of solid free base. This material was dissolved in EtOH (75 mL). The solution was treated with 7.5 N HCl in 2-propanol (2 mL, 15 mmol) and then diluted with Et_2O (100 mL). Filtration gave 4.9 g (66%) as the first crop of title compound, mp 225–228 °C. Recrystallization from EtOH–Et_2O raised the melting point to 228–231 °C.

6-Methoxy-4-methyl-8-nitro-5-[[3-(trifluoromethyl)benzyl]oxy]quinoline (9). A 12-L flask was charged with 5-hydroxy-6-methoxy-4-methyl-8-nitroquinoline[1] (225 g, 0.961 mol), 3-(trifluoromethyl)benzyl chloride (225 g, 1.16 mol), tetrabutylammonium hydroxide (40% in water, 700 g), and chlorobenzene (5 L). The mixture was stirred at 60–65 °C for 5 days, cooled, and filtered. The filtrate was diluted with methylene chloride (4 L), washed with water (2 × 5 L), dried ($MgSO_4$), and concentrated to a thick syrup, which was chromatographed on an aluminum oxide column and eluted with methylene chloride. The product fraction was collected and concentrated to a thick oil, which was slurried in ether–petroleum ether (1:1) to give the title compound, 171 g (45%), mp 105–107 °C. This material was used without further purification in the next step.

Similarly prepared was **5-(1-hexyloxy)-6-methoxy-4-methyl-8-nitroquinoline (18)** (Table II).

8-Amino-6-methoxy-4-methyl-5-[[3-(trifluoromethyl)benzyl]oxy]quinoline (10). A 2-L Parr bottle was charged with 8-nitroquinoline **9** (50 g, 0.127 mol) in warm (45 °C) THF–ethanol (750 mL:200 mL). Platinum oxide (3.75 g) was added to the solution and the mixture was hydrogenated at 50 psig until 3.1 equiv of H_2 was absorbed (about 5–7 min). The reaction mixture was cooled and filtered (Celite). The filtrate was concentrated to an oil, which was slurried in hexane to yield crude product. The crude products from three runs were combined, dissolved in ether, and treated with charcoal. After filtering (Celite), the filtrate was concentrated and diluted with hexane to yield the title compound, 89 g (64%), mp 80–82 °C. This material was used without further purification.

8-Amino-5-(1-hexyloxy)-6-methoxy-4-methylquinoline (19). This material was prepared via the reduction conditions reported by Campbell et al.[6] A mixture of 8-nitroquinoline **18** (88.3 g, 0.277 mol), water (140 mL), dibutyl ether (140 mL), and acetic acid (140 mL) was heated on a steam bath to give a homogeneous solution. The solution was cooled to 70 °C and iron filings (140 g, 2.5 mol) were added portionwise over a 20-min period. The mixture exothermed to 95 °C and was allowed to cool for 60 min. The mixture was then heated at 95 °C for 18 h, cooled, and filtered. The solid was slurried with ether (3 × 1800 mL) and the slurry was filtered. The combined ether extracts were concentrated to 500 mL, washed with 2% aqueous NaOH, dried ($MgSO_4$), treated with Norit A, and filtered (Celite). The filtrate from the original reaction mixture was extracted with ether (2 × 500 mL). The combined ether extract was washed with 2% NaOH and dried ($MgSO_4$). The ether layers were combined and concentrated to a green semisolid (140 g). This material was recrystallized from petroleum ether to give 58 g (72.5%) of pure product, mp 70–71 °C.

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Synthesis and Antiviral Activity of 3′-*C*-Cyano-3′-deoxynucleosides

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A series of 3′-*C*-cyano-3′-deoxynucleosides have been synthesized and evaluated as antiviral agents. Reaction of 2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuranos-3′-ulosyl derivatives of uracil, 4-*N*-acetylcytosine, and adenine with sodium cyanide gave a mixture of epimeric cyanohydrins, which after 3′-deoxygenation yielded the corresponding 3′-*C*-cyano-3′-deoxy-β-D-*xylo*-pentofuranosyl derivatives **10**. These compounds were epimerized to the corresponding β-D-*ribo*-pentofuranosyl derivatives **11**. Desilylation of **10** and **11** gave the deprotected 3′-*C*-cyano-3′-deoxy-β-D-*xylo*- and -*ribo*-pentofuranosyl nucleosides. These derivatives of uridine, cytidine, and adenine, as well as the 3′-*C*-cyano-3′-deoxy-β-D-*xylo*- and -*ribo*-pentofuranosyl, 3′-*C*-cyano-2′,3′-dideoxy-β-D-*threo*- and -*erythro*-pentofuranosyl, and 3′-*C*-cyano-2′,3′-dideoxy-β-D-*glycero*-pent-2′-enofuranosyl derivatives of thymine, were evaluated for their antiviral activity. None of the compounds proved active against the replication of retroviruses (human immunodeficiency virus, murine sarcoma virus) at concentrations that were not toxic to the host cells. However, the 3′-*C*-cyano-3′-deoxy-β-D-*xylo*- (**12e**) and -*ribo*-pentofuranosyl (**13e**) derivatives of adenine showed activity against some DNA (i.e., vaccinia) and RNA (i.e., Sindbis, Semliki forest) viruses at concentrations well below the cytotoxicity threshold.

A number of sugar-modified nucleosides show antiviral activity.[1] These compounds may interfere with viral encoded enzymes which catalyze reactions that only occur in the virus-infected cell.[2] This is the case for the potent and selective anti-human immunodeficiency virus (HIV) agents 2′,3′-dideoxynucleosides **1–4**, which in their 5′-triphosphate form interfere with the HIV reverse transcriptase,[3,4] an enzyme specific for retroviruses. Other sugar-modified nucleosides, such as various arabinofuranosyl,[5,6]

