SYNTHESIS OF NUCLEOSIDES OF URONIC ACIDS.

V.* SYNTHESIS AND ANTIVIRUS ACTIVITY OF NUCLEOSIDES OF D-XYLURONIC ACID

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Uronic and aminodesoxyuronic acids are components of biologically active compounds of a nucleoside nature. The nucleoside antibiotics gougerotin, blasticidin S, and polyoxins [25] (active with respect to tumors, bacteria, and fungi) have a broad spectrum of biological activity. Substances that display activity against tumors [8, 17] and viruses [6, 12, 18, 23] have been observed among synthetic nucleosides of uronic acids.

Esters and amides of adenosine-5'-carboxylic acid [21, 22] and their derivatives [7] have pronounced hypotensive vasodilating, cardiotonic, and antiaggregation activity.

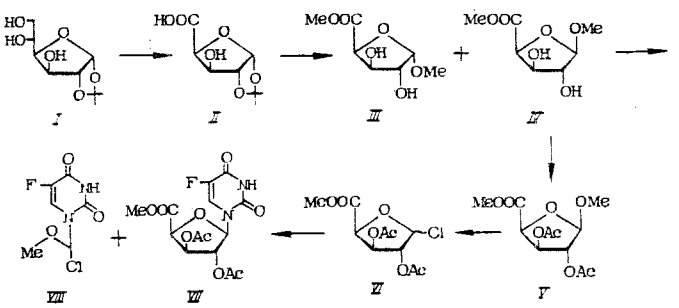
The aim of the present research was to develop methods for the synthesis of nucleosides of xyluronic acid and to study their antivirus activity. It is known that xylofuranosyl nucleosides have appreciable anticancer and antivirus activity [1, 13, 16].

The most preferred and general method for the synthesis of nucleosides with a β-D-xylo configuration is glycosylation of heterocyclic bases by the corresponding derivatives of D-xylofurano ə [2, 10, 13, 16].

In the synthesis of nucleosides of D-xyluronic acid we started from 1,2-O-isopropylidene-α-D-glucofuranose (I), the oxidation of which with potassium permanganate in an alkaline medium led to the formation of 1,2-O-isopropylidene-α-D-xyluronic acid (II) in 83% yield [26].

Treatment of acid II with a 3% solution of gaseous HCl in methanol at 40°C for 15 h gave a mixture of anomeric methyl-O-D-xylofuranuronosides, which could be separated by means of column chromatography on silica gel. The methyl (methyl-β-D-xylofuranoside)uronate structure (IV) was assigned to the chromatographically more mobile compound on the basis of PMR data (Table 1). The spin-spin coupling constant (SSCC) $J_{1,2} < 0.4$ Hz in the PMR spectrum of this compound constitutes evidence for its β-anomeric configuration. The $J_{1,2}$ SSCC in the PMR spectrum of less mobile III is 4.0 Hz and is in good agreement with its α-anomeric configuration. The SSCC of the other protons of the furanose ring observed in the PMR spectra are in good agreement with the constants of the α- and β-anomeric O-methylxylosides described in [11].

Diacetate V was obtained by acetylation of IV with Ac_2O in pyridine.



*See [4] for Communication IV.

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TABLE 1. Data from the PMR Spectra of the Synthesized Compounds

