stirred at room temperature for 48 h. MeOH (1 mL) was added to the reaction, and the mixture was filtered through a Celite pad. The filtrate was concentrated, and the residue was chromatographed ($CHCl_3$). The nucleoside fractions were collected and concentrated, and the residue was treated with 3% HCl/MeOH for 24 h. After the solvent was removed by evaporation, the residue was crystallized from water to give 107 mg (33%) of **8B**, mp 124–125 °C.

In a similar manner, the 2′-bromo analogue (**8C**), mp 134–136 °C, was obtained via condensation of bis(trimethylsilyl)thymine (**8**) with the bromo sugar (**C**). For the ^1H NMR data of **8B** and **8C**, see Table II.

1-(2-Deoxy-2-fluoro-β-D-ribofuranosyl)-5-iodocytosine Hydrochloride (9, 2′-Fluoro-2′-deoxy-5-iodocytidine).[10] 2′-Fluoro-2′-deoxycytidine[8] (390 mg, 1.6 mmol) was dissolved in 3% HCl/MeOH (10 mL), and the solution was concentrated to dryness. The residue was suspended in AcOH (10 mL), and AcCl (2 mL) was added. The mixture was stirred for 30 min at 90–95 °C and then concentrated in vacuo. The residue was dissolved in water (2 mL), and to this solution were added I_2 (194 mg, 0.8 mmol), HIO_3 (56 mg), CCl_4 (2 mL), and AcOH (3 mL), and the mixture was stirred for 24 h at 50–55 °C. The mixture was concentrated in vacuo, and the residue triturated several times with CCl_4 and then crystallized from EtOH to give 150 mg of crude 3′,5′-di-*O*-acetyl-2′-deoxy-2′-fluoro-5-iodocytidine hydrochloride which was dissolved in 10% HCl/MeOH and stirred for 24 h at room temperature. After concentration of the mixture in vacuo, the residue was triturated several times with Et_2O, the insoluble solid was dissolved in water and filtered, and the filtrate was lyophilized to give **9** as a fluffy solid (62 mg). The ^1H NMR spectral data are given in Table II.

Antiviral Activity. Antiviral activity was determined for HSV-1 (strain 2931) and HSV-2 (strain G) on monolayers of Vero cells by the plaque-reduction assay.[2] A dose that reduced the number of virus plaques by 50% (ED_{50}) was determined.

Cytotoxicity. In other experiments (data not presented), we have found that inhibition of lymphocytic proliferation in response to the mitogen PHA demonstrated levels of cytotoxicity similar to those obtained with the inhibition of Vero cell proliferation.[2] Lymphocyte proliferation was quantitated by [^3H]thymidine incorporation after a 4-h pulse.[11]

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Registry No. **1A**, 56632-83-8; **1B**, 58461-30-6; **1C**, 67036-66-2; **1C**·HCl, 83966-85-2; **2**, 83966-86-3; **2A**, 69123-93-9; **2B**, 80791-95-3; **2B**·HCl, 83966-87-4; **2B** diacetate, 83966-88-5; **2C**, 83966-89-6; **2C**·HCl, 83966-90-9; **2C** diacetate, 83966-91-0; **3**, 83966-92-1; **3A**, 69123-90-6; **3A** (α isomer), 83999-91-1; **3B**, 80791-94-2; **3C**, 83966-93-2; **3C**·HCl, 83966-94-3; **4A**, 89636-53-0; **4A** 3-*O*-acetate 5-*O*-benzoate, 83966-95-4; **4B**, 80791-96-4; **4C**, 83966-96-5; **4C**·HCl, 83966-97-6; **5A**, 69123-94-0; **6A**, 69123-97-3; **7A**, 69123-98-4; **8**, 7288-28-0; **8A**, 69256-17-3; **8B**, 80791-97-5; **8C**, 83966-98-7; **9**, 80791-93-1; **9** diacetate HCl, 83966-99-8; $(Me_3Si)_2NH$, 32713-31-8; cytosine, 71-30-7; 5-iodocytosine, 1122-44-7; 1,3-di-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinofuranose, 84025-00-3; 1-(3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-fluoro-β-D-arabinofuranosyl)-5-iodocytosine, 83967-00-4; 5-methylcytosine, 554-01-8; 1,3,5-tri-D-acetyl-2-chloro-2-deoxy-α-D-arabinofuranose, 30589-74-3; 5-bromocytosine, 2240-25-7; 1,3,5-tri-D-acetyl-2-bromo-2-deoxy-α-D-arabinofuranose, 83967-01-5; 3,5-di-*O*-acetyl-2-chloro-2-deoxy-D-arabinofuranosyl bromide, 84025-01-4; 3,5-di-*O*-acetyl-2-bromo-2-deoxy-D-arabinofuranosyl bromide, 84025-02-5; 2-fluoro-2′-deoxycytidine, 10212-20-1.

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Carbocyclic Analogues of 5-Substituted Uracil Nucleosides: Synthesis and Antiviral Activity

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Carbocyclic analogues of 3′-deoxyuridines, 3′-deoxyuridines, and uridines with substituents at position 5 of the uracil moiety were prepared by direct halogenation (5-bromo and 5-iodo groups) and by displacement of the 5-bromo group by amino and substituted-amino groups. The analogue of 5-(hydroxymethyl)uridine was prepared via reaction of the isopropylidene derivative of the uridine analogue with paraformaldehyde. The carbocyclic analogues of thymidine and of 5-bromo-, 5-iodo-, and 5-(methylamino)-2′-deoxyuridine were highly active in vitro against herpes simplex virus, types 1 and 2. The corresponding analogues of 5-substituted 3′-deoxyuridines and of 5-substituted uridines were not active in this assay.

Several pyrimidine nucleosides, notably 1-β-D-arabinofuranosylcytosine (*ara*-C)[1,2] and 5-fluoro-2′-deoxyuridine,[3,4] have useful anticancer activity. Many pyrimidine nucleosides have antiviral activity;[5-10] among the antiviral pyrimidine nucleosides, a great variety of 5-substituted 2′-deoxyuridines (**1**) inhibit the replication of herpes viruses. Because of the anticancer, antiviral, and other types of biological activity found among pyrimidine nucleosides, there is a continuing interest in this type of structure.

