Russian Journal of Organic Chemistry, Vol. 39, No. 9, 2003, pp. 1248–1255. Translated from Zhurnal Organicheskoi Khimii, Vol. 39, No. 9, 2003, pp. 1322–1329.

Adamantyl-Substituted Amino Alcohols. Synthesis and Functionalization at the Nitrogen and Oxygen Nucleophilic Centers

L. I. Kas'yan[1], E. A. Golodaeva[1], and A. O. Kas'yan[2]

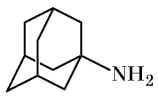
[1] *Dnepropetrovsk National University, per. Nauchnyi, 13, Dnepropetrovsk, 49005 Ukraine*

[2] *Institut für organische Chemie, Rheinisch Westfälische Technische Hochschule, Aachen, Germany*

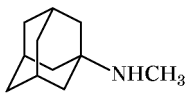
Received April 2, 2003

Abstract—1-Aminoadamantanes and 1-aminomethyladamantanes were brought into reactions with *p*-nitrophenyloxirane and 9-carbazolylmethyloxirane. The reactions occurred in a regioselective fashion according to the Krasusky rule, which was confirmed by the ^{1}H and ^{13}C NMR data. The resulting amino alcohols having a *p*-nitrophenyl moiety were subjected to functionalization at the nitrogen and oxygen nucleophilic centers using *p*-nitrobenzenesulfonyl chloride, *p*-nitrobenzoyl chloride, and hexamethyldisilazane, and *N*,*O*-bisacyl derivative was synthesized. The structure of the products was proved by IR and ^{1}H NMR spectroscopy.

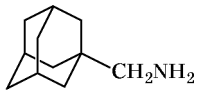
Amines and amides having adamantane fragments exhibit antiviral properties and are active in the treatment of Parkinson's disease [1, 2]. The biological activity of aminoadamantanes is believed to originate from the presence of a bulky and highly lipophilic cage-like fragment which is capable of directly interacting with biological membranes containing a lipid layer and also with hydrophobic fragments of proteins, including those constituting receptor structure [1, 3].



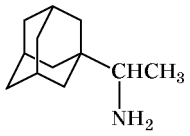
I



II



III



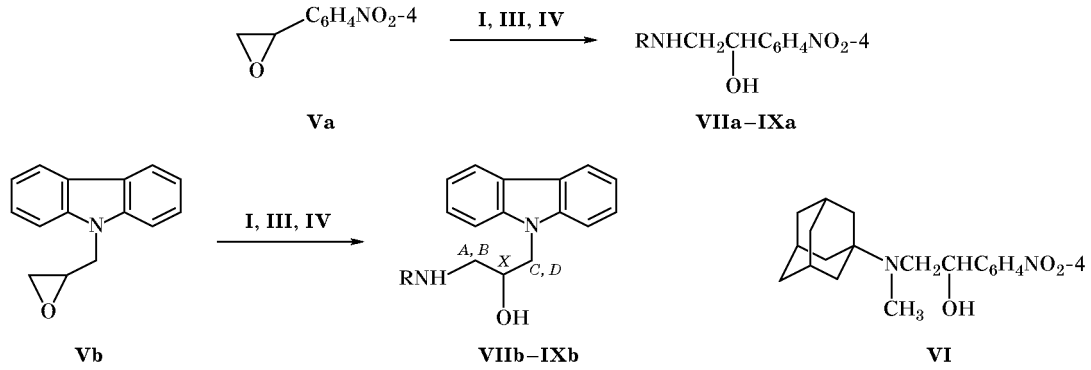
IV

Compounds **I**–**IV** are among the most extensively studied amines of the adamantane series. Amine **I** and **IV** hydrochlorides are known as medical preparations Amantadine (Midantanum) and Remantadin. Biological properties of such amines stimulates studies in the field of further modification of the amino group therein and search for new compounds with a pronounced biological activity. Reactions of amines **I**–**IV** with sulfonyl chlorides [4–6], endic anhydride [7], aryl isocyanates, aryl isothiocyanates [5, 8], and dichlorophosphinoyl isocyanate [9] have been reported. Their structure and conformations were studied by molecular mechanics [4], and electron density distribution in their molecules was analyzed by quantum-chemical methods [4, 10]. According to the results of AM1 semiempirical calculations [4], the basicity of the above amines decreases in the series **II** > **I** > **IV** > **III**. However, it was presumed [10] that the reactivity of these compounds is determined mainly by steric effects of the bulky cage-like fragments rather than by electron density distribution in their molecules.