Compound	Solvent	Chemical shifts, δ, ppm							SSCC, J, Hz				
		H-6 H-8	H-5 H-2	H-1′	H-2′	H-3′	H-4′	others	1,2	2,3	3,4	5,6 H-F	1′-F
III	$CDCl_3$+CD_3OD	—	—	5,04 d	4,06 dd	4,36 dd	4,68 d	3,76 s COOMe	4,0	5,0	6,0	—	—
IV	d_6-DMSO	—	—	4,96 d	4,16 dd	4,76 m		3,28 s OMe 3,40 s COOMe 5,96 d OH 5,10 d OH	1,0	2,0	6,0	—	—
V	$CDCl_3$	—	—	5,28 s	5,0 d	4,60 dd	4,94 d	3,36 s COOMe 3,34 s OMe	0	3,0	5,0	—	—
VII	CD_3COCD_3	8,70 d	—	6,18 dd	5,52 dd	5,76 dd	5,24 d	3,86 s COOMe	2,0	2,0	4,5	7,0	1,5
VIII	$CDCl_3$	7,92 d	—	8,0 d	—	—	—	3,60 s OMe	—	—	—	6,5	1,5
XII	CD_3COCD_3	8,46 d	5,88 d	6,22 d	5,50 dd	5,78 dd	5,22 d	3,86 s COOMe	2,0	2,0	4,5	8,0	—
XIII	$CDCl_3$	8,72 s	—	6,28 d	5,66 d	6,08 dd	5,52 d	8,0—7,72 Bz	2,0	2,0	4,5	—	—
XIV	d_6-DMSO	8,46 d	—	5,70 dd	4,08 s	4,20 d	4,60 dd	7.54 and 7.30 $CONH_2$	0	0	4,0	7,0	1,5
XV	d_6-DMSO	8,30 d	5,56 d	5,72 s	3,98 s	4,12 d	4,56 d	7,50 and 7.36 $CONH_2$	0	0	3,5	8,0	—
XVI	d_6-DMSO	8,36 s	8,08 s	5,90 s	3,90 s	4,18 d	4,48 d	7,36 s and 7.22 s $CONH_2$ 7,22 s NH_2	0	0	4,0	—	—
XVIII	$CDCl_3$	8,08 d	—	5,88 d	5,28 d	5,28 m	3,92 d	7,72 d and 7.32 d Ts 3,76 s COOMe 2,40 s Me 2,06 s Ac	2,0	2,0	4,0	7,0	1,0
XIX	$CDCl_3$	7,16 d	—	6,40 dd	5,92 dd	6,14 d	—	3,84 s COOMe 2,10 s Ac	3,0	3,0	—	6,0	1,0

TABLE 2. Data from the UV and Raman Spectra of the Synthesized Compounds

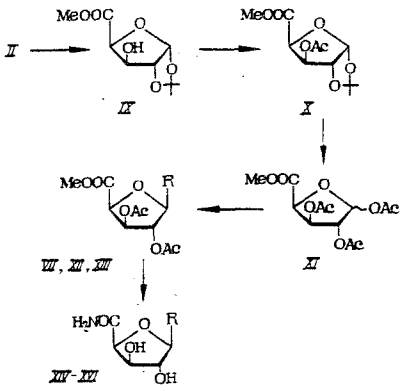
Compound	Solvent	UV spectrum		Raman spectrum	
		λ_{max} ($\varepsilon \cdot 10^{-3}$)	λ_{min} ($\varepsilon \cdot 10^{-10}$)	$B_{2u}\lambda$ ($[\theta] \cdot 10^{-3}$)	$B_{1u}\lambda$ ($[\theta] \cdot 10^{-3}$)
VII	Alcohol	267 (8,6) 207 (9,3)	235 (2,1)	260 (+15,0) 264 (+13,0)	215 (—4,7)
	Dioxane				
XII	Alcohol	260 (10,2) 207 (10,0)	231 (2,6)	257 (+15,7)	220 (—2,4)
	Dioxane			260 (+7,7)	
XIV	Alcohol	270 (6,2) 203 (7,7)	235 (1,5)	268 (+4,8)	230 (—2,4)
XV	»	262 (9,3) 203 (9,7)	231 (2,0)	263 (+5,8)	232 (—8,7)
XVI	»	261 (17,4)	230 (3,1)	260 (—7,9)	216 (—7,9)
XVIII	»	275sh (10,0) 265 (11,0) 227 (15,5)	247 (5,3)	272 (+13,3)	245 (—2,4)
XIX	»	255 (10,9) 213 (7,0)	227 (6,0)	255 (—42,7)	220 (—21,3)
XX	»	259 (13,9) 209 (12,0)	230 (4,0)	250 (+14,2)	212 (—17,4)
	Dioxane			250 (+7,4)	212 (—11,1)

The reaction of V with a mixture of Ac_2O, AcOH, and concentrated H_2SO_4 (~20% of the latter) for 24 h at room temperature led, according to the PMR data, only to partial acetolysis of the 1-O-methylxyluronoside. An increase in the reaction time was accompanied by significant resinification of the reaction mixture and a decrease in the yield of the isolatable acetolysis products.

