derivatives enhances antimicrobial action against Staphylococcus aureus and anthracoid spores. Blockage of the ether residue in the ethyl ester of this acid by hydrazine or hydrazone groups also resulted in greater antimicrobial activity.

LITERATURE CITED

1. A. P. Grekov and V. V. Shevchenko, Zh. Org. Khim., 4, No. 12, 1213-2116 (1968).
2. A. I. Gurevich and V. P. Sheynker, Optik. Spektrosk., 12, No. 1, 42-53 (1962).
3. V. P. Maksimets and O. N. Popilin, Khim. Geterotsikl. Soed., No. 2, 191-193 (1970).
4. A. A. Martynovskii, L. A. Shtoyko, N. N. Malovichko, et al., 4th Congress of Pharmacists of the Ukrainian SSR: Titles of Papers [in Russian], Zaporozh'e (1984), p. 148.
5. A. A. Martynovskii, L. A. Shtoyko, and I. A. Mazur, Farm. Zh., No. 4, 40-42 (1984).
6. A. A. Martynovskii, L. I. Borodin, N. N. Malovichko, et al., 5th Congress of Pharmacologists of the Ukrainian SSR: Titles of papers [in Russian], Zaporozh'e (1985), p. 101.
7. A. A. Martynovskii, N. N. Malovichko, and I. A. Mazur, Synthesis and Biological Activity of 2-Chloroacridinyl-9-thioacetic Acid and its Salts, Farm. Zh., No. 1, 33-36 (1986).
8. B. Murzubraimov and G. I. Shtrempler, Zdravookhr. Kirgiz., No. 2, 22-24 (1982).
9. O. M. Cherntsov, Zh. Obshch. Khim., 14, No. 3, 186-193 (1944).
10. D. K. Shakha, Synthesis, Properties, and Biological Activity of Acridine Derivatives: Dissertation for Candidate of Pharm. Sciences degree [in Russian], L'vov (1984).
11. R. S. Asquith and D. L. Hammich, J. Chem. Soc., 14, 1181-1183 (1948).
12. A. Edinger, Chem. Ber., 33, No. 3, 3769-3770 (1900).
13. S. Lolia and M. Ionescu, Stud. Univ. Babes. Bolyai. Ser. Chem., 17, No. 1, 77-84 (1972).
14. E. Ochiai and J. Irbai, J. Pharm. Soc. Jpn., 69, 413-415 (1949).

SYNTHESIS AND ANTIVIRAL ACTIVITY OF NITROGEN-CONTAINING ADAMANTANE DERIVATIVES

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

UDC 615.281.8:547.592.1].012.1

It is known [1, 2, 5] that nitrogenous functional derivatives of the adamantane series have distinct antiviral activity which, apparently, is caused by the high lipophilicity of the adamantyl radical. For example, N-adamantyl substituted ureas [5], carbamates [3], and carboxylic amides [6] are active. Therefore, the synthesis and study of the antiviral activity of compounds containing both adamantyl and amide fragments in their molecules seemed to be an important task.

To determine the relationship of the virus-inhibiting effect and the structure, we have synthesized acylamino, carbamoylamino, and alk(thio)oxycarbonylamino derivatives of adamantane.

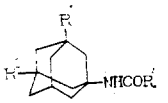
Reaction of adamantane with an excess of 98% HNO_3 in AcOH with subsequent addition of aliphatic and aromatic nitriles to the reaction mixture leads to the formation of acylaminoadamantanes (I-VII) (see scheme on following page).

In the reaction with an excess of succinonitrile, concurrent with addition of the adamantyl cation according to Ritter [7], a conversion of the second C≡N group to an amide group takes place through subsequent protonation and hydrolysis, which leads to the preparation of 1-[(2-carbamoylethyl)carbonylamino]adamantane (II). In case of shortage of

Kuibyshev Polytechnical Institute, Belorussian Scientific Research Institute of Microbiology and Epidemiology, Minsk.

Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 23, No. 4, pp. 418-421, April, 1989. Original article submitted February 23, 1988.

0091-150X/89/2304-0304 $12.50



I-XIII

R' = CH_2CH_2OMe (I), $CH_2CH_2CONH_2$ (II), $CH_2CH_2CONHAd$ (III), CH_2CONH_2 (IV), $C_6H_4NO_2$-m (V), $(CH_2)_3COOEt$ (VI), C_6H_4Cl-o (VII), OEt (VIII-X), $CONH_2$ (XI), SEt (XII, XIII); R^1 = H (I-VIII, XII), Me (IX, X, XIII), Et (XI), R^2 = H (I-IX, XI, XII), Me (X, XIII).

succinonitrile, the product of diadamantylization, the bis(adamantyl-1)amide of succinic acid (III), is produced. In the case of β-cyanoethyl malonate the reaction product contains only one ester group.

N-adamantyl substituted carbamates (VIII-X) are prepared by reacting adamantane or alkyl substituted adamantanes with 98% HNO_3 and then with ethyl esters of carbamic acids.

In the same way, the reaction of 1-ethyladamantane with a mixture of 98% HNO_3, AcOH, and urea yields 1-carbamoylamino-3-ethyladamantane (XI).

Reaction of nitro derivatives of the adamantane series with ethyl thiocyanate in concentrated H_2SO_4 leads to the preparation of N-adamantyl substituted thiocarbamates (XII and XIII).

The IR spectra of acylamino derivatives I-VII contain three characteristic absorption bands in the regions 2200-3360, 1635-1660, and 1520-1545 cm^{-1}, which correspond with the valence vibrations of the secondary amido group. In the spectra of carbamates VIII-X, the absorptions at 3340-3385, 1705-1715, and 1520-1535 cm^{-1} correspond with the valence vibrations of the bonds in the —NHCOO— group. In the IR spectra of thiocarbamates XII and XIII, the bands at 3235-3250, 1645-1665, and 1510-1525 cm^{-1} are characteristic of the valence vibrations of the NH, C=O, and C—N bonds (amide I and amide II bands). Also the PMR spectra of compounds I-XIII unambiguously confirm their chemical structures.

EXPERIMENTAL (CHEMICAL)

IR spectra were recorded on a IKS-29 spectrometer in KBr and thin films. The purity of the compounds was checked by chromatography on Silufol UV-254 plates (Czechoslovakia). Characteristics of the prepared compounds are listed in Table 1. Found and calculated values of the elemental analyses correspond.

TABLE 1. Characteristics of Compounds I-XIII

Compound	Yield, %	mp, °C	Empirical formula
I	73	91—2	$C_{14}H_{23}NO_2$
II	75	166—7	$C_{14}H_{22}N_2O_2$
III	49	272—3 (dec.)	$C_{24}H_{36}N_2O_2$
IV	35	166—7	$C_{13}H_{20}N_2O_2$
V	55	160—2	$C_{17}H_{20}N_2O_3$
VI	57	176—7	$C_{17}H_{27}NO_3$
VII	63	148—51	$C_{17}H_{20}NClO$
VIII	81	90,5—1,0	$C_{13}H_{21}NO_2$
IX	65	164/15 mm *	$C_{14}H_{25}NO_2$
X	85	156/9 mm**	$C_{15}H_{25}NO_2$
XI	43	144—5	$C_{13}H_{22}N_2O$
XII	78	119—20	$C_{13}H_{21}NOS$
XIII	81	53—3,5	$C_{15}H_{25}NOS$

*n_D^{20} 1.4888.
**n_D^{20} 1.4914.

