H) band at 3350 cm^{-1} in their IR spectrum. However, in the case of IV with X = H_2, which were isolated as oils and crystals, the N−H absorption is manifested as a broad band with two maxima at 3220 and 3550 cm^{-1}. This is due to the presence of isomeric forms of the amides [2]. The ν (C = 0) band for all of the amides is found at 1650 ± 5 cm^{-1}.

*See [3] for Communication III.

Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSSR, Erevan. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1670-1673, December, 1970. Original article submitted May 5, 1969.



Dihydroquinolines V, which, after separation from the starting amide, were reduced with lithium aluminum hydride to the corresponding tetrahydroquinolines (II), were obtained by Bischler–Napieralski cyclization of the amides. All II were isolated as crystalline hydrochlorides. Their IR and UV spectra are characteristic for benzyltetrahydroisoquinoline derivatives.

Amides IV were reduced with lithium aluminum hydride in ether to obtain the open analogs of the tetrahydroisoquinolines viz., amines VI. The compounds were isolated as the hydrochlorides, which were recrystallized from alcohol-ether (Table 3).

The results of the pharmacological investigations will be published separately.

EXPERIMENTAL

The IR and UV spectra were obtained under the direction of L. V. Khazhakyan, and the elementary analyses were performed by S. N. Tonakanyan. The IR spectra in mineral oil were obtained with a UR-10 spectrophotometer. The UV spectra in alcohol were obtained with an SF-4 spectrometer.

3,4-Dialkoxyphenylethylamines. These were obtained by hydrogenation of the corresponding nitriles [4] in alcohol with a fourfold excess of hydrazine hydrate in the presence of a nickel catalyst. The yields of the amines were 70-75% [5].

The synthesis of amides IV via the method in [2], viz., by condensation of the amines with acid at 180-200 deg, gave low yields of hard-to-purify products because of considerable resinification.

3-Methoxy-4-alkoxyphenylethylamides of Diphenylacetic Acid (IV. R^1 = OAlk, R^2 = OCH_3, X = H_2). A solution of 0.1 mole of 3-methoxy-4-alkoxyphenylethylamide and 0.11 mole of anhydrous pyridine in 50 ml of absolute benzene was added dropwise to a solution of 0.1 mole of diphenylacetyl chloride in 80 ml of absolute benzene. The mixture was stirred for 1 h and then refluxed on a water bath for 3 h. After the

TABLE 1. Compounds of the IV Type

R^1	R^2	X	Mp	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
CH_3O	CH_3O	H_2	105—106	$C_{24}H_{25}NO_3$	77,0	6,7	3,6	76,7	6,7	3,7	89
C_2H_5O	CH_3O	H_2	113—114	$C_{25}H_{27}NO_3$	77,3	7,3	3,8	77,0	6,9	3,5	90
C_3H_7O	CH_3O	H_2	120—121	$C_{26}H_{29}NO_3$	77,2	6,9	3,5	77,3	7,2	3,4	79
i-C_3H_7O	CH_3O	H_2	94—95	$C_{26}H_{29}NO_3$	77,0	7,5	3,5	77,3	7,2	3,4	97
C_4H_9O	CH_3O	H_2	107—108	$C_{27}H_{31}NO_3$	78,1	7,1	3,0	77,6	7,4	3,3	96
i-C_4H_9O	CH_3O	H_2	90—91	$C_{27}H_{31}NO_3$	77,4	7,4	3,4	77,6	7,4	3,3	93
H	H	—$(CH_2)_4$—	134—135	$C_{26}H_{27}NO$	84,3	7,6	4,1	84,5	7,3	3,7	81
CH_3O	H	—$(CH_2)_4$—	138—139	$C_{27}H_{29}NO_2$	81,0	7,2	3,8	81,1	7,3	3,5	48
C_2H_5O	H	—$(CH_2)_4$—	90—91	$C_{28}H_{31}NO_2$	80,8	7,6	3,8	81,3	7,5	3,3	94
C_4H_9O	H	—$(CH_2)_4$—	110—111	$C_{30}H_{35}NO_2$	82,0	7,9	3,4	81,6	7,9	3,1	99
i-C_4H_9O	H	—$(CH_2)_4$—	131—133	$C_{30}H_{35}NO_2$	81,5	7,8	3,4	81,6	7,9	3,1	98

TABLE 2. Compounds of the II Type (hydrochlorides)