One method for obtaining acylhalogenoses is the reaction of peracylated sugars and 1-O-alkylglycosides with 1,1-dichlorodimethyl ether in the presence of catalytic amounts of $ZnCl_2$ [19]. The reaction of V with 1,1-dichlorodimethyl ether and $SnCl_4$ and condensation of the resulting glycosyl chloride VI with 2,4-O-bis(trimethylsilyl)-5-fluorouracil gave N^1-(methyl 2,3-di-O-acetyl-β-D-xylofuranosyluronate)-5-fluorouracil (VII) (21% yield) and a small amount of N^1-[(methoxy)chloromethyl]-5-fluorouracil (VIII), which was also synthesized from equimolar amounts of 1,1-dichlorodimethyl ether and 2,4-O-bis(trimethylsilyl)-5-fluorouracil in anhydrous dichloroethane. Replacement of a second chlorine atom was not observed when 2 moles of 2,4-O-bis(trimethylsilyl)-5-fluorouracil per mole of the ether was introduced into the reaction, nor was the formation of an N^1,N^3-dialkylated product observed.

In another synthetic scheme acid II was treated with an ether solution of diazomethane, the resulting ester IX was acetylated with Ac_2O in pyridine, acetate X was treated with a mixture of AcOH, Ac_2O, and concentrated H_2SO_4, and methyl D-xyluronate triacetate (XI) was obtained in 74% yield in the form of an anomeric mixture, which was then used for the synthesis of nucleosides. A singlet of the 1-H proton of the β anomer (6.20 ppm) and a doublet of the 1-H proton of the α anomer (6.60 ppm, $J_{1,2}$ 4.5 Hz) are observed in the PMR spectrum of XI: α: β = 1:2.

Glycosylation of trimethylsilyl derivatives of 5-fluorouracil, uracil, and N^6-benzoyladenine with XI in acetonitrile in



R = 5-fluoro-uracilyl (VII, XIV), 1-uracilyl (XII, XV), N^6-benzoyl-9-adeninyl (XIII), 9-adeninyl (XVI).

TABLE 3. Physicochemical Properties of the Compounds

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calc., %			$[\alpha]_D^{20}$
			C	H	N		C	H	N	
III	31	114—6	43,55	6,20	—	$C_7H_{12}O_6$	43,75	6,25	—	—14,0° (C 1,0 EtOH)
IV	58	155—7	43,59	6,27	—	$C_7H_{12}O_6$	43,75	6,25	—	+7,0° (C 1,0, EtOH)
V	85	194—6	47,78	5,73	—	$C_{11}H_{16}O_8$	47,82	5,80	—	+4,0° (C 1,0, $CHCl_3$)
VII	54	Amorphous	44,58	3,83	7,23	$C_{14}H_{15}FN_2O_9$	44,92	4,01	7,48	+43,0° (C 1,0, $CHCl_3$)
VIII	51	227—30	34,16	2,71	13,24	$C_8H_9FClN_3O_3$	34,53	2,88	13,43	—
XII	38	Amorphous	46,88	4,62	7,71	$C_{14}H_{16}N_2O_9$	47,19	4,49	7,87	36,0° (C 1,0, $CHCl_3$)
XIII	33	176—84	54,54	4,27	14,27	$C_{22}H_{21}N_6O_8$	54,66	4,35	14,49	176,0° (C 1,0, $CHCl_3$)
XIV	65	245—52	39,30	3,38	15,03	$C_9H_{10}FN_3O_6$	39,27	3,64	15,27	0,5° (C 1,0, C_2O)
XV	61	125—30	39,52	4,78	15,06	$C_9H_{11}N_3O_6 \cdot H_2O$	39,27	4,73	15,27	0,5° (C 1,0, H_2O)
XVI	31	198—204	37,95	4,88	26,39	$C_{10}H_{12}N_6O_4 \cdot 2H_2O$	37,97	5,06	26,58	—24,0° (C 1,0, DMSO)
XVIII	53	95—7	46,80	3,77	5,72	$C_{19}H_{19}FN_2O_{10}$	46,91	3,91	5,76	+50,0° (C 1,0, $CHCl_3$)
XIX	67	146—8	45,75	3,44	8,74	$C_{12}H_{11}FN_2O_7$	45,86	3,50	8,91	—167,0° (M 2,15, $CHCl_3$)

