Systematic Synthesis and Biological Evaluation of α- and β-D-Xylofuranosyl Nucleosides of the Five Naturally Occurring Bases in Nucleic Acids and Related Analogues[1]

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The α- and β-D-xylofuranosyl analogues of the naturally occurring nucleosides, as well as other D-xylofuranosyl derivatives, have been the subject of a systematic synthesis and examination of their biological, i.e. antiviral antimetabolic, and cytostatic properties. The β anomers were prepared by glycosylation of purine and pyrimidine aglycons with peracylated 1-*O*-acetyl-α-D-xylofuranoses, followed by removal of the blocking groups. The α anomers were obtained by a multistep synthesis with use of 2-amino- or 2-mercapto-α-D-xylofuran[1′,2′:4,5]-2-oxazoline as starting material. The xylofuranosyl nucleosides were tested for their activity against a variety of RNA and DNA viruses and for inhibition of cell growth and macromolecule synthesis. Three compounds, 9-(β-D-xylofuranosyl)adenine, 9-(β-D-xylofuranosyl)guanine, and 1-(β-D-xylofuranosyl)cytosine, showed marked biological activity.

There has been considerable interest in nucleosides modified on the sugar moiety as potential antiviral and antitumor agents.[2] However, one class of sugar-modified analogues, the xylofuranonucleosides, has received relatively limited attention. A thorough literature survey of this series revealed several important points. A comprehensive chemical study of the α- and β-D-xylofuranonucleosides has not yet appeared, and several of the reported products are equivocal or imperfectly characterized. Furthermore, there is a lack of biological data for the α anomers. In part this may be attributed to the difficulty in synthesizing glycosides with the *cis*-1′,2′ configuration, as well as the generally accepted notion that α-nucleosides are inactive. The latter concept, however, may require reconsideration since several α-nucleosides are now known to exhibit significant antimetabolic properties.[3] Apart from a few notable examples,[4-9] most biologically evaluated β-D-xylofuranonucleosides possess modified aglycon structures,[7-30] rather than the five natural bases. In general, the biological evaluations have centered on antitumor activity[6,9-19,31] and enzyme substrate or inhibitory activity.[8,19-26,32-37] Antiviral[5,27,28] and antibacterial[4,25,38] properties have received less attention.

One xylofuranonucleoside, 9-(β-D-xylofuranosyl)adenine (β-XyloA) is well recognized for its antitumor[30,31,39,40] and antiviral[41] effects. The antiproliferative activity of β-XyloA, which can be amplified by simultaneous inhibition of adenosine deaminase,[30,42-46] is related to its inhibitory effects on various metabolic reactions.[33,39,45-58]

In view of the general paucity of both chemical and biological information, we have undertaken a systematic study of all the α- and β-D-xylofuranosyl analogues of the naturally occurring nucleosides, as well as some related compounds.

Chemistry. Synthesis of β-D-Xylofuranosyl Nucleosides. Direct condensation of a suitably protected D-xylofuranose and the purine or pyrimidine bases was employed to prepare the β (trans-1′,2′) nucleosides. In accord with Baker's rule,[59] a 2′-*O*-acyl-D-xylofuranose was required for preferential or exclusive formation of the β anomers. Initially we intended to use tetra-*O*-acetyl-D-xylofuranose, previously described as a noncrystalline anomeric mixture.[60-65] But this compound was consistently contaminated with pyranose and hexaacetylated forms which proved difficult to remove on a preparative scale.[66] Two other xylose derivatives were more amenable and were used interchangeably: 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-α-D-xylofuranose (1)[7,67,68] and 1,2-di-*O*-acetyl-3,5-

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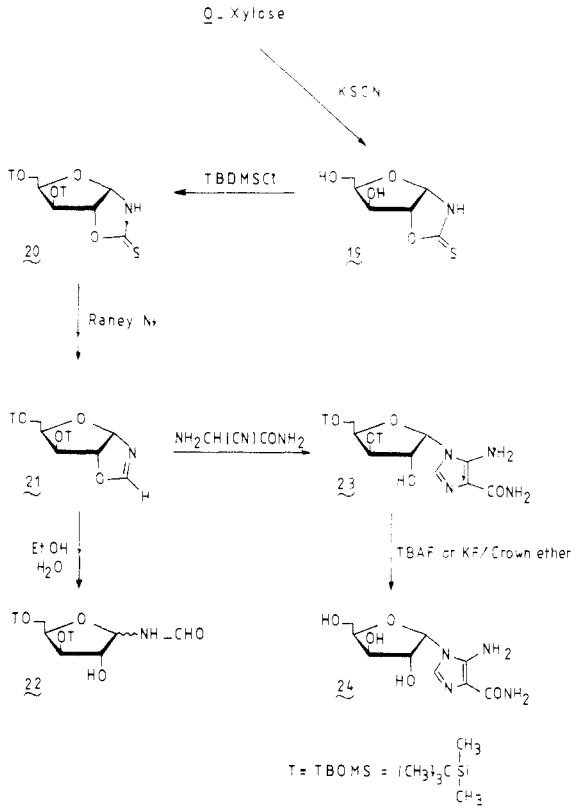
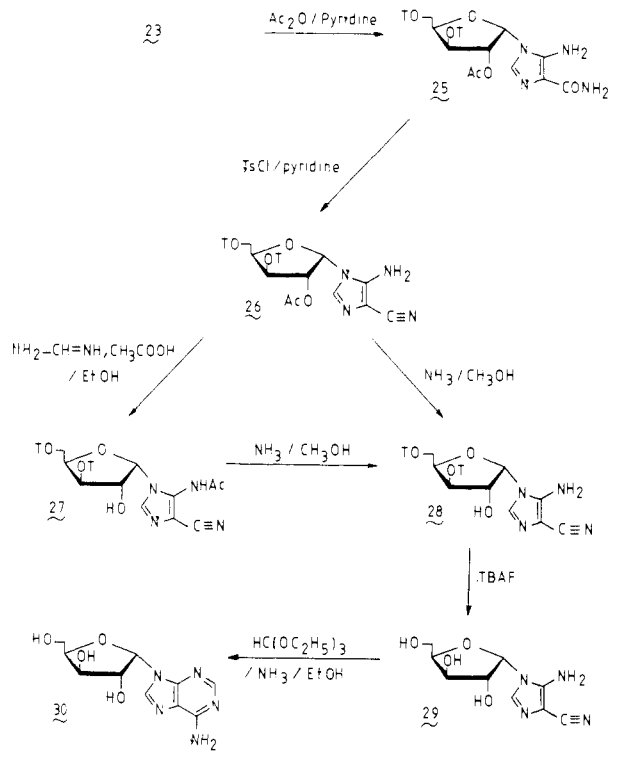
Scheme I

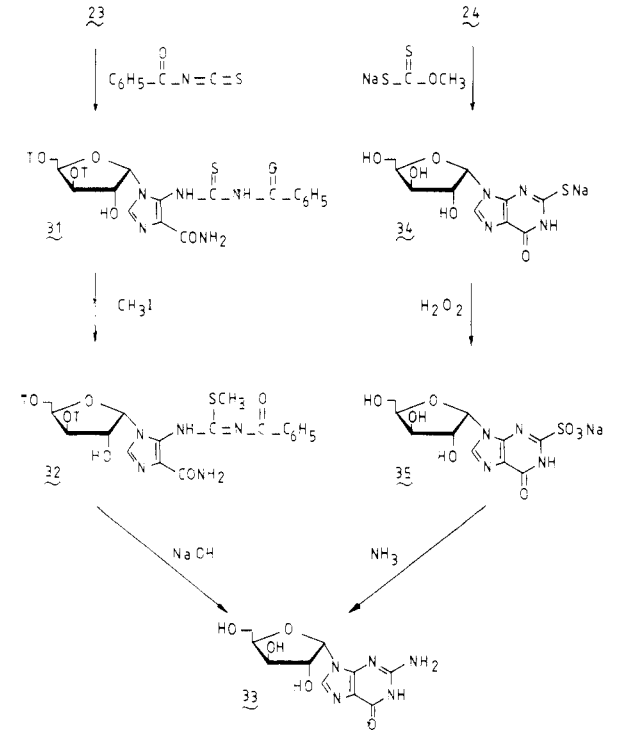


di-*O*-benzoyl-α-D-xylofuranose (**2**), which we had prepared earlier[69] for another purpose.[70]

Scheme II



Scheme III



Glycosylation was effected by two procedures, neither of which required prior protection of the heterocyclic bases.

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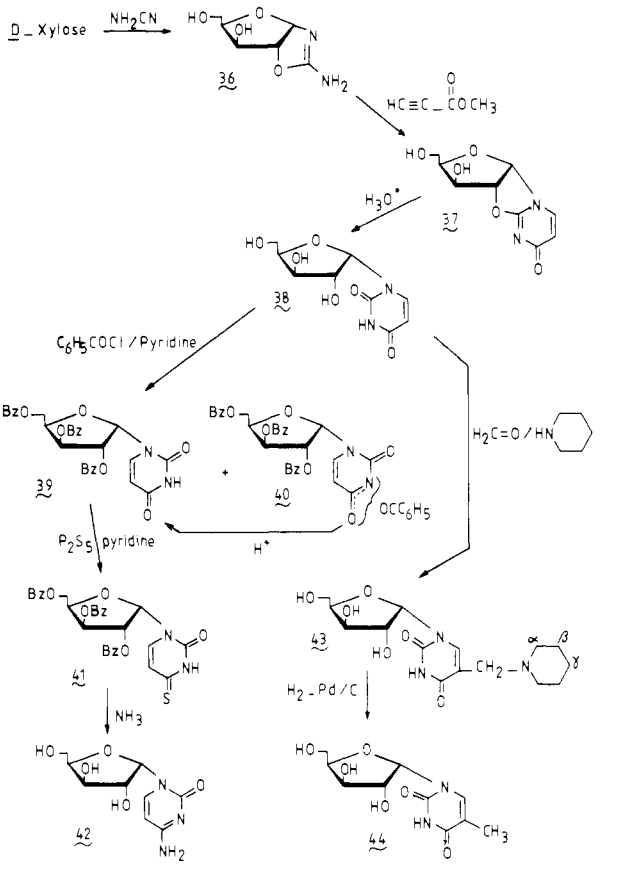
The method of Saneyoshi et al.[7,71] was only successful with adenine and cytosine; the other nucleosides were obtained by the Vorbruggen procedure.[72] From adenine and the pyrimidine bases only the expected β-9-N- (3) and β-1-N- (4–6) protected nucleosides were isolated in satisfactory yield. Removal of the acyl blocking groups with methanolic sodium methoxide then afforded the desired β-D-xylofuranonucleosides 11–14.

