ethyl acetate. The ethyl acetate solution was washed with water, dried with $MgSO_4$, and evaporated to give 0.62 g of an oil, which was chromatographed on silica gel under gradient-elution conditions ($CHCl_3$–2% MeOH in $CHCl_3$) to give 0.44 g of I in the form of an oil.

N-[1-Methoxycarbonyl-2-(8-quinolyl)ethyl]-DL-alanyl-L-proline (II). This compound was similarly obtained from 0.28 g (1.5 mmole) of IV, 0.83 g (3.6 mmole) of β-(8-quinolyl)-α-alanine methyl ester, 2.5 g of molecular sieves, and 0.12 g (1.92 mmole) of $NaCNBH_3$ in 5 ml of THF. The residue obtained after removal of the molecular sieves by filtration and evaporation of the solvent was washed with ethyl acetate and ether by decantation and dissolved in 4 ml of 8% $NaHCO_3$. The solution was extracted with ethyl acetate, and the aqueous layer was acidified to pH 6.0-7.0, and the substance was extracted with ethyl acetate. Some of the substance that remained in the aqueous solution was isolated after lyophilization to give a total of 0.44 g of a substance, chromatography of which on silica gel under gradient-elution conditions ($CHCl_3$–30% MeOH in $CHCl_3$) gave 0.24 g of II in the form of an oil.

LITERATURE CITED

1. V. N. Konyukhov, L. N. P'yankova, and K. Yu. Bobarykina, Khim. Geterotsikl. Soedin., No. 1, 141-144 (1965).
2. H. Arold, S. Reissman, and M. Eule, J. Prakt. Chem., 316, No. 1, 93-102 (1974).
3. Drugs in the Future, 11, 647-649 (1986).
4. Ibid., 10, 636-637 (1985).
5. Ibid., 12, 507-509 (1987).
6. S. H. Kubo and R. J. Cody, Clin. Pharmacokinet., 10, 377-391 (1985).
7. J. A. Marshall, T. F. Schlaf, and J. G. Csernansky, Synth. Commun., 5, 237-249 (1975).
8. M. W. Pantoliano, B. Holmquist, and J. F. Riordan, Biochemistry, 23, 1037-1042 (1984).
9. A. A. Patchett, E. Harris, E. W. Tristram, et al., Nature, 288, 280-283 (1980).
10. A. A. Patchett, E. E. Harris, M. J. Wyvratt, and E. W. Tristram European Patent No. 0012401 (1984).
11. I. Schechter and A. Berger, Biochem. Biophys. Res. Commun., 27, 157-162 (1967).
12. W.-E. Siems, G. Heder, and N. W. Komissarova, Z. Med. Lab. Diagn., 26, 230-234 (1985).
13. M. J. Wyvratt and A. A. Patchett, Med. Res. Rev., 5, 483-531 (1985).

SYNTHESIS AND INVESTIGATION OF VIRAL-INHIBITORY ACTIVITY OF NITROGEN-CONTAINING DERIVATIVES OF ADAMANTANE

Yu. N. Klimochkin, I. K. Moiseev, G. V. Vladyko, L. V. Korobchenko, and E. I. Boreko

UDC 615.281.8:547.592.1].012.1

Nitrogen-containing functional derivatives of the adamantane series display a wide spectrum of antiviral activity [2, 3]. In the course of work to search for new viral inhibitors [1, 4], we have synthesized urethanes, amides, aminoamides, and aminoesters containing adamantane in their structural framework, and have studied their antiviral activity.

1-Methoxycarbonylamino-3-ethyladamantane (I) and 1-ethoxycarbonylamino-3-isopropyladamantane (II) were obtained by reacting the corresponding alkyladamantanes with nitric acid and then with esters of carbamic acid, by a previously described method [4].