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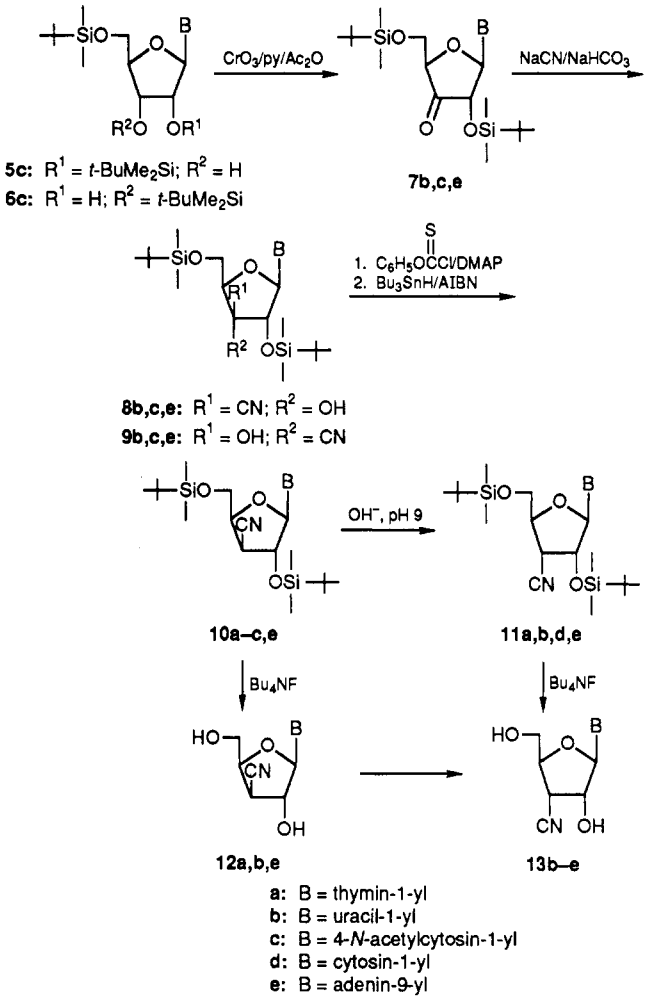
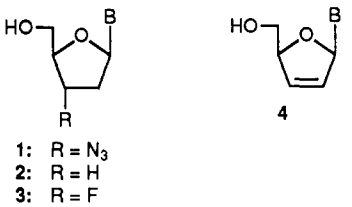
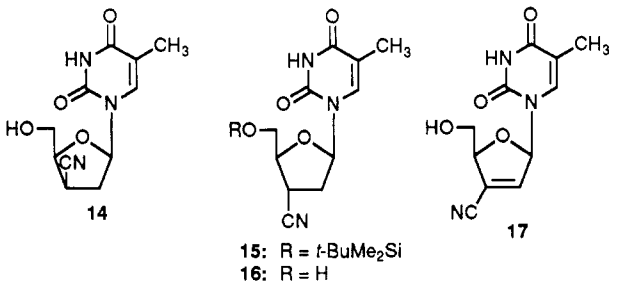
Scheme I



acyclic,[5–7] and carbocyclic[5,6,8] derivatives, may produce a selective antiviral activity by interference with enzymes that normally also occur in the host cell.



Some members of the branched-chain sugar nucleosides also show antiviral activity. Thus, oxetanocin,[9] a naturally occurring nucleoside, and its derivatives are active against HIV[10] and herpes viruses.[9,11] 3′-*C*-Methylcytidine and 2′- and 3′-*C*-methyladenosines are effective as anti-vaccinia agents in mice[12] and also inhibit the growth of KB cells in vitro.[13] These reports stimulated our interest in the branched-chain sugar nucleosides and prompted us to synthesize and evaluate 3′-*C*-cyano-3′-deoxynucleosides for their antiviral effects. Of this series, 3′-*C*-Cyano-3′-deoxythymidine (**16**) is structurally related to 3′-azido-3′-deoxythymidine (AZT, Retrovir) (**1**, B = thymin-1-yl), which has recently been licensed as an anti-AIDS agent in humans. Several recent papers from this and other laboratories reported different approaches for the synthesis of *C*-cyano branched-chain sugar nucleosides.[14–17] Our approach[16] involved the reaction of 1-[2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuranos-3′-ulosyl]-thymine with sodium cyanide followed by deoxygenation of the cyanohydrin formed. We have used this procedure for the synthesis of a variety of 3′-*C*-cyano-3′-deoxy-derivatives of 1-(β-D-pentofuranosyl)thymine, such as **10a**, **11a**, **12a**, and **14–17**.[16] In the present paper we extend this procedure for the synthesis of 3′-*C*-cyano-3′-deoxypento-furanosyl derivatives of uracil, cytosine, and adenine and report the antiviral effects of the 3′-*C*-cyanonucleoside derivatives of all four mentioned bases.



Chemistry

Reaction of 4-*N*-acetylcytidine[21] with 3 equiv of *tert*-butyldimethylsilyl chloride afforded a mixture of the two possible 2′,5′- and 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl) derivatives **5c** and **6c** in 65% and 10% yield, respectively (see Scheme I). Oxidation of **5c** with CrO_3/pyridine/Ac_2O[22] gave the 4-*N*-acetyl-1-(β-D-*erythro*-pentofuranos-3′-ulosyl)cytosine **7c** in 75% yield. Treatment of the 3′-ketonucleosides derived from uracil **7b**,[22] 4-*N*-acetylcytosine **7c**, and adenine **7e**[22] with sodium cyanide in a two-phase ethyl ether/water system, in the presence of sodium bicarbonate, gave in each case a (1:10) mixture of the two epimeric nucleoside 3′-cyanohydrins **8** and **9**. These cyanohydrins, on standing in solution, reversed to the corresponding ketonucleosides **7**, used as starting materials. Thus, they were not isolated, and they were used without further purification for the next step. Deoxygenation[23,24] at the 3′-position of the mixtures **8** + **9**,

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Table I. Antiretroviral Activity of 3′-*C*-Cyano-3′-deoxy Derivatives of Adenosine, Cytidine, Uridine, and Thymidine

	HIV-induced cytopathogenicity in MT-4 cells			MSV-induced transformation of C3H cells		
compd	ED_{50},[a] μM	CD_{50},[b] μM	therapeutic index (ratio ID_{50}/ED_{50})	ED_{50},[c] μg/mL	MCC,[d] μg/mL	therapeutic index (ratio MIC/ED_{50})
10b	>0.64	1.6 ± 0.3	<2.5	2.2 ± 0.7	≥3.2	≥1.5
10c	>3.2	4.8 ± 2.8	<1.5	>3.2	≥3.2	≤1
10e	>16	25 ± 2.3	<1.6	>16	80	<5
11b	3.2	6.6 ± 0.01	2.1	5.6 ± 1.1	≥8	≥1.4
11d	>3.2	6.1 ± 0.3	<1.9	>1.6	8	<5
11e	2.1 ± 0.6	5.1 ± 2.3	2.4	>1.6	8	<5
12a	>250	232 ± 25	<0.9	>250	>250	
12b	>400	>400		260 ± 20	400	1.5
12e[e]	>1.6	2.9 ± 0.7	<1.8	6.6 ± 1.3	≥40	≥6.1
13b	>80	147 ± 2.0	<1.8	>200	>200	
13d	>10	22.7 ± 0.1	<2.3	43 ± 7.8	>200	>4.7
13e[e]	>1.6	3.8 ± 0.1	<2.4	8.5 ± 6.7	≥40	≥4.7
14	>250	>250		>250	>250	
15	>16	31 ± 3.8	<1.9	>16	80	<5
16	>16	30 ± 7.7	<1.9	>16	80	<5
17	>50	24 ± 1.1	<0.5	191 ± 9	>250	>1.3

[a] 50% effective dose, achieving a 50% protection of MT-4 cells against the cytopathic effect of HIV. [b] 50% cytotoxic dose, required to reduce the viability of normal uninfected MT-4 cells by 50%. [c] Effective dose, achieving a 50% reduction in the MSV-induced transformation of C3H cells. [d] Minimal cytotoxic concentration, resulting in a microscopically visible alteration of cell morphology. [e] An aqueous solution of compound **12e** epimerized to **13e** by 50% after 3 days.

by treatment with (phenyloxy)thiocarbonyl chloride and 4-(dimethylamino)pyridine followed by reaction with tributyltin hydride in the presence of α,α′-azobis[isobutyronitrile], afforded stereoselectively the 3′-*C*-cyano-3′-deoxyxylofuranosyl derivatives of uracil **10b**, 4-*N*-acetylcytosine **10c**, and adenine **10e**, in 68%, 65%, and 63% yield, respectively.