the presence of three equivalents of $SnCl_4$ for 24 h at room temperature led to the formation of nucleoside VII, its uracil analog XII, and N^9-(methyl 2,3-di-O-acetyl-β-D-xylofuranosyluronate)-N^6-benzoyladenine (XIII), which, after the usual workup, were isolated in the individual state by means of column chromatography on silica gel.

The structures of the synthesized nucleosides VII, XII, and XIII follow unequivocally from the PMR spectral data (see Table 1). In the PMR spectrum of XII four signals of protons of the carbohydrate fragment of the molecule are observed in the form of a doublet (1'-H), a quartet (3'-H), a triplet (2'-H), and a doublet (4'-H).

Similar spectra were obtained for XII and XIII. The $J_{1',2'}$ SSCC of 2.0 Hz in the PMR spectra, as well as the positive Cotton effect (CE) of the B_{2u} absorption band in the Raman spectra of the pyrimidine nucleosides (Table 2), is a confirmation of the β-anomeric configuration of the xyluronic nucleosides.

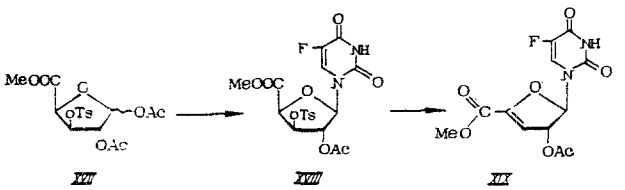
Treatment of protected nucleosides VII, XII, and XIII with a solution of ammonia in methanol led to their deacylation and the formation of the corresponding β-D-xylofuranosyluronamidenucleosides XIV-XVI.

The structures of the synthesized amides are in complete agreement with data from the UV, Raman, and PMR spectra. The correspondence of VII, XII, XIV, and XV to the structure of N^1-substituted nucleosides is demonstrated, first, by the absence in their UV spectra of a shift of the long-wave absorption maximum at 300 nm when the solution is made alkaline [24] and, second, by the positive Cotton effect of the B_{2u} band in the Raman spectra [20].

The presence in the UV spectrum of nucleoside XVI of an absorption maximum at 260 nm and the absence of changes in the spectrum that are characteristic for the N^7 isomer on passing from pH 7.0 to pH 1.0 [2] constitute evidence for its N^9-isomeric structure.

The absence of spin-spin coupling between the 1'-H, 2'-H, and 3'-H protons is characteristic for the amides obtained (see Table 1).

We obtained N^1-(methyl 2-O-acetyl-β-D-glyceropent-3-desoxy-3-enofuranosyluronate)-5-fluorouracil (XIX) by condensation of methyl 3-O-(p-tolylsulfonyl)-1,2-di-O-acetyl-D-xylofuranuronate (XVII) [10] with 2,4-O-bis(trimethylsilyl)-5-fluorouracil in acetonitrile in the presence of $SnCl_4$ with subsequent treatment of intermediate tosylate XVIII with pyridine.