N-Adamantylated carbamates III-VII were synthesized by the thermolysis of N(1-adamantyl)-S-ethylthiocarbamate at 130-200°C in hydroxylic solvents, which may be the first example of this kind of conversion. Apparently, the bulky adamantyl radical promotes the ready decomposition of the thiocarbamate, with the intermediate formation of 1-adamantylisothiocynate.

$$AdNHCOSC_2H_5 \xrightarrow[C_2H_5SH]{} AdNCO \xrightarrow{ROH} \underset{\text{III—VII}}{AdNHCOOR}$$

Ad-adamantyl-1

R=$(CH_2)_2Br$ (III), $(CH_2)_2OC_2H_5$ (IV), $(CH_2)_2N(CH_3)_2$ (V), $(CH_2)_2OH$ (VI), $CH_2C_6H_5$ (VII)

Kuibyshev Polytechnic Institute; Belorussian Scientific-Research Institute of Epidemiology and Microbiology, Minsk.

Translated from Khimiko-farmatsevitcheskii Zhurnal, Vol. 25, No. 7, pp. 46-49, July, 1991. Original article submitted July 6, 1990.

TABLE 1. Physicochemical and Spectral Characteristics of Compounds I-XVII

Compound	Yield, %	mp (bp), °C	Empirical formula	Spectral characteristics	
				IR, ν_{max}, cm^{-1}	PMR, δ, ppm, DMSO-d_6
I	71	24—25	$C_{14}H_{23}NO_2$	3360, 1715, 1520	0,77t (3H); 1,10 q (2H); 1,25—2,25m (14H); 3,53s (3H); 5,25 s (1H)
II	67	180—182/12 mm	$C_{16}H_{27}NO_2$	3350, 1720, 1510	0,81d (6H); 1,18 t 3H); 1,23—2,30m)№:H); 4,04q (2H); 6,98s (1H)
III	61	155—157/19 mm	$C_{13}H_{20}NBrO_2$	3350, 1735, 1510	1,40—2,35m (15H); 4,15t(2H); 3,42 t(2H); 6,89s (1H)
IV	70	28—30	$C_{15}H_{25}NO_3$	3350, 1715, 1520, 1155	1,05t (3H); 1,61s (6H); 1,93s (9H); 3,40q (2H); 3,55t (2H); 4,09t (2H); 5,44s (1H)
V	79	173—175	$C_{15}H_{26}N_2O_2 \cdot HCl$	3430, 3220, 1705, 1540	1,75s (6H); 2,08s (9H); 2,92s (6H); 3,47t (2H); 4,46t (2H); 7,68s (1H); 12,70s (1H)
VI	58	77—78	$C_{13}H_{21}NO_3$	3320, 1695, 1545, 1070	1,67s (6H); 2,00s (9H); 2,42 s (1H); 3,62t (2H); 3,98t (2H); 5,73s (1H)
VII	55	29—31	$C_{18}H_{23}NO_2$	3340, 1710, 1505, 735	1,65s (6H); 2,00s (9H); 4,97s (2H); 5,89s (1H); 7,34s (5H)
VIII	35	180—183	$C_{12}H_{18}N_2O_2$	3430, 3335, 1675, 1530	1,67s (6H); 2,05s (9H); 7,31s (1H); 7,45s (1H)
IX	56	234—235	$C_{22}H_{32}N_2O_2$	3360, 1670, 1495	1,67s (12H); 1,97s (18H); 7,67s (2H)
X	94	205—208	$C_{17}H_{28}N_2O_2 \cdot HCl$	3190, 1640, 1550	1,62s (6H); 1,91 s(9H); 2,64t (2H); 3,15t (2H); 3,25s (4H); 3,92s (4H); 7,70s (1H); 11,35s (1H)
XI	71	156—159	$C_{12}H_{18}NIO$	3260, 1640, 1550	1,67s (6H); 1,99s (9H); 3,75s (2H); 6,14s (1H)
XII	54	220—223	$C_{17}H_{26}N_2O \cdot HCl$	3180, 1675, 1555	1,50—2,30m (20H); 2,92s (4H); 3,85s (2H); 8,38s (1H); 10,08 s(1H)
XIII	45	247—248	$C_{16}H_{28}N_3O \cdot 2HCl$	3240, 1675, 1560	1,6 s(6H); 1,97s (9H); 3,50 s(8H); 3,86s (2H); 7,43 s(1H); 8,20s(1H); 10,10s (2H)
XIV	87	237—238	$C_{16}H_{26}N_2O_2 \cdot HCl$	3200, 1680, 1550, 1125	1,61s (6H); 1,95 s(9H); 3,38 s(4H); 3,85 s(2H); 3,90 s(4H); 8,32 s(1H); 10,65s (1H)
XV	62	175—180	$C_{16}N_{28}N_2O_3 \cdot HCl$	3260, 1665, 1540, 1085	1,60 s(6H); 2,05 s(9H); 3,28s (4H); 3,88 s(4H); 3,78 s(2H); 4,78 s(2H); 6,25s (1H); 8,82 s(1H)
XVI	82	175—180	$C_{15}H_{25}NO_2 \cdot HCl$	3340, 1715, 1220	1,69s (6H); 1,91 s(9H); 3,05 s(6H); 3,84 t(2H); 4,41t (2H); 11,98s (1H)
XVII	71	30—32	$C_{17}H_{29}NO_2 \cdot HCl$	3300, 1710, 1215	0,77t (3H); 1,14q (2H); 1,35—2,25m (14H); 2,90s(6H); 3,63 s(2H); 4,54 s(2H); 11,86s (1H)