R^1	R^2	X	Mp	Empirical formula	Found, %				Calc., %				Yield, %
					C	H	Cl	N	C	H	Cl	N	
CH_3O	OCH_3	H_2	223—225	$C_{24}H_{25}NO_2 \cdot HCl$	72,6	6,4	8,3	3,4	72,8	6,6	8,0	3,5	42
C_2H_5O	OCH_3	H_2	260—261	$C_{25}H_{27}NO_2 \cdot HCl$	72,9	6,5	8,6	3,7	73,2	6,8	8,6	3,4	58
C_3H_7O	OCH_3	H_2	241—242	$C_{26}H_{29}NO_2 \cdot HCl$	73,8	7,4	7,9	3,6	73,6	7,1	8,3	3,3	50
i-C_3H_7O	OCH_3	H_2	264—265	$C_{26}H_{29}NO_2 \cdot HCl$	73,9	6,9	8,3	3,3	73,6	7,1	8,3	3,3	54
C_4H_9O	OCH_3	H_2	234—235	$C_{27}H_{31}NO_2 \cdot HCl$	73,9	7,5	8,4	3,1	74,0	7,3	8,0	3,1	34
i-C_4H_9O	OCH_3	H_2	250—251	$C_{27}H_{31}NO_2 \cdot HCl$	73,9	7,4	8,3	3,5	74,0	7,3	8,0	3,1	50
H	H	$-(CH_2)_4-$	157—158	$C_{26}H_{27}N \cdot HCl$	80,3	7,6	9,1	4,1	80,0	7,2	9,0	3,5	38
CH_3O	H	$-(CH_2)_4-$	199—200	$C_{27}H_{29}NO \cdot HCl$	80,8	7,1	8,3	3,6	80,2	7,4	8,7	3,4	65
C_2H_5O	H	$-(CH_2)_4-$	233—234	$C_{28}H_{31}NO \cdot HCl$	77,6	8,0	8,4	3,3	77,4	7,4	8,1	3,2	37
C_4H_9O	H	$-(CH_2)_4-$	224—225	$C_{30}H_{35}NO \cdot HCl$	77,7	8,0	8,1	3,5	77,9	7,8	7,6	3,0	41
i-C_4H_9O	H	$-(CH_2)_4-$	224—226	$C_{30}H_{35}NO \cdot HCl$	77,3	8,1	7,9	3,3	77,9	7,8	7,6	3,0	38

TABLE 3. Compounds of the VI Type (hydrochlorides)

R^1	R^2	X	Mp	Empirical formula	Found, %				Calc., %				Yield, %
					C	H	Cl	N	C	H	Cl	N	
OCH_3	OCH_3	H_2	144—145	$C_{24}H_{27}NO_2 \cdot HCl$	72,4	6,8	8,8	3,3	72,4	7,0	8,9	3,5	41
OC_2H_5	OCH_3	H_2	174—175	$C_{25}H_{29}NO_2 \cdot HCl$	73,0	7,6	8,9	3,9	72,8	7,3	8,6	3,4	26
OC_3H_7	OCH_3	H_2	126—127	$C_{26}H_{31}NO_2 \cdot HCl$	73,6	7,6	7,9	3,6	73,3	7,5	8,3	3,2	16
i-OC_3H_7	OCH_3	H_2	147—148	$C_{26}H_{31}NO_2 \cdot HCl$	73,8	7,6	8,5	3,7	73,3	7,5	8,3	3,2	40
OC_4H_9	OCH_3	H_2	111—112	$C_{27}H_{33}NO_2 \cdot HCl$	73,7	7,8	8,1	3,4	73,6	7,7	8,0	3,1	54
i-OC_4H_9	OCH_3	H_2	103—104	$C_{27}H_{33}NO_2 \cdot HCl$	73,7	8,1	7,7	2,9	73,6	7,7	8,0	3,1	48
H	H	$-(CH_2)_4-$	169—170	$C_{26}H_{29}N \cdot HCl$	79,1	8,1	9,2	4,1	79,6	7,7	9,0	3,5	60
OCH_3	H	$-(CH_2)_4-$	212—213	$C_{27}H_{31}NO \cdot HCl$	77,3	7,2	7,9	3,7	76,8	7,6	8,4	3,3	22
OC_2H_5	H	$-(CH_2)_4-$	94—95	$C_{28}H_{33}NO \cdot HCl$	77,2	7,8	7,8	3,6	77,1	7,8	8,1	3,2	19
OC_4H_9	H	$-(CH_2)_4-$	175—177	$C_{30}H_{37}NO \cdot HCl$	77,5	7,9	7,6	3,1	77,6	8,2	7,6	3,0	19
i-OC_4H_9	H	$-(CH_2)_4-$	203—205	$C_{30}H_{37}NO \cdot HCl$	77,2	8,2	8,0	3,5	77,6	8,2	7,6	3,0	20