The synthesis of nucleoside XIX enabled us to unequivocally assign the signals of the 1'-H and 3'-H protons in the PMR spectra of the unsaturated nucleosides of this series [3, 9, 10]. In the PMR spectra of these compounds the signals of the 1'-H and 3'-H protons are represented in the form of doublets with close $J_{1',2'}$ and $J_{2',3'}$ values; thus the spectra have degenerate character. Our previous assignments [3, 9, 10] of the signals were based on the postulate that the weak-field signal belongs to the vinyl 3'-H proton. In the PMR spectrum of nucleoside XIX, owing to the characteristic long-range spin-spin coupling of the 1'-H and F nuclei with J = 1.5 Hz, the 1'H-proton becomes "labeled," is easily identified, and is observed at weaker field than the vinyl 3'-H proton (see Table 1).

An analysis of the data from the PMR spectra of the nucleosides obtained reveals a significant anisotropic effect of the methoxycarbonyl and carboxamido groups on the 6-H proton of the pyrimidine heteroring, which is manifested in its deshielding and the shift of its signal in the PMR spectrum to weak field. This phenomenon is due to the definite orientation of the carbonyl group and the 6-H proton relative to one another. Thus in the case of nucleosides of D-glucofuranurono-6,3-lactone [8] the fixed position of the carbonyl group in the bicyclic system, as well as its orientation relative to the 6-H proton of the heteroring, excludes its deshielding, while opening of the lactone ring leads to realization of the effect under discussion. In the case of VIII and XIX the chemical shift of the 6-H proton has the standard value and does not exceed 8.0 ppm, since an alkoxycarbonyl group is absent in VIII , whereas in the case of XIX interaction is impossible because of

steric limitations. In [15] this phenomenon is discussed from the point of view of the formation of an intramolecular hydrogen bond between the carbonyl group of the alkoxycarbonyl grouping and the 6-H atom of the heteroring, which occupies primarily an anti conformation around the N-glycoside bond relative to the carbohydrate fragment of the molecule. According to these concepts, nonpolar aprotic solvents should promote population of the anti conformation. In the Raman spectra that we obtained for samples of VII, XII, and N^1-(tert-butyl 2,3-O-isopropylidene-β-D-ribofuranosyluronate)uracil (XX) [14] in dioxane we observed a significant decrease in the molar ellipticity of the B_{2u} absorption band as compared with that of corresponding samples dissolved in alcohol (see Table 2). The mole fraction of the syn conformer, which has a negative Cotton effect and a lower dipole moment than the anti conformer, evidently increases in solution in nonpolar dioxane; this leads to the observed decrease in the molar ellipticity. In our opinion, a definitive conclusion regarding the nature of such interactions can be drawn only after additional investigations.

Thus we have developed methods for the synthesis of pyrimidine and purine nucleosides of D-xyluronic acid with the use, as glycosylating agents, of acetates of methyl esters of 1-OMe, 1-OAc, and 1-Cl derivatives of D-xyluronic acid, which were obtained by methanolysis and acetolysis of methyl 1,2-O-isopropylidene-α-D-xyluronate and treatment of the methyl-O-xyluronoside with 1,1-dichlorodimethyl ether. Biological tests of the nucleosides obtained were carried out, and pronounced antiherpetic activity was observed for the adenine nucleoside of D-xyluronamide; the promising character of the search for biologically active compounds in series of nucleosides of D-xyluronic acid was demonstrated.

EXPERIMENTAL (CHEMICAL)

The PMR spectra were obtained with the IMM PS-100 spectrometer (Japan) at an operating frequency of 100 MHz with Me_4Si as the internal standard. The UV spectra were recorded with a Specord UV-VIS spectrophotometer (East Germany). The Raman spectra and the angles of rotation were recorded with a JASCO-20 spectropolarimeter (Japan). The melting points were determined with a Boetius stage (East Germany). The course of the reactions and the individuality of the compounds obtained were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates (Czechoslovakian SSR) in $CHCl_3$–methanol systems [9:1 (A) and 4:1 (B)]. Silica gel L 100/400 μ (Czechoslovakian SSR) was used for column chromatography. The drying and purification of the organic solvents and reagents were carried out by standard methods.

