SYNTHESIS AND ANTIVIRAL ACTIVITY OF SULFUR-CONTAINING DERIVATIVES OF ADAMANTANE

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Antiviral activity is displayed by a large number of adamantane derivatives containing sulfur atoms in a functional group. There are reports on antiviral activity of adamantyl-containing thioureas [6, 7], thioamides [3], isothiuronic salts [5], and adamantylisothiocyanates [2].

The aim of the present work was to study the viral-inhibitory activity of a series of new adamantane derivatives. For this, we developed methods to obtain adamantyl-substituted thiocarbamates, selenocarbamates, sulfamides, dithiocarbamates, and isothiocyanates.

N-Adamantylated thiocarbamates I-VII were obtained from nitroxy derivatives by a previously described method [1].

3-R^1-5-R^2-1-AdNHCOSR^3
I—VII
R^1=H (I—III, V), CH_3 (IV, VII), C_2H_5 (VI), R^2=H (I, VI), CH_3 (II, IV, V, VII), C_2H_5 (III); R^3=CH_3 (I—IV), $CH_2C_6H_5$ (V—VII);
1-Ad=adamantyl-1 (I—VII), and also for IX—XVI

2-Methylthiocarbonylaminoadamantane (VIII) was synthesized by the reaction of 2-adamantol with a solution of methylthiocyanate in sulfuric acid, which excluded isomerization to a 1-substituted derivative, characteristic of adamantane compounds [8]. The PMR spectrum of thiocarbamate VIII contains a doublet of an α-proton at 3.99 ppm ($J_{H_\alpha H_N}$ 6 Hz), which confirms the bond of the nitrogen atom with the bridge carbon atom of the adamantane nucleus.

The reaction of hydroxylated adamantane derivatives with methylselenocyanate in concentrated sulfuric acid has, for the first time, resulted in the N-adamantylation of the selenocyano group by the Ritter reaction [9], to give selenocarbamates IX and X.

$$3\text{-}R^1\text{-}5\text{-}R^2\text{-}1\text{-}AdOH \xrightarrow[H_2SO_4]{CH_3SeCN} 3\text{-}R^1\text{-}5\text{-}R^2\text{-}1\text{-}AdNHCOSeCH_3$$

R_1=R^2=H (IX), R^1=R^2=CH^3 (X).

The IR spectra of I-X contain absorption bands in the regions 3240-3330, 1645-1655, and 1510-1530 cm^{-1}, characteristic respectively of valence vibrations of the NH bond, valence vibrations of the carbonyl group, and deformation vibrations of the NH bond together with valence vibrations of the C—N bond in the —NHCOS— fragment.

The reaction of 1-adamantol with arylsulfamides in 94% sulfuric acid at 60°C gave N-adamantylated products of the formula 1-$AdNHSO_2$-p-C_6H_4R [R = H (XI), CH_3 (XII)].

Adamantyl-containing dithiocarbamates XIII and XIV and isothiocyanates XV and XVI were synthesized by reacting the corresponding hydroxy and nitroxy derivatives with sodium diethyldithiocarbamate and potassium thiocyanate in a mixture of sulfuric and acetic acids.

$$3\text{-}R^1\text{-}5\text{-}R^2\text{-}1\text{-}AdOH \xrightarrow[H_2SO_4-AcOH]{(C_2H_5)_2NCSSNa} 3\text{-}R^1\text{-}5\text{-}R^2\text{-}1\text{-}AdSCSN(C_2H_5)_2$$
R^1=H (XIII, XIV), R^2= =H (XIII), C_2H_5 (XIV)

$$3\text{-}R^1\text{-}5\text{-}R^2\text{-}1\text{-}AdONO_2 \xrightarrow[H_2SO_4-AcOH]{KSCN} 3\text{-}R^1\text{-}5\text{-}R^2\text{-}1\text{-}AdNCS$$
R^1=H (XV), CH_3 (XVI); R^2=CH_3 (XV, XVI)

The structures of compounds XI-XVI were confirmed by IR and PMR spectral data. Physicochemical and spectral characteristics of the compounds synthesized are given in Table 1.