TABLE 2. Antiviral Properties of Nitrogen-Containing Adamantane Derivatives

Compound	virus	Plaque reduction test: concentration studied, μg/ml	virus titer, lg pfu/ml	difference with control, lg pfu/ml	ED_{50}, μg/ml	CTI
I	RSV	200*	≤5,15	≥1,61		
		100	6,64	0,12	>156,34	1
		50	6,73	0,03		
		0	6,76	—		
I	VEEV	200	Toxicity			
		100	≤6,00	≥1,40		
		50	≤6,00	≥1,40	>34,21	2
		25	7,23	0,17		
		0	7,40	—		
II	HSV	400	Toxicity			
		200	≤4,00	≥1,80		
		100	5,18	0,62	<50,00	1
		50	5,36	0,44		
		0	5,80	—		
II	CBPV	400	≤3,00	≥1,49		
		200	≤3,00	>1,49	48,72	2
		100	3,60	0,89		
		50	4,20	0,29		
		0	4,49	—		
II	ECHO	400	Toxicity			
		200	≤4,00	≥1,72		
		100	4,85	0,87	122,34	1
		50	5,34	0,38		
		0	5,72	—		
III	HSV	800	≤4,00	≥1,80		
		400	5,41	0,79		
		200	5,62	0,18	128,50	1
		100	5,70	0,10		
		0	5,80	—		
VIII	VOV	100	≤3,00	≥1,57		
		50	4,07	0,40	16,31	1
		25	4,39	0,18		
		12,5	4,53	0,04		
		0	4,57	—		
IX	VOV	100	≤3,00	≥1,57		
		50	4,34	0,23	89,38	1
		25	4,43	0,14		
		12,5	4,51	0,06		
		0	4,57	—		
IX	CBPV	100	≤4,00	≥1,53		
		50	≤4,00	≥1,53	6,43	2
		25	5,77	0,76		
		12,5	5,84	0,69		
		0	6,53	—		
X	HSV	200	Toxicity			
		100	6,35	0,75	<50	0—1
		50	6,44	0,66		
		0	7,1	—		
X	VSV	200	Toxicity			
		100	6,89	0,77		
		50	6,89	0,77	35,97	0—1
		25	7,56	0,10		
		0	7,66	—		
XI	HSV	12,5	5,91	0,93		
		0	6,84	—	<12,5	1
XI	NDV	12,5	6,47	1,23		
		6,25	7,0	0,70		
		3,12	7,27	0,43	<3,12	1
		0	7,7	—		
XIII	HSV	200	≤3,0	≥1,74		
		100	4,15	0,59	78,24	1
		50	4,54	0,20		
		25	4,36	0,38		
		0	4,74	—		
XIII	VSV	200	≤3,0	≥1,81		
		100	4,38	0,43	27,24	1
		50	4,49	0,32		
		25	4,62	0,19		
		0	4,81	—		
XIII	VEEV	200	≤6,0	≥1,4		
		100	6,48	0,92	75,32	1
		50	7,28	0,12		
		25	7,3	0,10		
		0	7,4	—		

Note. An asterisk indicates MBC for FCE. ED_{50} is the mean effective dose.

1-[(2-Methoxyethyl)carbonylamino]adamantane (I). To a mixture of 15 ml (0.35 mole) of 98% HNO_3 and 5 ml of glacial AcOH is added 5 g (0.036 mole) of adamantane, the mixture is kept at 25°C for 0.5 h, and to the solution obtained is added 5 ml (0.061 mole) of β-methoxypropionitrile, the mixture is kept at room temperature for 1.5 h, and poured out on ice. The precipitate is filtered off, washed with water, and dried. Pure I is obtained by crystallization from hexane.

Compounds II-VII are prepared in the same way by using other nitriles.

1-Ethoxycarbonylaminoadamantane (VIII). To 15 ml (0.35 mole) of 98% HNO_3 is added 5 g (0.036 mole) of adamantane, the mixture is kept at 25°C for 15 min, then 14 g (0.16 mole) of ethyl carbamate is added with cooling, the mixture is kept at room temperature for 1 h, and poured out on ice. The precipitate is filtered off, washed with water, dried, and crystallized from hexane to yield pure VIII.

