itself. Their MSC for Staphylococci are 0.3-0.5 μg/ml, for *Escherichia coli* 50-100 μg/ml, for for protozoa 100 μg/ml, and for *Bacillus pyocyaneus* 100 μg/ml.

LITERATURE CITED

1. Cl. Mariel, Rev. Med. (Paris), 21, 1595-1598 (1980).
2. S. Takahashi, K. Nitta, S. Honio, et al., J. Antibiot. (Tokyo), 26, 513-520 (1973).
3. W. A. Slusarchyke, I. L. Bouchard-Fwirg, and F. L. Weisenborn, J. Antibiot. (Tokyo), 26, 391-393 (1973).
4. U. S. Pat. No. 3825529 (1971); Ref. Zh. Khim., No. 10 "O", No. 264P (1975).
5. W. Moronowich, D. J. Lamb. H. A. Karnes, et al., J. Pharm. Sci., 58, 1485-1589 (1969).
6. V. I. Yudelevich and V. M. Tikhonova, in: Study of Biologically Active Compounds, Metabolites of Microorganisms, Part 2, [in Russian] Leningrad (1976), p. 37; V. I. Yudelevich, L. B. Sokolov, and B. I. Ionin, Usp. Khim., 49, 92-117 (1980).
7. H. Umezawa, Recent Advances in the Chemistry and Biochemistry of Antibiotics, Microbial Products Research Institute, Tokyo (1964).
8. W. Kump and H. Bickel, Helv. Chem. Acta, 56, 2323-2347 (1973).

SYNTHESIS AND STUDY OF THE ANTIVIRAL ACTIVITY OF THIENYL DERIVATIVES OF ADAMANTANE

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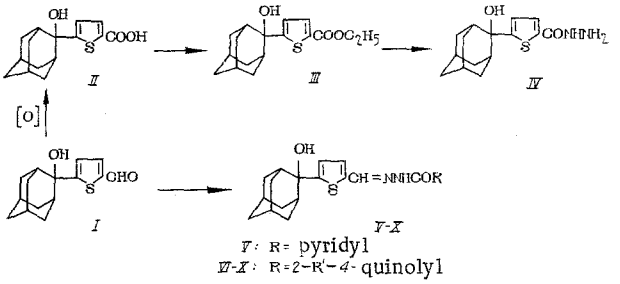
Adamantane derivatives are known as physiologically active substances with a wide spectrum of action. Among them are compounds showing antibacterial [1], antiviral [2], anticonvulsant [3], antisecretory [4], and vasodilating [5] action.

The synthesis of 2-(adamantyl-2-ol-2)-5-formylthiophene and derivatives of it has been carried out by the following scheme with the aim of studying antiviral properties in the 2-thienyladamantane series.



EXPERIMENTAL BIOLOGICAL PART

The antiviral activity of the 2-thienyladamantane derivatives was studied in relation to RNA- and DNA-containing viruses. Investigations were carried out with viruses of group A/Rostok/34 (HavINI), parainfluenza type 3, Venezuelan encephalomyelitis of the horse, ECHO type 6, adenovirus type 3, herpes simplex, and smallpox vaccine. The virus-inhibiting action of compounds was determined by the agar diffusion method in Petri dishes and also by the reduction of the cytopathogenic action of viruses. Compounds were studied on trypsinized cultures of chick fibroblasts and transplanted skin-muscle cells of human embryo. Assessment of the activity of preparations was carried out according to the scheme proposed by V. I. Votyakov and co-workers [6].

The investigated substances mainly possessed insignificant toxicity. Maximum tolerated concentrations of substances were within the limits 100-10 μg/ml. The studied substances

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possessed no marked antiviral properties. Weak antiviral action was shown by compound (II) on vaccinia virus.

