SYNTHESIS AND ANTIVIRAL ACTIVITY OF THE HYDROCHLORIDES OF ALICYCLIC MONO- AND DIAMINES

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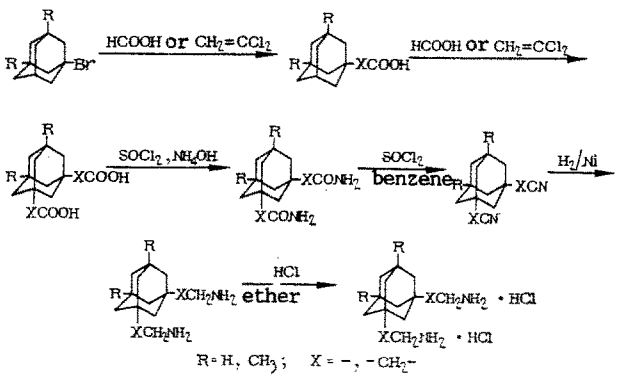
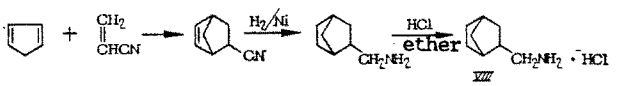
A considerable number of publications have been devoted to the study of the antiviral activity of derivatives of the alicyclic series [2, 4, 5, 7]. Antiviral preparations of the given class, such as midantane – 1-aminoadamantane hydrochloride – and remantadine – α-methyl-1-aminomethyladamantane hydrochloride – have recently found wide application in medicine. In this connection, it was of interest to synthesize and the study the antiviral activity of the hydrochloride salts of mono- and diamines of the adamantane, 1,3-dimethyladamantane, and bicyclo[2.2.1]heptane series.

The synthesis of mono- and dicarboxylic acids of the adamantane and 1,3-dimethyladamantane series was accomplished starting from the corresponding bromo derivatives in the mixture of sulfuric and nitric acids according to the following scheme:



When the resulting mono- and dicarboxylic acids were treated sequentially with thionyl chloride and ammonia, the corresponding mono- and diamides were obtained; the last react with thionyl chloride in benzene to give adamantane-containing mono- and dinitriles. The reduction of the latter on Raney Ni in ethyl alcohol and the treatment of the synthesized mono- and diamines with hydrogen chloride permit the isolation of high yields of the hydrochlorides of mono- and diamines of the adamantane and 1,3-dimethyladamantane series.

The hydrochloride (VIII) of 2-aminomethylbicyclo[2.2.1]-heptane was synthesized by the scheme:



The composition and the structure of the resulting hydrochlorides of the alicyclic mono- and diamines were confirmed by the data of the elemental analysis and the IR spectra. Some physico-chemical constants of the compounds obtained are presented in Table 1.

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TABLE 1. Physicochemical Characteristics of the Hydrochlorides of Alicyclic Mono- and Diamines

