3. Yu. K. Vasilenko, L. I. Lisevichkaya, L. M. Frolova et al., Farmakol. Toksikol, 5, 66-70 (1982).
4. V. V. Veinberg, Collected Works, in: Society of Russian Physicians in St. Petersburg in 1909-1910 [in Russian], St. Petersburg (1910), pp. 269-277.
5. V. A. Galkin and V. A. Maksimov, Biochemical Changes in Bile in Certain Diseases of the Digestive Organs. Scientific Survey [in Russian], Nauch. obzor., Moscow (1975).
6. Yu. M. Dererer, N. N. Krylova, and G. G. Ustinov, Choletithiasis [in Russian], Moscow (1983).
7. V. T. Zaichev, Z. A. Gurevich, and V. G. Pocherchov, Cholelithiasis [in Russian], Khar'kov (1979).
8. V. G. Kolb and V. S. Kamyshnikov, Manual of Clinical Chemistry [in Russian], Minsk (1982), pp. 31-35.
9. Ibid., pp. 73-75.
10. Ibid., pp. 111-116.
11. Ibid., pp. 251-253.
12. V. G. Kolb and V. S. Kamyshnikov, Byull. Éksp. Biol. Med., No. 6, 750-752 (1980).
13. J. Magyar, Diseases of the Liver and Bile Ducts [Russian translation], Vol. 2, Budapest (1962), pp. 247-303.
14. M. D. Mashkovskii, Drugs [in Russian], 8th Edn., Part 1, Moscow (1977), p. 327.
15. V. P. Miroshnichenko, Investigation of the Cholatocholesterol Function of the Liver in Viral Hepatitis and Cholelithasis by a New Method of Photometric Analysis. Dissertation for the Degree of Candidate of Medical Sciences [in Russian], Zaporosh'e (1978).
16. I. A. Oivin, Pat. Fiziol., No. 4, 78-85 (1960).
17. M. I. Prokhorova and Z. N. Tupikova, Large Manual of Carbohydrate and Lipid Metabolism [in Russian], Leningrad (1965), pp. 53-54.
18. A. S. Saratikov and N. P. Skakun, Bile Formation and Cholagogic Agents [in Russian], Tomsk (1977).
19. D. S. Sarkisov and P. I. Remezov, Experimental Reproduction of Human Diseases [in Russian], Moscow (1960), pp. 177-178.
20. S. K. Agarwa and P. Rastogi, Phytochemistry, 13, 2623-2645 (1974).
21. B. Borkowski and B. Pasich, Farm. Pol., 18, 49-54 (1962).
22. A. Vachon, J. D. Boyer, H. Slacni, et al, Lyon Med., 242, 173-178 (1979).

SYNTHESIS OF POTENTIAL DRUGS BASED ON HYDROPHOSPHORYL COMPOUNDS. VI. SYNTHESIS AND ANTIVIRAL ACTIVITY OF UNSATURATED ORGANOPHOSPHORUS DERIVATIVES OF INOSINE DIALDEHYDE

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A large number of analogs of nucleic acid components is known, including nitrogen bases, nucleosides, and nucleotides, modified in the heterocyclic or carbohydrate fragments [3]. To this class of substances belong a series of known antiviral preparations with a marked biological effect the basis of which is the action of cellular nucleic acid synthesis [3]. To such drugs belong for example cytosar [3, 12], virazole (ribavirin) [3, 11, 14], and the phosphorus containing preparation vidarapin phosphate [10]. The search for new antiviral preparations has also been conducted among phosphorus containing nucleosides which may particularly be obtained on the basis of hypophosphites [6, 7].

The interaction has been effected of propadienephosphonous acid and inosine dialdehyde (ID) in the presence of primary amines in the present work. As a result of the reaction the formation occurred of inosine dialdehyde 9-[morpholyl-3'-hydroxy-4'alkyl(cycloalkanyl,

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TABLE 1. Unsaturated Organophosphorus Derivatives of ID