Synthesis of the guanine nucleosides was achieved with 2-amino-6-chloropurine, since use of this base allowed preparation of not only the guanine but also the 6-thioguanine derivatives.[9,73–75] Compounds of this type have exhibited striking biological properties.[9,31,76,77] Glycosylation of 2-amino-6-chloropurine resulted in a chromatographically separable mixture of the β-9-N (7) and β-7-N (8) isomers which were subsequently converted to the unprotected 9- and 7-β-D-xylofuranonucleosides of guanine (15, 16) and 6-thioguanine (17, 18).

Scheme IV



The results of these condensations and the physical properties of the β-D-xylofuranonucleosides are presented in Table I.

Synthesis of α-D-Xylofuranosyl Nucleosides. Preparation of the α anomers required a regioselective and stereospecific strategy. As in other series,[38,94–115] these aims

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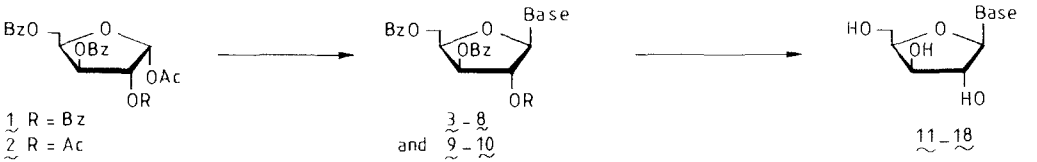
Table I. Preparation and Physical Properties of β-D-Xylofuranonucleosides



compd[a]	R	base	method[b]	yield,[c] %	mp, °C	λ_{max},[d] nm ($\epsilon \times 10^{-3}$)	^{1}H NMR spectral data: $[\alpha]^{20}_D$, deg	solvent[e]	H-1′	$J_{1'2'}$, Hz	other characteristic peaks	formula[f]
3	Ac	9-adenine	A	70 (a)	108–110 (diethyl ether)	258 (13.0) 230 (25.1)	+46.0 (*c* 1.00, $CHCl_3$)	F	6.26 (d)	2.5	2.16 (s, Ac); 6.1 (s, NH_2); 8.12 and 8.23 (s, H-2 and H-8)	$C_{26}H_{23}N_5O_7$
4	Bz	1-cytosine	A	33 (a)	140–141 (EtOH)	272 (8.9) 232 (4.09)	+63.4 (*c* 0.6, $CHCl_3$)	F	6.23 (s)	0	5.83 (d, H-5; $J_{5,6}$ = 7.5 Hz)	$C_{30}H_{25}N_3O_8 \cdot C_2H_5OH$
5	Ac	1-uracil	B	82 (b)	white foam	261 (11.4) 235 (25.8)	*g*	F	6.07 (d)	2.6	2.13 (s, Ac); 7.67 (d, H-6; $J_{5,6}$ = 8.4 Hz); 9.6 (s, NH-3)	*g*
6	Bz	1-thymine	B	72 (c)	196–198 (ethyl acetate)	266 (9.5) 232 (37.3)	+50.6 (*c* 0.85, $CHCl_3$)	G	6.28 (d)	3.3	1.77 (s, CH_3); 11.5 (s, NH-3)	$C_{31}H_{26}N_2O_9$
7	Bz	9-(2-amino-6-chloropurine)	B	42 (d)	white foam	309 298[g] 224	*g*	F	6.3[h]	*h*	5.3 (s, NH_2); 8.15 (s, H-8)	*g*
8	Bz	7-(2-amino-6-chloropurine)	B	34 (d)	white foam	323 273[g] 228	*g*	F	6.67 (s)	0	5.7 (s, NH_2); 8.67 (s, H-8)	*g*
9	Bz	9-(2-amino-6-mercaptopurine)	C	72	241–243 ($CHCl_3$/MeOH)	345 (25.9) 274 (8.6) 230 (45.9)	−16.4 (*c* = 0.67, Me_2SO)	G	6.0–6.3[i]	*i*	6.8 (s, NH_2); 8.23 (s, H-8); 12.0 (s, NH-1)	$C_{31}H_{25}N_5O_7S$
10	Bz	7-(2-amino-6-mercaptopurine)	C	66	178 dec (isobutyl alcohol)	355 (16.7) 268 (sh) 230 (48.3)	+26.5 (*c* 0.83, $CHCl_3$)	G	7.2–8.3[j]	*j*	6.6 (s, NH_2); 8.68 (s, H-8); 12.0 (s, NH-1)	$C_{31}H_{25}N_5O_7S$[f]
11		9-adenine	D	78	145–147 (MeOH)	258 (14.6)	−41.2 (c 1.31, H_2O)	G	5.86 (d)	1.8	7.3 (s, NH_2); 8.15 and 8.26 (s, H-2 and H-8)	$C_{10}H_{13}N_5O_4 \cdot 0.5H_2O$
12		1-cytosine	D	74	240–242 ($EtOH/H_2O$)	273 (7.5)	−20.0 (*c* 0.75, Me_2SO)	G	5.57 (s)	0	5.73 (d, H-5; $J_{5,6}$ = 7.8 Hz); 7.2 (s, NH_2); 7.73 (d, H-6)	$C_9H_{13}N_3O_5$
13		1-uracil	D	77 (e)	158–160 (MeOH)	263 (9.4)	+27.0 (c 1.00, H_2O)	G	5.63 (s)	0	5.60 (d, H-5; $J_{5,6}$ = 8.1 Hz); 7.77 (d, H-6); 11.2 (s, NH-3)	$C_9H_{12}N_2O_6$
14		1-thymine	D	51	(softens 98) 160 (MeOH)	268 (9.8)	0 (*c* 0.83, H_2O)	G	5.68 (d)	1.3	1.77 (s, CH_3); 7.67 (s, H-6); 11.3 (s, NH-3)	$C_{10}H_{14}N_2O_6 \cdot 0.33H_2O$
15		9-guanine	E	41	236–240 (H_2O)	275 (sh) 253 (13.2)	−68.1 (*c* 0.72, Me_2SO)	G	5.68 (d)	1.5	6.4 (s, NH_2); 7.90 (s, H-8); 10.8 (s, NH-1)	$C_{10}H_{13}N_5O_5 \cdot 0.66H_2O$
16		7-guanine	E	52	262–264 (H_2O)	285 (6.6) 244 (sh)	−33.3 (*c* 0.57, Me_2SO)	G	6.08 (d)	1.6	6.3 (s, NH_2); 8.14 (s, H-8); 11.2 (s, NH-1)	$C_{10}H_{13}N_5O_5 \cdot 0.5H_2O$
17		9-(2-amino-6-mercaptopurine)	D	35	212–214 (H_2O)	341 (24.8) 260 (7.8) 225 (12.8)	−94.7 (*c* 0.57, Me_2SO)	G	5.67 (d)	1.7	6.8 (s, NH_2); 8.03 (s, H-8); 12.0 (s, NH-1)	$C_{10}H_{13}N_5O_4S \cdot H_2O$[f]
18		7-(2-amino-6-mercaptopurine)	D	33	209–211 (H_2O)	352 (20.3) 223 (14.9)	+76.8 (*c* 0.56, Me_2SO)	G	7.00 (s)	0	6.5 (s, NH_2); 8.37 (s, H-8); 12.0 (s, NH-1)	$C_{10}H_{13}N_5O_4S \cdot 0.5H_2O$

[a] Reference of previously described compounds: **3**,[69] **6**,[9,67,78–80] **9**,[7] **11**,[35,41,60,63,69,81–85] **12**,[86,87] **13**,[9,88–90] **14**,[9,67,78,79] **15**,[7,75,91,93] **17**.[7] [b] See Experimental Section; A, $SnCl_4/CH_3CN$; B, HMDS, TMSCl, $SnCl_4/CH_3CN$; C, $NH_2C(S)NH_2/C_2H_5OH$; D, CH_3ONa/CH_3OH; E, $HSCH_2CH_2OH$, CH_3ONa, H_2O/CH_3OH. [c] Yeilds are based on directly crystallized pure samples or are calculated after silica gel column chromatography with the following eluents: (a) CH_2Cl_2/MeOH (96:4, v/v), (b) $CHCl_3$/MeOH (98:2, v/v), (c) CH_2Cl_2/MeOH (99:1, v/v), (d) $CH_2Cl_2/(C_2H_5)_2O$ (9:1, v/v), (e) $CHCl_3$/MeOH (9:1, v/v). [d] UV spectra of all *O*-acyl-protected compounds were determined in EtOH and of all deprotected nucleosides in H_2O, except for **11** in EtOH. [e] F: chloroform-d_6; G: dimethyl-d_6 sulfoxide. [f] Chemical formulas are given for compounds that were analyzed for all the elements except oxygen, and with the exception of **10** and **17** all analytical results were within ±0.4% of the theoretical values. Anal. Calcd for **10**: C, 60.87; H, 4.12; N, 11, 45; S, 5.24. Found: C, 59.46; H, 4.11; N, 11.23; S, 5.48. Anal. Calcd for **17**: C, 37.85; H, 4.77; N, 22.07; S, 10.11. Found: C, 37.96; H, 4.18; N, 22.52; S, 10.35. [g] These compounds were used directly without further characterization for the preparation of **13**, **9–10**, **15**, **16**. [h] Hidden under the signal of H-2′ or H-3′. [i] Hidden under the signals of H-2′ and H-3′. [j] Hidden under the signal of benzoyl.

were accomplished by constructing the heterocyclic moiety from a xylose derivative possessing a 2-oxazoline ring fused in the α-(cis-1′,2′) configuration.