In the IR spectra of urethanes I-VII, there are bands from the valence vibrations of the carbonyl group in the region of 1695-1735 cm^{-1}, and amide II bands at 1505-1540 cm^{-1}. Absorption corresponding to the valence vibrations of the N—H bond is present at 3320-3430 cm^{-1}.

Reacting a solution of adamantane in a mixture of nitric and acetic acids with an excess of oxamide at 70°C leads to the formation of a mixture of mono- (VIII) and diadamantylated (IX) products, which were separated by fractional recrystallization from isopropanol.

$$AdH \xrightarrow[2.\ (CONH_2)_2]{1.\ HNO_3-AcOH} \underset{VIII}{AdNHCOCONH_2} + \underset{IX}{AdNHCOCONHAd}$$

Analogously, addition of β-morpholinopropionitrile to a solution of adamantane in a mixture of nitric and acetic acids allows one to obtain, by a Ritter reaction, 1-(β-morpholinopropionyl)aminoadamantane, which was isolated as the chlorhydrate (X).

Reacting 1-adamantol with α-iodoacetamide in concentrated sulfuric acid gives N-(1-adamantyl)-iodoacetamide (XI), from which, by reacting with different amino derivatives, we synthesized a series of adamantane aminoamides XII-XV, isolated as the corresponding hydrochlorides.

$$AdOH \xrightarrow[H_2SO_4]{NH_2COCH_2I} \underset{XI}{AdNHCOCH_2I} \xrightarrow[Na_2CO_3]{R^1R^2NH} \underset{XII—XV}{AdNHCOCH_2NR^1R^2}$$

$R^1+R^2=(CH_2)_5$ (XII), $(CH_2)_2NH(CH_2)_2$ (XIII), $(CH_2)_2O(CH_2)_2$ (IV); $R^1—R^2=CH_2CH_2OH$ (XV)

The IR spectra of VIII-XV display absorption bands characteristic of secondary amides at 3180-3430, 1640-1680, and 1495-1560 cm^{-1}; the PMR spectra of XII-XV contain absorptions corresponding to the protons of the $COCH_2N^+$ fragment at 3.78-3.86 ppm.