The β-D-xylo nucleosides **10b** and **10e** were epimerized to the corresponding β-D-ribo epimers **11b** (72%, reflux) and **11e** (78%, room temperature) by treatment with a methanolic NaOH solution up to pH 9. The same basic treatment of **10c** at room temperature resulted in 3′-epimerization and 4-N-deacetylation of the starting compound to afford **11d** in 71% yield.

Finally, treatment of **10b**, **10e**, **11b**, **11d**, and **11e** with tetrabutylammonium fluoride afforded the corresponding 3′-*C*-cyano-β-D-xylo deprotected nucleosides **12b** and **12e** and 3′-*C*-cyano-β-D-ribo deprotected nucleosides **13b**, **13d**, and **13e**, respectively. The deprotected xylo derivatives **12b** and **12e** were somewhat unstable and, on standing in dimethyl sulfoxide or water solution at room temperature, slowly epimerized to the corresponding ribo epimers **13**. Epimerization did not occur to a noticeable extent during crystallization from boiling ethyl acetate. In crystalline form the compounds are stable. The analytical and spectral data reported for partly unstable compounds **12b** and **12e** are reliable since they have been obtained from crystalline compounds or from freshly prepared solutions. The deprotected β-D-xylo derivative of 4-*N*-acetylcytidine **12c** was very unstable and could not be isolated. Thus, reaction of **10c** with tetrabutylammonium fluoride, as before, gave not only removal of the 2′ and 5′ silyl groups but also epimerization of the 3′-*C*-cyano group to afford **13c** in 72% yield. This β-D-ribo compound, which was stable, was 4-N-deacetylated to give 3′-*C*-cyano-3′-deoxycytidine (**13d**), in 70% yield, by treatment with a solution of NaOH in methanol.

The presence of a 3′-*C*-cyano-3′-deoxy grouping in nucleosides **10b**,**c**,**e**, **11b**,**d**,**e**, **12b**,**e**, and **13b**–**e** was demonstrated as follows. The IR spectra showed a band at 2225–2235 cm^{-1} characteristic of CN group. The ^1H NMR spectra of **10b**,**c**,**e**, **11b**,**d**,**e**, **12b**,**e**, and **13b**–**e** showed the presence of H-3′, as a doublet of doublets by coupling with H-2′ and H-4′, at δ 3.19–3.85, and the ^{13}C NMR spectra showed a signal at δ 114.95–120.24 assigned to the CN carbon atom and a signal at δ 34.83–38.98 assigned to C-3′.

The assignment of absolute configuration at C-3′ of the xylo and ribo 3′-*C*-cyanonucleosides **10b**,**c**,**e**–**13b**–**e** was made by comparing their ^1H and ^{13}C NMR parameters with those previously reported for the thymidine derivatives **10a**, **11a**, and **12a**, the stereochemistry of which had been unequivocally determined.[16] The coupling constants of the furanose ring protons observed for the 3′-*C*-cyano-3′-deoxy-β-D-*xylo*- (**10b**–**e**) ($J_{1',2'}$ = 4.0–6.5, $J_{2',3'}$ = 5.5–7.5, $J_{3',4'}$ = 7.0–7.5 Hz) and -*ribo*-pentofuranosyl nucleosides (**11b**–**e**) ($J_{1',2'}$ = 0, $J_{2',3'}$ = 4–4.5, $J_{3',4'}$ = 10–12.5 Hz) are in agreement with those reported for **10a** ($J_{1',2'}$ = 6, $J_{2',3'}$ = 7.3, $J_{3',4'}$ = 8 Hz) and **11a** ($J_{1',2'}$ = 0.8, $J_{2',3'}$ = 4.4, $J_{3',4'}$ = 10.0 Hz).[16] These coupling constants are also in a reasonably good agreement with those reported in the literature for other 3′-*C*-branched-3′-deoxy-β-D-*xylo*- ($J_{1',2'}$ = 5.1–7.2, $J_{2',3'}$ = 8.8–11.4, $J_{3',4'}$ = 8.8 Hz)[26] and -*ribo*-pentofuranosyl nucleosides ($J_{1',2'}$ = 0–1.5, $J_{2',3'}$ = 5–5.5 Hz).[25,28-30] This suggests that these coupling constant values could be used to assign the C-3′ configuration of an unknown 3′-*C*-branched-chain sugar nucleoside.

The stereochemical assignments for the present 3′-*C*-cyano-3′-deoxynucleosides are in agreement with the mechanisms accepted for the transformations **7** → **13**. The xylo configuration of compounds **10**, resulted from 3′-deoxygenation of cyanohydrins **8** and **9**, can be explained by the relative steric hindrance of the α and β faces of the furanose ring, which facilitates the approach of the tributyltin hydride from the less hindered side of the molecule.[23] In this case, the hydrogen enters from the α face, opposite to the base and the 5′-O-substituent. The assignment of the α face as the less hindered side of the

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Table II. Cytotoxicity and Antiviral Activity of 3'-C-Cyano-3'-deoxynucleoside Derivatives in Primary Rabbit Kidney Cell Cultures

compd	min cytotoxic concn,[a] μg/mL	min inhibitory concn[b] (MIC), μg/mL			
		herpes simplex virus 1 (KOS)	herpes simplex virus 2 (G)	vaccinia virus	vesicular stomatitis virus
10b	≥4	>1	>1	>1	>1
10c	≥4	>1	>1	>1	2
10e	≥100	>40	>40	>40	>40
11b	≥10	>4	>4	>4	>4
11d	≥10	>4	>4	>4	>4
11e	10	>4	>4	>4	>4
12a	400	150	150	150	>200
12b	≥200	>200	>200	>200	>200
12e[c]	200	>200	>200	4	>200
13b	>200	>200	>200	>200	>200
13d	≥100	70	70	40	>100
13e[c]	100	>40	>40	4	>100
14	>400	>400	>400	>400	>400
15	100	>40	>40	>40	>40
16	100	>40	20	20	>40
17	200	>100	>100	>100	>100
tubercidin	≥0.4	0.4	0.4	>0.1	0.07
(S)-DHPA	≥400	>400	>400	20	20
ribavirin	>400	>400	>400	10	300
carbocyclic 3-deazaadenosine	>400	>400	>400	2	0.7

[a] Required to cause a microscopically detectable alteration of normal cell morphology. [b] Required to reduce virus-induced cytopathogenicity by 50%. [c] An aqueous solution of compound **12e** epimerized to **13e** by 50% after 3 days.

furanose ring is in agreement with the epimerizations of **10** to **11**, and of **12** to **13**, in which the cyano group easily moves from the β face to the α face, to give the thermodinamically more stable β-D-ribo nucleosides **11** and **13**.