Compound	Yield, %	Mp, °C (decomposition)	Found, %			Empirical formula	Calculated, %			IR spectrum, ν, cm^{-1}			UV spectrum, λ, nm
			C	H	P		C	H	P	P=O	C=N	C=C=C	
I	54	185—188	38,90	4,44	4,51	$C_{24}H_{30}N_9O_{12}P \cdot 4H_2O$	38,97	5,14	4,20	1225	1685	1940	197, 250, 454
II	16	180—183	40,54	4,75	4,76	$C_{27}H_{32}N_9O_{16}P \cdot 2H_2O$	40,25	4,47	3,85	1245	1680	1935	197, 250, 477
III	26	181—184	37,00	5,16	2,68	$C_{27}H_{33}N_{10}O_{15}P \cdot 6H_2O$	36,98	5,13	3,54	1230	1655	1935	197, 250
IV	18	172—175	42,00	5,21	4,10	$C_{28}H_{38}N_{11}O_{12}P \cdot 2H_2O$	42,69	5,34	3,94	1260	1685	1935	197, 247, 477
V	30	185—187	37,78	4,40	3,87	$C_{25}H_{30}N_9O_{14}P \cdot 4H_2O$	38,31	4,85	3,96	1235	1670	1950	197, 245, 292
VI	27	170—173	43,50	6,20	3,51	$C_{28}H_{39}N_9O_{14}P \cdot 2H_2O$	42,58	5,07	3,93	1265	1680	1950	197, 245, 492
VII	21	186—189	43,68	5,09	3,95	$C_{29}H_{38}N_9O_{14}P \cdot 2H_2O$	43,33	5,23	3,86	1230	1680	1935	197, 248, 492
VIII	23	188—191	43,56	5,15	3,54	$C_{29}H_{38}N_9O_{14}P \cdot 2H_2O$	43,33	5,23	3,86	1245	1680	1935	197, 250, 500
IX	53	218—222	49,88	5,89	3,79	$C_{34}H_{44}N_9O_{12}P \cdot H_7O$	49,82	5,62	3,78	1685	1685	1960	197, 257, 500
X	37	190—192	49,45	5,87	3,84	$C_{35}H_{47}N_{10}O_{12}P \cdot H_2O$	49,52	5,90	3,66	1245	1685	1935	197, 257, 500
XI	80	221—224	42,76	7,26	5,09	$C_{20}H_{35}N_5O_7P \cdot 3H_2O$	43,16	7,37	5,57	1235	1685	1940	197, 248, 452
XII	75	239—242	28,41	4,40	14,68	$C_{14}H_{24}N_5O_{14}P \cdot H_2O$	28,14	4,36	15,60	1245	1670	1950	197, 249, 486
XIII	26	149—152	43,16	4,79	4,21	$C_{28}H_{34}N_9O_{14}P \cdot H_2O$	43,69	4,79	4,03	1245	1680	1935	197, 248, 477
XIV	41	234—237	44,09	4,51	3,82	$C_{31}H_{36}N_9O_{14}P \cdot H_2O$	44,33	4,53	5,57	1240	1680	1945	197, 248, 468

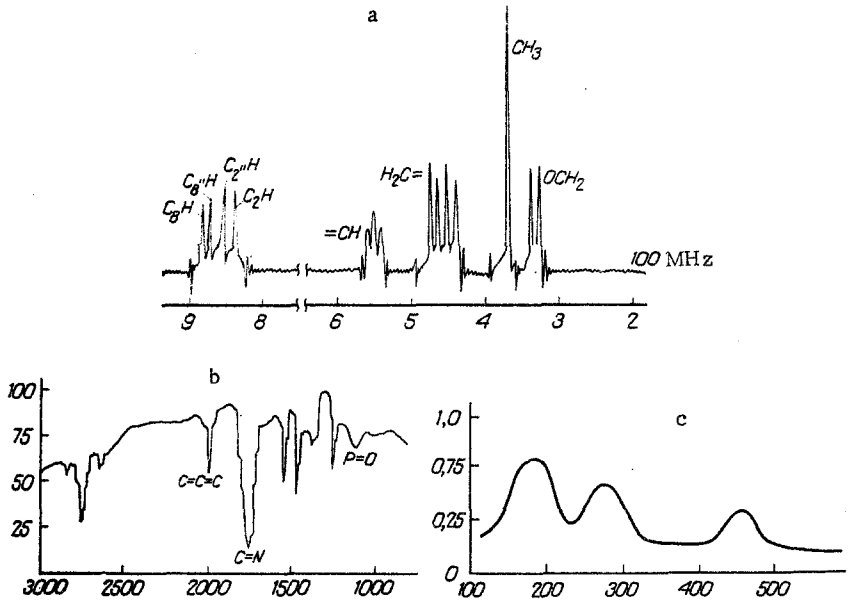


Fig. 1. a) PMR, b) IR, and c) UV spectrum of inosine dialdehyde 9-(morpholyl-3'-hydroxy-4'-methyl-5'-propadienephosphinate-6'-hydroxymethyl-2')-hypoxanthine (I). On the abscissa axis is shown a) the chemical shift (in ppm), b) wavenumber (in cm^{-1}), and c) wavelength (nm); and on the ordinate b) transmission (%), and c) optimal density (in relative units).