TABLE 2. Antiviral Activities of Compounds I-XVII

Compound	Antiviral activity against						
	HSV	VV	FPV	VSV	VEEV	RSV	ECHO 6
I	–	–	–	–	–	–	–
II	–	–	–	–	–	–	–
III	–	+	+	+	–	–	–
IV	–	+	–	–	–	+	++
V	–	–	++	–	–	++	–
VI	++	++	–	–	+	+	–
VII	–	–	–	–	–	–	–
VIII	–	++++	+++	–	–	–	–
IX	–	++++	–	–	–	–	–
X	++	+	–	–	–	–	–
XI	–	–	–	–	–	–	–
XII	–	+	–	–	–	–	–
XIII	–	–	+	–	–	–	–
XIV	–	–	–	–	–	–	–
XV	+	–	++++	–	–	–	–
XVI	++	++	++	++	–	–	–
XVII	–	–	–	–	–	–	–

Notes. –) Denotes absence of activity; +, ++) weak activity; +++) intermediate activity; and ++++) high activity.

Aminoester chlorhydrates of adamantanecarboxylic acids XVI and XVII were obtained by reacting the chlorhydrates of 1-adamantanecarboxylic and 3-ethyladamantanecarboxylic acids with dimethylaminoethanol.

Physicochemical and spectral characteristics of the compounds synthesized are given in Table 1.

EXPERIMENTAL (CHEMISTRY)

IR spectra were taken on an M-80 spectrophotometer (Germany), from KBr tablets or thin films. PMR spectra were recorded on a Bruker WP-80DS spectrometer (80 MHz, FRG), with HMDS as internal standard. Purity of compounds was monitored by chromatography on Silufol UV-254 plates (Czechoslovakia). Values found in elemental analyses agreed with those calculated.

N-(1-Adamantyl)benzylcarbamate (VII). A mixture of 2 g (8.4 mmoles) N-(1-adamantyl)-S-ethylthiocarbamate and 3 ml (29 mmoles) was refluxed for 1 h, excess benzyl alcohol was distilled, and the residue was sublimed under vacuum at 203-205°C/2 mm Hg. Following recrystallization from pentane, 1.31 g of urethane VII was obtained. Compounds III-VI were prepared similarly.

Synthesis of VIII, IX. To a mixture of 10 ml (220 mmoles) 98% nitric acid and 5 ml (90 mmoles) acetic acid at 20-25°C was added 3.5 g (26 mmoles) of adamantane; this was let stand 1 h and at 25°C was added 5 g (57 mmoles) of oxamide, which was let stand 2 h at 70°C, poured onto ice, the precipitate filtered, washed with water, dried, and recrystallized from isopropanol. Obtained was 2.6 g N,N^1-bis(1-adamantyl)oxamide (IX). After evaporating the mother liquor and recrystallization from acetone, 2.0 g N-(1-adamantyl)oxamide (VIII) was isolated.

1-(β-Morpholinopropionyl)aminoadamantane Hydrochloride (X). To a mixture of 25 ml (590 mmoles) 98% nitric acid and 5 ml (90 mmoles) acetic acid was added 5 g (37 mmoles) of adamantane. This was let stand 0.5 h, 7 g (50 mmoles) β-morpholinopropionitrile was added dropwise at 25-30°C, and incubation continued for 4 h. The reaction was poured onto ice, neutralized with NaOH, extracted with benzene, and the benzene extract was washed with water, dried with KOH, and dry HCl passed through. After filtration, 11 g of amide X was obtained.

N-(1-Adamantyl)-α-iodoacetamide (XI). To 15 ml (265 mmoles) of 94% sulfuric acid was added 3 g (20 mmoles) of 1-adamantol. After dissolution, 10 g (54 mmoles) α-iodoacetamide was then added, the mixture was incubated 2 h at 25°C and poured onto ice, and the precipitate was filtered, washed with water, dried, and recrystallized from benzene–hexane to give 4.5 g of compound XI.

1-(α-Morpholylacetyl)aminoadamantane Hydrochloride (XIV). A mixture of 4 g (12.5 mmoles) of amide XI, 4 g (38 mmoles) anhydrous sodium carbonate, and 4 ml (47 mmoles) morpholine in 40 ml of ethanol was refluxed 3 h and poured into 200 ml of water. The precipitate was extracted with ether (3 × 50 ml), the ethereal extract dried over NaOH, and dry HCl passed through. After filtration, 3.4 g of amide XIV was obtained. Amides XII, XIII, and XV were prepared similarly.