Compounds IX and X are prepared in much the same way.

1-Carbamoylamino-3-ethyladamantane (XI). To a mixture of 16 ml (0.38 mole) of 98% HNO_3 and 10 ml of glacial AcOH is added 4 ml (0.023 mole) of 1-ethyladamantane, the mixture is kept at 25°C for 1 h, then 8 g (0.13 mole) of urea is added with cooling, the mixture is heated at 60°C for 1 h, and poured out on ice. The precipitate is filtered off, washed with water, and dried. Pure XI is obtained by crystallization from $CHCl_3$.

N-Adamantyl-1-S-ethyl Thiocarbamate (XII). To a solution of 8.5 g (0.043 mole) of 1-nitroxyadamantane in 25 ml of 96% H_2SO_4 is added, at a temperature not exceeding 0°C, 5 ml (0.057 mole) of ethyl thiocyanate, the mixture is kept at −10°C for 1 h, and poured out on ice. The precipitate is filtered off, washed with water, dried, and crystallized from hexane to yield pure XII.

Thiocarbamate XIII was prepared in the same way.

EXPERIMENTAL (BIOLOGICAL)

Antiviral properties of the compounds were determined in experiments with tissue cultures with regard to the viruses: herpex simplex type I virus (HSV), variolo vaccine virus (VOV), classical birds pest virus (CBPV), Newcastle disease virus (NDV), respiratory syncytial virus (RSV), vesicular stomatitis virus (VSV), Venezuelan equine encephalomyelitis virus (VEEV), and ECHO-6 virus by the primary screening method ("screening test") and the reduction of plaques under an agar overlayer. With the ECHO virus experiments were carried out with a monolayer culture of transferred musculocutaneous cells of human embryos, with RSV with interwoven cells of rabbit lung (RL/33), and with the other viruses with primary trypsinized fibroblasts of chicken embryos (FCE).

The presence of an inhibition zone in the formation of plaques when the screening test was used, and also the decrease in virus titer under the influence of the compounds under investigation in comparison with untreated controls when the reduction of plaques was studied served as criteria for antiviral activity. The chemotherapeutic (CTI) index was calculated as the ratio of maximum bearable concentration (MBC) of a compound for cell cultures to its minimal concentration causing a lowering of the titer to the extent of 1.25 log pfu/ml.

The investigation method and the evaluation of the obtained results are described earlier in [4].

It has been established that compounds I-III, VIII-XI, and XIII have antiviral properties often with regard to two viruses and more (Table 2). However, low values of the CTI at best point to weak expression of these properties (I, II, IX). Basically, the same lowering of the virus titers in comparison with untreated controls was observed in the presence of the compounds at concentrations that correspond with the maximum bearable ones for the cell systems, which makes it possible to consider the observed antiviral activity as bordering on the toxic activity.

LITERATURE CITED

1. S. D. Isaev, A. G. Yurchenko, and S. S. Isaev, Fiziol. Akt. Veshchestva (Kiev), No. 15, 3-15 (1983).
2. E. I. Kovalev, Khim.-farm. Zh., No. 3, 19-27 (1977).
3. French Pat. 1,588,472; Chem. Abstr., 74, 53176w (1971).
4. V. I. Votyakov, E. I. Boreko, G. V. Vladyko, et al., Primary Investigation of Antiviral Properties of Synthetic and Natural Compounds (Methodic Recommendations) [in Russian], Minsk (1986).
5. R. C. Fort, Adamantane: The Chemistry of Diamond Molecules, New York (1976), p. 334.
6. G. May and D. Peteri, Arzneim.-Forsch., 23, 718-721 (1973).
7. J. J. Ritter and P. P. Minieri, J. Am. Chem. Soc., 70, 4045-4048 (1948).