Previously, we have reported the synthesis of carbocyclic analogues of uracil nucleosides[11] (**2a**, **3a**, and **4a**), thymidine nucleosides[12,13] (**2b**, **3b**, and **4b**), 5-fluorouracil nu-

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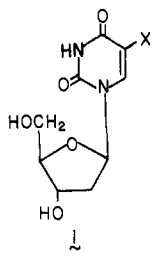
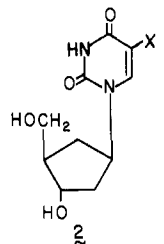


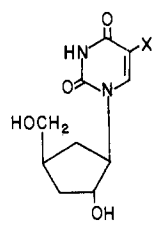
1



2

a: H
b: CH_3
c: F
d: Br
e: I

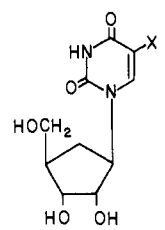
f: NH_2
g: $-NHCH_3$
h: $-NHC_4H_9$
i: $-N(CH_3)_2$



3

a: H
b: CH_3
c: F
d: Br

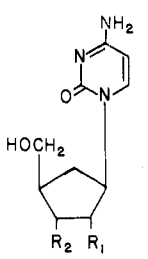
e: I
f: NH_2
g: $-NHCH_3$



4

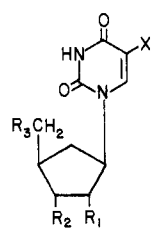
a: H
b: CH_3
c: F
d: Br

e: I
f: NH_2
g: $-NHCH_3$
h: $-CH_2OH$



5

R_1 = H, R_2 = OH
R_1 = OH, R_2 = H
R_1 = R_2 = OH



6

a: R_1 = H, R_2 = R_3 = OAc, X = Br
b: R_1 = R_3 = OAc, R_2 = H, X = Br
c: R_1 = R_2 = R_3 = OAc, X = Br
d: R_1 = H, R_2 = R_3 = OAc, X = I
e: R_1 + R_2 = O O, R_3 = X = H

cleosides[14] (**2c**, **3c**, and **4c**), and cytosine nucleosides (**5**).[15,16] In tests against leukemia L1210 in mice, the carbocyclic analogues of thymidine, cytidine, and 1-β-D-arabinofuranosylcytosine caused increases in life span of 32,[13] 82,[17] and 104%,[18] respectively. The carbocyclic analogue of cytidine is highly active against human influenza virus in vitro, and the *ara*-C and 2,2′-anhydro-*ara*-C carbocyclic analogues are modestly active against influenza virus.[19]

Table I. Evaluation of Carbocyclic Analogues of 5-Substituted Uracil Nucleosides against Herpes Simplex Virus[a]

		type 1, strain 377		type 2, strain MS	
compd	X	VR[b]	MIC_{50}, mcg/mL	VR[b]	MIC_{50}, mcg/mL
2a	H	0			
2b	CH_3	5.4	0.8	3.2	7.0
2c	F	0		0	
2d	Br	6.2	0.3	1.5	32
2e	I	6.5	0.4	2.9	32
		7.1	0.3	3.4	20
		7.9	0.1		
		7.4	0.4		
2f	NH_2	0.1			
2g	$NHCH_3$	4.2	10	1.2	229
		3.9	15		
		4.5	25		
2h	NHC_4H_9	2.0	290	0.7	1000
2i	$N(CH_3)_2$	0			
3a	H	0			
3b	CH_3	0.4		0	
3c-3g		0			
4a-4g		0			
4h	CH_2OH	0.3		0	
6a	Br	1.3	92		
		0.9	100		
6b	Br	0			
6d	I	2.4	10		
		1.6	25		
IdUrd		7.4	0.3	5.0	1.0
ara-A		2.7	9.8	2.3	20.1

[a] Antiviral assays were performed with HSV-1 and HSV-2 replicating in primary rabbit kidney cell cultures. [b] VR = virus rating. See text and Experimental Section.

Because of these observations of activity by carbocyclic analogues of pyrimidine nucleosides and because of the selective antiviral activity of 5-substituted uracil nucleosides, we extended our studies to include carbocyclic analogues of various 5-substituted uracil nucleosides (**2–4**).

(±)-5-Bromo-(1α,3β,4α)-1-[3-hydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (**2d**) was prepared, by procedures similar to those of Visser[20] for the preparation of 5-bromo-2′-deoxyuridine (BrdUrd), by bromination of **2a** diacetate in acetic acid and deacylation of **6a**. The carbocyclic analogues (**3d** and **4d**) of 5-bromo-3′-deoxyuridine and of 5-bromouridine were prepared similarly. The carbocyclic analogue (**2e**) of 5-iodo-2′-deoxyuridine (IdUrd) and 5-iodouracil derivatives **3e** and **4e** were prepared from the parent uracil derivatives (**2a**, **3a**, and **4a**) by iodination in nitric acid according to the procedure of Prusoff[21] for IdUrd. The carbocyclic analogue (**2f**) of 5-amino-2′-deoxyuridine was isolated by ion-exchange chromatography after reaction of the 5-bromo diacetate derivative **6a** with methanolic ammonia at 100 °C, and the 5-(methylamino)-2′-deoxyuridine analogue (**2g**) was obtained similarly after treatment of bromo derivative **2d** with methylamine. Likewise, other 5-amino derivatives (**2h,i**, **3f,g**, and **4f,g**) were obtained from 5-bromouracil (**2d**, **3d**, and **4d**) or 5-bromouracil *O*-acetyl (**6a–c**) derivatives. The 5-(hydroxymethyl)uridine analogue (**4h**) was synthesized by preparing the 2′,3′-isopropylidene analogue (**6e**), hydroxymethylating **6e** with paraformaldehyde in basic solution,[22,23] and deblocking as usual.

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The carbocyclic analogues (2–4) of 5-substituted uracil nucleosides were tested for selective inhibition of herpes simplex virus (HSV) replication in secondary rabbit kidney cells in culture. A standard assay for inhibition of virus-induced cytopathogenic effects (CPE), which has been described previously,[19,24] was used to evaluate these analogues against herpes simplex virus type 1 (HSV-1), strain 377; compounds that were active against HSV-1 were subsequently tested for activity against herpes simplex virus type 2 (HSV-2) in the same manner. Certain compounds active against strain 377 of HSV-1 were also evaluated against strain HF/TK$^-$, a mutant strain of HSV-1 deficient in its ability to induce a virus-specific thymidine kinase in infected cells.

