SYNTHESIS AND PROTECTIVE PROPERTIES OF PHENYLADAMANTANE WITH RESPECT TO RABIES VIRUS

G. I. Danilenko,[1] E. A. Shablovskaya,[1] L. A. Antonova,[2] S. V. Guzhova,[2] I. A. Lobanova,[2] A. P. Dyachenko,[2] and A. I. Panasyuk[2]

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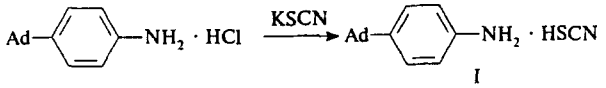
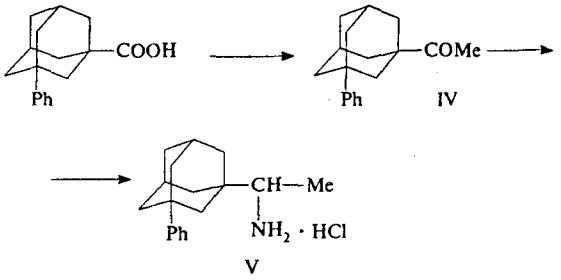
At present, the development of rabies disease is prevented only by antirabic vaccine and gamma-globulin. There are rare indications that drugs capable of providing effective chemotherapy against rabies may also exist. In particular, alkylaminoalkyl esters of fluorenonedicarboxylic acid, as well as the alkoxy and alkylthio derivatives of fluorene and fluorenone, are known to be active with respect to some viruses, including the rabies virus [1, 2]. It was reported that the introduction of reserpine at the instant of infection increased the lifetime of test animals [3], while ketamine inhibited the synthesis of viral nucleoprotein and glycoprotein [4]. 4-Adamantylaninile hydrochloride exhibited protective properties in mice infected with rabies virus [5].

Therefore, it was expedient to continue with the search for new inhibitors of rabies virus in the series of phenyladamatanes. 4-(1-Adamantyl)phenylammonium thiocyanate (I) was synthesized from 4-adamantylaniline using the reaction



I

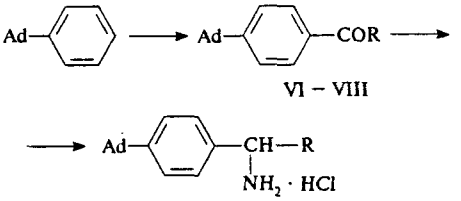
We have also synthesized 1-phenyl-3-aminoadamantane (II) as described in [6] and 1-(4-tolyl)-3-aminoadamantane (III) according to [7]. 1-Phenyl-3-(1-aminoethyl)adamantane hydrochloride (V) was obtained by the scheme



V

Condensation of 1-phenyladamantane-3-carboxylic acid with ethoxymagnesium malonate, followed by acid hydrolysis, led to 1-phenyl-3-acetyladamantane (IV), which can be converted into amine V by the Leuckart reaction.

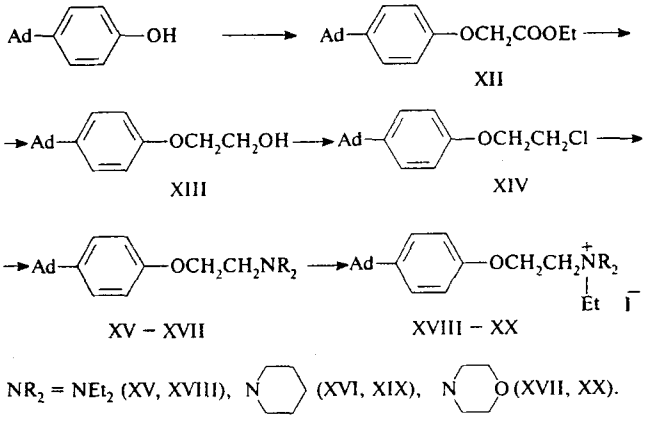
4-Adamantylaniline homologs were obtained from phenyladamantane by the following scheme:



R = Me (VI, IX), Et (VII, X), *n*-Pr (VIII, XI).