EXPERIMENTAL CHEMICAL PART*

2-(Adamantyl-2-ol-2)-5-formylthiophene (I). Phosphorus oxychloride (9.6 g:0.064 mole) was added to a solution of 2-(adamantyl-2-ol-2-)thiophene (1.1 g:0.005 mole) in dimethylformamide (DMF) (4.6 g:0.064 mole) with cooling in ice water. The reaction mixture was heated on a water bath for 1 h, cooled, poured onto ice, and neutralized with sodium carbonate. Bright yellow needles of (I), which had precipitated after cooling the reaction mixture, were filtered off, washed with water, and air dried. Yield was 1.14 g (85 %), mp 164-165°C (from heptane). Found, %: C 66.7; S 11.5. $C_{15}H_{18}O_2S$. Calculated, %: C 67.2; S 12.0. IR spectrum, ν, cm^{-1}: 3420 (OH); 3120, 2920, 2865 (CH_2); 1670 (CO).

2-(Adamantyl-2-ol-2-)-5-thiophene Carboxylic Acid (II). Compound (I) (3.1 g: 0.011 mole) was added to a solution of NaOH (3.6 g) in water (36 ml) with vigorous stirring, a solution of $KMnO_4$ (2.44 g) in water (38 ml) was poured in at 10-15°C, stirred a further 15 min, and the reaction mixture was heated almost to boiling by passing steam through it. The precipitate of MnO_2 was filtered off, the filtrate neutralized with 10% hydrochloric acid solution, and evaporated in a porcelain dish. Yield of (II) was 2.2 g (78%), mp 285-286°C (from ethanol). Found, %: C 64.0; S 6.1. $C_{15}H_{18}O_3S$. Calculated, %: C 64.5; S 6.4. IR spectrum, ν, cm^{-1}: 3370 (OH), 2940 (CH_2), 1690 (CO).

2-(Adamantyl-2-ol-2)-5-thiophene Carboxylic Acid Ethyl Ester (III). Compound (II) (0.5 g: 0.002 mole) was dissolved in ethanol (10 ml), then H_2SO_4 (sp. gr. 1.84) (0.26 mole) was added with cooling, the mixture was heated for 5-6 h on a water bath, cooled, poured onto ice, and neutralized with sodium carbonate. The product was extracted with ether, the ether solution was decolorized with activated carbon, dried over anhydrous Na_2SO_4, and evaporated. The oily (III) obtained was put into the hydrazinolysis reaction without additional purification.

2-(Adamantyl-2-ol-2-)-5-thiophene Carboxylic Acid Hydrazide (IV). Ethyl ester (III) was dissolved in ethanol (20 ml), hydrazine hydrate (4 ml) was added, and the mixture boiled for 5 h. The white crystalline solid, which precipitated on cooling, was filtered off, washed with alcohol, and air dried. Yield was 0.34 g [58% calculated on initial acid (II)], mp 208-208.5°C (from ethanol). Found, %: C 60.8; S 10.8. $C_{15}H_{20}N_2O_2S$. Calculated, %: C 61.2; S 10.8. IR spectrum, ν, cm^{-1}: 3350 (OH); 3260 (NH); 2920 (CH_2); 1660 (CO).

Isonicotinoyl-5-(adamantyl-2-ol-2-)-2-formylthiophene Hydrazone (V). Isonicotinic acid hydrazide (0.28 g: 0.002 mole) was dissolved in alcohol (100 ml), (I) (0.5 g : 0.002 mole) was added, and the mixture boiled for 4 h. The bright yellow finely crystalline substance precipitated after cooling was filtered off, washed with alcohol, and air dried. Yield was 0.4 g (54 %) mp 250-251°C (from ethanol). Found, %: C 65.8; N 11.5. $C_{21}H_{23}N_3O_2S$. Calculated, %: C 66.1; N 11.0. IR spectrum, ν, cm^{-1}: 3380 (OH); 3300 (NH); 2930 (CH_2); 1675 (CO).

Compounds (VI-X) were obtained similarly (see Table 1).

*IR spectra of compounds were measured by N. A. Kabo on a UR-20 spectrophotometer (East Germany) in KBr pellets.