The antiviral activity of each compound was expressed in terms of a virus rating (VR), and the potency was measured as a minimum inhibitory concentration (MIC_{50}). The VR, determined by a modification of the method of Ehrlich et al.,[25] is a weighted measurement of antiviral activity that takes into account the degree of inhibition of virus-specific CPE and the degree of cytotoxicity produced by the test compound. A VR $\geq$ 1.0 indicates definite antiviral activity, a VR = 0.5–0.9 indicates marginal to moderate antiviral activity, and a VR < 0.5 usually indicates no significant antiviral activity. The MIC_{50} is the concentration of test compound required to inhibit virus-induced CPE by 50%.

The carbocyclic analogue (**2e**) of IdUrd was the most active compound against HSV-1 with a VR in the range of 6.5 to 7.9 and an MIC_{50} in the range of 0.1 to 0.4 μg/mL (Table I). Other carbocyclic analogues of 5-substituted 2′-deoxyuridines that displayed high antiherpes activity were the analogue (**2d**) of BrdUrd with a VR of 6.2 and MIC_{50} of 0.3 μg/mL, the analogue (**2b**) of thymidine[12,13] with a VR of 5.4 and MIC_{50} of 0.8 μg/mL, and the analogue (**2g**) of 5-(methylamino)-2′-deoxyuridine with a VR of 3.9 to 4.5 and MIC_{50} of 10 to 25 μg/mL (Table I). The 5-(butylamino) analogue (**2h**) was quite active (VR = 2.0) but was much less potent (MIC_{50} = 290 μg/mL). These same analogues demonstrated highly significant antiviral effects against HSV-2 (strain MS) in vitro but were uniformly inactive against the TK$^-$ variant of HSV-1 (strain HF). This finding indicates that these antiviral carbocyclic analogues are activated by the virus-induced thymidine kinase in infected cells,[26–29] just as the true nucleoside analogues of this type are known to be. This virus-specific mechanism of drug activation is known to result in a high degree of antiviral selectivity. The diacetates (**6a** and **6d**) of **2d** and **2e** also showed significant activity against HSV-1 (strain 377), but they were less active than **2d** and **2e**.

The parent deoxyuridine analogue[11] (**2a**) and the carbocyclic analogues of 5-fluoro-,[14] 5-amino-, and 5-(dimethylamino)-2′-deoxyuridine were not active. Also, the carbocyclic analogues (**3** and **4**) of 3′-deoxyuridines and uridines were devoid of significant activity in this assay. During evaluations of these carbocyclic analogues (**2–4**), two well-known antiviral drugs, IdUrd and 1-β-D-arabinofuranosyladenine (*ara*-A), were included as positive controls. Typical values of VR and MIC_{50} for IdUrd and *ara*-A are also listed in Table I.

Experimental Section

General Methods. Melting points were determined in capillary tubes heated in a Mel-Temp apparatus. Ultraviolet spectra (UV) were recorded with a Cary Model 17 spectrophotometer, and maxima are reported in nanometers. Solutions for ultraviolet determinations were prepared by diluting an aliquot of an ethanol solution with 0.1 N hydrochloric acid, phosphate buffer (pH 7), or 0.1 N sodium hydroxide; absorption maxima of these solutions are reported as being determined in 0.1 N HCl, at pH 7, or in 0.1 N NaOH, respectively. Mass spectral data (MS) were taken from low-resolution spectra determined at 70 eV with a Varian/MAT Model 311A spectrometer equipped with a combination electron-impact, field-ionization, and field-desorption ion source. The peaks listed are those due to the molecular ion (M), those attributable to the loss of certain fragments from the molecular ion (M – fragment), and some other prominent peaks. Unless indicated otherwise, infrared spectra were recorded with a Perkin-Elmer Model 521 or 621 spectrophotometer from samples in potassium bromide disks; w = weak, sh = shoulder. Nuclear magnetic resonance spectra were determined with a Varian Model XL-100-15 spectrometer operating at 100.1 MHz for proton (^{1}H NMR) and at 25.2 MHz for carbon-13 (^{13}C NMR) spectra. The internal standard was $(CH_3)_4Si$; s = singlet, d = doublet, m = multiplet. Thin-layer chromatography (TLC) was performed on plates of silica gel,[30] and developed plates were examined by UV light (254 nm). Other pertinent information (amount applied, developing solvent) are given parenthetically at the appropriate places in the experimental procedures.

(±)-5-Bromo-1-[(1α,3β,4α)-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (2d). A solution of 540 mg of diacetate **6a** in 25 mL of ammonia–methanol (10% ammonia) was stirred at room temperature for 72 h and then concentrated to dryness under reduced pressure. The residue was dissolved in hot water (10 mL), the solution was treated with activated charcoal and filtered, and the filtrate (plus washings) was concentrated to about one-half of the original volume. After the concentrated solution had been stored at low temperature (about 5 °C), the white crystalline product was collected by filtration, washed sparingly with water, and dried in vacuo at 78 °C: yield 251 mg (52%); mp 188–193 °C. After the filtrate had been concentrated and refrigerated, an additional quantity (60 mg, total yield 73.7%) of **2d** was obtained in the same manner: mp 189–194 °C; UV max 284 (ϵ 10 000) and 212 nm (ϵ 9400) at pH 1, 284 (ϵ 10 000) and 212 nm (ϵ 9600) at pH 7, 280 nm (ϵ 7400) at pH 13; MS, *m/e* 304 (M), 286 (M – H_2O), 274, 255 (M – H_2O – CH_2OH), 247, 217 (5-bromouracilyl group + C_2H_4), 191 (5-bromouracilyl group + 2H), 190 (5-bromouracilyl group + H); IR (1800–1300 cm^{-1} region) 1695, 1685, 1645, 1630 (sh), 1610, 1505 (w), 1460, 1445, 1425, 1415 (sh), 1375, 1345, 1310 cm^{-1}. Anal. ($C_{10}H_{13}BrN_2O_4$) C, H, N.