The starting material, xylofuranothioxooxazolidine **19**, obtained by minor modification of a published procedure,[116] was first transformed to the α-XyloAICA derivatives **23** and **24** (Scheme I) and then cyclized to α-XyloA (**30**, Scheme II) and α-XyloG (**33**, Scheme III).

To enhance solubility in organic solvents, the hydroxyl groups of **19** were protected by *tert*-butyldimethylsilylation with TBDMSCl, affording **20**. Treatment with Raney nickel in dioxane quantitatively produced the unstable oxazoline **21**. Since this compound hydrolyzed readily to *N*-formyl-D-xylofuranosylamine (**22**), the next step was conducted without isolation or purification of **21**. Rather, a methanolic solution of crude **21** was directly reacted with α-amino-α-cyanoacetamide to give the protected α-AICA xyloside **23**, isolated in 40% yield after chromatographic purification. Desilylation was achieved with either tetra-*n*-butylammonium fluoride (TBAF) or by heating with potassium fluoride, giving the desired 1-(α-D-xylofuranosyl)-4-carbamoyl-5-aminoimidazole (**24**)[117] in yields of better than 70% (Scheme I).

Protection of the 2′-position of **23** was required for synthesis of α-XyloA (**30**), as indicated in Scheme II. Since introduction of a TBDMS group proved difficult,[66] presumably due to steric hindrance, acetylation (acetic anhydride in pyridine) was employed to give **25**. Dehydration with *p*-toluenesulfonyl chloride[118-120] then afforded nitrile **26**. Attempted direct ring closure[121] with formamidine acetate[122-124] was unsuccessful, giving only the 2′-deprotected, N-acetylated product **27**, apparently *via* O → N acetyl migration. On the other hand, the deprotected nucleoside **29**, obtained easily from either **26** or **27** by successive treatment with methanolic ammonia and TBAF, cyclized in satisfactory yield with triethyl orthoformate in ethanolic ammonia[125-127] to the desired α-XyloA (**30**).

Earlier reports have mentioned α-XyloA as a side-product obtained after condensation with 1,2,3,5-tetra-*O*-acetyl-D-xylofuranose.[63,81,82,128] However, neither Lee et al.[81] nor Ikehara et al.[82,128] isolated the compound in the pure state; the former reported its 3′,5′-*O*-isopropylidene derivative and the latter an anomeric mixture. A crystalline product assigned this structure by Magnani et al.[63] appears different (melting point, ^{1}H NMR) from **30**. Examination of the reported ^{1}H NMR data[63,82] suggests that Magnani's compound is 9-β-D-xylopyranosyladenine.[129] In view of the previously mentioned pyranose contamination of the starting sugar, this result is not surprising.

On the basis of literature procedures,[130] two different cyclization routes were used to prepare α-XyloG (Scheme III). Although this compound has been reported, it was previously obtained in yield too low to permit full characterization.[92] The first method[131-137] involved condensation of the α-AICA derivative **23** with benzoyl isothiocyanate to give **31** (67%) and subsequent methylation to **32** (81%). Base-induced cyclization of **32** occurred with concomitant loss of the TBDMS protecting groups to afford the desired α-XyloG (**33**). To improve the yield and to provide an unequivocal structure proof, a second approach was investigated.[138-140] Treatment of the unprotected α-AICA xyloside **24** with carbon disulfide in methanolic sodium hydroxide at 180 °C gave **34** which, without isolation, was oxidized with hydrogen peroxide to **35**. Animation with ammonia then afforded **33**, identical with the prepared sample, in overall 29% from **24**.

The synthesis of the α-D-xylofuranosyl pyrimidine nucleosides is presented in Scheme IV. Although α-XyloU[38] (**38**) and α-XyloC[141,142] (**42**) have been described in varying detail, α-XyloT (**44**) was hitherto unknown. The starting

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material, 2-aminooxazoline **36**, was prepared by the procedure employed by Hessler[111] in the arabinose series. The $O^2,O^{2'}$-anhydro-1-α-D-xylofuranosyluracil (**37**) was obtained by the method of Holy[38] and then heated with dilute aqueous hydrochloric acid to produce α-XyloU (**38**). After protection of the hydroxyl groups by benzoylation, the resulting nucleoside **39** was converted in two steps to α-XyloC (**42**), employing methods previously used in the ribose series.[143]

In view of the known conversion of uracil nucleosides to their 5-methyl derivatives,[102,144-154] α-XyloT (**44**) was prepared from α-XyloU (**38**). Mannich reaction with formaldehyde and piperidine gave **43** which underwent catalytic hydrogenolysis to α-XyloT (**44**). Structural assignments for the reported compounds are based on elemental analysis and their physical properties. Unless otherwise noted, our data were in accord with literature values for previously described compounds.

Biological Evaluation

All the prepared α- and β-D-xylofuranonucleosides **11–18**, **24**, **30**, **33**, **37**, **38**, **42**, and **44** were evaluated in vitro against various viruses in four cell systems (Table II).

From these studies it is apparent that three compounds, namely β-XyloA (**11**), β-XyloC (**12**), and β-XyloG (**15**), exhibited significant antiviral activity against several DNA viruses (HSV-1, HSV-2, vaccinia). Noteworthy also was the activity of α-XyloA (**30**) against another (+)RNA virus, rhinovirus-9.

With the exception of β-XyloA (**11**), none of the test compounds caused a microscopically detectable alteration of host-cell morphology at a concentration of 200 or 400 μg/mL (Table II).

β-XyloA (**11**), β-XyloC (**12**), and β-XyloG (**15**) inhibited host-cell growth as well as DNA and RNA synthesis within the concentration range of 10–100 μg/mL, β-XyloA (**11**) being the most inhibitory of the three compounds (Table III). Based on the ratio of the minimum inhibitory concentration for host-cell growth to the minimum antiviral (herpes simplex) concentration, the antiviral indices of compounds **11**, **12**, and **15** in primary rabbit kidney cells may be estimated at 0.5, 3.6, and 1.1, respectively.

In additional experiments it was ascertained that β-XyloA (**11**), β-XyloC (**12**), and β-XyloG (**15**) inhibited the

Table II. Antiviral Activity of D-Xylofuranonucleosides against Different Viruses in Different Cell Systems

	minimum cytotoxic concn,[a] μg/mL				minimum inhibitory concentration,[b] μg/mL													
					primary rabbit kidney cells			HeLa cells	African green monkey kidney (Vero B) cells							human diploid (WI-38) cells		
compd	PRK cells	HeLa cells	Vero B cells	Wi-38 cells	herpes simplex virus-1 (KOS)	herpes simplex virus-2 (G)	vaccinia virus	vesicular stomatitis virus	polio virus-1	Coxsackie virus B4	parainfluenza virus-3	Reo virus-1	Sindbis virus	Semliki forest virus	rhino-virus 1A	rhino-virus-9
β-XyloA (11)	⩾100	100	>100	200	>40	>40	>40	>40	>40	>40	>40	>40	>40	>40	20	20
β-XyloC (12)	⩾200	200	>200	>400	20	20	>100	>100	>100	>100	>100	>100	>40	>200	>400	>400
β-XyloU (13)	⩾400	>400	>400	>400	300	300	150	>200	>400	>400	>400	>400	>400	>400	>400	>400
β-XyloG (15)	⩾200	400	>400	>400	70	70	10	>200	>200	>200	>400	>400	>400	>400	>400	>400
7-β-XyloG (16)	>400	>400	⩾400	⩾400	>400	>400	>400	>400	>400	>200	>200	>200	>200	>200	>200	>200
9-β-XyloTG (17)	>400	⩾200	⩾200	⩾400	>400	>400	>400	>200	>200	>200	>200	>200	>200	>200	>200	>200
α-XyloAICA (24)	>400	>400	>400	>400	>400	>400	>400	>400	>400	>300	>400	>400	>400	>400	>400	>400
α-XyloA (30)	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400
α-XyloT (44)	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	40
tubercidin	⩾0.4	⩾1	⩾0.4	0.4	>0.1	>0.1	>0.1	0.07	0.2	0.2	>0.1	0.2	>0.1	>0.4	0.01	0.007
(S)-DHPA	>400	>400	>400	>400	>400	>400	20	20	70	>400	100	>400	100	>400	150	>400
ribavirin	>400	⩾400	⩾400	>400	>400	>400	7	100	20	70	70	20	7	70	150	70
carbocyclic 3-deazaadenosine	>400	⩾400	⩾400	>400	>400	>400	2	0.7	2	>400	0.7	0.2	2	>400	>400	>400
β-ara-A	⩾200	⩾200	⩾200	⩾100	20	10	2	70	150	>100	>100	150	150	>100	>100	>100

[a] Required to cause a microscopically detectable alteration of normal cell morphology, when incubated with cells for the same duration as required to measure antiviral activity. [b] Required to reduce virus-induced cytopathogenicity by 50%. Viral cytopathogenicity was recorded as soon as it reached completion in the control virus-infected cell cultures. The multiplicity of infection (MOI) was invariably 100 × $CCID_{50}$, that is 100 times the virus dose needed to infect 50% of the cell.