TABLE 1. Hydrazones of 2-R-Cinchoninoyl-5-(adamantyl-2-ol-2-)-2-formylthiophene

Compound	R'	Yield, %	mp, °C	N found, %	Empirical formula	N calculated, %	IR spectrum, ν, cm^{-1}			
							OH	NH	CO	NO_2
VI	Methyl	89	238—240	9,6	$C_{26}H_{24}N_3O_2S$	9,3	3410	3270	1675	—
VII	2-Furyl	98	228—230	8,4	$C_{29}H_{27}N_3O_3S$	8,4	3450	3160	1690	—
VIII	Phenyl	94	240—242	9,8	$C_{31}H_{29}N_3O_2S$	8,4	3400	3270	1650	—
IX	5-Nitro-2-thienyl	91	240—242	6,5	$C_{29}H_{26}N_4O_4S$	6,6	3500	3180	1660	1340
X	p-Nitrophenyl	79	237—239	10,1	$C_{31}H_{28}N_4O_4S$	10,0	3460	3320	1650	1350

LITERATURE CITED

1. Japanese Patent No. 52-46949 (1977). Ref. Zh. Khim., No. 20079p (1978).
2. Swiss Patent No. 586663 (1977); Ref. Zh. Khim., No. 23060p (1977).
3. A. L. Fridman, V. S. Zalesov, I. K. Moiseev, et al., Khim.-farm. Zh., No. 7, 6-8 (1974).
4. British Patent No. 1466130 (1977); Ref. Zh. Khim., No. 21054p (1977).
5. Japanese Patent No. 52-144682 (1977); Ref. Zh. Khim., No. 210117p (1978).
6. V. I. Votyakov and E. I. Boreko, in Methodological Problems in the Scientific Development of Antiviral Agents [in Russian], Minsk (1977), p. 10.

SYNTHESIS AND ANTIVIRAL ACTIVITY OF N-SUBSTITUTED AMINOADAMANTANES

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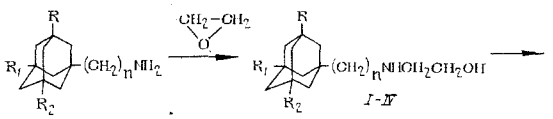
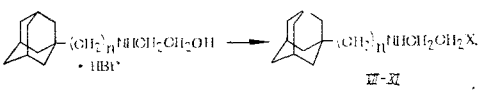
The initial data on the antiviral activity of derivatives of 1-aminoadamantane derivatives were published in 1964 [1]. Up to the present time several hydroxy and aminoethyl derivatives of aminoadamantane have been synthesized, however they are significantly superseded by 1-aminoadamantane in antiviral activity [2]. With the aim of searching for new compounds active against influenza virus, derivatives of 1- and 2-aminoadamantane and of 1-aminoethyladamantane having a substituted ethyl residue on the nitrogen atom have been synthesized and studied.

The synthesis of the hydroxyethyl derivatives (I-IV) has been described by us previously in [3]. Replacement of the hydroxyl group by a bromine atom was effected by the action of phosphorus tribromide or hydrobromic acid. On reacting bromides (V) and (VI) with thiourea, sodium thiosulfate, or sodium thiophosphate compounds (VII-X) were obtained.



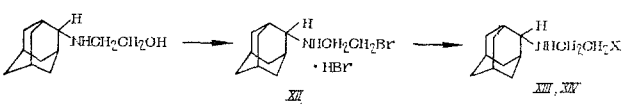
I: $R = R_1 = R_2 = H$, $n = 0$; II: $R = R_1 = R_2 = H$, $n = 1$; III: $R = CH_3$, $R_1 = R_2 = H$, $n = 1$; IV: $R = R_1 = R_2 = CH_3$, $n = 1$.



V: $n = 0$, VI: $n = 1$; VII: $n = 0$, $X = SC(NH_2)_2^+Br \cdot HBr$;
VIII: $n = 0$, $X = SPO_3HNa$; IX: $n = 0$, $X = SH \cdot HCl$;
X: $n = 1$, $X = SSO_3H$; XI: $n = 1$, $X = SPO_3HNa$.

Compound (XI) was not obtained since (VI) hydrobromide was insoluble in water and in organic solvents containing water and heating to more than 50°C was inadmissible in this case due to the thermal instability of (XI).

The derivatives of 2-aminoadamantane (XIII, XIV) were obtained in a similar manner.



XIII: $X = SC(NH_2)_2^+Br^- \cdot HBr$; XIV: $X = SSO_3H$.

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