1-(2-Dimethylamino)ethoxycarbonyladamantane Hydrochloride (XVI). To a solution of 2 g (10 mmoles) of 1-adamantanecarboxylic acid chloroanhydride in 5 ml benzene was added a solution of 1 ml (10 mmoles) dimethylaminoethanol in 5 ml of absolute benzene. This was boiled 10 h, the benzene distilled, and the sediment recrystallized from acetone–hexane to yield 2.45 g of hydrochloride XVI. Compound XVII was obtained similarly.

EXPERIMENTAL (BIOLOGY)

Antiviral properties of compounds were determined in experiments in tissue culture against herpes simplex type I (HSV), vaccinia (VV), classical fowl plague (FPV), respiratory syncytial (RSV), vesicular stomatitis (VSV), Venezuelan equine encephalomyelitis (VEEV), and ECHO 6 viruses using a screening test and plaque reduction beneath an agar overlay. Studies with ECHO 6 virus were carried out on passaged cultures of human embryonic skin-muscle cells, with respiratory syncytial virus on cultures of rabbit lung connective tissue cells, and with the other viruses on primary trypsinized chick embryo fibroblasts.

The criteria for antiviral activity were the presence of a zone of supression of plaque formation (the so-called screening test), and a decreased viral titer caused by the compound under investigation, compared to the untreated control (the plaque-reduction method).

Similar methods were used by us to obtain the results in studies described previously [5].

Experimental data characterizing the viral-inhibitory activity of the studied nitrogen-containing adamantane derivatives are presented in Table 2.

Of the 17 compounds tested, 11 had antiviral activity, often expressed in different degrees against two or more types of viruses. The presence of an alkyl substituent (ethyl, isopropyl) at the junctional position of the adamantane skeleton causes the disappearance of activity (XVII compared to XVI, I and II compared to III-VI), which is confirmed by literature data [6] on the decrease in activity in a series of amino derivatives of alkyladamantanes.

Compounds VI, X, XV, and XVI had the ability to inhibit the growth of herpes virus. It is interesting that of the three synthesized analogs (V, XVI, and XVII) of the known antiherpetic drug Tromandatine [7] having a dimethylaminoethoxy group in their structures, only one was found to be active. Most compounds were active against vaccinia and fowl plague viruses. The three carbamates were effective against RSV. The greatest activity was displayed by amides VIII and IX against vaccinia virus, and by XV against FPV.

The data obtained, along with previous findings on the antiviral activity of the nitrogen-containing derivatives, may serve to justify the further search for viral-inhibitory substances from among the functional derivatives of adamantane.

LITERATURE CITED

1. Z. V. Vlasova, R. S. Belen'kaya, A. E. Lipkin, et al., Khim.-farm. Zh., No. 7, 808-810 (1982).
2. G. A. Galegov, Zh. Vses. Khim. O-va, 18, No. 2, 200-202 (1973).
3. S. D. Isaev, A. G. Yurchenko, S. S. Isaeva, Physiologically Active Substances [in Russian], No. 15, Kiev (1983), pp. 3-15.
4. Yu. N. Klimochkin, I. K. Moiseev, E. I. Boreko, et al., Khim.-farm. Zh., No. 4, 418-421 (1989).
5. V. I. Votyakov, E. I. Boreko, G. V. Vladyko, et al, Primary Study of the Antiviral Properties of Natural and Synthetic Compounds (Recommended Methods) [in Russian], Minsk (1986).
6. P. E. Aldrich, E. S. Hermann, W. E. Meir, et al., J. Med. Chem., 14, 535-543 (1971).
7. D. Peteri and W. Stermer, Arzneimittel-Forsch., 23, 577-581 (1973).