Antiviral Activity

The 3'-C-cyano-3'-deoxy derivatives of adenosine, cytidine, uridine, and thymidine were evaluated on their inhibitory effects of the replication of a number of viruses including HIV in human MT-4 cells, Moloney murine sarcoma virus (MSV) in murine C3H embryo fibroblast cells (Table I), herpes simplex virus type 1, herpes simplex virus type 2, vaccinia virus and vesicular stomatitis virus in primary rabbit kidney cell cultures (Table II), vesicular stomatitis virus, Coxsackie virus B4 and polio virus 1 in HeLa cells (Table III), and parainfluenza 3 virus, reovirus 1, Sindbis virus, Coxsackie virus B4, and Semliki forest virus in vero cell cultures (Table IV).

None of the compounds showed marked anti-HIV or anti-MSV activity at a concentration that was significantly below their toxicity threshold (Table I). The cyanonucleosides 3'-C-cyano-3'-deoxythymidine (**16**) and 1-(3'-C-cyano-2',3'-dideoxy-β-D-*glycero*-pent-2'-enofuranosyl)-thymine (**17**), albeit structurally related to the potent anti-HIV compounds 3'-azido-3'-deoxythymidine (AZT) (1, B = thymin-1-yl)[30] and 1-(2',3'-dideoxy-β-D-*glycero*-pent-2'-enofuranosyl)thymine (D4T) (4, B = thymin-1-yl),[31] were devoid of any anti-retrovirus activity at subtoxic concentrations (Table I).

With most of the 3'-C-cyano-substituted 3'-deoxynucleoside derivatives little, if any, specificity was noted in their antiviral activity against vesicular stomatitis virus, Coxsackie virus B4, polio virus 1, or parainfluenza 3 virus (Tables II–IV). However, compounds **12e** and **13e** proved effective against Sindbis virus and Semliki forest virus at concentrations (10 and 20 μg/mL, respectively) that were well below the cytotoxicity threshold (200 and 100 μg/mL, respectively) (Table IV). Compounds **12e** and **13e** were also endowed with a marked activity against vaccinia virus (MIC 4 μg/mL), again at a concentration well below the cytotoxicity threshold (200 and 100 μg/mL, respectively) (Table II).

Table III. Cytotoxicity and Antiviral Activity of 3'-C-Cyano-3'-deoxynucleoside Derivatives in HeLa Cell Cultures

compd	min cytotoxic concn,[a] μg/mL	min inhibitory concn[b] (MIC) μg/mL		
		vesicular stomatitis virus	Coxsackie virus B4	polio virus 1
10b	4	>1	>4	>4
10c	≥4	>1	2	>4
10e	≥100	>40	>40	>40
11b	≥40	>10	>10	>10
11d	≥4	2	>4	>4
11e	≥4	>1	>1	>1
12a	400	150	>200	>200
12b	≥400	>200	>200	>200
12e[c]	400	150	>200	>200
13b	>200	>200	>200	>200
13d	100	70	>40	>40
13e[c]	≥200	>100	200	>100
14	>400	>400	>400	>400
15	100	>40	>40	>40
16	200	>100	>100	>100
17	400	150	>200	>200
tubercidin	≥0.4	0.07	0.4	0.4
(S)-DHPA	>400	2	>400	>400
ribavirin	≥200	20	70	70
carbocylic 3-deazaadenosine	>400	1	>400	>400

[a] Required to cause a microscopically detectable alteration of normal cell morphology. [b] Required to reduce virus-induced cytopathogenicity by 50%. [c] An aqueous solution of compound **12e** epimerized to **13e** by 50% after 3 days.

Concerning the reliability of the biological data reported for the partly unstable compounds **12b** and **12e**, it should be mentioned that their presence during the first 24–48 h in virus-infected cell cultures is crucial to exert the antiviral action. At these time periods, the major amounts of the test compounds are not yet converted to the epimerized forms. The epimerization of **12b** in water solution is not significant after 12 h. After 5 days **12b** is still the major compound. Thus, the negative data reported for **12b** and its stable epimer **13b** are reliable. The epimerization of **12e** to **13e** is faster. After 3 days the content of **12e** and **13e** in a water solution is about 50/50. The antiviral activities reported for **12e** and **13e** are the same against

(31) Balzarini, J.; Baba, M.; Pauwels, R.; Herdewijn, P.; De Clercq, E. *Biochem. Pharmacol.* **1988**, *37*, 2847.

Table IV. Cytotoxicity and Antiviral Activity of 3′-*C*-Cyano-3′-deoxynucleoside Derivatives in Vero Cell Cultures

compd	min cytotoxic concn,[a] μg/mL	min inhibitory concn[b] (MIC), μg/mL				
		parainfluenza 3 virus	reovirus	Sindbis virus	Coxsackie virus B4	Semliki forest virus
10b	4	>1	>1	>1	>1	>1
10c	≥4	>4	>4	>4	>4	>4
10e	≥40	>10	>10	20	20	>40
11b	≥10	>4	>4	>4	>4	>4
11d	10	>4	>4	>4	>4	>4
11e	10	>4	>4	>4	>4	>4
12a	≥200	>100	>200	150	>100	300
12b	400	>200	>200	>200	>200	>200
12e[c]	200	70	>100	10	100	20
13b	>200	>100	>100	>100	>100	>100
13d	200	>100	>100	>100	>100	>100
13e[c]	100	>100	>40	10	>100	20
14	>400	>200	>200	>400	>400	>400
15	>100	>100	20	>100	>100	>100
16	≥10	>10	>10	>10	>10	>10
17	>100	>40	>40	>100	>100	>40
tubercidin	0.4	>0.1	>0.1	0.2	>0.1	>0.1
(*S*)-DHPA	400	150	7	>400	100	>400
ribavirin	>400	40	70	70	100	300
carbocyclic 3-deazaadenosine	400	4	7	300	100	>400

[a] Required to cause a microscopically detectable alteration of normal cell morphology. [b] Required to reduce virus-induced cytopathogenicity by 50%. [c] An aqueous solution of compound **12e** epimerized to **13e** by 50% after 3 days.

vaccinia virus, Sindbis virus, and Semliki forest virus, but **12e** is less toxic. Thus, taking into account that **13e** is stable, the antiviral activity data (Tables II and IV) are reliable, but **12e** could be less toxic than reported.