Published data on the reactions of aminoadamantanes with epoxy derivatives are very scanty, though the spectrum of biological action of amino alcohols is fairly wide and a number of medicines contain the above structural fragments [11, 12]. *N*,*N*-Bis(1-hydroxyethyl)- and *N*,*N*-bis(1-hydroxypropyl)-1-adamantylamine hydrochlorides were synthesized by heating of amine **I** with 1,2-epoxyethane and 1,2-epoxypropane, respectively (6 h, 70–75°C) [13]. Addition products of *p*-nitrophenyloxirane (**Va**), 9-carbazolylmethyloxirane (**Vb**), and 1,2-epoxycyclohexane to *N*-methyl-1-adamantylamine (**II**) were also reported [5]. The goal of the present work was to examine reactions of amines **I**, **III**, and **IV** with oxiranes **Va** and **Vb** and to study the reactivity of the resulting amino alcohols, as well as of previously described compound **VI** (Scheme 1).

1070-4280/03/3909-1248 $25.00 © 2003 MAIK "Nauka / Interperiodica"

Scheme 1.



VII, R = 1-Ad; **VIII**, R = 1-AdCH$_2$; **IX**, R = 1-AdCH(CH$_3$).

The aminolysis of epoxy derivatives **Va** and **Vb** was carried out in isopropyl alcohol at room temperature with equimolar amounts of the reactants [5, 14]. Amino alcohols **VII**–**IX** were isolated in 71–88% yield; their properties are given in Table 1. Compounds **VII**–**IX** are crystalline substances with R_f values of 0.6–0.9 for those derived from **Va** and 0.4–0.6 for carbazole derivatives (from **Vb**). In the IR spectra of most of the products we observed two absorption bands in the region 3460–3300 cm^{-1}, which were assigned to stretching vibrations of the O–H and N–H bonds; all amino alcohols showed in the spectra absorption bands belonging to the aromatic fragment; and compounds **VIIa**–**IXa** were also characterized by nitro group absorption at 1523–1518 and 1349–1341 cm^{-1} [15].

Table 2 contains parameters of the ^{1}H NMR spectra of the amino alcohol fragments in **VII**–**IX**, which

Table 1. Yields, melting points, R_f values, IR spectra, and elemental analyses of amino alcohols **VII**–**IX** and their *N*- and *O*-functionalized derivatives **X**–**XV**

Comp. no.	Yield, %	mp, °C	R_f (ether)	IR spectrum, ν, cm^{-1}	Found N, %	Formula	Calculated N, %
VIIa	84.6	108–110	0.68	3430, 3299, 3083, 1518, 1348, 1311, 1227, 1106, 1170	8.82	$C_{18}H_{24}N_2O_3$	8.86
VIIb	82.0	97–99	0.40	3420, 3346, 3065, 1640, 1552, 1240, 1146	7.59	$C_{25}H_{30}N_2O$	7.49
VIIIa	75.3	145–146	0.62	3302, 3051, 1604, 1522, 1349, 1212, 1108, 1065	8.40	$C_{19}H_{26}N_2O_3$	8.48
VIIIb	73.2	94–96	0.46	3417, 3293, 3051, 1457, 1124, 1024	7.29	$C_{26}H_{32}N_2O$	7.22
IXa	71.4	110–112	0.59	3302, 3051, 1604, 1523, 1346, 1220, 1109, 1072	8.21	$C_{20}H_{28}N_2O_3$	8.14
IXb	82.5	76–77	0.45	3460, 3297, 3065, 1465, 1140, 1080	6.89	$C_{27}H_{34}N_2O$	6.96
Xa	88.2	149–151	0.46	3430, 3054, 1640, 1525, 1350, 1112	8.97	$C_{25}H_{27}N_3O_6$	9.03
Xb	75.0	122–124	0.40	3471, 3060, 1645, 1520, 1345, 1110	8.84	$C_{26}H_{29}N_3O_6$	8.77
XIa	30.1	125–126	0.43	3420, 3030, 1609, 1530, 1350, 1258, 1125, 1148	8.30	$C_{24}H_{27}N_3O_7S$	8.38
XIb	35.4	101–103	0.37	3434, 3045, 1600, 1525, 1338, 1246, 1135	8.21	$C_{25}H_{29}N_3O_7S$	8.15
XIIb	93.3	190–191	0.61	3240, 3064, 1721, 1587, 1525, 1339, 1280	9.09	$C_{25}H_{27}N_3O_6$	9.03
XIIIb	90.1	204–210	0.67	3060, 1718, 1590, 1530, 1335, 1267	8.81	$C_{26}H_{29}N_3O_6$	8.77
XIVb	96.1	184–186	0.60		8.71	$C_{26}H_{29}N_3O_6$	8.77
XV	80.0	143–145	0.75	1719, 1600, 1535, 1348, 1276	9.09	$C_{32}H_{30}N_4O_9$	9.12