The physicochemical properties of the synthesized compounds are presented in Table 3.

1,2-O-Isopropylidene-α-D-xyluronic Acid (II). Potassium permanganate [20.0 g (0.126 mole)] was added in small portions with constant stirring to a solution of 1,2-O-isopropylidene-α-D-glucofuranose (I) [11.0 g (0.05 mole)] in 300 ml of water in the course of 4 h while maintaining the temperature of the reaction mixture at 15°C. The flask was then placed in a refrigerator, and its contents were stirred at 5°C for another 20 h. The resulting MnO_2 was removed by filtration and washed throughly with hot water. The filtrate was evaporated with a vacuum rotary evaporator to a volume of 50 ml, and this concentrate was applied to a column packed with KU-2 (H^+) cation exchange resin (50 ml). Evaporation of the eluate gave 8.5 g (83%) of acid II with mp 70°C (Lit. value, 70°C, [26].

Methyl (Methyl-α- and -β-D-xylofuranoside) uronates (III, IV). Acid I [2.0 g (0.813 mole)] was dissolved in a 3% solution of gaseous HCl in anhydrous methanol, which was obtained by the careful addition of AcCl (2.5 ml) to cooled (to 0°C) methanol (50 ml), and the reaction mixture was heated without access to moisture and air at 40°C for 15 h. It was then neutralized with barium carbonate and concentrated. The residue was extracted with ethyl acetate, the combined extracts were evaporated to a small volume, and the concentrate was applied to a column packed with silica gel. Elution with chloroform gave 0.6 g of III, with R_f 0.15 (A), and 1.1 g of IV with R_f 0.20 (A). Analytical samples were obtained by crystallization of III and IV from ethyl acetate.

Methyl (Methyl-2,3-di-O-Acetyl-β-D-xylofuranoside)uronate (V). Compound IV (0.5 g) was dissolved in a mixture of pyridine (5 ml) and Ac_2O (2 ml) and the reaction mixture was maintained at room temperature for 24 h. It was then evaporated to dryness with the addition of 5 ml each of alcohol and toluene, and this operation was repeated until the pyridine and Ac_2O were removed completely. Crystallization of the residue from alcohol gave 0.61 g of acetate V.

N^1-(Methyl 2,3-di-O-acetyl-β-D-xylofuranosyluronate)-5-fluorouracil (VII). Compound V [0.55 g (2 mmole)] was dissolved in a mixture of CH_2Cl_2 and 1,1-dichlorodimethyl ether [2 ml (1:1)], and the solution was heated for 0.5 h at 50°C in the presence of a catalytic amount of $SnCl_4$. Chloride VI was dissolved in 5 ml of anhydrous acetonitrile, and 2,4-O-bis(trimethylsilyl) 5-fluorouracil [0.6 g (2.2 mmole)] and $SnCl_4$ [1.4 g (6 mmole)] were added to the solution. After 24 h, the reaction mixture was neutralized with a saturated solution of $NaHCO_3$ and extracted with $CHCl_3$ (three 30-ml protions). The combined extracts were washed with water, dried with Na_2SO_4, and evaporated to dryness. The syrupy residue was applied to a column packed with silica gel and eluted successively with $CHCl_3$ and $CHCl_3$–methanol (85:5) to give 0.03 g of VIII and 0.16 g (21%) of VII.

N^1-[(Methoxy)chloromethyl]-5-fluorouracil (VIII). 2,4-O-Bis-(trimethylsilyl)-5-fluorouracil [2.7 g (10 mmole] was added to a solution of 1,1-dichlorodimethyl ether [1.2 g (10 mmole)] in anhydrous dichloroethane (25 ml). After 24 h, the reaction mixture was evaporated, and the residue was applied to a column packed with silica gel in a small volume of $CHCl_3$. Elution with $CHCl_3$ gave 1.1 g of crystalline VIII.