The findings obtained here for **12e** and **13e** suggest that these compounds are worthy of further evaluation for their antiviral potential, i.e., their mechanism of antiviral action and their efficacy in animal model infections.

Experimental Section

Chemical Procedures. Melting points were measured with a Kofler hot-stage apparatus. ^{1}H NMR spectra were recorded with a Varian EM-390 and a Bruker AM-200 spectrometer operating at 90 and 200 MHz and ^{13}C NMR spectra with a Bruker WP-80-SY and a Varian XL-300 spectrometer operating at 20 and 75 MHz, with Me_4Si as internal standard. IR spectra were recorded with a Shimadzu IR-435 spectrometer. Analytical TLC plates were purchased from Merck. Flash column chromatography was performed with silica gel 60, 230–400 mesh (Merck). Compounds were detected by UV light (254 nm) or by spraying the plates with 30% H_2SO_4 in ethanol and heating.

4-*N*-Acetyl-2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)cytidine (5c) and 4-*N*-Acetyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-cytidine (6c). A mixture of 4-*N*-acetylcytidine (1.42 g, 5 mmol), pyridine (10 mL), and *tert*-butyldimethylsilyl chloride (2.26 g, 15 mmol) was stirred at room temperature for 48 h and then evaporated to dryness. The residue dissolved in chloroform was washed with cold (4 °C) 1 N HCl (50 mL) and water (2 × 50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by column chromatography using hexane/ethyl acetate (1:1) as the eluent. The fastest moving band afforded 1.66 g (65%) of **5c** which crystallized from ethyl acetate/hexane: mp 191–192 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.80 (s, 18 H, *t*-Bu), 2.09 (s, 3 H, NAc), 2.33 (bs, 1 H, 3′-OH), 5.75 (d, 1 H, H-1′, $J_{1',2'}$ = 1 Hz), 7.33 (d, 1 H, H-5), 8.30 (d, 1 H, H-6), 10.30 (bs, 1 H, 4-NH); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 18.04, 18.44 (C–Si), 25.81, 25.92 [(CH_3)$_3$C], 61.48 (C-5′), 68.76 (C-2′), 76.99 (C-3′), 84.46 (C-4′), 90.54 (C-1′), 96.61 (C-5), 144.79 (C-6), 155.03 (C-2), 163.28 (C-4), 171.33 (4-NHCO). Anal. ($C_{23}H_{43}N_3O_6Si_2$) C, H, N.

The slowest moving band gave a solid which crystallized from ethyl acetate/hexane to give 0.25 g (10%) of **6c**: mp 127–128 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.90, 0.93 (2 s, 18 H, *t*-Bu), 2.26 (s, 3 H, NAc), 3.35 (bs, 1 H, 2′-OH), 5.97 (d, 1 H, H-1′, $J_{1',2'}$ = 2 Hz), 7.42 (d, 1 H, H-5), 8.30 (d, 1 H, H-6), 10.56 (bs, 1 H, 4-NH); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 17.94, 18.26 (C–Si), 25.59, 25.83 [(C-H_3)$_3$C], 61.46 (C-5′), 70.33 (C-2′), 76.10 (C-3′), 84.86 (C-4′), 91.12 (C-1′), 96.69 (C-5′), 144.32 (C-6), 155.43 (C-2), 163.09 (C-4), 171.27 (4-NHCO). Anal. ($C_{23}H_{43}N_3O_6Si_2$) C, H, N.

4-*N*-Acetyl-1-[2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuranos-3′-ulosyl]cytosine (7c). To a solution of CrO_3 (0.6 g, 6 mmol), pyridine (1 mL, 12 mmol), acetic anhydride (0.6 mL, 6 mmol), and methylene chloride (14 mL) was added **5c** (1.02 g, 2 mmol). The resulting mixture was stirred at room temperature for 45 min and concentrated to dryness. The residue was treated with ethyl acetate (10 mL) and filtered through a short silica gel (15 g) column using ethyl acetate as the eluent. The filtrate was evaporated to dryness and the residue coevaporated with ethanol (3 × 5 mL). The residue was purified by column chromatography using ethyl acetate/hexane (1:2) as the eluent to yield 0.76 g (75%) of **7c** as a syrup: IR (Nujol) 1770 cm^{-1} (furanose C=O); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.75 (s, 18 H, *t*-Bu), 2.26 (s, 3 H, NAc), 3.85 (m, 2 H, H-5′), 4.10 (d, 1 H, H-2′, $J_{1',2'}$ = 8 Hz), 4.20 (m, 1 H, H-4′), 6.33 (d, 1 H, H-1′), 7.43 (d, 1 H, H-5), 8.05 (d, 1 H, H-6); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 57.75 (C-5′), 73.30, 76.99 (C-2′, C-4′), 81.59 (C-1′), 92.43 (C-5), 139.21 (C-6), 158.06 (C-2), 166.15 (C-4), 170.84 (4-NHCO), 202.88 (C-3′). Anal. ($C_{23}H_{41}N_3O_6Si_2$) C, H, N.

General Procedure for the Synthesis of 2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-3′-*C*-cyano-3′-deoxy-β-D-xylofuranosyl Nucleosides (10). A mixture of the 3′-ketonucleoside **7** (1 mmol), water (4 mL), ethyl ether (8 mL), sodium bicarbonate (0.16 g, 2 mmol), and sodium cyanide (0.05 g, 1 mmol) was stirred vigorously at 15 °C for 16 h. The organic phase was separated, and the aqueous phase was washed with ethyl ether (2 × 8 mL). The combined ethereal phases were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue, a mixture of two epimeric cyanohydrins, was dissolved in dry acetonitrile (10 mL). To this solution were added 4-(dimethylamino)pyridine (0.25 g, 2 mmol) and (phenyloxy)thiocarbonyl chloride (0.2 mL, 1.1 mmol). The mixture was stirred at room temperature for 2 h, and the solvent was evaporated under reduced pressure. The residue, suspended in toluene (20 mL), was transferred to a three-necked flask, α,α′-Azobis[isobutyronitrile] (0.03 g, 0.2 mmol) was added, oxygen-free N_2 was bubbled through the suspension for 15 min, and then tributyltin hydride (0.4 mL, 1.5 mmol) was added. The flask was heated in an oil bath at 70 °C for 4 h while the N_2 bubbling was maintained. The reaction mixture was allowed to reach room temperature. Then, it was washed with water (20 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue was purified by column chromatography.