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

Compound	Yield, %	mp (bp), °C	Empirical formula	Spectral characteristics	
				IR, ν max, cm^{-1}	PMR, δ, ppm, acetone-d_6
I	85	125—126	$C_{19}H_{19}HOS$	3300, 1655, 1510, 1205	1,67s (6H); 1,99s (6H); 2,07s (3H); 5,14s (1H)
II	78	83—85	$C_{13}H_{21}NOS$	3280, 1650, 1520, 1205	0,81s (3H); 1,36—2,05 m (14H); 2,18s (3H); 6,69s (1H)
III	70	118—120	$C_{14}H_{23}NOS$	3240, 1645, 1530, 1210	0,77t (3H); 1,15q (2H); 1,35—2,15 m (14H); 2,15s (3H); 6,55s (1H)
IV	79	117—118	$C_{14}H_{23}NOS$	3270, 1655, 1530, 1215	0,83s (6H); 1,41—2,12m (13H); 2,21s (3H); 6,59s (1H)
V	55	92—93	$C_{19}H_{25}NOS$	3320, 1655, 1510, 1200	0,76s (3H); 1,30—2,30 m (14H); 4,12s (2H); 5,05s (1H); 7,30s (5H)
VI	49	71—73	$C_{20}H_{27}NOS$	3280, 1650, 1515, 1195	0,75t (3H); 1,18q (2H); 1,31—2,25 m (14H); 4,10 (2H); 7,30s (5H); 5,05s (1H)
VII	61	85—86	$C_{20}H_{27}NOS$	3330, 1655, 1510, 1195	0,83s (6H); 1,1—2,3 m (13H); 4,10s (2H); 5,10s (1H); 7,28s (5H)
VIII	54	98—99,5	$C_{12}H_{19}NOS$	3270, 1645, 1525, 1205	1,55—2,10 m (15H); 2,21s (3H); 3,99s (1H); 7,10s (1H)
IX	76	122—124	$C_{12}N_{19}NOSe$	3260, 1655, 1520, 1210	1,66s (6H); 2,01s (9H); 2,23s (3H); 5,17s (1H)
X	76	108—111	$C_{14}H_{21}NOSe$	3300, 1655, 1525, 1205	0,84s (6H); 1,0—1,9 m (13H); 2,21s (3H); 5,19s (1H)
XI	61	119—120	$C_{16}H_{21}NO_2S$	3180, 1315, 1155	1,55s (6H); 1,86s (6H); 1,96s (3H); 6,27s (1H); 7,49—8,03 m (5H)
XII	66	160—161	$C_{17}H_{23}NO_2S$	3220, 1320, 1145, 795	1,60s (6H); 1,83s (6H); 1,93s (3H); 6,13s (1H); 7,35 (2H); 7,75s (2H)
XIII	53	92—94	$C_{15}H_{25}NS_2$	1455, 1400, 1295, 1250	1,25t (6H); 1,74s (6H); 2,18s (3H); 2,40s (6H); 3,85q (4H)
XIV*	76		$C_{17}H_{29}NS_2$	1460, 1410, 1265, 1210	0,8t (3H); 1,21t (6H); 1,05—2,60 m (16H); 3,89 (4H)
XV	60	90	$C_{12}H_{17}NS$	2070, 1110, 810, 670	0,8s (3H); 1,3—2,1m (14H)
XVI**	64	140/3mm	$C_{13}H_{19}NS$	2065, 1190, 895, 675	0,82s (6H); 1,35—2,15 m (13H)

*Isolated by column chromatography on silica gel. Eluent — hexane, n_D^{20} 1.5781 R_f 0.58 (chloroform).
**n_D^{20} 1.5474.

TABLE 2. Antiviral Properties of Compounds I-XVI

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

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

EXPERIMENTAL (CHEMISTRY)

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

2-Methylthiocarbonylaminoadamantane (VIII). To 15 ml (265 mmoles) of 94% sulfuric acid at 20°C was added 4 g (55 mmoles) methylthiocyanate dropwise, followed by 2 g (13 mmoles) of 2-adamantol. This was incubated 30 min at 20°C, poured onto ice, and extracted with ether. The ethereal extract was washed with water and dried with sodium sulfate, and following distillation of the ether and recrystallization of the residue from hexane, 1.6 g of thiocarbamate VIII was obtained.

N-(1-Adamantyl)-Se-methylselenocyanate (IX). To 10 ml (177 mmoles) 94% sulfuric acid was added 2.2 g (14.5 mmoles) of 1-adamantol, and following dissolution of this, 1 ml (14.5

mmoles) methylselenocyanate was added dropwise at −10°C. This was incubated 2 h at −5°C and poured onto ice, and the residue was filtered, washed with water, and dried. Following recrystallization from hexane, 3 g of compound IX was obtained. Selenocarbamate X was obtained similarly.

N-(1-Adamantyl)benzolsulfamide (XI). To 20 ml (354 mmoles) 94% sulfuric acid was added 5 g (33 mmoles) 1-adamantol and 11 g (70 mmoles) benzosulfamide. This was incubated for 2 h and poured onto ice, the precipitate was filtered, washed with water, and dried, and following recrystallization from benzene, 5.85 g of sulfamide XI was obtained. Compound XII was prepared similarly.