Compound	mp., °C	Empirical formula	Found, %				Calculated, %				IR spectra; absorption ν, cm^{-1}
			C	H	N	Cl	C	H	N	Cl	
1-Aminomethyladamantane hydrochloride (I)	>300	$C_{11}H_{20}ClN$	65,84	10,03	6,79	17,64	65,51	9,93	6,95	17,62	Broad bands 3350—3450, 2600, 3100, 2310, 1620, 1510, 1417, 1380, 830
1-Aminoethyladamantane hydrochloride (II)	>300	$C_{12}H_{22}ClN$	66,89	10,14	6,40	16,35	66,82	10,21	6,50	16,48	Broad bands 3400—3550, 2550—3150, 1680, 1605, 1490, 1380, 850
1,3-Dimethyl-5-aminomethyladamantane hydrochloride (III)	258—260 (with decomp.)	$C_{13}H_{24}ClN$	68,08	10,58	6,22	15,61	67,97	10,46	6,10	15,47	3220, 3200, Broad bands 2760—3110, 2745—2300, 2055, 2010, 1620, 1595, 1505, 1470, 1380, 1170, 1145, 940
1,3-Dimethyl-5-aminomethyladamantane hydrochloride (IV)	263—265 (with decomp.)	$C_{14}H_{26}ClN$	69,12	10,80	5,91	14,42	68,99	10,68	5,75	14,58	3050, Broad bands 2800—3000, 2400—1990, 1750, 1720, 1600, 1535, 1470, 1390, 1180, 950
1,3-Bis(aminomethyl)adamantane hydrochloride (V)	>300	$C_{12}H_{24}Cl_2N_2$	53,80	9,08	10,31	26,71	53,93	8,99	10,49	26,59	Broad bands 3400—3500, 2400—3100, 1690, 1605, 1520, 1470, 1385, 880
1,3-Bis(aminoethyl)adamantane hydrochloride (VI)	>300	$C_{14}H_{28}Cl_2N_2$	57,00	9,31	9,62	24,19	56,95	9,49	9,49	24,07	Broad bands 2360—3450, 2500—3200, 2370, 1605, 1470, 1380, 1350, 830
1,3-Dimethyl-5-aminomethyl-7-aminoethyladamantane hydrochloride (VII)	294—296 (with decomp.)	$C_{15}H_{30}Cl_2N_2$	58,35	9,88	9,29	23,19	58,25	9,71	9,06	22,98	Broad band 2730—3200, 2650, 2070, 2020, 1620, 1530, 1470, 80, 1250
2-Aminomethylbicyclo[2.2.1] heptane hydrochloride (VIII)	210—215 (with decomp.)	$C_8H_{16}ClN$	59,60	9,93	8,71	28,03	59,44	9,91	8,67	27,98	Broad band 2800—3200, 2650, 1590, 1510, 1470, 1385, 1050

TABLE 2. Antiviral Activity of the Hydrochlorides of Alicyclic Mono- and Diamines

Compound	Virus	Diameters of zones in the investigation by the method of the primary screening, mm		Dose-dependent effects					
				investigated concentration, μg/ml	test of the reduction of plaques		investigation with introduction into the composition of the supporting medium		
		toxicity	suppression of the formation of plaques		viral titer, log PFU/ml	difference from the control, log PFU/ml	CPE, %	viral titer, log PFU/ml	difference from the control, log PFU/ml
I	VCBP	0	30	12*	6,06	0,44	...	...	...
				6	5,89	0,61			
				3	5,98	0,52			
				0	6,50	—			
VI	VCBP	0	24	200*	5,48	1,30	100	...	...
				100	5,18	1,60	100		
				50	5,28	1,50	100		
				25	5,49	1,29	100		
				12	5,61	1,17	100		
				6	5,64	1,14	100		
				3	5,76	1,02	100		
				1,5	5,71	1,07	100		
				0	6,78	—			
VIII	VSV	0	22	100*	3,50	1,68	50	4,00	2,60
				50	3,50	1,68	75	4,30	2,30
				25	3,50	1,68	75	5,40	1,20
				12	3,98	1,20	100	6,40	0,20
				6	4,80	0,38	100	6,60	—
				0	5,18	—			
VIII	VCBP	0	40	100	6,30	1,38	50	5,20	0,84
				50	5,70	1,98	50	5,50	0,54
				25	6,48	1,20	50	5,72	0,32
				12	7,28	0,40	75	5,28	0,76
				3	7,60	0,48	75	5,30	0,74
				0	7,68	—	100	6,04	
VIII	NDV	0	12	100	5,78	0,87	100	...	...
				50	6,00	0,65	100		
				25	5,95	0,70	100		
				12	6,26	0,39	100		
				0	6,65	—			
VIII	VVS	0	12	100	5,00	2,23	100	...	...
				50	5,90	1,33	100		
				25	6,48	0,75	100		
				12	6,41	0,82	100		
				6	6,34	0,89	100		
				0	7,23	—			
VIII	VVEE	0	14	100	9,25	0,04	75	8,08	1,21
				50	9,24	0,04	75	8,13	1,16
				25	9,24	0,04	75	9,18	0,11
				12	9,19	0,09	50	9,29	0
				0	9,28	—		9,29	

*MTC.