Table 2. ^{1}H NMR parameters (chemical shifts δ, ppm, and coupling constants *J*, Hz) of the amino alcohol fragment in adamantane derivatives **VII**–**X**, **XIIb**, **XIIIb**, **XIVb**, and **XV**

Compound no.	H_X	H_A, H_B	H_C, H_D	Substituent	NH	OH
VIIa	4.59, $^3J_{X,A}$ = 8.8, $^3J_{X,B}$ = 3.8	2.94, 2.48, $^2J_{A,B}$ = 12.1	–	8.13, 7.47 (4H, H_{arom})	2.02	3.10
VIIb	3.93, $^3J_{X,A}$ = 8.8, $^3J_{X,B}$ = 3.8	2.68, 2.45, $^2J_{A,B}$ = 12.0	4.48, 4.27, $^2J_{C,D}$ = 15.9, $^2J_{D,X}$ = 5.2, $^2J_{C,X}$ = 3.3	7.16–8.00 (8H, carbazole)	3.23	4.19
VIIIa	4.67, $^3J_{X,A}$ = 9.5, $^3J_{X,B}$ = 3.6	2.66, 2.51, $^2J_{A,B}$ = 12.2	–	8.13, 7.47 (4H, H_{arom})	2.60	2.82
VIIIb	4.09, $^3J_{X,A}$ = 8.8, $^3J_{X,B}$ = 3.6	2.68, 2.42, $^2J_{A,B}$ = 11.9	4.26, 4.17, $^2J_{C,D}$ = 15.8, $^2J_{D,X}$ = 5.0, $^2J_{C,X}$ = 3.6	7.16–7.99 (8H, carbazole)	3.00	3.22
IXa	4.12, $^3J_{X,A}$ = 9.9, $^3J_{X,B}$ = 3.6	3.11, 2.55, $^2J_{A,B}$ = 12.1	–	8.13, 7.48 (4H, H_{arom})	2.70	2.85
IXb	4.67, $^3J_{X,A}$ = 9.5, $^3J_{X,B}$ = 3.6	2.66, 2.51, $^2J_{A,B}$ = 12.0	4.42, 4.35, $^2J_{C,D}$ = 15.0, $^2J_{D,X}$ = 5.5, $^2J_{C,X}$ = 3.6	7.24–8.09 (8H, carbazole)	1.94	2.00
Xa	4.67, $^3J_{X,A}$ = 9.0	3.12, 2.76, $^2J_{A,B}$ = 12.0	–	7.50–8.35 (8H, H_{arom})	–	3.25
Xb	4.76, $^3J_{X,A}$ = 9.3, $^3J_{X,B}$ = 3.6	3.16, 2.91, $^2J_{A,B}$ = 12.3	–	8.24, 8.17, 8.01, 7.74 (8H, H_{arom})	–	2.82
XIIb	5.12	3.35, 3.27	–	8.27, 8.21, 7.89, 7.76 (8H, H_{arom})	3.12	–
XIIIb	5.30	3.47, 3.40	–	7.80–8.50 (8H, H_{arom})	–	–
XIVb	5.25	3.34, 3.31	–	8.26, 8.11, 7.94, 7.84 (8H, H_{arom})	3.24	–
XV	5.56	3.56, 3.49	–	7.70–8.35 (12H, H_{arom})	–	–

support the assigned structures and indicate that the aminolysis of epoxy derivatives **Va** and **Vb** occurs according to the Krasusky rule [16]. The ^{1}H NMR spectrum of each compound contains a one-proton multiplet (doublet of doublets) at δ 4.0–4.7 ppm from the H_X proton on the carbon atom bearing the hydroxy group, and two signals are observed in the region δ 2.4–3.1 ppm from the H_A and H_B protons located on the carbon atom attached to the amino group. Table 2 also gives chemical shifts of the H_C and H_D protons of the methylene group neighboring to the carbazole nitrogen atom in compounds **VIIb**–**IXb** (δ 4.2–4.5 ppm). Protons of the two methylene groups (H_A/H_B and H_C/H_D) are nonequivalent in pairs due to diastereotopicity arising from the presence of a chiral carbon center between those methylene groups.