(±)-1-[(1α,3β,4α)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione (2e). A solution of iodine (2.49 g) in chloroform (13 mL) was added to a solution of 2.175 g of the carbocyclic analogue (**2a**) of 2′-deoxyuridine in 1 N nitric acid (22 mL), and the resulting mixture was heated under reflux for 2 h and then stored overnight at about 5 °C. The chloroform layer was separated, and the water layer, which then contained a white solid, was again refrigerated. The white crystalline solid was collected by filtration, washed with cold water, and dried in vacuo at room temperature. The crude product (2.914 g) was dissolved in hot water (75 mL); the solution was filtered and then refrigerated; and the recrystallized product was collected

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(30) Analytical TLC was performed with plates of silica gel GF. [Precoated thin-layer chromatography plates (fluorescent), 250 μm in thickness, were purchased from Analtech Inc., Blue Hen Industrial Park, Newark, DE 19711]. Preparative TLC was performed with precoated plates of silica gel (Whatman PLK5F, 20 × 20 cm, 1 mm in thickness, Whatman Inc., Clifton, NJ 07014).

by filtration, washed with cold water, and dried in vacuo at 78 °C: yield 2.58 g (76%); mp 197–199 °C; UV max 292 (ε 8900) and 217 nm (ε 10 900) at pH 1, 293 (ε 8700) and 217 nm (ε 11 000) at pH 7, 283 nm (ε 6400) at pH 13; MS, *m/e* 352 (M), 334 (M – H_2O), 322, 303 (M – H_2O – CH_2OH), 295, 293, 265 (5-iodouracilyl group + C_2H_4), 260, 239 (5-iodouracilyl group + 2 H), 238 (5-iodouracilyl group + H), 225 (M – I); IR (1800–1300 cm^{-1} region) 1690, 1640, 1600, 1505, 1460, 1420, 1400 (sh), 1345, 1330 (sh), 1305 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.2–1.7 and 1.7–2.3 (overlapping multiplets 2 C*H*$_2$ and C*H*CH_2OH), 3.48 (m, CH_2OH), 4.0 (m, C*H*OH), 4.6 (m, CH_2O*H*), 4.7 (m, CHO*H*), 4.9 (m, C*H* at position 1 of cyclopentane ring), 8.13 (s, C*H* at position 6 of pyrimidine ring), 11.58 (s, NH). Anal. ($C_{10}H_{13}IN_2O_4$) C, H, N.

(±)-5-Amino-1-[(1α,3β,4α)-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (2f) Sulfate. A solution of 500 mg of **6a** in 30 mL of an ammonia–methanol solution (20% ammonia) was heated at 100 °C for 20 h in a sealed stainless-steel bomb. The reaction solution was removed from the chilled bomb, concentrated with a current of nitrogen to remove ammonia, and concentrated in vacuo to a yellow syrup. A water (50 mL) solution of the syrup was subjected to ion-exchange chromatography on a column of a cation-exchange resin (Amberlite CG-120, H^+ form). The resin column was washed thoroughly with water, and the 5-amino-2′-deoxyuridine analogue (**2f**) was then eluted with 1 N aqueous ammonia. The basic eluate was concentrated to remove ammonia and then lyophilized. Sulfuric acid (2 N, 0.25 mL) was added to an ethanol (3 mL) solution of the lyophilization residue. Addition of acetonitrile to the acidic solution and refrigeration of the mixture caused the formation of a precipitate (weight, 109 mg), and addition of acetonitrile to the filtrate and refrigeration of the mixture furnished a second crop of solid (206 mg). Acetonitrile was added to a hot, heterogeneous mixture of ethanol and the two crops of solid, and the resulting mixture was stored in a freezer (about −15 °C) and filtered to collect a precipitate, which was washed with acetonitrile and dried in vacuo at 78 °C: yield 136 mg. Concentration of the filtrate produced a second crop: yield 63 mg. The two crops were combined (total yield of the hemisulfate dihydrate = 56%): UV max 270 nm (ε 9300) at pH 1, 298 (ε 7500) and 226 nm (ε 7000) at pH 7, 291 (ε 6400) and 230–235 nm (slight shoulder) at pH 13; MS, *m/e* 241 (M), 223 (M – H_2O), 127 (5-aminouracilyl group + H); IR (1800–1300 cm^{-1} region) broad bands centered at 1700, 1535, 1520, 1480, 1435, 1400, 1375, 1275 cm^{-1}. Anal. ($C_{10}H_{15}N_3O_4 \cdot 0.5H_2SO_4 \cdot 2H_2O$) C, H, N.

(±)-1-[(1α,3β,4α)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-5-(methylamino)-2,4(1*H*,3*H*)-pyrimidinedione (2g). A solution of 175 mg of **2d** in a 50% solution (30 mL) of methylamine in methanol was heated at 90–100 °C for 20 h in a sealed, stainless-steel bomb. The reaction solution was removed from the chilled bomb, concentrated with a current of nitrogen, and then concentrated in vacuo to a foam. A water (25 mL) solution of the residue was chromatographed on a column of a cation-exchange resin (Amberlite CG-120, H^+ form). The resin column was washed thoroughly with water, and the 5-(methylamino)-2′-deoxyuridine analogue (**2g**) was eluted from the column with 1 N aqueous ammonia. The basic eluate was concentrated to dryness in vacuo, ethanol (3 mL) was added to the residue, the cloudy solution was filtered, and the clear filtrate was diluted carefully with ether (10 mL). A white solid was collected by filtration, washed with ether, and dried in vacuo at 78 °C: yield 37 mg. The filtrate was diluted with ether, and a second crop of white solid was then obtained in the same way: yield 73 mg (total yield as **2g** hemihydrate = 65.8%). The two crops of product were combined in hot ethanol, the solution was filtered, and the hot filtrate was diluted with ether. The white precipitate was collected by filtration, washed with ether, and dried in vacuo at 78 °C: recovery 73%; UV max 270 nm (ε 9400) at pH 1, 303 (ε 6400) and 236 nm (ε 6800) at pH 7, 294 (ε 5800) and 230–240 nm (slight shoulder) at pH 13; MS, *m/e* 256 (M + 1), 255 (M), 237 (M – H_2O), 224 (M – CH_2OH), 206 (M – H_2O – CH_2OH), 167, 141 [5-(methylamino)uracilyl group + H]; IR (1800–1300 cm^{-1} region) 1700, 1660, 1635, 1595, 1585 (sh), 1510, 1500, 1475, 1465, 1455, 1440, 1425, 1395, 1370, and 1320 cm^{-1}. Anal. ($C_{11}H_{17}N_3O_4 \cdot 0.5H_2O$) C, H, N.