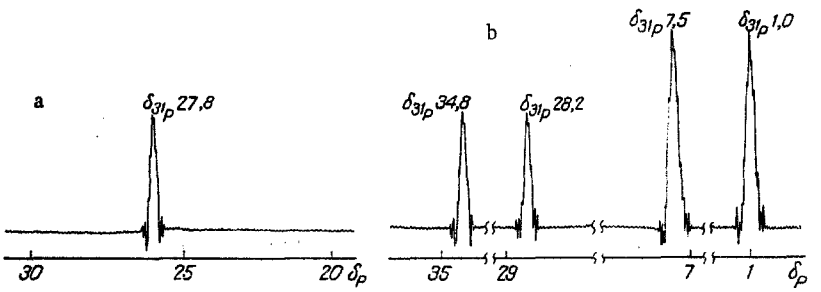


Fig. 2. ^{31}P NMR spectra of a) compounds (I) and b) (XII). δ is chemical shift (ppm).

heteryl)-5'-propadiene phosphinate-6'-hydroxymethyl-2']-hypoxanthine, i.e., the carbohydrate fragment is transformed into a morpholine ring containing an unsaturated phosphinate group in the 5' position and primary amine residues in the 4' position.

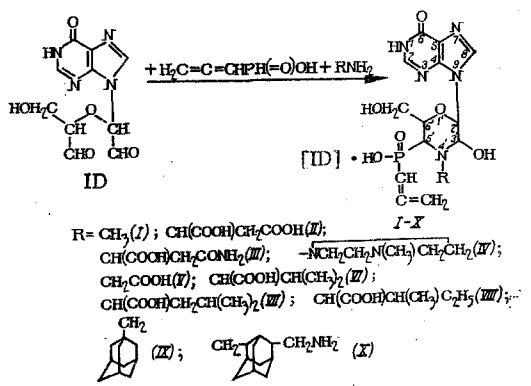


TABLE 2. Toxicity and Antiviral Activity of Organophosphorus Derivatives of ID

Compound	Toxicity in ovo		Index of protection, %				
			vaccinia virus		RSV		
	LD_{50}, mg/embryo	MTD, mg/embryo	prophylactic regime	therapeutic regime	prophylactic regime	therapeutic regime	influenza A virus
I	4,5	3,5	47,5	46,5	33,2	43,4	18,6
II	4,5	3,0	75,7	63,5	35,3	65,6	16,6
III	4,5	3,5	58,9	45,0	28,8	2,1	0
IV	2,5	1,5	49,4	69,7	2,6	0	41,6
V	5,0	4,0	82,6	71,0	10,5	0	45,0
VI	4,0	3,0	77,4	67,9	50,6	66,4	35,0
VII	1,0	—	52,2	44,1	60,9	62,2	47,5
VIII	2,0	1,5	46,8	42,6	58,8	46,5	60,0
IX	2,5	1,5	82,7	78,9	62,7	76,8	39,7
X	3,5	3,0	64,0	42,0	59,0	52,4	—
Ribamide	3,0	2,0	98,0	85,9	78,0	86,0	—
Rimantadine	4,0	—	—	—	—	—	78

The studied reaction may be considered as a variation of the Kabachnik—Fields reaction [2, 8].

Propadienephosphonous acid, obtained by the esterification of hypophosphorous acid with propargyl alcohol according to [1], was used as phosphorylating agent. The following primary amines were used in the work, 1) the amino acids glycine, valine, leucine, isoleucine, aspartic acid, asparagine, 2) 1-amino-4-methylpiperazine, 3) aminomethyladamantane, and 1,3-bis(aminomethyladamantane).

The reactions of propadienephosphonous acid, ID, and primary amines were carried out in methanolic or aqueous methanolic medium at 55-60°C for 5-7 h.