4-Adamantylacetophenone (VI) was synthesized as described in [8]; a similar procedure was used for the synthesis of ketones VII and VIII. Using the Leuckart reaction, ketones VI – VIII were converted into 4-adamantyl-1-(1-formamidoalkyl)benzenes, which were hydrolyzed (without purification) to amines IX – XI.

The adamantyl derivatives of dialkylaminoethanol were synthesized proceeding from 4-adamantylphenol described in [8]:



NR_2 = NEt_2 (XV, XVIII), N⟨⟩ (XVI, XIX), N⟨O⟩ (XVII, XX).

The condensation of 4-adamantylphenol with ethyl ester of bromoacetic acid yields 4-adamantylphenoxyacetic acid ethyl ester (XII). Ester XII was reduced by lithiumaluminum-

[1] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kiev, Ukraine.
[2] Institute of Epidemiology and Infectious Diseases, Ministry of Health of Ukraine, Kiev, Ukraine.

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hydride to 4-adamantylphenoxyethanol (XIII). Compound XIII was converted into 2-(4-adamantylphenoxy)-1-chloroethane (XIV) by the reaction with thionyl chloride in pyridine. Heating chloride XIV with diethylamine, piperidine, or morpholine in anhydrous ethanol in the presence of catalytic amounts of sodium iodide led to amines XV – XVII, and the subsequent quaternization yielded salts XVIII – XX. Properties of the synthesized compounds are given in Table 1.

EXPERIMENTAL CHEMICAL PART

The IR spectra of synthesized compounds were measured in KBr disks on a UR-20 spectrophotometer. The ^1H NMR spectra were recorded on a Varian VXR-300 (300 MHz) spectrometer using DMSO-d_6 as the solvent and HMDS at the internal standard. The data of elemental analyses agree with the results of analytical calculations using the empirical formulas.

4-(1-Adamantyl)phenylammonium thiocyanate (I). To a solution of 5 g 1-(4-aminophenyl)adamantane hydrochloride in 20 ml of methanol was added over 10 min with stirring a solution of 1.54 g potassium rhodanate in 30 ml of methanol. The mixture was stirred for another 20 min and filtered. The filtrate was evaporated in vacuum at a temperature not exceeding 20°C to obtain 5 g (92%) of compound I; m.p., 155 – 157°C; IR spectrum (ν_{max}, cm^{-1}): 3000 – 3080 (NH_3^+, CH phenyl), 2850, 2940 (CH, CH_2 adamantane), 2080 (SCN), 810, 840 (1,4-disubstituted benzene).

3-Acetyl-1-phenyladamantane (IV). A mixture of 3 g 1-phenyladamantane-3-carboxylic acid and 5 ml thionyl chloride was treated at 50 – 55°C for 3 h, after which the excess $SOCl_2$ was distilled off in vacuum and the residue was dissolved in 20 ml benzene. Ethoxymagnesium malonate, obtained from 0.4 g magnesium, 2.5 ml of anhydrous ethanol, and 2.6 ml malonic ester, was dissolved in 30 ml benzene. To this solution was added the above chloroanhydride solution, and the mixture was boiled for 2 h and cooled to room temperature. Then 10 ml of 5% aqueous sulfuric acid was added, the mixture was shaken, the organic layer separated, and the solvent distilled off. To the residue was added a mixture of 12 ml acetic acid, 8 ml water, and 1.5 ml concentrated sulfuric acid. The resulting mixture was boiled with stirring until carbon dioxide ceased to evolve. Upon cooling, 100 ml of water was added and the mixture extracted with ether. The extract was washed with a sodium bicarbonate solution, the solvent was distilled off, and the residue distilled at 101 – 103°C (1 Torr). The distillate solidifies to yield compound IV; m.p., 35 – 36°C; IR spectrum (ν_{max}, cm^{-1}): 1715 (CO).

TABLE 1. Characteristics of Compounds XV – XX

Compound	Yield, %	M.p., °C (solvent)
XV	72	47 – 48 (CCl_4)
XVI	37	88 – 90 (acetone)
XVII	73	110 – 112 (2-propanol)
XVIII	62	189 – 190 (2-propanol)
XIX	62	198 – 199 (2-propanol)
XX	44	203 – 204 (2-propanol)

1-Phenyl-3-(1-aminoethyl)adamantane hydrochloride (V). A mixture of 1 g ketone IV and 10 ml formamide was boiled for 10 h. Upon cooling, 20 ml of water was added. The precipitate was separated, mixed with 10 ml of concentrated hydrochloric acid, boiled for 7 h, and cooled on ice. The precipitate was separated and crystallized from 2-propanol to obtain 0.53 g (48%) of compound V; m.p., 253 – 254°C; IR spectrum (ν_{max}, cm^{-1}): 3020 – 3040 (NH_3^+), 2860, 2920 (CH, CH_2 adamantane), 1380, 1440, (CH_3).