(±)-5-(Butylamino)-1-[(1α,3β,4α)-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (2h) Sulfate. A solution of 400 mg of **6a** in butylamine (25 mL) was heated under reflux for 20 h and then concentrated in vacuo to a gummy residue. Water (20 mL) was added to the residue, and the aqueous mixture was extracted three times with 20-mL portions of ether and then concentrated in vacuo to a colorless syrup (yield 280 mg). A water (50 mL) solution of the residual syrup was chromatographed on a column of a cation-exchange resin as described for **2g**, and the basic eluate was concentrated in vacuo to a syrup that was dissolved in ethanol. The ethanol solution was filtered and concentrated to a colorless syrup: yield 248 mg (81% yield calculated as **2h** free base). The free base was converted to a sulfate salt as follows: 1 N sulfuric acid (1 mL) was added to an ethanol (20 mL) solution of the free base, the solution was concentrated to a low volume, the addition of ethanol and the concentration of the resulting solution were repeated several times to remove water, and ether was then added to the concentrated solution. A white, hygroscopic solid, collected in two crops, was separated by filtration, washed with ether, and dried in vacuo at 78 °C: yield 170 mg (44% calculated as a sulfate 1.25-hydrate); MS, *m/e* 297 (M), 279 (M – H_2O), 254 (M – C_3H_7), 236 (M – C_3H_7 – H_2O), 183 [5-(butylamino)uracilyl group + H]; IR (1800–1000 cm^{-1} region) broad bands centered at 1690, 1585, 1495, 1465, 1440, 1395, 1380 (sh), 1310 (sh), 1280, 1210, 1165, 1115, 1040 cm^{-1}. Anal. ($C_{14}H_{23}N_3O_4 \cdot 0.5H_2SO_4 \cdot 1.25H_2O$) C, H; N: calcd, 11.40; found, 11.85.

(±)-5-(Dimethylamino)-1-[(1α,3β,4α)-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (2i). A solution of 160 mg of **6a** in 15 mL of a solution of dimethylamine in methanol (20% dimethylamine) was heated in a sealed, stainless-steel bomb at 100 °C for 24 h. The reaction product was isolated by the procedure described for **2g**; the basic eluate from the resin column was concentrated in vacuo to remove dimethylamine and then lyophilized. An ethanol (10 mL) solution of the residue was filtered, concentrated to a low volume, diluted with a small amount of ether, and stored at about 5 °C. The precipitated 5-(dimethylamino)uracil derivative (**2i**) was collected by filtration, washed with an ethanol–ether mixture (1:1), and dried in vacuo: yield 90 mg (76%). This compound may be reprecipitated by the addition of ether to an ethanol solution: mp 137–142 °C dec; UV max 270 nm (ε 9500) at pH 1, 294 (ε 6600) and 230 nm (ε 7600) at pH 7, 284 (ε 5800) and 230–235 nm (slight shoulder) at pH 13; MS, *m/e* 270 (M + 1), 269 (M), 251 (M – H_2O), 181, 155 [5-(dimethylamino)uracilyl group + H]; IR (1800–1300 cm^{-1} region) 1700 (sh), 1685, 1640, 1615 (sh), 1600 (sh), 1515, 1475, 1460, 1455, 1430, 1395, 1365, 1315 cm^{-1}. Anal. ($C_{12}H_{19}N_3O_4 \cdot 0.75H_2O$) C, H, N.

(±)-5-Bromo-1-[(1α,2β,4α)-2-hydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (3d). Diacetate **6b** (270 mg) was treated with 10% methanolic ammonia (15 mL) according to the procedure described for the preparation of **2d**. The crude product was recrystallized from a small amount of water. Two crops of crystals (**3d**) were collected: total yield 160 mg (75.8%); mp 199–202 °C; UV max 284 (ε 10 000) and 211 nm (ε 9700) at pH 1, 284 (ε 9900) and 210 nm (ε 9800) at pH 7, 280 nm (ε 7600) at pH 13; MS, *m/e* 304 (M), 286 (M – H_2O), 276 (M – CO), 255 (M – H_2O – CH_2OH), 217 (5-bromouracilyl group + C_2H_4), 191 (5-bromouracilyl group + 2H), 190 (5-bromouracilyl group + H); IR (1800–1300 cm^{-1} region) 1700, 1670, 1610, 1500 (w), 1455, 1410, 1390, 1375, 1350, 1335 (sh), 1310 (sh), 1300 cm^{-1}. Anal. ($C_{10}H_{13}BrN_2O_4 \cdot 0.5H_2O$) C, H, N.

(±)-1-[(1α,2β,4α)-2-Hydroxy-4-(hydroxymethyl)cyclopentyl]-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione (3e). A solution of 500 mg of the carbocyclic analogue (**3a**) of 3′-deoxyuridine in 5 mL of 1 N nitric acid was added to a solution of 500 mg of iodine in chloroform (3 mL), and the resulting mixture was heated under reflux for about 20 h. A crystalline precipitate that had formed in the reaction mixture was collected by filtration, washed with cold water and with ether, and dried in vacuo at 78 °C: yield 565 mg (73%); mp 208–210 °C. Recrystallization of this material from water (10 mL) furnished white crystals: yield 418 mg; mp 210–212 °C; UV max 293 (ε 8700) and 217 nm (ε 10 900) at pH 1, 294 (ε 8700) and 217 nm (ε 11 000) at pH 7, 284 nm (ε 6400) at pH 13; MS, *m/e* 352 (M), 334 (M – H_2O), 324 (M – CO), 303 (M – H_2O – CH_2OH), 265 (5-iodouracilyl group + C_2H_4), 239 (5-iodouracilyl group + 2H), 238 (5-iodouracilyl group + H); IR (1800–1300 cm^{-1} region) 1695, 1665, 1605, 1490 (w), 1445, 1410, 1400, 1385, 1340,

1305 (sh), 1295. Anal. ($C_{10}H_{13}IN_2O_4 \cdot 0.25H_2O$) C, H, N.