Amino alcohols **VII**–**IX** show in the ^{13}C NMR spectra (Table 3) signals from carbon atoms attached to the hydroxy group (δ_C 71–72 ppm) and amino group (δ_C 47–58 ppm). The above spectral data suggest regioselective attack by the amino group of adamantane derivatives **I**, **III**, and **IV** on the terminal carbon atoms of the epoxy fragments in compounds **Va** and **Vb** to afford the most substituted carbinols according to the Krasusky rule. The observed regioselectiviety in opening of the oxirane ring in compounds **Va** and **Vb** is consistent with the generally accepted veiws on the mechanism of bimolecular

Table 3. ^{13}C NMR parameters (chemical shifts δ_C) of the amino alcohol fragment in compounds **VII**–**IX**

Compound no.	CHOH	NCH_2	CH_2N (carbazole)	Substituent
VIIa	71.4	51.1	–	150.6, 147.4, 126.7, 123.8
VIIb	71.5	56.4	47.6	141.1, 126.4, 126.1, 120.6, 119.4, 109.3
VIIIa	70.4	57.8	–	150.5, 147.4, 126.7, 123.8
VIIIb	72.0	57.3	47.7	141.0, 126.2, 126.0, 120. 5, 119.6, 109.4
IXa	72.1	56.9	–	150.5, 150.4, 126.7, 123.8
IXb	70.9	57.2	47.6	141.0, 126.2, 126.1, 120.5, 119.5, 109.3

Table 4. Parameters of the ^1H NMR spectra (chemical shifts δ, ppm, and coupling constants J, Hz) of compounds **VII**–**X**, **XIIb**, **XIIIb**, **XIVb**, and **XV** (adamantane fragment)

Compound no.	Adamantane fragment			CH_3	Ad**C**H_2N (AdCHN)
	3H (CH)	6H (CH_2)	6H (CH_2)		
VIIa	2.07	2.01	1.69	–	–
VIIb	1.90	1.52	1.40	–	–
VIIIa	1.91	1.61	1.46	–	2.21, 2.19, $^2J_{H,H}$ = 11.5
VIIIb	1.93	1.68	1.52	–	2.41, 2.31, $^2J_{H,H}$ = 13.7
IXa	1.92	1.61	1.41	0.92	(2.03)
IXb	1.69	1.56	1.39	0.89	(1.98)
Xa	2.17	2.00	1.67	–	–
Xb	2.04	1.71	1.60	–	2.47, 2.34, $^2J_{H,H}$ = 11.3
XIIb	2.07	1.98	1.66	–	–
XIIIb	2.20	2.00	1.65	2.59	–
XIVb	2.01	1.69	1.54	–	2.33, 2.25, $^2J_{H,H}$ = 11.5
XV	2.29	2.15	1.78	–	–

Table 5. Parameters of the ^{13}C NMR spectra (chemical shifts δ_C) of compounds **VII**–**IX** (adamantane fragment)

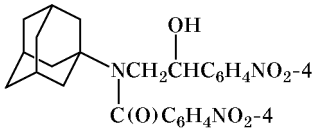
Comp. no.	Adamantane fragment				CH_3	Ad**C**H_2N	CH
VIIa	48.2	43.2	36.8	29.8	–	–	–
VIIb	50.9	43.2	36.9	29.8	–	–	–
VIIIa	37.9	33.9	30.1	28.7	–	70.4	–
VIIIb	50.8	41.7	37.1	28.5	–	72.1	–
IXa	55.3	39.0	36.4	28.8	14.6	–	70.4
IXb	52.7	39.0	36.6	28.8	14.3	–	70.1

nucleophilic substitution (S_N2) which involves attack by nucleophile on the most accessible terminal carbon atom [17].

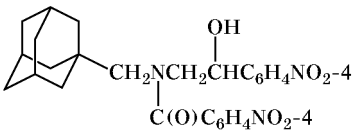
Tables 4 and 5 contain parameters of the ^1H and ^{13}C NMR spectra for some structural fragments of the prepared compounds, including adamantane moiety and contiguous methyl, methylene, and methine groups. The methylene protons are nonequivalent and are coupled through a geminal constant of 11.5 and 13.7 Hz for amino alcohols **VIIIa** and **VIIIb**, respectively. The substituents in compounds **IXa** and **IXb** give rise to quartets at δ 2.03 and 0.92 ppm and

doublets of doublets at δ 1.98 and 0.89 ppm, respectively. Carbon nuclei of the methylene and methine groups resonate in the region δ_C 70–72 ppm.