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Table III. Effects of Compounds 11, 12, and 15 on Cell Proliferation and Macromolecule Synthesis in Primary Rabbit Kidney Cells

compd	ID_{50},[a] μg/mL: cell growth	DNA synth: [^{3}H-*methyl*]dThd incorporation	RNA synth: [^{3}H-5]Urd incorporation	protein synth: [$^3H_2$-4,5]leucine incorporation
β-XyloA (11)	23	17	46	37
β-XyloC (12)	72	84	60	>200
β-XyloG (15)	62	71	61	148
β-ara-A	27	31	15	>200
β-ara-C	0.04	0.05	0.03	>200

[a] 50% inhibitory dose, or dose required to reduce the cell number or DNA, RNA, or protein synthesis by 50%.

Table IV. Effects of Compounds 11, 12, and 15 on the Proliferation of Mouse Myeloma Cells SP2

compd	no. of living cells (× 10^{-3}) at 0 h	48 h	96 h
control 1	123	1064	1856
control 2	123	916	1856
β-XyloA (11) (100 μg/mL)	123	8	0
β-XyloA (11) (10 μg/mL)	123	48	400
β-XyloA (11) (1 μg/mL)	123	864	1368
β-XyloC (12) (100 μg/mL)	123	56	0
β-XyloG (15) (100 μg/mL)	123	24	0

replication of herpes simplex virus-1 (KOS) in primary rabbit kidney cells: i.e. when assayed at 100 μg/mL, compounds 11, 12, and 15 reduced the 24-h virus yield from 6.6 log pfu/mL to 0, 2.8, and 3.2 log pfu/mL, respectively (data not shown).

The antiherpetic activity of β-XyloA (11) and β-XyloG (15) has been previously noted[5,41,154,155] as have been the antitumor properties of 11.[30,31,39,40] Compounds 11, 12, and 15 brought about a marked suppression of the growth of mouse myeloma cells (Table IV), and again, the inhibitory effect of compound 11 on tumor cell growth was more pronounced than that of the two other compounds.

Compound 12 (β-XyloC) was remarkably nontoxic in vivo: LD_{50} (50% lethal dose), > 2 g/kg (Table V). For compound 15 (β-XyloG) the LD_{50} was markedly lower. Preliminary findings with a rather small number (six) of animals per group indicate that compounds 12 and 15 might be effective against herpetic encephalitis in mice at subtoxic doses (Table V). These findings remain to be corroborated.

Experimental Section

Chemical Synthesis. General Procedures. Evaporation of solvents was done with a rotary evaporator under reduced pressure (water aspirator). Melting points were determined on a Büchi 510 apparatus and are uncorrected. Ultraviolet spectra (UV) were recorded on an Optica Model 10 spectrophotometer; numbers in parentheses are extinction coefficients ($\epsilon \times 10^{-3}$). Infrared spectra were determined with a Perkin-Elmer 298 instrument. Proton nuclear magnetic resonance were determined at ambient temperature on Varian EM 360, EM 390, or HA 100 spectrometers. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. The presence of exchangeable protons was confirmed by exchange with D_2O followed by reintegration. Mass spectra (MS) were measured with a JEOL JMSD 100 instrument, at 75 eV by direct probe sample introduction. Optical rotations were measured in a 1-cm cell on a Perkin-Elmer Model 241 spectropolarimeter in the indicated solvents. Elemental analyses were determined by the Service de Microanalyse du CNRS, Division de Vernaison, France. Where analyses are indicated only by symbols of the elements, the analytical results obtained for those elements were within ±0.4% of the theoretical values. Thin-layer chromatography (TLC) was performed on precoated aluminum sheets of silica gel 60 F_{254} (Merck, no. 5554), visualization of products being accomplished by UV absorbance followed by charring with 10% ethanolic sulfuric acid and heating. Short column chromatography was performed with silica gel 60 H (Merck, no. 7736) under weak nitrogen pressure (≃4 psi). High-pressure liquid chromatographic (HPLC) studies were carried out on a Waters Associates unit equipped with an U_6K injector, 6000 A and M-45 pumps, a M-720 solvent programmer, a 440 UV detector operating at 254 nm, a R-401 differential refractometer, and a M-730 microprocessor-controlled data system.

General Procedures for the Preparation of Protected β-D-Xylofuranosyl Nucleosides 3–10. Method A.[7,71] Aglycon (adenine or cytosine) was suspended in a solution of protected starting sugar 1 or 2 (1 equiv) in anhydrous acetonitrile (30 mL/mmol of aglycon). Stannic chloride (2 equiv) in anhydrous acetonitrile (6 mL/equiv) was added and the mixture was stirred at room temperature (15 h for adenine, 65 h for cytosine) with exclusion of moisture. The reaction mixture was concentrated, and sodium hydrogen carbonate (0.58 g/mmol of aglycon) and water (3.4 mL/g of $NaHCO_3$) were carefully added with stirring. When the evolution of carbon dioxide had ceased, the mixture was evaporated to dryness. The residue was then triturated with boiling $CHCl_3$ and filtered through a sintered funnel. This operation was repeated three times. The combined filtrates were washed with water, dried over sodium sulfate, and evaporated. Chromatography of the residue on a silica gel column led, after evaporation of the appropriate fractions, to the isolation of pure 3 and 4.

Method B.[72] To a mixture of the aglycon (uracil, thymine, 2-amino-6-chloropurine) and of the protected starting sugar 1 or 2 (1 equiv) in anhydrous acetonitrile (15 mL/mmol of aglycon) were added consecutively hexamethyldisilazane (HMDS, 0.8 equiv), trimethylchlorosilane (TMSCl, 0.8 equiv) and $SnCl_4$ (1.2 equiv). For thymine and 2-amino-6-chloropurine, the resulting clear solution was refluxed for 20 min; for uracil, the solution was stirred at ambient temperature for 21 h, then more $SnCl_4$ (0.5 eq.) was added and the stirring continued for an additional 24 h. The reaction mixtures were concentrated to a small volume, diluted with methylene chloride (ca. 30 mL/mmol of aglycon), then twice washed with the same volume of saturated $NaHCO_3$ solution and finally with water. The organic layers were dried over sodium sulfate, filtered through Celite, and evaporated. The resulting crude material was purified by silica gel column chromatography to give pure 5–8.

Method C. Compound 7 or 8 (2.0 g, 3.26 mmol), obtained by method B, was dissolved in 50 mL of anhydrous ethanol containing 0.7 g (9.2 mmol) of thiourea. The solution was refluxed for 1 h and then evaporated to dryness. The crude material obtained was dissolved in chloroform (200 mL) and the resulting solution washed twice with water (100 mL). The organic layer was dried over sodium sulfate, filtered, and evaporated. Crystallization from chloroform–ethanol gave 1.44 g (72%) of pure 9; precipitation from isobutyl alcohol gave 1.31 g (66%) of pure 10.

General Procedures for the Preparation of Unprotected β-D-Xylofuranosyl Nucleosides 11–18. Method D. The protected nucleosides 3–6, 9, 10 were dissolved with stirring in a freshly prepared solution (ca. 50 mL/4 mequiv of nucleoside) of 0.3 N sodium methoxide. When TLC indicated the reaction was complete (ca. 3 h), an equivalent volume of water was added and the solution was neutralized to pH 6–7 by the addition of DOWEX 50 Wx2 (pyridinium form) ion-exchange resin. The resin was filtered and washed with warm MeOH and water, and the com-

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Table V. Toxicity of Compounds 12 and 15 for Mice and Their Effect on Herpetic Encephalitis

compd	toxicity (no. of dead mice)[a] dose, mg/kg 100	250	750	1200	2000	LD_{50}, mg/kg	efficacy (no. of surviving mice)[b] dose, mg/kg per day (4 days) 0	75	150
β-XyloG (15)	2	5	8	ND[c]	ND	280	0	3	toxic
β-XyloC (12)	0	0	0	0	1	>2000	0	1	2
β-ara-A	0	0	0	ND	ND	>750	0	ND	ND
acyclovir	0	0	1	7	7	1250	0	ND	ND

[a] Ten mice per group. [b] Six virus-infected mice per group. [c] ND: not determined.

bined filtrates were evaporated to dryness. The residue was dissolved in water and repeatedly washed with $CHCl_3$ and Et_2O. The aqueous phase was then filtered and evaporated to dryness to afford the deblocked nucleosides 11–14, 17, 18, which could be further purified by either column chromatography or crystallization.

Method E. To a solution of 1.5 g (2.44 mmol) of compound 7 or 8 in methanol (20 mL) were added 0.65 mL (9.32 mmol) of 2-mercaptoethanol, 8.7 mL of 1 M methanolic sodium methoxide, and 0.08 mL of water. The stirred mixture was refluxed for 3.5 h during which time the sodium salt of 15 or 16 began to precipitate. After cooling to 5 °C overnight, these sodium salts were collected and suspended in 15 mL of methanol. To these suspensions was added with stirring 1.2 mL of acetic acid. After 15 min the precipitates were filtrated and recrystallized from water to afford 0.28 g (41%) of pure 15 and 0.36 g (52%) of pure 16.