EXPERIMENTAL CHEMICAL

The IR spectra of the compounds synthesized were taken on a UR-20 spectrophotometer (GDR) in mineral oil.

1-Aminoethyladamantane (II). The mixture of 60 g of 1-carboxymethyladamantane and 110 ml of thionyl chloride is boiled under a reflux condenser until the complete solution of the acid is effected. The excess of thionyl chloride is distilled; the reamining traces are removed by the azerotropic distillation with benzene. The resulting acid chloride of 1-carboxymethyladamantane is dissolved in 30 ml of dry benzene, and is slowly added, with cooling, to 200 ml of a concentrated aqueous solution of ammonia. The precipitated residue is filtered offf, washed with water, and dried. To the product obtained are added 60 ml of thionyl chloride and 150 ml of benzene; the mixture is boiled for 8 h. The mixture is then poured into water. The organic layer is separated and washed with a 2% solution of NaOH and water until neutrality is reached; it is dried over Na_2SO_4. The benzene is distilled, and the nitrile of 1-carbony-methyladamantane is recrystallized from ethanol.

Into a reactor equipped with a stirrer, a reflux condenser, and a dropping funnel are placed 19 g of $LiAlH_4$ and 500 ml of dry tetrahydrofuran; the mixture is heated to boiling.

TABLE 3. Antiviral Activity of the Hydrochlorides of Alicyclic Mono- and Diamines*

Compound	VHS	VSV	VCBP	NDV	VVS	VVEE	ECHO
I	—	—	+++	—	—	—	—
II	—	—	—	—	—	—	—
III	—	—	—	—	—	—	—
IV	—	—	—	—	—	—	—
V	—	—	—	—	—	—	—
VI	—	—	+++	—	—	—	—
VII	—	—	—	—	—	—	—
VIII	—	++	+++	—	+	++	—

*According to the scheme of evaluation in [2].

A solution of the nitrile of carboxymethyladamantane in 100 ml of tetrahydrofuran is added dropwise with stirring. To the cooled reaction mass are further sequentially added 20 ml of water, 15 ml of a 20% of NaOH, and 50 ml of water. The residue is filtered off; the resulting solution of the diamine is concentrated, and the residue is distilled in vacuo. The yield of 1-aminoethyladamantane is 75.5% based on 1-carboxymethyladamantane. The product has bp 132-135°C at 3-4 mm of Hg stem.

The synthesis of the compounds (I) and (III)-(VII) is accomplished by an analogous method.

2-Aminomethylbicyclo[2.2.1]heptane (VIII). Into an autoclave equipped with a jacket, a stirrer, a thermometer, and a connecting pipe for the dosing of hydrogen are placed 50 g of the nitrile of 2-carboxybicyclo[2.2.2]hept-5-ene [6], 300 ml of ethyl alcohol, and 5 g of Raney Ni. Nitrogen is blown through the autoclave; gaseous ammonia is added to the pressure of 3 atm. The hydrogenation is carried out at the temperature of 50-60°C for 6-8 h with the pressure of hydrogen at 8-10 atm. At the end of the reaction, the contents of the autoclave are taken out; they are filtered off from the catalyst. The solvent is evaporated, and the residue is distilled in vacuo. The product has bp 48-51°C (4-5 mm of Hg stem). The yield is 91-95%.

General Method for the Synthesis of the Hydrochlorides of the Amines. The amine (10 g) is dissolved in 200 ml of diethyl ether; dry hydrogen chloride is bubbled through with stirring for 3-4 h. The resulting precipitate of the hydrochloride is filtered off; it is washed with diethyl ether and acetone, and dried. The yields of the hydrochlorides are close to quantitative.