Molecules of amino alcohols contain two nucleophilic centers capable of reacting with electrophilic reagents. The reactions of compounds **VIIa** and **VIIIa** with *p*-nitrobenzoyl chloride occurred at the more nucleophilic amino groups of the former to afford *N*-*p*-nitrobenzoyl derivatives **Xa** and **Xb**, respectively:



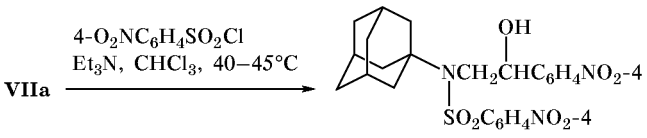
Xa



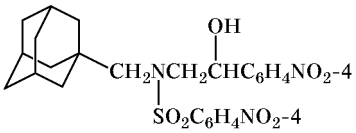
Xb

Unlike *p*-nitrobenzoyl chloride which smoothly reacts with amino alcohols under mild conditions (20°C) in the presence of triethylamine (the yields of **Xa** and **Xb** are 88 and 75%), the reaction of **VIIa** and **VIIIa** with *p*-nitrobenzenesulfonyl chloride in chloroform in the presence of the same base requires heating to 40–45°C, and the corresponding sulfonamides **XIa** and **XIb** are formed in 30 and 35% yield, respectively (Scheme 2). Our attempt to obtain compound **XIa** by the procedure reported in [4] (in a two-phase system using sodium hydroxide as a base; this procedure turned out to be very advantageous for the reaction of amines **I**–**IV** with arenesulfonyl chlorides) was even less successful: the yield of sulfonamide **XIa** was as low as 19%. The structure of N-substituted amino alcohols follows from analysis of their spectral parameters. The IR spectra of **X** and **XI** retain

Scheme 2.



XIa

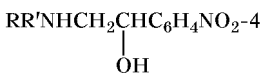


XIb

absorption bands in the region 3471–3420 cm^{-1}, which belong to O–H stretching vibrations, while bands corresponding to sulfonamide and tertiary amide groups appear (at 1645 and 1640 cm^{-1} for the latter; Table 1) [15]. The selective N-acylation is also confirmed by the ^1H NMR spectra of compounds **Xa** and **Xb**; in particular, signals from protons of the methylene group on the nitrogen atom (H_A and H_B rather than H_X) shift appreciably downfield relative to their position in the spectra of initial amino alcohols **VIIa** and **VIIIa** (Table 2). Also, a downfield shift of signals from the methylene group contiguous to the adamantane fragment in **Xb** was observed. The signals from the adamantane protons in the spectra of both acylation products **Xa** and **Xb** did not change their position (Table 4).

Alternative functionalization of the hydroxy group was effected with amino alcohols **VI**, **VIIa**, and **VIIIa** via a two-step process including the synthesis of crystalline trimethylsilyl ethers **XIIa**–**XIVa** and their subsequent transformation into *O*-acyl derivatives **XIIb**–**XIVb** (Scheme 3).

Scheme 3.



VI, VIIa, VIIIa

XIIa–XIVa

XIIb–XIVb

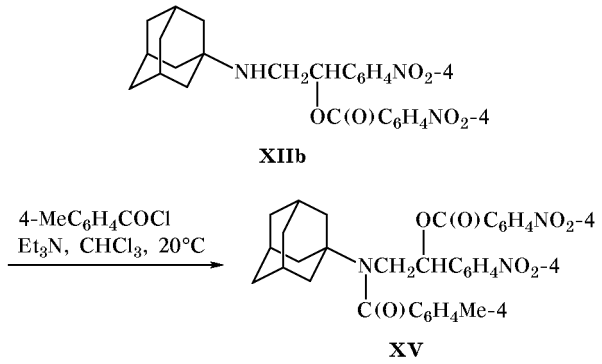
VIIa, **XIIa**, **XIIb**, R = 1-Ad, R′ = H; **VI**, **XIIIa**, **XIIIb**, R = 1-Ad, R′ = Me; **VIIIa**, **XIVa**, **XIVb**, R = 1-AdCH$_2$, R′ = H; HMDS is hexamethyldisilazane.