2-Thioxo-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-α-D-xylofuran[1′,2′:4,5]-2-oxazolidine (20). To 10 g (52.3 mmol) of 19[116,156] in 80 mL of anhydrous dimethylformamide was added 17.82 g (262.1 mmol) of imidazole, followed by 19.73 g (131.2 mmol) of *tert*-butyldimethylsilyl chloride. The mixture was stirred for 3 h in a stoppered flask, poured into stirred cold water (400 mL), and after 15 min extracted with ether (2 × 300 mL). The combined organic layers were evaporated to dryness. To the residue was added water (300 mL) and compound 20 was extracted with hexane (3 × 200 mL). The combined organic layers were dried over sodium sulfate, filtered, and evaporated to dryness. The resulting syrup was dried at 40 °C under a high vacuum to afford 20.2 g (92%) of pure 20 as a crystalline mass: mp 102–104 °C. This compound was used directly without further purification for the preparation of 21. An analytical sample of 20 was recrystallized from hexane–DMF: mp 87–89 °C; UV (MeOH) λ_{max} 244 nm (18.8); ^1H NMR ($CDCl_3$) δ 0.08 (s, 6 H, 2 $SiCH_3$), 0.13 and 0.16 (2 s, 2 × 3 H, 2 $SiCH_3$), 0.90 (s, 18 H, 2 $SiC(CH_3)_3$), 3.7–4.2 (m, 3 H, H-4′,5′, 5″), 4.50 (d, 1 H, H-3′; $J_{3',4'}$ = 3.0 Hz), 5.03 (d, 1 H, H-2′), 5.92 (d, 1 H, H-1′; $J_{1',2'}$ = 5.3 Hz), 7.9 (br s, 1 H, NH). Anal. ($C_{18}H_{37}NO_4SSi_2 \cdot C_3H_7NO$) C, H, N.

3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-α-D-xylofuran-[1′,2′:4,5]-2-oxazoline (21). Compound 20 (20 g, 47.65 mmol) was dissolved in anhydrous dioxane (160 mL) and magnetically stirred with ca. 120 g of Raney nickel (Merck Art. 820876), which had been freshly activated with 18 N acetic acid and then extensively washed with absolute ethanol and anhydrous dioxane. The mixture was refluxed for 45 min with efficient stirring. The suspension was filtered through Celite at room temperature and the filtrate was evaporated to dryness to afford 19 g of a greenish oil which was used without further purification for the preparation of 22 and 23: ^1H NMR ($CDCl_3$) δ 0.06 (s, 6 H, 2 $SiCH_3$, 0.13 and 0.15 (2 s, 2 × 3 H, 2 $SiCH_3$), 0.91 (s, 9 H, $SiC(CH_3)_3$), 0.95 (s, 9 H, $SiC(CH_3)_3$), 3.4–3.9 (m, 3 H, H-4′, 5′, 5″), 4.25 (d, 1 H, H-3′; $J_{3',4'}$ = 2.3 Hz), 4.55 (d, 1 H, H-2′), 6.12 (d, 1 H, H-1′; $J_{1',2'}$ = 5.4 Hz), 7.03 (s, 1 H, H-2).

***N*-Formyl-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-D-xylofuranosylamine (22).** A solution of oxazoline 21 (0.5 g, ca 1.29 mmol) in ethanol (50 mL) with powdered charcoal was refluxed for 15 min and then filtered through Celite. The filtrate was evaporated to dryness and the residue crystallized from ethanol–water to afford 0.21 g (40%) of pure 22: mp 181–183 °C; ^1H NMR ($CDCl_3$) δ 0.00 (s, 6 H, 2 $SiCH_3$) 0.04 (s, 6 H, 2 $SiCH_3$), 0.85 (s, 18 H, 2 $SiC(CH_3)_3$), 3.6–4.4 (m, 6 H, H-2,3,4,5,5′ + OH-2), 5.36 (dd, H-1 anti; $J_{(HN,H-1)anti}$ = 10.5 Hz; $J_{(1,2)anti}$ = 3.5 Hz, after D_2O exchange), 5.85 (dd, H-1 syn; $J_{(NH,H-1)syn}$ = 9.0 Hz; $J_{(1,2)syn}$ = 3.5 Hz, after D_2O exchange), 6.8–7.2 (m, 1 H, NH), 8.22 (s, 1 H; CHO syn), 8.22 (d, 1 H, CHO anti; $J_{(NH,CHO)anti}$ = 11.7 Hz); $[\alpha]^{20}_D$ 0° (c 1.54, $CHCl_3$). Anal. ($C_{18}H_{39}NO_5Si_2$) C, H, N.

1-[3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-α-D-xylofuranosyl]-4-carbamoyl-5-aminoimidazole (23). A solution of oxazoline 21 (18.0 g, ca. 46.4 mmol) and α-amino-α-cyanoacetamide[157] (3.8 g, 38 mmol) in anhydrous methanol (200 mL) was heated under reflux for 1 h. TLC (CH_2Cl_2/CH_3COCH_3, 6:4) showed one major Bratton–Marshall[158] active spot at R_f 0.18. The solution was evaporated to a gum which was chromatographed on a silica gel column using CH_2Cl_2/CH_3COCH_3 (6:4) to afford 9.0 g (40%) of 23. This compound was crystallized from diethyl ether: mp 190–191 °C; UV (MeOH) λ_{max} 266 nm (16.3); ^1H NMR ($CDCl_3$) δ 0.00 (s, 6 H, 2 $SiCH_3$), 0.05 (s, 6 H, 2 $SiCH_3$), 0.85 (s, 18 H, 2 $SiC(CH_3)_3$), 3.78 (d, 2 H, 2 H-5′; $J_{4',5'}$ = 5.4 Hz), 4.2–4.6 (m, 3 H, H-2′,3′,4′), 5.1 (br s, 2 H, NH_2), 5.75 (d, 1 H, H-1′; $J_{1',2'}$ = 3.1 Hz), 5.6–6.4 (br s, 3 H, NH_2 + OH-2′), 7.10 (s, 1 H, H-2); $[\alpha]^{20}_D$ +28.1 (c 1.21, $CHCl_3$). Anal. ($C_{21}H_{42}N_4O_5Si_2$) C, H, N.

1-α-D-Xylofuranosyl-4-carbamoyl-5-aminoimidazole (24). Method A.[159] To 4.0 g (8.22 mmol) of 23 in 20 mL of anhydrous THF at room temperature was added with stirring 20 mL of a 1 M solution of tetra-*n*-butylammonium fluoride (TBAF) in anhydrous THF. The resulting mixture was stirred for 4 h, and the obtained precipitate was washed with THF and recrystallized from ethanol to give 1.5 g (71%) of pure 24: mp 217–219 °C (lit.[117] (222–223 °C). Anal. ($C_9H_{14}N_4O_5$) C, H, N.

Method B.[160] To flame-dried KF (7.17 g, 123.4 mmol) were added dibenzo-18-crown-6 (2.97 g, 8.22 mmol) and anhydrous benzene (1.6 L). Most of the benzene (75%) was distilled from the mixture, which was then cooled to room temperature and treated with 23 (4.0 g, 8.22 mmol) dissolved in anhydrous CH_3CN (120 mL) plus acetic acid (4 mL). The reaction was refluxed for 20 h, cooled, treated with ethanol (200 mL), and evaporated to dryness. The residue was chromatographed on a silica gel column using MeOH/$CHCl_3$ (3:7) to afford 1.6 g (76%) of pure 24. This compound was identical in all respects with that obtained by using method A, and its physical properties were in close agreement with literature data.[117]

1-[2′-*O*-Acetyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-α-D-xylofuranosyl]-4-carbamoyl-5-aminoimidazole (25). To a stirred solution of 23 (3.0 g, 6.16 mmol) in anhydrous pyridine was added acetic anhydride (0.8 mL, 8.46 mmol). After 4 h at room temperature, routine treatment followed by chromatography on a silica gel column using MeOH/$CHCl_3$ (2:98) led, after evaporation of the appropriate fractions, to the isolation of 25 (3.0 g, 92%), which was crystallized from diethyl ether–petroleum ether: mp 154–155 °C; UV (MeOH) λ_{max} 267 nm (26.9); ^1H NMR ($CDCl_3$) δ 0.00 (s, 12 H, 2 $Si(CH_3)_2$), 0.84 and 0.87 (2 s, 2 × 9 H, 2 $SiC(CH_3)_3$), 1.81 (s, 3 H, CH_3CO), 3.80 (d, 2 H, 2 H-5′; $J_{4',5'}$ = 3.0 Hz), 4.25 (m, 1 H, H-4′), 4.57 (t, 1 H, H-3′; $J_{3',4'}$ = 5.6 Hz), 4.9 (br s, 2 H, NH_2-5), 5.30 (t, 1 H, H-2′; $J_{2',3'}$ = 5.6 Hz), 6.03 (d, 1 H, H-1′; $J_{1',2'}$ = 5.6 Hz), 5.0–7.0 (br s, 2 H, $CONH_2$), 7.01 (s, 1 H, H-2); mass spectrum, *m/z* 259 (M^+·); $[\alpha]^{20}_D$ +22.8 (c 0.57, $CHCl_3$).

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Anal. ($C_{23}H_{44}N_4O_6Si_2$) C, H, N, Si.