The obtained compounds (I-X) were solid substances crystallizing well from water or a methanol—water mixture. The homogeneity of the obtained susbtances was demonstrated by thin layer chromatography on Silufol. Compounds (I-X) did not have sharp melting points, they decomposed on heating. The phosphorylated derivatives of ID (I-X) dissolved well in dimethylsulfoxide and dimethylformamide, they (except IX, X) were soluble in water, had limited solubility in alcohols (methanol, ethanol propanol), and were insoluble in acetone, ether, chloroform, benzene, and hexane.

The physicochemical constants, data of elemental analysis, and spectral characteristics of the obtained compounds are given in Table 1. The structure of the synthesized substances was established with the aid of NMR, IR, and UV spectroscopy and was demonstrated additionally by chemical conversions.

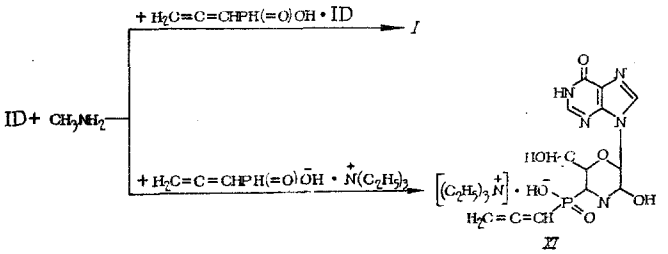
Signals were recorded in the PMR spectrum of compound (I) (Fig. 1) for protons of an allene system, represented as a triplet for the methine proton (HC=) and a pair of doublets for the terminal methylene protons (H_2C=). Signals were also present for the protons of a purine base and a morpholine ring, for protons of a methyl group (singlet, CH_3), and a methylene group (doublet OCH_2).

Similar PMR spectra were obtained for the compounds synthesized from the other amines. In the spectra of compounds (II-X) signals were recorded for the protons of the corresponding amines in addition to the signals of protons characteristic of compound (I) (with the exception of the signal for the methyl group protons).

Absorption bands were observed for C=C=C, P=O, C=N, and other groups of the purine ring in the IR spectra of compounds (I-X).

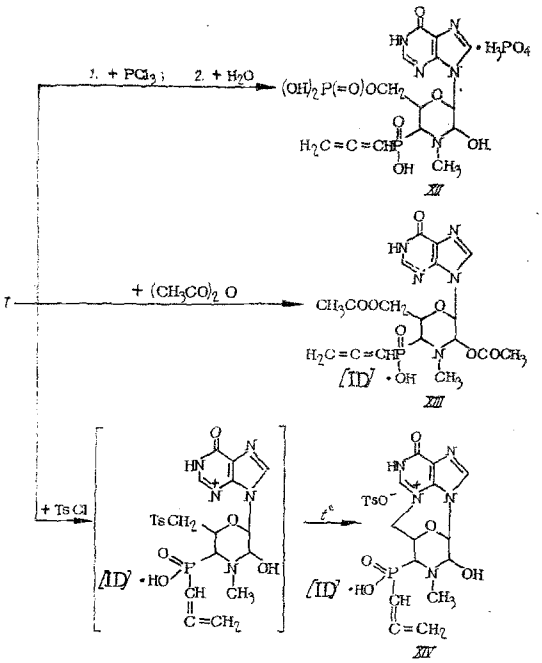
All compounds (I-X) had two absorption maxima in the UV region at 197 and 248-252 nm characteristic of nitrogen bases. In the case of the brightly colored products the absorption appeared in the visible region at 452-500 nm.

Chemical demonstration of the structure of (I-X) was carried out in the example of the model compound inosine dialdehyde 9-(morpholyl-3'-hydroxy-4'-methyl-5'-propadienephosphinate-6'-hydroxymethyl-2')-hypoxanthine (I) obtained as a result of the interaction of propadienephosphonous acid with ID and methylamine. The formation of inosine dialdehyde phosphinate salt was confirmed by two alternate syntheses. In the first case the triethylammonium salt of propadienephosphonous acid was formed in the reaction with ID and methylamine. In the second case reaction was carried out with the inosine dialdehyde salt of propadienephosphonous acid. As a result of these reactions the corresponding salts (I) and (XI) were formed while in the second case the yield of product was increased to double in comparison with the applied method of synthesis.



To determine the location of the phosphinate and hydroxyl groups on the morpholine ring compound (I) was treated with phosphorus trichloride in the presence of oxygen from the air. Under these conditions the reaction proceeds selectively at the primary hydroxyl group according to [4, 5] and subsequent hydrolysis leads to the formation of phosphate (XII).