The silylation of amino alcohols **VI**, **VIIa**, and **VIIIa** with hexamethyldisilazane (HMDS) in the presence of a catalytic amount of chlorotrimethylsilane was performed in toluene under mild conditions [18]. The silyl ethers thus obtained were converted (without purification) into the corresponding *O*-acyl derivatives by treatment with *p*-nitrobenzoyl chloride in dry chloroform at room temperature in the absence of a base. The successful reaction with amino alcohols

possessing both secondary (**VIIa**, **VIIIa**) and tertiary amino groups (**VI**) indicates a weak effect of that group on the silylation of the hydroxy group.

Bis-acylated product **XV** was synthesized by reaction of *O*-acyl derivative **XIIb** with *p*-nitrobenzoyl chloride in the presence of triethylamine as shown in Scheme 4.

Scheme 4.



XIIb **XV**

The properties of the crystalline O-acylated products are presented in Table 1. The IR spectra of **XIIb**, **XIIIb**, and **XV** contain absorption bands at 1721–1719 cm^{-1} due to stretching vibrations of the ester carbonyl groups [15], while hydroxy group absorption is lacking. In the IR spectrum of **XV** we observed no absorption bands assignable to hydroxy or amino group, but an amide carbonyl band was present at 1600 cm^{-1}. The overall intensity of the aromatic proton signals in the ^1H NMR spectra strictly corresponds to the number of *p*-substituted benzene rings in their molecules (8 protons in **XIIb**, **XIIIb**, and **XIVb** and 12 protons in **XV**). Change of the position of the H_X, H_A, and H_B signals with rise in the number of acyl groups should be noted. For example, the chemical shifts of H_X in compounds **Xa** (*N*-acyl group), **XIIb** (*O*-acyl group), **XV** (two acyl groups), and **VIIa** (no acyl group) are as follows: δ 4.59, 4.67, 5.12, and 5.56 ppm.

EXPERIMENTAL

The IR spectra were recorded on a Specord 75-IR spectrometer from samples pelleted with KBr. The ^1H NMR spectra were obtained on Varian and Bruker DRX spectrometers with operating frequencies of 200, 400, and 500 MHz; chloroform-*d* or DMSO-d_6 was used as solvent, and hexamethyldisiloxane or tetramethylsilane, as internal reference. The ^{13}C NMR spectra were measured on a Varian Gemini-BB instrument operatng at 100.7 MHz. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using diethyl ether as eluent; spots were visualized by treatment with iodine vapor. The elemental compositions were determined using a Carlo Erba analyzer.

Amines **I**–**III** were synthesized by the procedures described in [19–21], and amine **IV** was isolated from the corresponding hydrochloride. Their properties were in agreement with published data [9, 19–21].

***N*-(1-Adamantyl)-2-amino-1-(*p*-nitrophenyl)-ethanol (VIIa).** A mixture of 0.80 g (0.005 mol) of *p*-nitrophenyloxirane (**Va**) and 0.76 g (0.005 mol) of 1-adamantylamine was dissolved in 10 ml of isopropyl alcohol. When the reaction was complete (TLC), the precipitate was filtered off, washed with isopropyl alcohol on a filter, dried, and recrystallized from a mixture of isopropyl alcohol and water (2 : 1).

Amino alcohols **VIIIa** and **IXa** were synthesized by a similar procedure (Table 1).

***N*-(1-Adamantyl)-1-amino-3-(9-carbazolyl)-2-propanol (VIIb).** A mixture of 0.67 g (0.003 mol) of *N*-(2,3-epoxypropyl)carbazole (**Vb**) and 0.46 g (0.003 mol) of 1-adamantylamine was dissolved in 10 ml of isopropyl alcohol. The reaction completion was determined by TLC. The product was purified by recrystallization from 2-propanol–benzene (2 : 1).

Compounds **VIIIb** and **IXb** were synthesized in a similar way (Table 1).

***N*-(1-Adamantyl)-*N*-(*p*-nitrobenzoyl)-2-amino-1-(*p*-nitrophenyl)ethanol (Xa).** A solution of 0.19 g (0.001 mol) of *p*-nitrobenzoyl chloride in 5 ml of dry chloroform was added dropwise with stirring to a mixture of 0.31 g (0.001 mol) of amino alcohol **VIIa** and 0.30 g (0.003 mol, 0.41 ml) of triethylamine in 15 ml of dry chloroform. The mixture was stirred at room temperature until the reaction was complete (TLC) and washed in succession with three portions of water, 20% hydrochloric acid, and water again. The organic layer was separated and dried over calcined magnesium sulfate. The solvent was removed, and the residue was recrystallized from 2-propanol–water (2 : 1). Amide **Xb** was synthesized by a similar procedure (Table 1).