1-[2′-*O*-Acetyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-α-D-xylofuranosyl]-4-cyano-5-aminoimidazole (26). To 3.0 g (5.67 mmol) of **25** in anhydrous pyridine (28 mL) was slowly added with stirring and exclusion of moisture a solution of 0.54 g (2.83 mmol) of *p*-toluenesulfonyl chloride in anhydrous pyridine (4 mL). The solution was stirred at ambient temperature for 12 h and then more *p*-toluenesulfonyl chloride (1.08 g, 5.66 mmol) in anhydrous pyridine (8 mL) was added and the stirring continued for an additional 6 h. The solution was poured into ice water (100 mL), stirred for 15 min, and extracted with chloroform (2 × 100 mL). The organic layers were washed with water (100 mL), dried over sodium sulfate, and filtered, and the filtrate was evaporated to dryness. The residue was chromatographed on a silica gel column using EtOAc/$CHCl_3$ (5:95) to afford 2.0 g (69%) of pure **26** as a syrup: IR ($CHCl_3$) 2220 cm^{-1} (CN); UV (MeOH) λ_{max} 246 nm (11.7); ^1H NMR ($CDCl_3$) δ 0.05 (s, 12 H, 2 $Si(CH_3)_2$), 0.85 and 0.88 (2 s, 2 × 9 H, 2 $SiC(CH_3)_3$), 1.83 (s, 3 H, CH_3CO), 3.8–3.9 (m, 2 H, H-5′,5″), 4.0 (br s, 2 H, NH_2-5), 4.3 (m, 1 H, H-4′), 4.55 (t, 1 H, H-3′; $J_{3',4'}$ = 5.3 Hz), 5.26 (t, 1 H, H-2′; $J_{2',3'}$ = 5.3 Hz), 6.08 (d, 1 H, H-1′; $J_{1',2'}$ = 5.3 Hz), 7.13 (s, 1 H, H-2); mass spectrum, *m/z* 510 ($M^{+\cdot}$); $[\alpha]^{20}_D$ +6 (*c* 1.0, $CHCl_3$). Anal. ($C_{23}H_{42}N_4O_5Si_2$) C, H, N.

1-[3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-α-D-xylofuranosyl]-4-cyano-5-acetamidoimidazole (27). A solution of **26** (0.7 g, 1.37 mmol) and formamidine acetate (0.42 g, 4.13 mmol) in absolute ethanol (11 mL) (or ethoxyethanol) was heated under reflux for 5 h, when TLC indicated complete reaction. The solvent was removed under vacuum and the residue was stirred with 20 mL of CH_2Cl_2. The precipitated ammonium acetate salt was removed and the filtrate was concentrated and chromatographed on a silica gel column using EtOAc/$CHCl_3$ (15:85) to afford 0.45 g (64%) of **27**. The compound was crystallized from diethyl ether–petroleum ether: mp 101–103 °C; IR ($CHCl_3$) 2238 cm^{-1} (CN); UV (MeOH) λ_{max} 270 nm (10.6), 239 nm (sh, 9.6); ^1H NMR ($CDCl_3$) δ 0.01 and 0.03 (2 s, 2 × 6 H, 2 $Si(CH_3)_2$), 0.8 (s, 18 H, 2 $SiC(CH_3)_3$), 2.1 (s, 3 H, CH_3CO), 3.75 (d, 2 H, 2 H-5′; $J_{4',5'}$ = 4.5 Hz), 4.3–4.8 (m, 4 H, H-2′,3′,4′ + OH-2′), 5.8 (d, 1 H, H-1′; $J_{1',2'}$ = 3.0 Hz), 7.6 (s, 1 H, H-2), 9.1 (br s, 1 H, NH-5); mass spectrum, *m/z* 510 ($M^{+\cdot}$); $[\alpha]^{20}_D$ −59.7 (*c* 0.72, $CHCl_3$). Anal. ($C_{23}H_{42}N_4O_5Si_2$) C, H, N, Si.

1-[3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-α-D-xylofuranosyl]-4-cyano-5-aminoimidazole (28). Compounds **26** or **27** (0.17 g, 0.33 mmol) were dissolved in methanolic ammonia (10 mL) (previously saturated at 0 °C) and heated in a bomb at 80 °C for 15 h. Solvent was evaporated under vacuum and the residue chromatographed on a silica gel column using EtOAc/$CHCl_3$ (2:8) to afford in each case 0.15 g (96%) of **28**. The compound was crystallized from diethyl ether: mp 225–227 °C; UV (MeOH) λ_{max} 244 nm; ^1H NMR ($CDCl_3$) δ 0.15 (s, 6 H, 2 $SiCH_3$), 0.21 and 0.25 (2 s, 2 × 3 H, 2 $SiCH_3$), 0.98 and 1.01 (2 s, 2 × 9 H; 2 $SiC(CH_3)_3$), 3.74 (d, 2 H, 2 H-5′; $J_{4',5'}$ = 4.8 Hz), 4.3 (m, 3 H, H-2′,3′,4′), 4.4 (br s, 2 H, NH_2-5), 5.75 (d, 1 H, H-1′; $J_{1',2'}$ = 3.0 Hz), 5.7 (br s, 1 H, OH-2′); mass spectrum, *m/z* 468 ($M^{+\cdot}$); $[\alpha]^{20}_D$ −32.2 (*c* 0.56, $CHCl_3$). Anal. [$C_{21}H_{40}N_4O_4Si_2 \cdot {}^1/_2(C_2H_5)_2O$] C, H, N.

1-α-D-Xylofuranosyl-4-cyano-5-aminoimidazole (29). To 1.0 g (2.13 mmol) of **28** in anhydrous THF (5 mL) at room temperature was added with stirring to a solution of 1 M TBAF in anhydrous THF (5 mL). The resulting mixture was stirred for 16 h and then evaporated under vacuum. The residue was chromatographed on a silica gel column using MeOH/$CHCl_3$ (15:85) to afford 0.45 g (88%) of **29** as a syrup; UV (MeOH) λ_{max} 249 nm (11.6); ^1H NMR (Me_2SO-d_6) δ 3.3–3.7 (m, 2 H, H-5′,5″), 4.0–4.4 (m, 3 H, H-2′,3′,4′), 4.0–6.2 (br s, 3 H, OH-2′,3′,5′), 5.84 (d, 1 H, H-1′; $J_{1',2'}$ = 3.0 Hz), 6.10 (br s, 2 H, NH_2-5), 7.16 (s, 1 H, H-2); mass spectrum, *m/z* (relative intensity) 240 ($M^{+\cdot}$, 2), 108 (100); $[\alpha]^{20}_D$ −22 (*c* 0.5, Me_2SO).

9-α-D-Xylofuranosyladenine (30). A mixture of **29** (0.24 g, 1.0 mmol), ethanolic ammonia (25 mL) (previously saturated at 0 °C), and triethyl orthoformate (0.15 g, 10.1 mmol) was heated at 150 °C for 18 h in a bomb. After cooling to room temperature, the solution was filtered through Celite and evaporated to dryness. The residue was chromatographed on a silica gel column using MeOH/$CHCl_3$ (2:8) to afford 0.17 g (64%) of **30**. The compound was crystallized from MeOH: mp 98–100 °C; UV (pH 1, 0.1 N HCl) λ_{max} 258 nm, λ_{min} 231 nm; UV (H_2O) λ_{max} 260 nm (21.8), λ_{min} 226 nm (3.5); UV (pH 13, 0.1 N NaOH) λ_{max} 260 nm, λ_{min} 230 nm; ^1H NMR (Me_2SO-d_6) δ 3.5–3.8 (m, 2 H, H-5′,5″), 4.0–4.3 (m, 2 H, H-3′,4′), 4.3–4.5 (m, 1 H, H-2′), 4.66 (t, 1 H, OH-5′), 5.42 (d, 1 H, OH-2′ or 3′; $J_{(H,OH)-2'or3'}$ = 4.1 Hz), 5.72 (d, 1 H, OH-2′ or -3′; $J_{(H,OH)-2'or3'}$ = 4.6 Hz), 6.34 (d, 1 H, H-1′; $J_{1',2'}$ = 3.7 Hz), 7.23 (br s, 2 H, NH_2), 8.10 and 8.14 (2 s, 2 × 1 H, H-2 and H-8); mass spectrum, *m/z* (relative intensity) 267 ($M^{+\cdot}$, 10), 178 (47), 164 (76), 148 (14), 136 (48), 135 (100), 108 (33); $[\alpha]^{20}_D$ +26.2 (*c* 0.61, Me_2SO). Anal. ($C_{10}H_{13}N_5O_4 \cdot {}^2/_3H_2O$), C, H, N.

1-[3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-α-D-xylofuranosyl]-4-carbamoyl-5-[(*N*-benzoylthiocarbamoyl)amino]imidazole (31). To a stirred solution of **23** (3.0 g, 6.16 mmol) in anhydrous acetone (90 mL), benzoyl isothiocyanate (1.1 g, 6.74 mmol) in anhydrous acetone (10 mL) was added dropwise. The mixture was then refluxed for 1 h. The solvent was removed under reduced pressure and the residue chromatographed on a silica gel column using absolute ethanol/$CHCl_3$ (5:95). Evaporation of the appropriate fractions led to the isolation of **31** (2.7 g, 67%). The compound was crystallized from $CHCl_3/(C_3H_7)_2O$: mp 188–189 °C; UV (MeOH) λ_{max} 248 nm (24.8), 276 nm (sh); ^1H NMR ($CDCl_3$) δ 0.07 (s, 12 H, 4 $SiCH_3$), 0.83 and 0.90 (2 s, 2 × 9 H, 2 $SiC(CH_3)_3$), 3.8–4.0 (m, 2 H, H-5′,5″), 4.3, 5.7, 7.1, 9.7, and 12.1 (5 br s, 5 × 1 H, all D_2O exchangeable), 6.03 (d, 1 H, H-1′; $J_{1',2'}$ = 3.3 Hz), 7.5–8.1 (m, 6 H, H-2 + COC_6H_5); $[\alpha]^{20}_D$ +6 (*c* 1.0, $CHCl_3$). Anal. ($C_{29}H_{47}N_5O_6SSi_2$) C, H, N, S.