(±)-5-Amino-1-[(1α,2β,4α)-2-hydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (3f). Compound **3f** was prepared from **3d** by the procedure described for the preparation of **2f**, but it was isolated as the free base rather than as a sulfate salt. After the base eluate from the resin column had been lyophilized, the residue was slurried with ethanol (30 mL/g), ether (60 mL/g) was added, and the mixture was stored at about 5 °C. A precipitate was collected, washed with ether, and dissolved in hot ethanol (100 mL/g). The ethanol solution was filtered to remove a slight turbidity, diluted with ether (160 mL/g), and stored again at about 5 °C. The solid product was collected by filtration, washed with ether, and dried in vacuo at 78 °C: UV max 271 nm (ε 8400) at pH 1, 297 (ε 6600) and 225 nm (shoulder, ε 6400) at pH 7, and 292 (ε 5800) and 230–235 nm (slight shoulder) at pH 13; MS, *m/e* 242 (M + 1), 241 (M), 223 (M − H_2O), 192 (M − H_2O − CH_2OH), 154 (5-aminouracilyl group + C_2H_4), 140, 128, and 127 (5-aminouracilyl group + 2H and H, respectively); IR (1800–1300 cm^{-1} region) broad bands centered at 1680, 1640, 1600, 1580 (sh), 1500, 1380, 1350 (sh), 1305 (sh) cm^{-1}. Anal. ($C_{10}H_{15}N_3O_4 \cdot H_2O$) C, H, N.

(±)-1-[(1α,2β,4α)-2-Hydroxy-4-(hydroxymethyl)cyclopentyl]-5-(methylamino)-2,4(1*H*,3*H*)-pyrimidinedione (3g). By the procedure described for the preparation of **2g**, compound **3g** was prepared from 550 mg of **6b** and a solution (15 mL) of methanolic methylamine (25% methylamine). The basic eluate from the resin column was concentrated in vacuo and then lyophilized, and an ethanol solution of the residue (288 mg) was filtered, concentrated to a low volume, diluted with a small amount of ether, and stored at about 5 °C. The precipitate was collected by filtration, washed with an ethanol–ether mixture (5:1), and dried in vacuo at 78 °C: yield 198 mg (55% calculated as $0.25H_2O$: mp 200–205 °C; UV max 272 nm (ε 10 000) at pH 1, 302 (ε 7200) and 234 nm (ε 7500) at pH 7, 294 (ε 6200) and 230–240 nm (slight shoulder) at pH 13; MS, *m/e* 256 (M + 1), 255 (M), 237 (M − H_2O), 206 (M − H_2O − CH_2OH), 167, 141 [5-(methylamino)uracilyl group + H]; IR (1800–1300 cm^{-1} region) 1675, 1660, 1640, 1525, 1475, 1445, 1420, 1385, 1340 (sh), 1295 cm^{-1}. Anal. ($C_{11}H_{17}N_3O_4 \cdot 0.25H_2O$) C, H, N.

(±)-5-Bromo-1-[(1α,2β,3β,4α)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (4d). Triacetate **6c** (471 mg) was treated with 10% methanolic ammonia (25 mL) according to the procedure described for the preparation of **2d**. Recrystallization of the crude product from water gave white crystals that were dried at 78 °C: yield 251 mg (74%); mp 229–232 °C; UV max 284 (ε 10 200) and 212 nm (ε 9600) at pH 1, 283 (ε 9900) and 211 nm (ε 9500) at pH 7, and 280 nm (ε 7800) at pH 13; MS, *m/e* 320 (M), 302 (M − H_2O), 271, 217 (5-bromouracilyl group + C_2H_4), 191 (5-bromouracilyl group + 2H); IR (1800–1300 cm^{-1} region) 1710 (sh), 1690, 1620, 1505, 1455, 1420, 1395, 1360, 1315, 1305 cm^{-1}. Anal. ($C_{10}H_{13}BrN_2O_5$) C, H, N.

(±)-1-[(1α,2β,3β,4α)-2,3-Dihydroxy-4-(hydroxymethyl)cyclopentyl]-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione (4e). Iodine (284 mg) was added to a well-stirred mixture of chloroform (1.42 mL), 304 mg of the carbocyclic analogue (**4a**) of uridine, and 1 N nitric acid (3 mL). The mixture was heated under gentle reflux for 2 h and then stirred at room temperature for 1 h. Additional iodine (142 mg) was added, and the mixture was stirred at room temperature overnight (during which time a white precipitate formed) and was chilled. The precipitate was collected by filtration, washed with cold water and then with chloroform, and dried at 78 °C: yield 270 mg (59%); mp 210–212 °C. The filtrate was neutralized (pH 7) with 6 N NaOH and then extracted with ethyl acetate in a continuous liquid–liquid extractor. From the ethyl acetate extract, 90 mg (mp 209–212 °C) of additional **4e** was obtained (total yield 78%). The two portions were combined and dissolved in hot water (6 mL), and the solution was cooled slowly to room temperature and then chilled. The white crystalline precipitate was collected by filtration, washed with cold water, and dried in vacuo at 78 °C: yield 282 mg (61%); mp 210–213 °C; UV max 293 (ε 8700) and 217 nm (ε 10 800) at pH 1, 292 (ε 8600) and 217 nm (ε 10 800) at pH 7, 284 nm (ε 6300) at pH 13; MS, *m/e* 368 (M), 350 (M − H_2O), 321, 319 (M − H_2O − CH_2OH), 265 (5-iodouracilyl group + C_2H_4), 239 and 238 (5-iodouracilyl group + 2H and H, respectively), 222 (M − H_2O − HI); IR (1800–1300 cm^{-1} region) 1700, 1680, 1615, 1500 (w), 1450, 1425 (sh), 1415, 1390, 1365 (sh), 1355, 1315 (sh), 1305 cm^{-1}. Anal. ($C_{10}H_{13}IN_2O_5$) C, H, N.

(±)-5-Amino-1-[(1α,2β,3β,4α)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (4f). The carbocyclic analogue (**6c**; 530 mg) of 5-bromouridine triacetate was treated with methanolic ammonia (30 mL of 50% methanol–ammonia) according to the procedure for the preparation of **2f**. After the basic eluate from the resin column had been lyophilized, the residual white solid was dissolved in hot ethanol (20 mL) with the aid of a small amount of water (2 mL). The solution was treated with activated charcoal and filtered, and the filtrate was diluted with ether (25 mL) and concentrated to about one-half of the original volume. The concentrated solution was diluted again with ether (25 mL) and concentrated again, and this process was repeated. The resulting mixture, containing a white solid, was placed in a refrigerator. The white precipitate was then collected by filtration, washed with ether, and dried in vacuo at 78 °C: yield 93 mg. By concentrating the filtrate and adding more ether, we obtained a second crop of product in the same way: yield 133 mg (total yield as a hydrate 69%). The two portions of hygroscopic product were blended and dried again at 78 °C: UV max 269 nm (ε 9200) at pH 1, 297 (ε 7400) and 225 nm (shoulder, ε 6900) at pH 7, 291 (ε 6300) and 230–235 nm (slight shoulder) at pH 13; MS, *m/e* 257 (M), 239 (M − H_2O), 128 and 127 (5-aminouracilyl group + 2H and H, respectively); IR (1800–1270) cm^{-1} region) broad bands centered at 1685, 1645, 1595, 1495, 1400, 1335 (w), 1300 (sh), 1270 cm^{-1}. Anal. ($C_{10}H_{15}N_3O_5 \cdot H_2O$) C, H, N.