***N*-(1-Adamantyl)-2-amino-*N*-(*p*-nitrophenylsulfonyl)-1-(*p*-nitrophenyl)ethanol (XIa).** *a*. A solution of 0.22 g (0.001 mol) of *p*-nitrobenzenesulfonyl chloride in 10 ml of dry chloroform was added dropwise with stirring to a mixture of 0.31 g (0.001 mol) of amino alcohol **VIIa** and 0.31 g (0.003 mol, 0.42 ml) of triethylamine in 15 ml of dry chloroform. The reaction was slow, so that the mixture was stirred

at 40–45°C. When the reaction was complete (TLC), the mixture was washed in succession with three portions of water, 20% hydrochloric acid, and water again. The organic layer was separated and dried over calcined magnesium sulfate. After removal of the solvent, the residue was purified by recrystallization from 2-propanol–benzene (1 : 1).

***N*-(1-Adamantylmethyl)-2-amino-*N*-(*p*-nitrophenylsulfonyl)-1-(*p*-nitrophenyl)ethanol (XIb)** was synthesized in a similar way (Table 1).

b. A solution of 0.22 g (0.001 mol) of *p*-nitrobenzenesulfonyl chloride in 10 ml of diethyl ether was added dropwise with stirring to a mixture of 0.31 g (0.001 mol) of amino alcohol **VIIa** in 10 ml of ether and 2 ml of a 20% aqueous solution of sodium hydroxide. The mixture was stirred at room temperature until the reaction was complete (TLC). The organic layer was separated and dried over calcined magnesium sulfate, the solvent was removed, and the product was purified by recrystallization from benzene. Yield 19.4%.

***N*-(1-Adamantyl)-2-amino-1-(*p*-nitrophenyl)-ethyl *p*-nitrobenzoate (XIIb).** A solution of 0.16 g (0.001 mol, 0.21 ml) of hexamethyldisilazane in 10 ml of anhydrous toluene containing a catalytic amount of chlorotrimethylsilane was added dropwise with stirring at room temperature to a solution of 0.31 g (0.001 mol) of amino alcohol **VIIa** in 10 ml of anhydrous toluene. The mixture was stirred until the reaction was complete (TLC), the solvent was removed under reduced pressure, and the product, silyl ether **XIIa**, was washed with dry benzene on a glass filter. A solution of 0.19 g (0.001 mol) of *p*-nitrobenzoyl chloride in 5 ml of dry chloroform was added dropwise with stirring to a mixture of 0.42 g (0.001 mol) of silyl ether **XIIa** and 15 ml of dry chloroform. The mixture was stirred at room temperature until the reaction was complete (TLC), the solvent was removed, and the product was purified by recrystallization from 2-propanol–water (2 : 1).

Trimethylsilyl ethers **XIIIa** and **XIVa** and the corresponding *O*-acyl derivatives **XIIIb** and **XIVb** were synthesized in a similar way (Table 1).

***N*-(1-Adamantyl)-2-amino-*N*-(*p*-toluoyl)-1-(*p*-nitrophenyl)ethyl *p*-nitrobenzoate (XV).** A solution of 0.19 g (0.001 mol) of *p*-toluoyl chloride in 5 ml of dry chloroform was added dropwise with stirring to a mixture of 0.48 g (0.001 mol) of compound **XIIb** and 0.30 g (0.003 mol, 0.41 ml) of triethylamine in 15 ml of dry chloroform. The mixture was stirred at room temperature until the reaction was complete (TLC). After appropriate treatment, the organic layer was separated and dried over calcined magnesium sulfate, the solvent was removed, and the product was recrystallized from aqueous ethanol (1 : 1).