Analysis of the ^{31}P NMR spectrum of compound (XII) revealed the presence of two phosphate groups with phosphorus chemical shifts of 1.0 and 7.5 ppm and two phosphinate groups with phosphorus chemical shifts of 28.2 and 34.8 ppm (Fig. 2, b), the ratio of intensities was 2:1. In the ^{31}P NMR spectrum of compound (I) (Fig. 2, a) only one signal was recorded and corresponded to the phosphinate group (δ ^{31}P 27.8 ppm). Such a picture for the ^{31}P NMR spectrum corresponds to the existence of the phosphate of the monophosphoric ester (XII) in the form of two conformers. We arrived at this conclusion for the following reasons. As a result of phosphorylation it is possible to assume the formation of a product with the phosphinate group at position 5' or 3' of the morpholine ring and in the latter case a compound is obtained which is capable of cyclization with the formation of a cyclic phosphate. To clarify the ability of compound (XII) to cyclize it was treated with dicyclohexylcarbodiimide. However in the ^{31}P NMR spectrum of the product of this reaction signals were recorded for phosphorus atoms with the same values of chemical shifts as for compound (XII). Thus compound (XII) was not capable of cyclization and the phosphinate group is found at position 5' of the morpholine ring and the hydroxyl at position 3'. The presence of two pairs of signals for the phosphorus atoms in the ^{31}P NMR spectrum may be explained by the existence of two conformers for compound (XII). On hydrolysis of the phosphorylation product phosphoric acid was formed which gave the phosphate salt of the corresponding nucleoside phosphate ester. This conclusion was confirmed by the ratio of intensities of the signals of phosphinate and phosphate groups in the ^{31}P NMR spectrum (see Fig. 2).



Compound (I) was treated with acetic anhydride to determine the quantity of hydroxyl groups. The acetylation reaction proceeded under mild conditions in dry dimethylformamide. According to data of PMR spectroscopy the obtained product (XIII) contained two acetyl groups (chemical shift δ 2.55, singlet $COCH_3$) in positions 3' and 7' of the morpholine ring. Absorption bands were apparent in the IR spectrum which were characteristic of CO groups (1755 cm^{-1}).

To establish the spatial structure of the obtained compounds the intramolecular alkylation of compound (I) was effected by the action of toluene-p-sulfonyl chloride. It is known that under conditions of a β-configuration of the glycosidic bond when the N^3 atom and the primary alcoholic group are drawn sterically close the cyclonucleoside was formed in [4, 5, 13]. Signals were contained in the PMR spectrum of compound (XIV) for protons of the phenyl ring (δ 7.10-7.45, multiplet C_6H_5) together with signals for two protons, confirming its structure. Absorption bands were recorded in the IR spectrum of product (XIV) which were characteristic of a C–N bond (1345 cm^{-1}) and a C_6H_5 group (1495 cm^{-1}). Results of potentiometric titration showed the development of a second acidic function while in compound (I) only one acidic function was recorded. Consequently it may be proposed that in modified compound (I) the morpholine ring retains the β configuration of the glycosidic bond in relation to the nitrogen base the same as for the ribose fragment in relation to hypoxanthine in the initial ID.

Therefore a combination of spectral and chemical methods has demonstrated the chemical structure of the whole series of compounds (I-X).

EXPERIMENTAL (CHEMICAL)

PMR spectra were obtained on a Tesla BS-497 C instrument (Czechoslovakia) with an operating frequency of 100 MHz. Solutions (20-25%) in $(CD_3)_2SO$ were investigated, internal standard was hexamethyldisiloxane, 40-45% solutions in D_2O were investigated with an external standard. ^{31}P NMR spectra were taken on a Varian CFT-20 instrument (USA) with an operating frequency of 20 MHz, chemical shifts were determined relative to 85% H_3PO_4 as external standard. IR spectra were recorded on an IKS-29 spectrophotometer (Czechoslovakia) in KBr disks. UV spectra were taken on a Specord UV-VIS instrument (East Germany). The purity of all the obtained compounds was checked by thin layer chromatography on Silufol UV-254 plates (Czechoslovakia) in the system butanol–ethanol–water (4:1:5). Substances were visualized on chromatograms with UV light and iodine vapor.