1-[4-(1-Adamantyl)phenyl]propan-1-one (VII). To a mixture of 4.9 g propanoyl chloride, 13.3 g aluminum chloride, and 70 ml dichloroethane at – 5°C was gradually (over 1 h) added with stirring a solution of 10 g 1-phenyladamantane in 30 ml dichloroethane. Then the mixture was stirred for another 1 h at – 5°C and 1 h at 20°C and poured onto 100 g ice. The organic layer was washed with water and dried with sodium sulfate. Finally, the solvent was distilled off to obtain 4.7 g (43%) of compound VII; m.p., 112 – 113°C (*n*-hexane); IR spectrum (ν_{max}, cm^{-1}): 2860, 2930 (CH, CH_2 alif.), 1710 (C=O), 810, 840 (1,4-disubstituted benzene).

1-[4-(1-Adamantyl)phenyl]butan-1-one (VIII). Compound VIII was obtained from 16.6 g butyric acid chloroanhydride, 20 g aluminum chloride, and 22.1 g of 1-phenyladamantane by a procedure analogous to that used for the synthesis of ketone VII. Yield of compound VIII, 14.2 g (52%); m.p., 81 – 82°C (*n*-hexane); IR spectrum (ν_{max}, cm^{-1}): 2860, 2920 (CH, CH_2), 1710 (CO).

4-(1-Adamantyl)-1-(1-aminoethyl)benzene hydrochloride (IX). A mixture of 5 g ketone VI, 3 ml formamide, and 2 ml of 99% formic acid was boiled for 10 h. Then 50 ml of water was added and the precipitate was separated and boiled for 4 h with 10 ml of concentrated hydrochloric acid. The reaction mixture was neutralized with Na_2CO_3 and extracted with ether. Finally, the amine was precipitated with a flow of dried hydrogen chloride to obtain 1.05 g (59%) of compound IX; m.p., 280 – 282°C (water); IR spectrum (ν_{max}, cm^{-1}): 2860, 2930 (CH, CH_2), 3000 (NH_3^+), 810, 840 (1,4-disubstituted benzene).

4-(1-Adamantyl)-1-(1-aminopropyl)benzene hydrochloride (X). Compound X was obtained from 2 g ketone VII, 5 ml formamide, and 2 ml of 99% formic acid by a procedure analogous to that used for the synthesis of amine IX. Yield of compound X, 1.2 g (50%); m.p., 266 – 268°C (water); IR spectrum (ν_{max}, cm^{-1}): 2850, 2920 (CH, CH_2), 3000 (NH_3^+), 810, 840 (1,4-disubstituted benzene).

4-(1-Adamantyl)-1-(1-aminobutyl)benzene hydrochloride (XI). Compound XI was obtained from 5 g ketone VIII, 20 ml formamide, and 4 ml of 99% formic acid by a procedure analogous to that used for the synthesis of amine IX. Yield of compound XI, 3.4 g (61%); m.p., 319 – 320°C (water); IR spectrum (ν_{max}, cm^{-1}): 2860, 2920 (CH, CH_2), 3000 (NH_3^+), 810, 840 (1,4-disubstituted benzene); ^1H NMR spectrum (δ, ppm): 8.53 (s, 3H), 7.38 (m, 4H), 4.06 (m, 1H),

2.00 (s, 3H), 1.80 (s, 6H), 1.68 (s, 6H), 1.13 (m, 2H), 1.03 (m, 2H), 0.78 (t, 3H).

4-Adamantylphenoxyacetic acid ethyl ester (XII). A mixture of 15 g 4-adamantylphenol, 7.4 ml bromoacetic acid ethyl ester, 14 g anhydrous K_2CO_3, and 150 ml acetone was boiled with stirring for 20 h. Then the precipitated was separated and the solvent distilled off to obtain 13.9 g (67%) of compound XII; m.p., 83 – 84°C (*n*-hexane); IR spectrum (ν_{max}, cm^{-1}): 1720 (CO).