1-[3′-,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-α-D-xylofuranosyl]-4-carbamoyl-5-[(*N*-benzoyl-*S*-methylisothiocarbamoyl)amino]imidazole (32). Compound **31** (1.0 g, 1.54 mmol) was dissolved in 0.3 N methanolic sodium methoxide (7.7 mL). Methyl iodide (0.26 g, 1.83 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. The solution was acidified (approximately pH 6) with glacial acetic acid and then evaporated to dryness. The residue was chromatographed on a silica gel column using $CHCl_3$ to afford 0.83 g (81%) of pure **32** as a foam: UV (MeOH) λ_{max} 238 nm (25.5); ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H, 2 $SiCH_3$), 0.13 and 0.15 (2 s, 2 × 3 H, 2 $SiCH_3$), 0.93 and 0.95 (2 s, 2 × 9 H, 2 $SiC(CH_3)_3$), 2.53 (s, 3 H, SCH_3), 3.8–4.1 (m, 2 H, H-5′,5″), 4.0, 5.8, 7.3, and 10.8 (4 br s, 4 × 1 H, all D_2O exchangeable), 4.3–4.6 (m, 3 H, H-2′,3′,4′), 6.17 (d, 1 H, H-1′; $J_{1'2'}$ = 3.0 Hz), 7.4–8.1 (m, 6 H, H-2 + COC_6H_5); $[\alpha]^{20}_D$ +34.9 (*c* 0.66, $CHCl_3$).

9-α-D-Xylofuranosylguanine (33). Method A. A solution of **32** (0.46 g, 0.69 mmol) in 6 N aqueous sodium hydroxide (3.5 mL) was heated to reflux for 1 h. After cooling to room temperature the solution was neutralized to pH ca. 7.0 by addition of 2 N hydrochloric acid and then filtered. TLC of the filtrate (*i*-PrOH/NH_4OH (20%)/H_2O, 6:3:1) showed a major spot (R_f 0.47) which corresponded to **33** and a minor spot (R_f 0.56). Purification of **33** was accomplished by HPLC: the column (61 cm × 7.8 mm i.d.) was packed with C_{18}/Porasil B Bondapak (37–75 μm); the eluent was H_2O at a flow rate of 10 mL/min. Evaporation of the appropriate fractions and trituration with H_2O gave 0.05 g (26%) of **33**: mp 186 °C, start of decomposition (lit.[92] mp 260–261 °C); UV (pH 1, 0.1 N HCl) λ_{max} 255 nm (11.6), 278 nm (sh, 7.9); λ_{min} 227 nm (2.8); UV (H_2O) λ_{max} 252 nm, 272 nm (sh); λ_{min} 224 nm; UV (pH 13, 0.1 N NaOH) λ_{max} 266 nm; λ_{min} 231 nm; ^1H NMR (Me_2SO-d_6) δ 3.6 (m, 2 H, H-5′,5″), 4.0, 4.2, and 4.3 (3 m, 3 × 1 H, H-2′,3′,4′), 4.6 (m, 1 H, OH-5′), 5.4 (m, 1 H, OH-2′ or -3′), 5.70 (d, 1 H, OH-2′ or -3′; $J_{(H,OH)-2'or3'}$ = 4.5 Hz), 6.11 (d, 1 H, H-1′; $J_{1',2'}$ = 3.8 Hz), 6.5 (br s, 2 H, NH_2), 7.67 (s, 1 H, H-8), 10.6 (br s, 1 H, NH-1); $[\alpha]^{20}_D$ −17.1 (*c* 0.76, Me_2SO) [lit.[92] $[\alpha]^{20}_D$ −15.3 (*c* 0.5, H_2O)]. Anal. ($C_{10}H_{13}N_5O_5 \cdot {}^2/_3H_2O$) C, H, N.

Method B. To a solution of sodium hydroxide (0.70 g, 17.45 mmol) in anhydrous methanol (6.5 mL) was added compound **24** (0.9 g, 3.49 mmol) and then carbon disulfide (1.33 g, 1.05 mL, 17.45 mmol). The reaction mixture was heated in a bomb at 180 °C for 3 h. After cooling to 0 °C, the bomb was opened and the reaction mixture was evaporated under vacuum. The residue was dissolved in water (11 mL) and 30% hydrogen peroxide (1.98 g, 1.8 mL, 17.45 mmol) was added at 5 °C with stirring. After 1 h, the solution was saturated with ammonia at 0 °C and then heated in a bomb at 120 °C for 2 h. The reaction mixture was evaporated to dryness and three times coevaporated with water. The residue was dissolved in water (20 mL) and TLC (*i*-PrOH/NH_4OH (20%)/H_2O, 6:3:1) showed three spots (R_f 0.53, 0.47, and 0.40),

that of R_f 0.47 corresponding to **33**. The pH of the solution was adjusted to ca. 7.0 by addition of Dowex 50 W×2 (pyridinium) ion-exchange resin. The resin was filtered and washed well with warm water. The combined washing and filtrate were evaporated to dryness, dissolved in a small quantity of water, and applied to a column (2 × 20 cm) of Dowex 50 W×2 (H^+) resin. The column was washed with water (ca. 5 L) until the eluate exhibited no UV_{254} absorption, and then compound **33** was eluted with an aqueous solution of 1.08 N ammonium hydroxide. Concentration of the latter eluate and precipitation from water afforded 0.29 g (29%) of **33**, identical with that obtained by using method A.

2-Amino-α-D-xylofuran[1′,2′:4,5]-2-oxazoline (36). A mixture of D-xylose (50 g, 333 mmol), cyanamide (17.3 g, 410 mmol), and powdered potassium bicarbonate (1.68 g, 20 mmol) was stirred at 90 °C for 1 h in DMF (330 mL). After cooling to room temperature, the solution was half-evaporated and stored for 20 h in the cold (−15 °C). The precipitate was collected and recrystallized from water and then from EtOH–H_2O (4:1) to give 18 g of **36**. The filtrate was concentrated under vacuum and recrystallized to give a second crop of crystals (7 g). The combined yield was 25 g (43%): mp 185–187 °C (lit. mp 164 °C;[38] 163–167 °C[161]). Its other physical properties were in close agreement with literature data.[38,161] Anal. ($C_6H_{10}N_2O_4$) C, H, N.

O^2,$O^{2'}$-Anhydro-1-α-D-xylofuranosyluracil (37). This compound was synthesized with only minor modification of the method of Holy.[38] From a mixture of **36** (15 g, 86.1 mmol) in 50% aqueous ethanol (200 mL) and methyl propiolate (25 g, 297.3 mmol), 8.2 g (42%) of pure **37** was obtained after crystallization from H_2O/MeOH: mp 265–267 °C (lit. mp >250 °C;[38] 255–260 °C[162]). Its other physical properties were in close agreement with literature data.[38,141] Anal. ($C_9H_{10}N_2O_5$) C, H, N.

1-α-D-Xylofuranosyluracil (38). A solution of **37** (6.12 g, 27.1 mmol) in 0.5 N hydrochloric acid (30 mL) was refluxed for 1 h. After cooling to room temperature, the pH of the solution was adjusted to ca. 8.0 by addition of Duolite A102D (OH^-) ion-exchange resin. The resin was filtered and washed well with warm water. The combined washing and filtrate were evaporated to dryness. The residue was chromatographed on a silica gel column using MeOH/$CHCl_3$ (15:85) to afford 4.7 g (71%) of **38** which crystallized from absolute ethanol: mp 192–194 °C (lit.[38] 208 °C). Anal. ($C_9H_{12}N_2O_6$) C, H, N.

1-(2′,3′,5′-Tri-O-benzoyl-α-D-xylofuranosyl)uracil (39). To a solution of **38** (2.0 g, 8.19 mmol) in anhydrous pyridine (40 mL) was added dropwise with stirring and cooling in an ice bath a solution of benzoyl chloride (3.18 mL, 27.0 mmol) in anhydrous pyridine (20 mL). The solution of the reactant and the reaction mixture were protected from atmospheric moisture. After the addition of the benzoyl chloride was complete, the reaction mixture was heated at 55–60 °C for 48 h. After routine treatment, TLC (MeOH/$CHCl_3$, 3:97) showed a mixture of the desired tribenzoyl derivative **39** and a tetrabenzoyl derivative **40** (minor amount). The surplus benzoyl group on the pyrimidine ring was then selectively removed in a weakly acidic medium as described in the carbocyclic series.[163] Chromatography on a silica gel column using CH_2Cl_2 led, after evaporation of the appropriate fractions, to the isolation of **39** (3.8 g, 83%) as a white foam: UV (EtOH) λ_{max} 260 nm (sh), 233 nm; ^1H NMR ($CDCl_3$) δ 4.64 (d, 2 H, 2 H-5′; $J_{4',5'}$ = 5.5 Hz), 5.1 (m, 1 H, H-4′), 5.62 (dd, 1 H, H-5; $J_{5,6}$ = 8.3 Hz); $J_{5,NH-3}$ = 1.9 Hz), 5.88 (dd, 1 H, H-2′ or -3′), 6.02 (dd, 1 H, H-2′ or -3′), 6.58 (d, 1 H, H-1′; $J_{1',2'}$ = 4.3 Hz), 7.3–8.2 (m, 16 H, 3 C_6H_5CO + H-6), 9.3 (br s, 1 H, NH-3). This compound was used directly without further purification for the preparation of **41**.