1-[2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-3′-*C*-cyano-3′-deoxy-β-D-*xylo*-pentofuranosyl]uracil (10b). The residue was chromatographed with ethyl acetate/hexane (1:5) as the eluent to give 0.32 g (68%) of **10b** as a white foam: IR (Nujol) 2230 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 3.20 (t, 1 H, H-3′, $J_{2',3'}$ = $J_{3',4'}$

= 7.5 Hz), 3.76 (m, 2 H, H-5′), 4.36 (m, 2 H, H-2′, H-4′), 5.62 (d, 1 H, H-5), 5.80 (d, 1 H, H-1′, $J_{1',2'}$ = 6.5 Hz), 7.61 (d, 1 H, H-6), 9.94 (bs, 1 H, 3-NH); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 38.07 (C-3′), 63.33 (C-5′), 76.89, 76.98 (C-2′, C-4′), 87.95 (C-1′), 102.86 (C-5), 116.29 (CN), 138.99 (C-6), 150.27 (C-2), 162.83 (C-4). Anal. ($C_{22}H_{39}N_3O_5Si_2$) C, H, N.

4-*N*-Acetyl-1-[2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-3′-*C*-cyano-3′-deoxy-β-D-*xylo*-pentofuranosyl]cytosine (10c). The residue was chromatographed with ethyl acetate/hexane (1:2) as the eluent to afford 0.34 g (65%) of **10c** as a foam: IR (Nujol) 2225 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.23 (s, 3 H, NAc), 3.20 (dd, 1 H, H-3′, $J_{2',3'}$ = 6.0, $J_{3',4'}$ = 7.0 Hz), 4.01 (m, 2 H, H-5′), 4.63 (m, 2 -, H-2′, H-4′), 5.95 (d, 1 H, H-1′, $J_{1',2'}$ = 4.0 Hz), 7.43 (d, 1 H, H-5), 8.13 (d, 1 H, H-6); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 38.71 (C-3′), 62.85 (C-5′), 78.84, 79.02 (C-2′, C-4′), 91.24 (C-1′), 79.09 (C-5), 116.28 (CN), 143.82 (C-6), 155.08 (C-2), 163.35 (C-4), 171.32 (4-NCO). Anal. ($C_{24}H_{42}N_4O_5Si_2$) C, H, N.

9-[2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-3′-*C*-cyano-3′-deoxy-β-D-*xylo*-pentofuranosyl]adenine (10e). The residue was purified with ethyl acetate/hexane (1:1) to give a solid which crystallized from hexane to afford 0.31 g (63%) of **10e**: mp 163–164 °C; IR (Nujol) 2235 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 3.33 (dd, 1 H, H-3′, $J_{2',3'}$ = 5.5, $J_{3',4'}$ = 7.0 Hz), 3.93 (d, 2 H, H-5′, $J_{4',5'}$ = 3.5 Hz), 4.43 (dt, 1 H, H-4′), 4.96 (dd, 1 H, H-2′, $J_{1',2'}$ = 5.5 Hz), 5.95 (d, 1 H, H-1′), 6.03 (bs, 2 H, NH_2), 8.13 (s, 1 H, H-2), 8.27 (s, 1 H, H-8); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 38.98 (C-3′), 63.54 (C-5′), 77.74, 78.36 (C-2′, C-4′), 88.31 (C-1′), 116.46 (CN), 119.33 (C-5), 137.85 (C-8), 149.95 (C-4), 153.07 (C-2), 155.89 (C-6). Anal. ($C_{23}H_{40}N_6O_3Si_2$) C, H, N.

General Procedure for the Synthesis of 2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-3′-*C*-cyano-3′-deoxy-β-D-ribofuranosyl Nucleosides (11) by Epimerization of the Corresponding Xylo Isomers (10). To a solution of the 3′-C-cyanoxylo nucleoside **10** (0.8 mmol) in methanol (15 mL) was added dropwise a 1 N solution of NaOH in methanol until the pH of the resulting solution was 9. The mixture was stirred at room temperature or at reflux for 3–6 h, neutralized with a 1 N solution of HCl in methanol, and evaporated to dryness. The residue was purified by column chromatography.

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-3′-*C*-cyano-3′-deoxyuridine (11b). A pH 9 solution of **10b** was heated according to the general procedure for 6 h under reflux. The residue was chromatographed with ethyl acetate/hexane (5:1) as the eluent to give a solid which was crystallized from hexane to yield 0.28 g (72%) of **11b**: mp 159–160 °C; IR (Nujol) 2225 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 3.20 (dd, 1 H, H-3′, $J_{2',3'}$ = 4, $J_{3',4'}$ = 12.5 Hz), 3.93, 4.30 (2 dd, 2 H, H-5′a, H-5′b), 4.60 (m, 2 H, H-2′, H-4′), 5.66 (d, 1 H, H-5), 5.73 (s, 1 H, H-1′), 8.01 (d, 1 H, H-6), 10.33 (bs, 1 H, 3-NH); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 34.83 (C-3′), 60.64 (C-5′), 77.30, 82.94 (C-2′, C-4′), 92.54 (C-1′), 101.90 (C-5), 114.95 (CN), 139.41 (C-6), 150.24 (C-2), 163.40 (C-4). Anal. ($C_{22}H_{39}N_3O_5Si_2$) C, H, N.

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-3′-*C*-cyano-3′-deoxycytidine (11d). Following the general procedure a basic solution of **8c** was stirred at room temperature for 3 h. The residue was chromatographed with ethyl acetate/hexane (3:1) as the eluent to give a solid which crystallized from chloroform/hexane to afford 0.27 g (71%) of **11d**: mp 121–122 °C; IR (KBr) 2235 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 3.43 (dd, 1 H, H-3′, $J_{2',3'}$ = 4.5, $J_{3',4'}$ = 10.0 Hz), 3.98, 4.28 (2 dd, 2 H, H-5′a, H-5′b), 4.55 (m, 1 H, H-4′), 4.73 (d, 1 H, H-3′), 5.73 (s, 1 H, H-1′), 5.82 (d, 1 H, H-5), 7.95 (d, 1 H, H-6); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 35.66 (C-3′), 62.25 (C-5′), 78.30, 83.32 (C-2′, C-4′), 94.13, 94.67 (C-1′, C-5), 116.76 (CN), 141.61 (C-6), 156.19 (C-2), 167.51 (C-4). Anal. ($C_{22}H_{40}N_4O_4Si_2$) C, H, N.