ID, a carbonyl derivative of inosine, was obtained by the oxidation of inosine with periodic acid by the method described in [9]. Propadienephosphonous acid was obtained by the previously developed procedure of [1].

The synthesized compounds (I-XIV) were dissolved in water, filtered, and freeze dried for the purpose of purifying them.

Inosine Dialdehyde 9-[Morpholyl-3'-hydroxy-4'-alkyl(cycloalkyl,heteryl)-5'-propadiene-phosphinate-6'-hydroxymethyl-2']-hypoxanthine (I-X). Amine (methylamine, 1-amino-4-methyl-piperazine, aminoadamantanes) (0.012 mole) in methanol was added with stirring to ID (0.01 mole) and propadienephosphonous acid (0.012 mole) in methanol (30 ml) or water (amino acid) and the reaction was carried out at a temperature of 55-60°C for 5-7 h. At the end of the reaction the cooled reaction solution was filtered, and an excess of acetone poured in. The precipitated solid was filtered off, washed with acetone, ether, and dried in vacuum at 30°C for 4 h. Compounds (I-X) were obtained as fine grained crystals of various color.

Alternative Synthesis of Compound (I) Based on the Inosine Dialdehyde Salt of Propadiene-phosphonous Acid. ID(0.04 mole) and propadienephosphonous acid (0.042 mole) in methanol (20 ml) was stirred at a temperature of 20°C for 0.5 h. ID(0.04 mole) and methylamine (0.042 mole) in methanol (20 ml) were added to the obtained inosine dialdehyde salt of propadiene-phosphonous acid. The reaction was carried out at a temperature of 60°C for 5 h. At the end of the interaction the reaction solution was filtered and excess acetone added. The preceipitated solid was filtered off, washed with acetone, with ether, and dried in vacuum. Compound (I) was obtained as fine grained yellow crystals.

Triethylammonium 9-(Morpholyl-3'-hydroxy-4'-methyl-5'-propadienephosphinate-6'hydroxy-methyl-2')-hypoxanthine (XI). The triethylammonium salt of propadienephosphonous acid was obtained by the method described in [1]. ID (0.07 mole) and methylamine (0.075 mole) were added with stirring to the triethylammonium salt of propadienephosphonous acid (0.07 mole) in methanol (30 ml). The synthesis was carried out at a temperature of 60°C for 5 h. At the end of the process the reaction solution was cooled, filtered, and an excess of ether poured in. The precipitated solid was filtered off, washed with ether, and dried in vacuum. Compound (XI) was obtained as fine grained bright yellow crystals.

9-(Morpholyl-3'-hydroxy-4'-methyl-5'propadienephosphinate-6'-methylenephosphate-2')-hypoxanthine Phosphate (XII). Compound (I) (0.05 mile) in dry dimethylformamide (50 ml) was cooled to a temperature of −2°C and phosphorus trichloride (0.1 mole) was added dropwise with stirring during 1 h. Reaction was carried out with vigorous stirring at a temperature of 0°C for 2 h, then at 20°C for 4 h. Hydrolysis of the obtained diacid chloride was effected with water (0.017 mole) and the reaction solution was stirred for 1 h. An excess of acetone was poured in, the precipitated solid was filtered off, washed with acetone, and dried in vacuum. Compound (XII) was obtained as fine yellow crystals.

To clarify the ability of the obtained product to form a cyclic phosphate, compound (XII) (0.017 mole) in dry dimethylsulfoxide (50 ml) was cooled to −1°C and dicyclohexyl-carbodiimide (0.03 mole) and triethylamine (0.03 mole) were added dropwise with stirring. The reaction was then conducted at a temperature of 20°C for 1 h and at 90°C for 3 h. An excess of acetone was added to the cooled solution, the precipitated solid was filtered off, washed with acetone, and dried in vacuum. The product was obtained as fine yellow crystals.

Inosine Dialdehyde 9-Morpholyl-3'-hydroxyacyl-4'- methyl-5'-propadienephosphinate-6'-hydroxyacyl-2'-hypoxanthine (XIII). Compound (I) (0.05 mole) in dry dimethylformamide (50 ml) was cooled to −1°C and acetic anhydride (0.14 mole) was added dropwise with stirring maintaining the temperature of the reaction mixture at −1 to +2°C. The reaction was then carried out at 20°C for 2 h and at 70°C for 2 h. At the end of the process the reaction solution was cooled, acetone added, the precipitated solid filtered off, washed with acetone, with ether, and dried in vacuum. Compound (XIII) was obtained as fine grained brown crystals.