1-[4-(4-Adamantyl)phenoxy]-2-hydroxyethane (XIII). A solution of 10 g of compound XII in 150 ml ether was gradually (over 3 h) added with stirring to a mixture of 1.2 g lithiumaluminumhydride with 100 ml ether. The excess of $LiAlH_4$ was decomposed with water, the mixture was filtered, and the filtrate evaporated to obtain 7.6 g (78%) of compound XIII; m.p., 116 – 117°C (*n*-heptane); IR spectrum, CCl_4 (ν_{max}, cm^{-1}): 3620 (OH).

1-[4-(1-adamantyl)phenoxy]-2-chloroethane (XIV). A mixture of 3.8 g alcohol XIII, 1.4 ml pyridine, and 1.1 ml thionyl chloride was boiled for 18 h. Upon cooling, 20 ml of dichloroethane was added. Then the mixture was washed with cold water and the excess water evaporated to obtain 2.5 g (67%) of compound XIV; m.p., 77 – 78°C (*n*-heptane).

General procedure for the synthesis of 1-[4-(1-adamantyl)phenoxy]-2-aminoethanes (XV – XVII). A mixture of 0.02 mole chloride XIV, 0.025 mole of the corresponding amine, 0.05 g sodium iodide, and 20 ml of anhydrous ethanol was boiled for 40 h. Then the reaction mass was poured into 100 ml of a 3% sodium hydroxide solution and cooled on ice. The precipitate was separated to obtain the target amine (Table 1).

General procedure for the synthesis of tertiary salts XVIII – XX. A mixture of 0.04 mole of the corresponding amine (XV – XVII), 0.05 mole ethyl iodide, and 20 ml of anhydrous ethanol was boiled for 6 h. Then the reaction mass was evaporated to dryness to obtain the target salts (Table 1).

EXPERIMENTAL BIOLOGICAL PART

The experiments were performed on white mongrel mice weighing 8 – 12 g inoculated with a rabies virus at a dose corresponding to 90 – 100% lethality (CVS virus, 4.4 log LD_{50} / 0.1 ml). Compounds I – III, V, IX – XI, XV – XX were introduced into the infection site at a single dose of 1, 5, or 50 mg / kg with an aqueous suspension of Tween-80. The reference drugs were 4-adamantylaniline hydrochloride and gamma-globulin. Every dose of each compound was tested in a group of not less than 15 animals.

It was established that most of the compounds studied (except XVIII – XX) increased to various extents (Table 2) the survival of test animals inoculated with the rabies virus. The most active compounds (IX – XI) exhibited a protective action exceeding that of 4-adamantylaniline hydrochloride.

The most active compound XI, injected at a dose of 50 mg / kg to the test mice 1, 2, 3, 4, and 5 days after inoculation with the rabies virus CVS (100 LD_{50}), increased the survival of animals to 79.9, 68.8, 61.5, 53.8, and 46.6% respectively (against 6.6% animals survived in the control group).

TABLE 2. Protective Action of the Synthesized Compounds with Respect to Rabies Virus in Mice

Compound	Percentage survival for the dose, mg / kg (s.c.)			
	0	1	5	50
I			40.0	51.7
II		–	–	17
III		–	–	20
V		–	10	22
IX		43.0	66.7	60.0
X		50.0	53.0	78.6
XI		56.2	60.0	87.5
XV		21	32	46.0
XVI		17	20	31
XVII		13	26	29
XVIII – XX		–	–	–
4-Adamantylaniline hydrochloride		27	37	43
Control	6.6			

Note. (–) no protection.

The injections of gamma-globulin to animals inoculated with the same dose of the rabies virus were effective only if made on the first to third day after infection. The level of protection varied between 30 and 70%.

In the test mice inoculated with a low dose of the rabies virus (2.5 LD_{50}, modeling the natural infection level), a single introduction of compound XI at a dose of 50 mg / kg led to a 90% survival (against 20% in the control group).

We believe this experiment to be the first successful attempt of the rabies virus chemotherapy under laboratory conditions.

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