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-3′-*C*-cyano-3′-deoxyadenosine (11e). A pH 9 solution of **10e** was stirred at room temperature for 6 h according to the general procedure, and the residue was chromatographed with ethyl acetate/hexane (1:2) as the eluent to give 0.31 g (78%) of **11e** as a foam: IR (Nujol) 2230 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 3.73 (dd, 1 H, H-3′, $J_{2',3'}$ = 4.5, $J_{3',4'}$ = 10.0 Hz), 3.91, 4.21 (2 dd, 2 H, H-5′a, H-5′b), 4.65 (m, 1 H, H-4′), 5.05 (d, 1 H, H-2′), 6.03 (s, 1 H, H-1′), 7.60 (bs, 2 H, 6-NH_2), 8.20 (s, 1 H, H-2), 8.36 (s, 1 H, H-8); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 35.36 (C-3′), 61.33 (C-5′), 76.68, 82.56 (C-2′, C-4′), 92.09 (C-1′), 115.47 (CN), 120.24 (C-5), 138.72 (C-8), 149.10 (C-4), 152.90 (C-2), 155.84 (C-6). Anal. ($C_{23}H_{40}N_6O_3Si_2$) C, H, N.

General Procedure for Removal of the Protecting Groups of the 2′,5′-Di-*O*-silyl-Protected 3′-*C*-Cyano-3′-deoxy-β-D-*xylo*- and -*ribo*-furanosyl Nucleosides 10 and 11. To a solution of the silyl-protected nucleoside **10** or **11** (1 mmol) in THF (15 mL) was added tetrabutylammonium fluoride trihydrate (Bu_4NF) (0.63 g, 2 mmol), and the mixture was stirred at room temperature from 20 to 60 min. The reaction mixture was filtered through a wet (THF) column of silica gel using THF as the eluent. The filtrate was evaporated to dryness, and the residue was purified by flash column chromatography.

1-(3′-*C*-Cyano-3′-deoxy-β-D-*xylo*-pentofuranosyl)uracil (12b). Following the general procedure, **10b** reacted with Bu_4NF for 60 min. The residue was chromatographed with ethyl acetate/methanol (50:1) as the eluent to give a solid which crystallized from ethyl acetate to afford 0.11 g (46%) of **12b**: mp 165–166 °C; IR (Nujol) 2225 cm^{-1} (CN); ^{1}H NMR [$(CD_3)_2SO$, 200 MHz] δ 3.43 (dd, 1 H, H-3′, $J_{2',3'}$ = 7, $J_{3',4'}$ = 9 Hz), 3.43 (m, 2 H, H-5′), 4.30 (m, 1 H, H-4′), 4.47 (dd, 1 H, H-2′, $J_{1',2'}$ = 6 Hz), 5.56 (d, 1 H, H-5), 5.70 (d, 1 H, H-1′), 7.80 (d, 1 H, H-6′). Anal. ($C_{10}H_{11}N_3O_5$) C, H, N.

9-(3′-*C*-Cyano-3′-deoxy-β-D-*xylo*-pentofuranosyl)adenine (12e). According to the general procedure **10e** reacted with Bu_4NF for 20 min. The residue was chromatographed with ethyl acetate/methanol (8:1) as the eluent to afford a solid which crystallized from methanol/ethyl acetate to yield 0.18 g (67%) of **12e**: mp 230–231 °C; IR (KBr) 2240 cm^{-1} (CN); ^{1}H NMR [$(CD_3)_2SO$, 200 MHz] δ 3.72 (m, 2 H, H-5′), 3.79 (dd, 1 H, H-3′, $J_{2',3'}$ = 8.6, $J_{3',4'}$ = 8.5 Hz), 4.47 (m, 1 H, H-4′), 5.08 (dd, 1 H, H-2′, $J_{1',2'}$ = 6.7 Hz), 5.81 (dd, 1 H, H-1′), 7.42 (bs, 2 H, 6-NH_2), 8.16 (s, 1 H, H-8), 8.34 (s, 1 H, H-2); ^{13}C NMR [$(CD_3)_2SO$, 75 MHz] δ 37.16 (C-3′), 62.25 (C-5′), 74.77, 77.55 (C-2′, C-4′), 88.45 (C-1′), 118.29 (CN), 119.43 (C-5), 139.96 (C-8), 148.99 (C-4), 152.64 (C-2), 156.34 (C-6). Anal. ($C_{11}H_{12}N_6O_3$) C, H, N.

3′-*C*-Cyano-3′-deoxyuridine (13b). Following the general procedure **11b** reacted with Bu_4NF for 60 min. The residue was chromatographed with ethyl acetate/methanol (50:1) as the eluent to give 0.13 g (52%) of **13b** as a white foam: IR (Nujol) 2230 cm^{-1} (CN); ^{1}H NMR [CD_3OD, 200 MHz] δ 3.69 (dd, 1 H, H-3′, $J_{2',3'}$ = 5.2, $J_{3',4'}$ = 10.0 Hz), 3.69, 4.20 (2 dd, 2 H, H-5′a, H-5′b, $J_{5'a,5'b}$ = 12.8 Hz), 4.64 (m, 1 H, H-4′), 4.78 (dd, 1 H, H-2′, $J_{1',2'}$ = 1.5 Hz), 5.85 (d, 1 H, H-5), 5.95 (d, 1 H, H-1′), 8.17 (d, 1 H, H-6); ^{13}C NMR [$(CD_3)_2SO$, 75 MHz] δ 35.03 (C-3′), 59.70 (C-5′), 74.03 (C-2′), 81.57 (C-4′), 91.68 (C-1′), 101.38 (C-5), 116.74 (CN), 140.46 (C-6), 150.23 (C-2), 162.98 (C-4). Anal. ($C_{10}H_{11}N_3O_5$) C, H, N.

3′-*C*-Cyano-3′-deoxycytidine (13d). From 11d. According to the general procedure, **11d** was treated with Bu_4NF for 20 min. The residue was chromatographed with ethyl acetate/methanol (5:1) as the eluent to afford 0.17 g (67%) of **13d** as a white foam: IR (Nujol) 2230 cm^{-1} (CN); ^{1}H NMR [$(CD_3)_2SO$, 200 MHz] δ 3.40 (dd, 1 H, H-3′, $J_{2',3'}$ = 6.9, $J_{3',4'}$ = 10.0 Hz), 3.59, 3.81 (2 dd, 2 H, H-5′a, H-5′b, $J_{5'a,5'b}$ = 12.7 Hz), 4.29 (m, 1 H, H-4′), 4.39 (dd, 1 H, H-2′, $J_{1',2'}$ = 1.6 Hz), 5.68 (d, 1 H, H-5), 5.69 (d, 1 H, H-1′), 7.80 (d, 1 H, H-6). Anal. ($C_{10}H_{12}N_4O_4$) C, H, N.