EXPERIMENTAL BIOLOGICAL

The antiviral properties were determined in experiments on tissue cultures infected with the viruses of Herpes simplex type 1, smallpox vaccine (VSV), classic bird plague (VCBP), Newcastle disease (NDV), vesicular stomatitis (VVS), Venezualan equine encephalomyelitis (VVEE), and ECHO 6 by the method of primary screening [8]. The quantitative parameters of the antiviral action shown were subsequently determined by the methods of the reduction of plaques under an agar convering, as well as the suppression of the cytopathic effect (CPE) and the accumulation of infective viral progeny, after the introduction of the compounds investigated into the supporting medium [1, 3]. The synthetic medium 199 was utilized as the supporting medium; the nutrient covering was prepared on the basis of this medium with the addition of 0.8% of the bactagar "Difco" and 0.005% neutral red. The multiplicity of the infection comprised 0.00003 PFE/cell in the experiments with all viruses. The results were estimated after incubation for 48-72 h in an incubator.

Calculation of the maximal tolerated concentration (MTC) for the tissue culture from the CPEs of the investigated substances at different concentrations, and from the capacity of the cells to absorb neutral red [9] after incubation for 96 h, preceded the determination of the quantitative characteristics of the antiviral effect.

The investigations with the ECHO virus were carried out on monolayer cultures of passaged human embryonic cutaneous-muscular cells; investigations with the remaining viruses were carried out on primary chicken embryo cells (CECs).

It was established that the compounds (I), (VI), and (VIII) possess antiviral properties (Table 2).

The substances indicated were mainly active in regard to the infection induced by VCBP. The hydrochloride of the amine (VIII) possesses a wide spectrum of activity, also showing inhibitory properties toward experimental infections of CECs induced by VSV, NDV, VVS, and VVEE.

LITERATURE CITED

1. V. M. Votyakov and E. I. Boreko, Methodical Problems of the Scientific Development of Antiviral Agents [in Russian], Minsk (1977), pp. 10-14.
2. I. Ya. Grava, Ya. Yu. Polis, M. Yu. Lidak, et al., Khim.-farm. Zh., No. 10, 42-45 (1980).
3. L. V. Denisova, L. I. Nikonovich, V. A. Saikovskaya, et al., Molecular Biology of Viruses: Chemotherapy and Chemoprophylaxis of Viral Infections [in Russian], Minsk (1974). pp. 111-119.
4. V. M. Plakhotnik, V. Yu. Kovtun, N. A. Leont'eva, et al., Khim.-farm. Zh., No. 9, 1060-1063 (1982).
5. K. Aigami, J. Inamoto, N. Takaishi, et al., J. Med. Chem., 18, 713-721 (1975).
6. H. A. Bruson, J. Am. Chem. Soc., 64, 2457-2461 (1942).
7. R. C. Fort, Adamantane: The Chemistry of Diamond Molecules, New York (1976), pp. 327-357.
8. P. Link, B. Rada, and D. Blaskovic, Ann. N.Y. Acad. Sci., 130, 31-43 (1965).
9. M. I. Marcialis, M. L. Schivo, P. Ucchedu, et al., Experientia, 29, 1442-1443 (1973).

SYNTHESIS AND ANTIVIRAL ACTIVITY OF 2-(1-ARYLOXY) AND 2-(1-ARYLAMINO-HYDROXYPROPYLAMINO)PYRIMIDINES AND THEIR ACYCLIC ANALOGS

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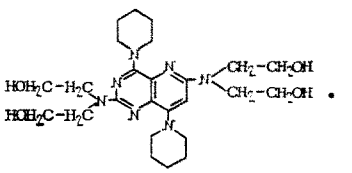
The search for antiviral drugs has been carried out amongst various types of chemical and biological compounds, and drugs in current use [4]. For example, antiviral activity has been found in dipyridamole, a coronary vasodilator and antithrombic drug:



Dipyridamole has been found to inhibit a wide range of viruses [11, 12], and some derivatives have been prepared and found to be possess antiviral activity [14]. In its mode of action, dipyridamole is an inhibitor of nucleoside transport in the cell, and totally suppresses the synthesis of viral RNA [13]. However, the synthesis of analogs of dipyridamole for this purpose has not been extensively pursued. For this reason, it appeared to us to be of interest to synthesize broader groups of pyrimidines and guanidines containing a propylamine moiety attached to nitrogen, which we regard as distant analogs of this drug.

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