Methyl 1,2-O-Isopropylidene-α-D-xyluronate (IX). A solution of diazomethane in ether was added to a solution of acid II (8.5 g) in 50 ml of methanol until a presistent yellow coloration developed. Removal of the solvent gave 9.07 g (100%) of ester IX with mp 106°C (mp 106°C, [26]).

Methyl 3-O-Acetyl-1,2-O-isopropylidene-α-D-xyluronate (X). A 35-ml sample of Ac_2O was added to a solution of ester IX (7.8 g) in 65 ml of anhydrous pyridine, and the reaction mixture was allowed to stand at room temperature for 24 h. It was then poured into 400 ml of a mixture of water and ice, and the liberated oil was extracted with CH_2Cl_2 (three 100-ml portions). The combined extracts were washed successively with 10% HCl, water, a saturated solution of $NaHCO_3$, and water, dried with Na_2SO_4, and evaporated to give acetate X in the form of a syrup [8.4 g, (90%)].

Methyl 1,2,3-Tri-O-acetyl-D-xyluronate (XI). Compound X (3.5 g) was stirred at room temperature for 24 h in a mixture of AcOH (105 ml), Ac_2O (12 ml), and concentrated H_2SO_4 (16 ml), after which the solution was poured into a mixture of water and ice (500 ml), and the resulting aqueous mixture was extracted with CH_2Cl_2 (three 50-ml portions). The extracts were washed with a saturated solution of $NaHCO_3$, dried with Na_2SO_4, and evaporated to dryness to give 3.03 g (74%) of triacetate XI, which was used for glycosylation of the silylated heterocycles.

N^1-(Methyl 2,3-di-O-acetyl-β-D-xylofuranosyluronate)-5-fluorouracil (VII). A solution of 2,4-O-bis(trimethylsilyl)-5-fluorouracil [1.64 g (5.94 mmole)] in 10 ml of acetonitrile was added to a solution of triacetate XI [1.5 g (4.93 mmole)] in 15 ml of anhydrous acetonitrile, and $SnCl_4$ [4.2 g (16.2 mmole)] was added dropwise. After 24 h, the reaction mixture was neutralized with a saturated solution of $NaHCO_3$ (35 ml) and extracted with CH_2Cl_2 (three 50-ml portions). The combined extracts were washed with water, dried with Na_2SO_4, and evaporated. The resulting syrupy residue was applied in $CHCl_3$ to a column packed with silica gel and eluted with $CHCl_3$ to give 1.0 g of nucleoside VII in the form of a solid foam.

N^1-(Methyl 2,3-di-O-acetyl-β-D-xylofuranosyluronate)uracil (XII). 2,4-O-Bis(trimethylsilyl)uracil [1.52 g (5.94 mmole)] and $SnCl_4$ [4.2 g (16.2 mmole)] were added to a solution of triacetate XI [15 g (4.93 mmole)] in 15 ml of acetonitrile. Under the conditions for the synthesis of nucleoside VII 0.67 g of nucleoside XII was obtained in the form of a solid foam.

N^9-(Methyl 2,3-di-O-acetyl-β-D-xylofuranosyluronate)-N^6-benzoyladenine (XIII). The trimethylsilyl derivative of N^6-benzoyladenine [4.86 g (12.5 mmole)] and $SnCl_4$ [9.0 g (34.5 mmole)] were added to a solution of triacetate XI [3.2 g (10.5 mmole)] in 35 ml of anhydrous acetonitrile, and the reaction mixture was maintained at room temperature for 2 days. Under the conditions used for the isolation and purification of VII 1.7 g of crystalline nucleoside XIII was obtained.