(±)-1-[(1α,2β,3β,4α)-2,3-Dihydroxy-4-(hydroxymethyl)cyclopentyl]-5-(methylamino)-2,4(1*H*,3*H*)-pyrimidinedione (4g). A solution of **6c** (530 mg) in a 50% solution (30 mL) of methylamine in methanol was heated at 100 °C for 18 h in a sealed, stainless-steel bomb, and **4g** was isolated by the method described for **2g**. It was recrystallized from ethanol–water–ether (8:1:15), washed with ethyl acetate, and dried in vacuo at 78 °C: yield 182 mg (53% as the monohydrate); mp indefinite (>105 °C); UV max 271 nm (ε 9100) at pH 1, 303 (ε 6300) and 235 nm (ε 6600) at pH 7, 294 (ε 6000) and 230–240 nm (slight shoulder) at pH 13; MS, *m/e* 271 (M), 253 (M − H_2O), 167, 141 [5-(methylamino)uracilyl group + H]; IR (1800–1300 cm^{-1} region) 1675 (broad), 1640, 1575 (sh), 1515, 1475, 1470 (sh), 1435, 1425, 1410 (sh), 1400, 1375, 1345, 1335, 1320, 1305 cm^{-1}. Anal. ($C_{11}H_{17}N_3O_5 \cdot H_2O$) C, N; H: calcd, 6.58; found, 6.17.

(±)-1-[(1α,2β,3β,4α)-2,3-Dihydroxy-4-(hydroxymethyl)cyclopentyl]-5-(hydroxymethyl)-2,4(1*H*,3*H*)-pyrimidinedione (4h). A solution of 190 mg of isopropylidene derivative **6e**, 50 mg of paraformaldehyde, and 2 mL of 0.5 N KOH was heated at 60–65 °C for 24 h and diluted at room temperature with 20 mL of water. A cation-exchange resin (Rexyn 101, H^+ form) was added in portions until the pH of the stirred mixture stabilized at about 3.5–4, the resin was separated by filtration and washed thoroughly with methanol, and the filtrate (including the washings) was concentrated to an amorphous residue (202 mg). Field-desorption and electron-impact mass spectra showed that the residue was the isopropylidene derivative of **4h** [*m/e* 312 (M), 297 (M − CH_3)] containing small amounts of **4h**, **4a**, and **6e**. A solution of the crude product in 20 mL of 50% acetic acid was boiled under reflux for 2 h to remove the isopropylidene group and concentrated to dryness in vacuo. A solution of the residue in 5 mL of 0.5 N KOH was heated at 46–48 °C for 3 h (to deacetylate the product) and treated with a cation-ion exchange resin (Rexyn 101, H^+ form) in portions to lower the pH to ca. 4. The resin was separated by filtration and washed thoroughly with methanol, and the water–methanol solution was concentrated in vacuo to a colorless syrup (162 mg). A methanol solution of the residue was applied to a preparative TLC plate of silica gel, the plate was developed with 3:1 $CHCl_3$–CH_3OH, the product band was removed and extracted in a Soxhlet extractor with methanol, the filtered extract was concentrated in vacuo to a colorless gum, and a warm ethanol solution of the residue was diluted with ether. A white, curdy solid was filtered from the chilled mixture, washed with ether, and dried in vacuo at 56 °C: yield 26 mg (hygroscopic); TLC, 1 spot (20 mcg on silica gel, developing solvent 3:1 $CHCl_3$–CH_3OH); HPLC, 98.9% (μ-Bondapak C_{18} column; 95:5 H_2O–acetonitrile, isocratic; monitored at 280 nm); MS (direct-probe temperature 250 °C), *m/e* 272 (M), 271 (M − H), 255 (M − OH), 242 (M −

CH_2OH + H), 143 [5-(hydroxymethyl)uracilyl + 2H], 125, 113. Anal. ($C_{11}H_{16}N_2O_6 \cdot 0.75H_2O$) C, H, N.

(±)-5-Bromo-1-[(1α,3β,4α)-3-hydroxy-4-(hydroxymethyl)-cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione Diacetate (6a). A mixture of acetic anhydride (11 mL) and 1.0 g of the carbocylic analogue (**2a**) of 2′-deoxyuridine was boiled under reflux until the mixture became a homogeneous solution. The solution was cooled to room temperature and was stirred and maintained at 25 °C while a solution of bromine (826 mg) in 1.1 mL of acetic acid was added dropwise. The resulting solution was stirred at room temperature for 3 h and then stored overnight at low temperature (about 5 °C) after additional reagent (206 mg of bromine in 0.3 mL of acetic acid) had been added. Volatile components were evaporated from the reaction solution under reduced pressure, and the crystalline residue was triturated with an ethanol–ether (1:1) mixture. The white solid was collected by filtration and dried under reduced pressure at 78 °C: yield 1.605 g (93%). Ultraviolet absorption data indicated that this material was comparable to an analytically pure specimen. This compound may be purified, if desired, by recrystallizing it from ethanol: recovery 84%; mp 164–167 °C; UV max 284 (ε 10 400) and 212 nm (ε 10 000) at pH 1, 282 (ε 9900) and 211 nm (ε 9600) at pH 7, and 280 nm (ε 7600) at pH 13; MS, *m/e* 388 (M), 328 (M − CH_3COOH), 285 (M − CH_3CO − CH_3COOH), 268 (M − $2CH_3COOH$), 190 (5-bromouracilyl group + H); IR (1800–1400 cm^{-1} region) 1740, 1720, 1700, 1680, 1620, 1500 (w), 1460 (sh), 1450, 1430, 1380, 1360, 1320 cm^{-1}. Anal. ($C_{14}H_{17}BrN_2O_6$) C, H, N.