Inosine Dialdehyde Toluene-p-sulfonate of 9-[Morpholyl-3'-hydroxy-4'-methyl-5'-propadiene-phosphinate-6'-(methylene-3)-2']-hypoxanthine (XIV). Pyridine (0.18 mole) was poured with stirring into compound (I) (0.03 mole) in dry dimethylformamide (35 ml). The reaction mixture was cooled to −1°C and toluene-p-sulfonyl chloride (0.037 mole) in dimethylformamide (15 ml) was added dropwise with stirring during 1 h. The reaction was then carried out at 20°C for 4 h and at 90°C for 3 h. The reaction solution was cooled, acetone poured in, the precipitated solid was filtered off, washed with acetone, with ether, and dried in vacuum. Compound (XIV) was obtained as fine grained brown crystals.

EXPERIMENTAL (BIOLOGICAL)

Study of the antiviral activity of the phosphorylated derivatives (I-X) of ID was carried out in relation to the oncogenic *Rous sarcoma* virus (RSV) and to the infections viruses of vaccinia and influenza. The antiviral action of compounds in relation to RSV (RSV strain RAV-1) and vaccinia virus (strain EM-63 manufactured by the Tomsk Scientific-Research Institute for Vaccines and Sera) was determined by therapeutic and prophylactic regimes by administration to the chorioallantoic membrane (CAM) of developing chick embryos. For prophylactic purposes vaccinia virus (10^{-3} BOE_{50}) and RSV ($10^{3.5}$ OD_{50}) in a volume of 0.1 ml was inoculated into an artificial air pocket at 1 h before injection or 1 h after injection of the virus (therapeutic regime). The quantity of pox marks on the CAM was estimated on the 2nd day, the number of foci of neoplastic transformation on the 8th day after administration of the compound. Physiological solution was administered to control embryos in place of the test substances.

To determine antiinfluenza action compounds were injected into the allantoic cavity at a dose of 1 mg in a volume of 0.2 ml into an embryo 1 h before inoculation of the virus. Physiological solution was administered to control embryos in place of the test substances. The results were calculated in comparison with the viral titer of test and control in the hemagglutination reaction by the generally accepted procedure with a 1% solution of chicken erythrocytes after 48 h inoculation of influenza A virus [strain A/Leningrad/110/072 (H3N2)].

The toxicity of the investigated substances was determined by administering a series of dilutions of compounds of various concentration to the chorioallantoic cavity or the CAM of 10-11 d developing chick embryos. About 5 embryos were used for each dilution, and were incubated in a thermostat at 37°C until hatching. They were scanned on the 2nd, 4th, and 10th days and the toxic dose of a compound was determined from the presence of dead embryos.

Study of antiviral activity of compounds (I-X) in relation to vaccinia virus and RSV was carried out in comparison with the known antiviral preparation ribamide and in relation to influenza A virus with one of the most active antiinfluenza drugs, viz., rimantadine.

As the biological tests showed all the studied compounds proved to have low toxicity on injection both into the allantoic cavity and also onto the CAM of developing chick embryos (Table 2). The data given in Table 2 showed that only compounds (VII-IX) were superseded in toxicity by the reference compound. It was shown that of the whole series of studied phosphorylated derivatives of ID compounds (II, V, VI, and IX) effectively suppressed the multiplication of vaccinia virus. It was established that in a series of cases the administration of substances by the prophylactic regime was appreciably more effective than by the therapeutic regime. The antiviral action of compounds (I, IV, and VIII) in relation to vaccinia virus proved to be almost half that of ribamide. The greatest suppression of foci of neoplastic transformation caused by RSV was observed on injecting compounds (VI-IX) both by the prophylactic and by the therapeutic regime of administration. The biological investigations showed that practically all the studied compounds displayed low antiinfluenza activity. The most appreciable antiinfluenza activity was detected only for compound (VIII) which proved to be 18% less than for rimantadine.

Thus the unsaturated organophosphorus derivatives of ID (I-X) possessed some antiviral activity in relation to RNA-and DNA-containing infectious and oncogenic viruses.