usual workup [1,3], the amide was recrystallized from acetone–ether (Table 1). Thin-layer chromatography on activity II aluminum oxide with a benzene–ethyl acetate (5:1) mobile phase exposed one spot. The average R_f values in this series were 0.45 ± 0.05. IR spectrum: 3320 ± 5, 3350 ± 5 cm^{-1} (N–H); 1645 ±5 cm^{-1} (C = O).

1-(N-Diphenylacetamido)methyl-1-(4-alkoxyphenyl)cyclopentanes (IV, R^1 = OAlk, R^2 = H, X = $(CH_2)_4$). These were obtained, like the previous amides, from diphenylacetyl chloride and 1-alkoxyphenyl-1-aminomethylcyclopentanes. The amides were recrystallized from benzene-petroleum ether (Table 1). Thin-layer chromatography on activity II aluminum oxide exposed one spot with an average R_f value of 0.70 ± 0.03 in benzene–ethyl acetate (5:1). IR spectrum: 3350 ± 5 cm^{-1} (N–H); 1650 ± 5 cm^{-1} (C=O).

1-Diphenylmethyl-6-methoxy-7-alkoxy-1,2,3,4-tetrahydroisoquinolines (II, X = H_2, R^1 = OAlk, R^2 = OCH_3) and 1-diphenylmethyl-7-alkoxy-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentanes (II, X = $-(CH_2)_4-$, R^1 = OAlk, R^2 = H). These were obtained via the method in [1-3] by refluxing 0.15 mole of amide IV in

toluene in the presence of 40 g of phosphorus oxychloride in 3 g of phosphorus pentoxide. The hydrochloride of V, which was converted to the base and reduced with lithium aluminum hydride in ether, was isolated. The substances were isolated in the form of hydrochlorides, which were recrystallized from ether–alcohol (Table 2). Chromatography on brand "S" paper from the Leningrad factory with butanol–acetic acid–water (10:1:3) exposed one spot with R_f 0.84 ± 0.04. Chromatography in a thin-layer of activity II aluminum oxide with chloroform as the mobile phase exposed one spot with R_f 0.70 ± 0.03 for compounds with $(CH_2)_4$ and with R_f 0.60 ± 0.05 for compounds with $X = H_2$ (Table 2). IR spectrum: 3300 ± 20, 1570 ± 5, 1600 ± 10, ±620 ± 5 cm^{-1}. UV spectrum: λ_{max} 280 ± 6 (log ε 3.55 ± 0.55); λ_{min} 250 ± 3 nm log ε 3.1 ± 0.05).

N-(β-Diphenylethyl)-N-(3-methoxy-4-alkoxyphenyl)ethylamines (VI, $X = H_2$, R^1 = OAlk, $R^2 = OCH_3$) and 1-(N-β-Diphenylethylaminomethyl)-1-(4'-alkoxyphenyl)cyclopentanes (VI, $X = -(CH_2)_4-$, R^1 = OAlk, R^2 = H). These compounds were obtained by reduction of amides IV with lithium aluminum hydride and ether via the method in [1-3]. They were isolated as the hydrochlorides, which were recrystallized from alcohol–ether (Table 3).

LITERATURE CITED

1. A. L. Mndzhoyan, É. A. Markaryan, T. M. Martirosyan, and S. S. Vasilyan, Khim. Geterotsikl. Soedin., 529 (1969).
2. A. L. Mndzhoyan, É. A. Markaryan, L. P. Solomina, and S. S. Vasilyan, Khim. Geterotsikl. Soedin., 827 (1969).
3. A. L. Mndzhoyan, É. A. Markaryan, and T. M. Martirosyan, Khim. Geterotsikl. Soedin., 1381 (1970).
4. E. R. Shepard and I. P. Noth, J. Am. Chem. Soc., 72, 4364 (1950).
5. A. Furst, R. C. Berlo, and S. Hooson, Chem. Rev., 65, 51 (1965).
6. M. D. Mashkovskii, Medicinals [in Russian], Vol. 1, Moscow (1967). p. 207.