From 10c. Following the general procedure, **10c** reacted with Bu_4NF for 45 min. The residue was chromatographed with ethyl acetate/methanol (10:1) as the eluent to give 0.21 g (72%) of **4-*N*-acetyl-3′-*C*-cyano-3′-deoxycytidine (13c)** as a white foam: ^{1}H NMR [CD_3OD, 200 MHz] δ 2.16 (s, 3 H, NAc), 3.42 (dd, 1 H, H-3′, $J_{2',3'}$ = 5, $J_{3',4'}$ = 10.5 Hz), 3.78, 4.16 (2 dd, 2 H, H-5′a, H-5′b, $J_{5'a,5'b}$ = 10.5 Hz), 4.50 (d, 1 H, H-2′), 4.50 (m, 1 H, H-4′), 5.80 (s, 1 H, H-1′), 7.36 (d, 1 H, H-5), 8 (d, 1 H, H-6). To a solution of compound **13c** (0.21 g, 0.72 mmol) in methanol (10 mL) was added dropwise a 1 N solution of NaOH in methanol until the pH of the resulting solution was 9. The mixture was stirred at room temperature for 30 min, neutralized with a 0.5 N solution of HCl in methanol, and evaporated to dryness. The residue was purified by flash column chromatography using ethyl acetate/methanol (5:1) as the eluent to afford 0.12 g (51% from **10c**) of **13d** identical with that obtained before.

3′-*C*-Cyano-3′-deoxyadenosine (13e). Following the general procedure, **11e** was treated with Bu_4NF for 20 min. The residue was chromatographed with ethyl acetate/methanol (8:1) as the eluent to give a solid which crystallized from methanol/ethyl acetate to afford 0.19 g (70%) of **13e**: mp 241–242 °C; IR (KBr)

2235 cm^{-1} (CN); ^{1}H NMR [$(CD_3)_2SO$ + CD_3OD (1:1), 200 MHz] δ 3.64, 3.83 (2 dd, 2 H, H-5′a, H-5′b, $J_{5'a,5'b}$ = 12.6 Hz), 3.85 (dd, 1 H, H-3′, $J_{2',3'}$ = 5.7, $J_{3',4'}$ = 8.9 Hz), 4.42 (m, 1 H, H-4′), 4.83 (dd, 1 H, H-2′, $J_{1',2'}$ = 2.3 Hz), 5.97 (d, 1 H, H-1′), 8.25, 8.10 (2 s, 2 H, H-8, H-2); ^{13}C NMR [$(CD_3)_2SO$, 75 MHz] δ 35.82 (C-3′), 60.54 (C-5′), 74.13, 81.92 (C-2′, C-4′), 90.55 (C-1′), 117.07 (CN), 119.10 (C-5), 139.28 (C-8), 148.80 (C-4), 152.57 (C-2), 156.06 (C-6). Anal. ($C_{11}H_{12}N_6O_3$) C, H, N.

Antiviral Assay Procedures. Human immunodeficiency virus (HIV) infection was carried out with the HTLV-III$_B$ strain. The virus was prepared from the culture supernatant of a persistently HTLV-III$_B$-infected HUT-78 cell line. The antiviral assays were based on an inhibition of HIV-induced cytopathogenicity in human MT-4 lymphocytes as described previously.[30]

Transformation of C3H mouse embryo cells by Moloney murine sarcoma virus (MSV) was carried out into 48-well Costar tissue culture cluster plates. C3H cells were seeded at 20 000 cells/mL per well and grown for 24 h. Cell cultures were then infected by 80 foci-forming units of MSV during 90 min, whereafter medium was replaced by 1 mL of fresh culture medium containing different concentrations of the test compounds. After 6–7 days, the transformation of the cell culture was examined microscopically.[30]

The antiviral assays, other than those for HIV and MSV, were based on the inhibition of virus-induced cytopathogenicity in either HeLa cells or Vero cells of primary rabbit kidney cell cultures, following established procedures.[32] Briefly, confluent cell cultures in microtiter trays were inoculated with 100 $CCID_{50}$ of virus. After 1 h of virus adsorption, residual virus was removed and the cell cultures were incubated in the presence of varying concentrations of the test compounds. Viral cytopathogenicity was recorded as soon as it reached completion in the control virus-infected cell cultures.

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Registry No. **5c**, 121055-61-6; **6c**, 121055-62-7; **7b**, 90813-54-0; **7c**, 121055-63-8; **7e**, 86734-95-4; **10b**, 121055-64-9; **10c**, 121055-65-0; **10e**, 121055-66-1; **11b**, 121055-67-2; **11d**, 121055-68-3; **11e**, 121055-69-4; **12a**, 117174-35-3; **12b**, 121123-89-5; **12e**, 121153-18-2; **13b**, 121123-90-8; **13c**, 121055-71-8; **13d**, 121055-70-7; **13e**, 121123-91-9; **14**, 117174-38-6; **15**, 117174-39-7; **16**, 116195-58-5; **17**, 118222-08-5; *N*-acetylcytidine, 3768-18-1.

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Prodrugs of the Selective Antiherpesvirus Agent 9-[4-Hydroxy-3-(hydroxymethyl)but-1-yl]guanine (BRL 39123) with Improved Gastrointestinal Absorption Properties

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Potential oral prodrugs of the antiherpesvirus acyclonucleoside 9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]guanine (**1**, BRL 39123) have been synthesized and evaluated for bioavailability of **1** in the blood of mice. Reduction of 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-amino-6-chloropurine (**13**) using ammonium formate and 10% palladium on carbon afforded the 2-aminopurine **14**, which was hydrolyzed to the monoacetate **15** and to 2-amino-9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]purine (**5**). The 2-aminopurine **5** was subsequently converted to additional monoester (**17**, **21**–**23**) and diester (**16**, **24**) derivatives and to its di-*O*-isopropylidene derivative **18**. Both **5** and its esters (**14**–**17**, **21**, **22**) and also **18** were well absorbed after oral administration and converted efficiently to **1**, the diacetyl (**14**) and dipropionyl (**16**) esters providing concentrations of **1** in the blood that were more than 15-fold higher than those observed after dosing either **1** or its esters (**25**–**27**). Some 6-alkoxy-9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]purines (**8**–**10**), the preparation of which has been reported previously, also showed improved absorption properties, but their conversion to **1** was less efficient than for the 2-aminopurine derivatives. On the basis of these results and subsequent experiments involving determinations of rates of conversion to **1** in the presence of rat and human tissue preparations, 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine (**14**, BRL 42810) was identified as the preferred prodrug of **1**. Oral bioavailability studies in healthy human subjects confirmed **14** as an effective prodrug, and this compound is now being evaluated in clinical trials.

The acyclonucleoside 9-[4-hydroxy-3-(hydroxymethyl)-but-1-yl]guanine (**1**, BRL 39123)[1,2] possesses potent and selective activity against herpes simplex virus types 1 and 2, varicella zoster virus, and Epstein–Barr virus in cell cultures[3] and in animals,[4] and its clinical efficacy in the treatment of herpetic infections is presently being evaluated.

However, after oral administration of **1** to mice only relatively low concentrations of the antiviral acyclonucleoside were detectable in the blood. The gastrointestinal absorption of acyclovir (**2**), which is also an acyclic analogue of guanosine, has similarly been reported[5,6] to be

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