(±)-5-Bromo-1-[(1α,2β,4α)-2-hydroxy-4-(hydroxymethyl)-cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione Diacetate (6b). The carbocyclic analogue (**3a**) of 3′-deoxyuridine was treated with acetic anhydride and with bromine in acetic acid according to the procedure described for **2a**. The crystalline product was recrystallized from ethanol: yield of **6b** from 0.5 g of **3a**, 820 mg (95%); mp 184–186 °C; UV max 283 (ε 10 100) and 211 nm (ε 9400) at pH 1, 283 (ε 10 000) and 212 nm (ε 9900) at pH 7, 280 nm (ε 7300) at pH 13; MS, *m/e* 388 (M), 328 (M − CH_3COOH), 285 (M − CH_3CO − CH_3COOH), 268 (M − $2CH_3COOH$), 249 (M − CH_3COOH − Br), 191 (5-bromouracilyl group + 2H), 190 (5-bromouracilyl group + H); IR (1800–1300 cm^{-1} region, Fourier transform spectrum determined with Nicolet Model MX-1 spectrometer) 1740, 1725, 1715, 1675, 1620, 1515 (w), 1465 (sh), 1460, 1450, 1425, 1405, 1390, 1370, 1360, 1345, 1320, 1300 cm^{-1}. Anal. ($C_{14}H_{17}BrN_2O_6 \cdot 0.25H_2O$) C, H, N.

(±)-5-Bromo-1-[(1α,2β,3β,4α)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione Triacetate (6c). The carbocyclic analogue (**4a**) of uridine was treated with acetic anhydride and with bromine in acetic acid according to the procedure described for **2a**. The crystalline residue remaining after volatile components had been evaporated from the reaction solution under reduced pressure was triturated with ether, collected by filtration, washed thoroughly with ether, and dried in vacuo at 78 °C: yield of **6c** from 1.91 g of the uridine analogue, 3.28 g (93%); mp 172–175 °C; MS, *m/e* 446 (M), 386 (M − CH_3COOH), 343 (M − CH_3COOH − CH_3CO), 307 (M − CH_3COOH − Br), 301, 284, 266, 191 (5-bromouracilyl group + 2H). Anal. ($C_{16}H_{19}BrN_2O_8$) C, H, N.

(±)-1-[(1α,3β,4α)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione Diacetate (6d). A solution prepared from 450 mg of **2e**, pyridine (20 mL), and acetic anhydride (1 mL) was stirred at room temperature for 3 days and then concentrated to a low volume. Cold water was added dropwise to the concentrated solution, and the resulting mixture, containing a gummy precipitate, was placed in a refrigerator to allow crystallization to occur. The crystalline precipitate was collected by filtration, washed well with cold water, and dried in vacuo at 78 °C: yield 550 mg (99%); mp 183–186 °C; UV max 293 (ε 8100) and 218 nm (ε 10 200) at pH 1, 292 (ε 8000) and 217 nm (ε 10 200) at pH 7, and 284 nm (ε 5800) at pH 13; MS, *m/e* 436 (M), 376 (M − CH_3COOH), 316 (M − $2CH_3COOH$), 303 (M − CH_3COOH − CH_2OCOCH_3), 265 (5-iodouracilyl group + C_2H_4), 239 (5-iodouracilyl group + 2H), 238 (5-iodouracilyl group + H); IR (1800–1300 cm^{-1} region) 1725, 1690, 1665, 1610, 1590, 1515 (w), 1445, 1435, 1420, 1375, 1355, 1345, 1320, 1305 cm^{-1}. Anal. ($C_{14}H_{17}IN_2O_6$) C, H, N.

Isopropylidene Derivative (6e) of the Carbocylic Analogue (4a) of Uridine. Perchloric acid (60%, 1.22 mL) was added to a mixture of 28.5 mL of anhydrous acetone and 0.78 mL of 2,2-dimethoxypropane, the solution was stirred at room temperature for 5 min, and the uridine analogue (**4a**; 484 mg) was added in one portion. The resulting solution was stirred at room temperature for 20 min, anhydrous pyridine (2.34 mL) was added, and the solution was concentrated to dryness in vacuo. A water (15 mL) solution of the residual syrup was extracted with $CHCl_3$ (3 × 30 mL), and the $CHCl_3$ extract was dried ($MgSO_4$) and concentrated to a gummy solid (245 mg). Recrystallization of the residue from ethyl acetate–ether furnished white crystals, which were washed with ether and dried in vacuo at 56 °C: yield 140 mg; mp 182–185 °C; TLC, 1 spot (silica gel, 9:1 $CHCl_3$–CH_3OH); MS, *m/e* 283 (M + 1), 267 (M − CH_3); IR 1700 and 1655 cm^{-1}. Anal. ($C_{13}H_{18}N_2O_5 \cdot 0.25H_2O$) C, H, N.

Antiviral Evaluations in Vitro. Compounds **2–4** were evaluated for antiviral activity in vitro exactly as described by Shannon et al.,[19] except that strain 377 of HSV-1, strain HF/TK⁻ of HSV-1, and strain MS of HSV-2 replicating in primary rabbit kidney cell cultures were employed as the challenge viruses.

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Registry No. **2a**, 62102-28-7; **2b**, 61849-27-2; **2c**, 78336-03-5; **2d**, 83967-02-6; **2e**, 83967-03-7; **2f**, 83967-04-8; **2f** 0.5-sulfate, 84025-03-6; **2g**, 83967-05-9; **2h** 0.5 sulfate, 83967-07-1; **2i**, 83967-08-2; **3a**, 62102-31-2; **3b**, 78795-26-3; **3c**, 78336-04-6; **3d**, 83983-96-4; **3e**, 83967-09-3; **3f**, 83967-10-6; **3g**, 83967-11-7; **4a**, 59967-83-8; **4b**, 78795-27-4; **4c**, 78336-05-7; **4d**, 83983-97-5; **4e**, 83967-12-8; **4f**, 83967-13-9; **4g**, 83967-14-0; **4h**, 83967-15-1; **4h** (isopropylidene deriv), 83983-98-6; **6a**, 83967-16-2; **6b**, 83967-17-3; **6c**, 83967-18-4; **6d**, 83967-19-5; methylamine, 74-89-5; butylamine, 109-73-9; dimethylamine, 124-40-3.