N,N-Diethyl(1-adamantyl)dithiocarbamate (XIII). To a mixture of 20 ml (354 mmoles) of 94% sulfuric acid and 5 ml (90 mmoles) acetic acid was added 4 g (26 mmoles) 1-adamantol. After dissolution at 15°C was added 6.8 g (40 mmoles) sodium N,N-diethyldithiocarbamate. This was incubated 1 h at 10-15°C, poured onto ice, and the residue filtered, washed with water, dried, and recrystallized from methanol, giving 3.5 g of XIII. Dithiocarbamate XIV was obtained similarly.

3-Methyl-1-adamantylisothiocyanate (XV). To a mixture of 20 ml (354 mmoles) 94% sulfuric acid and 5 ml (90 mmoles) acetic acid was added 5 g (24 mmoles) 1-nitroxy-3-methyladamantane, and following dissolution at 10-15°C, 3 g (30 mmoles) potassium thiocyanate was added. This was incubated 3 h at 15°C, poured onto ice, and extracted with ether, and the ethereal extract was washed with water, dried with sodium sulfate, and the ether distilled. After recrystallization of the residue from aqueous acetone, 3.0 g of compound XV was obtained. Isothiocyanate XVI was prepared 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 [4].

The antiviral properties of the synthesized sulfur-containing derivatives of adamantane are given in Table 2.

Of the 16 compounds prepared, 12 had various degrees of antiviral activity. Compounds I, IX, and X inhibited the growth of a wide range of viruses. The greatest activity was demonstrated by X, against classical fowl plague virus. It should be noted that thiourethane VIII, substituted at the bridge carbon of adamantane, displays a narrower range of antiviral activity than derivative I, substituted at the junctional position. Substituting an atom of selenium for sulfur in the urethane group causes increased viral-inhibitory activity (IX compared with I, and X with IV).

This group of compounds was characterized by the ability to inhibit the growth of ECHO 6 virus, and by the lack of inhibitory activity against vaccinia virus.

On the basis of the results obtained, we may conclude that sulfur- and selenium-containing derivatives of adamantane are of undoubted interest as potential inhibitors of viral activity.

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SYNTHESIS AND UTEROSTIMULATING ACTIVITY OF DERIVATIVES OF 1-DIALKYLAMINO-3-ALKOXY-2-PROPANOL

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These last few years β-adrenoblockers have been used for the treatment of uterine inertia [4], however, because of their effect on the cardiovascular system they have limited application in obstetric practice. The purpose of this investigation is the search for novel derivatives of alkoxyaminopropanol that have uterostimulating activity and essentially have no influence on the cardiovascular system, and are of general formula

$$R^1CH_2CH(OH)CH_2OR,$$

in which R=CH_3 (Ia), C_2H_5 (Ib), C_3H_7 (Ic), C_4H_9 (Id,e), $(CH_3)_2CH$ (If), $(CH_3)_2CHCH_2$ (Ig), $(CH_3)_3C$ (Ih), $PhCH_2$ (IIa,b), adamantyl-CH_2 (IIIa, b); R^1=$N(C_2H_5)_2$ (Ia-d,f,h, IIa, IIIa), morpholino (Ie, IIb, IIIb).

EXPERIMENTAL (CHEMICAL)

The synthesis of the compounds mentioned was carried out by three different methods. Compounds Ia-f were prepared by methods 1 and 2, compounds Ig-h by method 2, and compounds IIa, b and IIIa, b by method 3.

The hydrochlorides of these compounds, prepared by usual methods, are water-soluble oils, with the exception of IIIb, which is crystalline [6].

We have found that reactions of dialkylamino-2,3-epoxypropane with primary C_1-C_4 alcohols in the presence of $SnCl_4$ yield 1-dialkylamino-3-alkoxy-2-propanols in yields of 63-75%.

With secondary alcohols the final product is formed in a yield of 10% and with tertiary alcohols we failed to isolate the desired products.

It is convenient to carry out the reaction with low-molecular alcohols according to method 2, while reactions with aromatic or high-molecular alcohols proceed better according to method 3.

Method 1. To a mixture of 12.9 g (0.1 mole) of 1-diethylamino-2,3-epoxypropane and 37 g (0.5 mole) of butanol is added with stirring 0.5 ml of $SnCl_4$. The mixture is stirred at 75-80°C for 10 h. The excess of alcohol is distilled off, the residue is treated with 10 ml of 15% K_2CO_3, extracted with ether, and the extract is dried over potassium carbonate. The solution is filtered, the ether evaporated, and the residue distilled. Yield 15.2 g (75%) of Id, bp 117-118°C (1333 Pa), n_D^{20} 1.4354. Compounds Ia-c, e, f were prepared in much the same way.

Method 2. A mixture is prepared from 9.2 g (0.1 mole) of epichlorohydrin and 37 g (0.5 mole) of butanol. To this mixture is added with stirring 0.5 ml of $SnCl_4$. After 10-15 min the mixture is warmed up to 90-100°C. Then the reaction mixture is kept at that temperature for 20 min, the excess of butanol is evaporated, the residue is transferred to a dropping

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