N^1-(β-D-Xylofuranosyluronamide)-5-fluorouracil (XIV). Nucleoside VII (0.5 g) was dissolved in methanol (10 ml) saturated with ammonia in the cold, and the solution was allowed to stand in a refrigerator for 2 days. The mixture was then evaporated to dryness, and the residue was crystallized from alcohol to give 0.24 g of crystalline amide XIV.

N^1-(β-D-Xylofuranosyluronamide)uracil (XV). Nucleoside XII (0.4 g) was treated with ammonia under the conditions of the synthesis of XIV to give 0.175 g of amide XV.

N^9-(β-D-Xylofuranosyluronamide)adenine (XVI). Triethylamine (1 ml) was added to a solution of nucleoside XIII (0.85 g) in 20 ml of methanol. After 3 days, the solution was evaporated, and the residue was treated with methanol saturated with ammonia (15 ml) for 24 h. The mixture was evaporated, and the residue was applied to a column packed with silica gel. Successive elution with $CHCl_3$ (systems A and B) gave 0.156 g of crystalline nucleoside XVI.

N^1-(Methyl 3-O-(p-tolysulfonyl)-2-O-acetyl-β-D-xylofuranosyluronate)-5-fluorouracil (XVIII). A solution of 2,4-O-bis(trimethylsilyl)-5-fluorouracil [1.64 g (6 mmole)] in acetonitrile (5 ml) and $SnCl_4$ [4.2 g (16.2 mmole)] were added to a solution of sugar XVII [2.5 g (6 mmole)] in anhydrous acetonitrile (25 ml). Under the conditions for the synthesis of VII 1.53 g of crystalline nucleoside XVIII was obtained.

N^1-(Methyl 2-O-acetyl-β-D-glyceropent-3-desoxy-3-eno-furanosyluronate)-5-fluorouracil (XIX). A solution of nucleoside XVIII (1.0 g) in pyridine (10 ml) was refluxed for 4 h, after which it was evaporated to dryness, and the residue was dissolved in $CHCl_3$. The solution was applied to a column packed with silica gel and eluted with chloroform to give 0.4 g of crystalline nucleoside XIX.

EXPERIMENTAL (BIOLOGICAL)

The antivirus properties of XIV, XV, and XVI were determined in experiments on tissue cultures with respect to pox vaccine virus (PVV), herpes simplex virus (HSV), classical bird cholera virus (CBCV), Newcastle disease virus (NDV), vesicular stomatitis virus (VSV), Venezuelan equine encephalitis virus (VEEV), and ECHO 6 virus by the "screening-test" method and by reduction of patches under an agar coating. With the ECHO virus the investigations were carried out on monolayer cultures of passivated skin-muscle cells of human embryos, while the investigations with the remaining viruses were carried out on primary-trypsinized fibroblasts of chicken embryos (FCE). The size of the zone of suppression of the formation of patches, the decrease in the titer of the virus in the presence of various concentrations of the substances, and the chemotherapeutic index (CTI), which is calculated as the ratio between the maximal tolerance (for the tissue culture) concentration of the substance (MTD) and the concentration that decreases the titer of the virus by 1.25 log PFU/ml or more (the minimal active concentration (MAC)), served as indexes of the antivirus activity. The dose of compound that causes 50% suppression of propagation of the virus [the median effective dose (ED_{50})] was calculated by the method of Reed and Mench [5].

Compounds XV and XVI had antiviral properties. Both substances had low toxicity for the tissue culture of FCE (MTD $\geq$ 800 μg/ml). Compound XVI displayed the most pronounced antivirus activity with respect to HSV (MAC > 200 μg/ml, ED_{50} 25 μg/ml, CTI 2-4). In accordance with the adopted scheme of evaluation, its activity can be designated as moderate. The antivirus activity of the substance with respect to CBCV was manifested only in the presence of concentrations close to the MTD (MAC 800 μg/ml, ED_{50} 137 μg/ml, CTI 1). Compound XV inhibited the propagation of PVV also only at high concentrations (MAC 800 μg/ml, ED_{50} 200 μg/ml, CTI 1).

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