REFERENCES

1. Morozov, I.S., Petrov, V.I., and Sergeeva, S.A., *Farmakologiya adamantanov* (Pharmacology of Adamantanes), Volgograd: Volgogr. Med. Akad., 2001.
2. Moiseev, I.K., Makarova, N.V., and Zemtsova, M.N., *Usp. Khim.*, 1999, vol. 68, p. 1102; Moiseev, I.K., Makarova, N.V., and Zemtsova, M.N., *Russ. J. Org. Chem.*, 2001, vol. 37, p. 453; Aldrich, P.E., Hermann, E.C., Mejer, W.E., Paulshock, M., Prichard, W.W., Smydder, J.A., and Watts, J.C., *J. Med. Chem.*, 1971, vol. 14, p. 535.
3. Bagrii, E.M., *Adamantany: poluchenie, svoistva, primenenie* (Adamantanes: Synthesis, Properties, and Application), Moscow: Nauka, 1989; Indulen, M.K., Kalninya, V.A., Ryazantsava, G.M., and Bubovich, V.I., *Mekhanizmy antivirusnogo deistviya proizvodnykh adamantana* (Mechanisms of Antiviral Action of Adamantane Derivatives), Riga: Zinatne, 1981.
4. Kas'yan, A.O., Okovityi, S.I., Krasnovskaya, O.Yu., and Kas'yan, L.I., *Russ. J. Org. Chem.*, 1997, vol. 33, p. 985.
5. Kas'yan, L.I., Kas'yan, A.O., and Golodaeva, E.A., *Russ. J. Org. Chem.*, 2000, vol. 36, p. 1722.
6. Ivanov, A.I., Shmar'yan, M.I., and Skoldinov, A.P., *Khim.-Farm. Zh.*, 1969, no. 3, p. 13; Zakrewski, S.F., Bloch, A., and Nichol, C.A., *J. Med. Chem.*, 1968, vol. 11, p. 885; US Patent no. 3501511, 1970; *Ref. Zh., Khim.*, 1971, no. 9N267P.
7. Kas'yan, A.O., Krishchik, O.V., Krasnovskaya, O.Yu., and Kas'yan, L.I., *Russ. J. Org. Chem.*, 1998, vol. 34, p. 1731.
8. Kreutzberger, A. and Schroders, H.-H., *Arch. Pharm.*, 1975, vol. 308, p. 748; Kreutzberger, A. and Schroders, H.-H., *Tetrahedron Lett.*, 1969, p. 5101; Stetter, H. and Wulff, C., *Chem. Ber.*, 1962, vol. 95, p. 2302; Swiss Patent no. 424767, 1974; *Ref. Zh., Khim.*, 1975, no. 12O81P.
9. Kas'yan, L.I., Golodaeva, E.A., Danilenko, A.L., and Kas'yan, A.O., *Vopr. Khim. Khim. Tekhnol.*, 2002, no. 1, p. 31.
10. Novakov, I.A., Orlinson, B.S., Sabirov, Z.M., Urazbaev, V.N., and Monakov, Yu.B., *Vysokomol. Soedin.*, 1993, vol. 35, p. 2053.
11. Bergmeier, S.C., *Tetrahedron*, 2000, vol. 56, p. 2561; Lukevits, E.Ya., Libert, L.I., and Voronkov, M.G., *Usp. Khim.*, 1970, vol. 29, p. 2005.

12. Mashkovskii, M.D., *Lekarstvennye sredstva* (Medicines), Moscow: Novaya Volna, 2002, 14th ed., vols. 1, 2.

13. USSR Inventor's Certificate no. 368 236, 1973; *Ref. Zh., Khim.*, 1973, no. 22 N 302 P.

14. Kas'yan, A.O., Golodaeva, E.A., Tsygankov, A.V., and Kas'yan, L.I., *Russ. J. Org. Chem.*, 2002, vol. 38, p. 1606.

15. Nakanishi, K., *Infrared Absorption Spectroscopy. Practical*, San Francisco: Holden-Day, 1962.

16. Kirk, D.N., *Chem. Ind.*, 1973, p. 109; Krasuskii, K.A., *Zh. Obshch. Khim.*, 1936, vol. 6, p. 460.

17. Parker, R.N. and Isaacs, N.S., *Chem. Rev.*, 1959, vol. 59, p. 737.

18. Birgele, I.S., Kemme, A.A., and Kupge, E.L., *Kremniiorganicheskie proizvodnye aminospirtov: fiziko-khimicheskie issledovaniya* (Organosilicon Derivatives of Amino Alcohols: Physicochemical Studies), Riga: Zinatne, 1987; Kashutin, M.V., Ioffe, S.L., and Tartakovskii, V.A., *Usp. Khim.*, 1973, vol. 34, p. 1621; Kovalev, G.V., Rakhimov, A.I., and Sazhik, A.A., *Khim.-Farm. Zh.*, 1990, no. 5, p. 17.

19. USSR Inventor's Certificate no. 408 546, 1977; *Ref. Zh., Khim.*, 1978, no. 20 O 46 P.

20. USSR Inventor's Certificate no. 2 008 066, 1976; *Ref. Zh., Khim.*, 1977, no. 4 N 129 P.

21. Korolev, B.A., Khardin, A.P., Radchenko, S.S., Novakov, I.A., and Orlinson, B.S., *Zh. Org. Khim.*, 1978, vol. 14, p. 1632.