1-(2′,3′,5′-Tri-O-benzoyl-α-D-xylofuranosyl)-4-thiouracil (41). Phosphorus pentasulfide (3.99 g, 18.3 mmol) was added to a solution of 80 mL of pyridine containing 2.5 g (4.5 mmol) of **39**. The mixture was refluxed for 4 h, concentrated to approximately one-half of the volume, and poured with stirring into cold water (150 mL) and the solvent was decanted from an oily residue. The residue was dissolved in chloroform, washed twice with water, dried over sodium sulfate, filtered, and concentrated to dryness under vacuum. Chromatography on a silica gel column using $CHCl_3$ led, after evaporation of the appropriate fractions, to the isolation of **41** (2.3 g, 89%): UV (EtOH) λ_{max} 320 nm, 233 nm; ^1H NMR ($CDCl_3$) δ 4.66 (d, 2 H, 2 H-5′; $J_{4',5'}$ = 5.5 Hz), 5.1 (m, 1 H, H-4′), 5.95 (dd, 1 H, H-2′ or -3′), 6.04 (dd, 1 H, H2′ or -3′), 6.59 (dd, 1 H, H-5; $J_{5,6}$ = 7.8 Hz; $J_{5,NH-3}$ = 2.0 Hz), 6.55 (d, 1 H, H-1′; $J_{1',2'}$ = 4.0 Hz), 7.2–8.2 (m, 16 H, 3 C_6H_5CO + H-6), 9.9 (br s, 1 H, NH-3). This compound was used directly without further purification for the preparation of **42**.

1-α-D-Xylofuranosylcytosine (42). Compound **41** (1.2 g, 2.1 mmol) was treated with 80 mL of methanolic ammonia (previously saturated at 0 °C) in a bomb at 100 °C for 18 h. After cooling to room temperature, the solution was concentrated to dryness and the residue dissolved in water (150 mL). The aqueous solution was extracted successively with chloroform and carbon tetrachloride (3 × 100 mL each) to remove benzamide and methyl benzoate. The aqueous layer was treated with active charcoal, filtered through Celite, and evaporated to dryness. Chromatography of the residue on a silica gel column using MeOH/$CHCl_3$ (4:6) led, after evaporation of the appropriate fractions, to the isolation of pure **42** (0.39 g, 76%), which was crystallized from EtOH: mp 264–266 °C decomposition (lit. mp 263–264 °C decomposition[141-142]). Anal. Calcd for ($C_9H_{13}N_3O_5 \cdot {}^1/_3H_2O$) C, H, N.

1-α-D-Xylofuranosyl-5-(piperidinomethyl)uracil (43). To a solution of **38** (2.0 g, 8.19 mmol) and piperidine 6.28 mL, 65.6 mmol) in water (14 mL) was added dropwise, with stirring and cooling at ca. 5 °C, a solution of 35% aqueous formaldehyde (5.18 mL, 65.6 mmol). The mixture was heated at 60 °C for 16 h in a bomb and then cooled to room temperature. TLC (*tert*-butyl alcohol/methyl ethyl ketone/NH_4OH (20%)/H_2O, 20:15:5:10) revealed the presence of at least four new compounds, the main one having the highest R_f value. The residue obtained by evaporation to dryness was chromatographed on a silica gel column using MeOH/$CHCl_3$ (2:8) to afford 0.98 g (35%) of **43** as a hygroscopic powder after trituration with diethyl ether: mp 52 °C, start of decomposition; UV (pH 1, 0.1 N HCl) λ_{max} 268 nm, λ_{min} 234 nm; UV (H_2O) λ_{max} 268 nm, λ_{min} 234 nm; UV (pH 13, 0.1 N NaOH) λ_{max} 268 nm, λ_{min} 245; ^1H NMR (MeSO-d_6) δ 1.2–1.8 (m, 6 H, H-β,γ), 2.3–2.6 (m, 4 H, H-α), 2.9–3.1 (m, ≃1 H, no attributed signal), 3.1–3.3 and 3.5–3.7 (2 m, 2 × 2 H, H-5′,5″ and CCH_2N), 3.9–4.4 (m, 3 H, H-2′,3′,4′), 4.8–7.0 (br s, 4 H, OH-2′,3′,5′ + NH-3), 6.05 (d, 1 H, H-1′; $J_{1',2'}$ = 3.0 Hz), 7.40 (s, 1 H, H-6), 8.42 (s, 0.5 H, no attributed signal). This compound was sufficiently pure to be used without further purification for the preparation of **44**.

1-α-D-Xylofuranosylthymine (44). Compound **43** (0.32 g, 0.94 mmol) in 20 mL of 80% ethanol was hydrogenated over 10% palladium on carbon (50 mg) at 42 °C and atmospheric pressure for 48 h. The catalyst was removed and washed with warm 50% ethanol, and the combined washing and filtrate were evaporated to dryness. The residue was chromatographed on a silica gel column using MeOH/$CHCl_3$ (75:925) to afford 0.16 g (66%) of **44**. The compound crystallized from absolute ethanol: mp 196–197 °C; UV (pH 1, 0.1 N HCl) λ_{max} 268 nm, λ_{min} 235 nm; UV (H_2O) λ_{max} 269 nm (11.6), λ_{min} 236 nm (2.7); UV (pH 13, 0.1 N NaOH) λ_{max} 269 nm, λ_{min} 248; ^1H NMR (Me_2SO-d_6) δ 1.78 (s, 3 H, CH_3), 3.5–3.7 (m, 2 H, H-5′,5″), 3.9–4.1 (m, 2 H, H-4′ and -2′ or -3′), 4.2–4.4 (m, 1 H, H-2′ or -3′), 4.64 (t, 1 H, OH-5′; $J_{(H,OH)-5'}$ = 5.5 Hz), 5.28 (d, 1 H, OH-2′ or -3′; $J_{(H,OH)-2'or3'}$ = 3.8 Hz), 5.58 (d, 1 H, OH-2′ or -3′; $J_{(H,OH)-2'or3'}$ = 4.3 Hz), 6.01 (d, 1 H, H-1′; $J_{1',2'}$ = 3.1 Hz), 7.27 (s, 1 H, H-6), 11.2 (br s, 1 H, NH-3); mass spectrum, *m/z* (relative intensity) 258 (M^+, 22), 227 (21), 169 (20), 160 (23), 155 (25), 133 (19), 127 (78), 126 (100); $[\alpha]^{20}_D$ −56.7 (*c* 0.97, Me_2SO). Anal. ($C_{10}H_{14}N_2O_6$) C, H, N.

Biological Methods. Assays on Cell Culture. The origin of the viruses and the techniques used for measuring inhibition of virus-induced cytopathogenicity and virus replication have been described previously.[164] The methods for measuring inhibition of cell growth and cellular DNA, RNA, and protein synthesis have also been described.[165]

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The effects compounds 11, 12, and 15 on the multiplication of mouse myeloma cells SP2 was assessed by growing these cells in suspension and determining their number at 0, 48, and 96 h. The test compounds were dissolved in the growth medium at a concentration of 100, 10, or 1 μg/mL or less.

Assays on Animals. For evaluation of the acute toxicity for mice, the compounds were suspended with 0.2 g of Tween 80 and 0.2 g of (carboxymethyl)cellulose/100 mL of distilled water and administered intraperitoneally to Swiss mice (Iffa Credo, 20–24 g) as a single dose of 100–2.000 mg/kg. The follow-up period was 14 days.

For evaluation of the effects of the compounds on herpetic encephalitis, young mice, weighing 10 g, were inoculated intracerebrally with 0.03 mL of an herpes simplex virus suspension containing ca. 4 $CCID_{50}$. The compounds were administered at 75 or 150 mg/kg per day, given as two daily intraperitoneal injections, for 4 days. This treatment was started immediately after virus inoculation. The animals were observed during 21 days.

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Synthesis and Antiviral Activity of (*E*)-5-(2-Bromovinyl)uracil and (*E*)-5-(2-Bromovinyl)uridine

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(*E*)-5-(2-Bromovinyl)uracil (BVU) and (*E*)-5-(2-bromovinyl)uridine (BVRU) were synthesized starting from 5-formyluracil via (*E*)-5-(2-carboxyvinyl)uracil or starting from 5-iodouridine via (*E*)-5-(2-carbomethoxyvinyl)uridine and (*E*)-5-(2-carboxyvinyl)uridine, respectively. Depending on the choice of the cell system, BVU and BVRU exhibited a marked activity against herpes simplex virus type 1 (HSV-1) in vitro. Although BVU and BVRU were less potent than the reference compound (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU), their antiviral activity spectrum was remarkably similar to that of BVDU. The latter findings suggest that BVU and BVRU are metabolically converted to BVDU or a phosphorylated product thereof. In vivo, BVU protected mice against a lethal disseminated HSV-1 infection.

BVDU [(*E*)-5-(2-bromovinyl)-2′-deoxyuridine]ranks among the most potent and selective inhibitors of herpes simplex virus type 1 (HSV-1) and varicella-zoster virus (VZV) replication.[1-3] It appears to be a promising drug for the systemic (oral) treatment of VZV infections in immunosuppressed patients,[4-6] as well as for topical treatment of HSV-1 keratitis.[7,8] However, BVDU is not a very efficient inhibitor of herpes simplex virus type 2 (HSV-2),[2] and in attempts to potentiate its activity against HSV-2, several derivatives of BVDU have been prepared with modification in either the pyrimidine or sugar moiety: i.e. IVDU [(*E*)-5-(2-iodovinyl)-2′-deoxyuridine],[1] (*E*)-5-(1-propenyl)-2′-deoxyuridine,[9,10] (*E*)-5-(3,3,3-trifluoro-1-propenyl)-2′-deoxyuridine,[11] (*E*)-5-(2-bromovinyl)-2′-deoxycytidine,[12] 1-β-D-arabinofuranosyl-(*E*)-5-(2-bromovinyl)uracil,[13,14] (*E*)-5-(2-bromovinyl)-3′-amino-2′,3′-dideoxyuridine,[15] and the carbocyclic analogues of BVDU and IVDU.[16]

All these BVDU analogues share a common activity spectrum, in that they are very active against HSV-1 and VZV, much less active against HSV-2, and inactive against dThd kinase-deficient (TK^-) strains of HSV-1. It has also become obvious that these analogues follow a mechanism of action that is similar, if not identical, to that of BVDU itself. The mode of action of BVDU is essentially based upon (i) a specific affinity for the virus-encoded dThd

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