LITERATURE CITED

1. V. V. Belakhov, V. I. Yudelevich, E. V. Komarov, et al., Zh. Obshch. Khim., 53, No. 7, 1493-1503 (1983).
2. M. I. Kabachnik and T. Ya. Medved', Dokl. Akad. Nauk SSSR, 83, No. 3, 689-691 (1952).
3. C. Ya. Mel'nik and M. I. Preobrazhenskaya, Results of Science and Technology. Bioorganic Chemistry Series [in Russian], Vol. 1, Moscow (1984).
4. A. Michelson, Chemistry of Nucleosides and Nucleotides [Russian translation], Moscow (1966).
5. Z. A. Shabarova and A. A. Bogdanov, Chemistry of Nucleic Acids and Their Components [in Russian], Moscow (1978).
6. V. I. Yudelevich, L. G. Myasnikova, E. V. Komarov, et al., in: All-Union Conference on the Chemistry of Organophosphorus Compounds, No. 7. Summaries of Reports, Leningrad, 1982, p. 33.

7. V. I. Yudelevich, L. G. Myasnikova, M. S. Polyak, et al., in: Prospects for Bioorganic Chemistry in the Design of New Drugs [in Russian], Riga (1982), p. 147.
8. E. K. Fields, J. Am. Chem. Soc., 74, 1528-1531 (1952).
9. M. R. Murthy and P. A. Ranjekar, J. Chromatog., 76, 337-343 (1973).
10. J. R. Praes, International Publishers Annual Drug Data Report, Vol. 3, Barcelona (1981).
11. K. Smith and W. Kirkpatrick (editors), Ribavirin. A Broad Spectrum Antiviral Agent, New York (1980).
12. W. Shannon and F. M. Schabel Jr., Pharmacol. Ther., 11, 263-390 (1980).
13. E. Shaw, J. Am. Chem. Soc., 81, 6021-6026 (1959).
14. J. Witkowski, R. Robins, R. Sidwell, and L. Simon, J. Med. Chem., 15, 1150-1156 (1972).

ANTIMICROBIAL ACTIVITY OF DERIVATIVES OF BENZ-2,1,3-THIA- AND SELENADIAZOLES AND THEIR COMPLEX COMPOUNDS WITH COPPER [2+] CHLORIDE

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It is known [5] that several salts of Cu(2+) display antimicrobial activity in relation to a series of microorganisms.

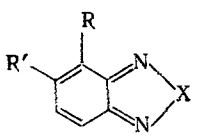
It seemed of interest to study the antimicrobial properties of the complex compounds of $CuCl_2$ with derivatives of benz-2,1,3-thia- and selenadiazoles which possess a wide spectrum of biological activity [3].

We subjected the derivatives of benz-2,1,3-thia- and selenadiazoles (I)-(X), and their complexes, to tests.

$[kCuCl_2 \cdot mL]_n$

(XI—XXIII)

XI: L = I; XII, XIII: L = II; XIV: L = III; XV: L = IV; XVI: L = V; XVII: L = VI; XVIII: L = VII; XIX: L = VIII; XX, XXI: L = IX; XXII, XXIII: L = X; XV, XXII, XXIII, polymers; XX, XXI, monohydrates XI—XXII: k = 1; XXIII: k = 2; XI, XII, XV, XX, XXII: m = 1; XIII, XIV, XVI—XIX, XXI: m = 2; XXIII: m = 3; XI—XIV, XVI—XVIII: n = 2; XIX—XXI: n = 1.



I—X

I, II: R = R′ = H; III, IV: R = H, R′ = OH; V: R = NO_2, R′ = H; VI, VII: R = H, R′ = NO_2; VIII: R = NH_2, R′ = H; IX: R = H, R′ = NH_2; X: R = R′ = NH_2; I, III, V, VI, VIII—X: X = S; II, IV, VII: X = Se.

Compounds (I), (VI), and (IX) were synthesized according to the method of [8]. Compound (II) was synthesized by the method of [12]. Compounds (III) and (VIII) were synthesized according to [7]. Compounds (IV), (V), (VII), and (X) were synthesized according to [11], [9], [10], and [6] respectively. The complexes (XI), (XVI), (XVII), and (XIX)-(XXIII) were synthesized according to the method of [1]; (XII), (XIII), and (XVIII) were synthesized according to [2].

The complexes (XIV) and (XV), which have not previously been described, were obtained by the reaction of anhydrous $CuCl_2$ with the appropriate ligand in abs. ethanol at 1:1 and 1:2 ratios of metal to ligand.

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