A. Damascus and his staff. Consultations on NMR analyses were with L. Swenton and P. Finnegan. All of the above persons are in the Physical Methodology Department of G.D. Searle R&D. Single-crystal X-ray analysis was performed by Dr. C. K. Schauer under the direction of Prof. Oren Anderson at Colorado State University, Ft. Collins, CO, using a Nicolet R3m-E diffractometer supplied by NSF CHE-8103011. Manuscript preparation was by G. Koek and P. Polin.

Registry No. 7, 111159-74-1; 8, 111159-75-2; 9, 111159-76-3; 10, 111159-77-4; 11, 23876-12-2; 11(aminoguanidine hydrazone), 111159-96-7; 12, 16634-91-6; 12(aminoguanidine hydrazone), 111159-95-6; 13, 111159-78-5; 13·2HCl, 111160-04-4; 14, 111159-79-6; 14·2HCl, 111160-03-3; 15, 111159-80-9; 15(aminoguanidine hydrazone), 111159-94-5; 16, 111159-81-0; 16·3HCl, 111160-02-2; 17, 111159-82-1; 17·HNO_3, 111160-12-4; 18, 111159-83-2; 19, 111159-84-3; 20, 111159-85-4; 20·HCl, 111159-97-8; 21, 111159-86-5; 21·HCl, 111160-01-1; 22, 111159-87-6; 23, 6928-06-9; 23·HCl, 111159-98-9; 24, 6928-07-0; 24·H_2SO_4, 111159-99-0; 25, 74618-23-8; 25·$1^1/_2H_2SO_4$, 111160-00-0; 26, 72189-66-3; 27, 111159-88-7; 27·HNO_3, 111822-63-0; 28, 111159-89-8; 28·H_2SO_4, 111160-06-6; 29, 111159-90-1; 29·H_2SO_4, 111160-08-8; 29·$^1/_2H_2SO_4$·$^1/_2H_2O$, 111822-62-9; 30, 111159-91-2; 30·H_2SO_4, 111160-10-2; 31, 111159-92-3; 32, 111159-93-4; 2,6-$(Me)_2C_6H_3CHO$, 1123-56-4; 2,6-$(Me)_2$-4-OH-1-$(CHO)C_6H_2$, 70547-87-4; $NH_2C(=NH)NHNH_2$·HNO_3, 10308-82-4; $NH_2C(=NH)NHNH_2$·$^1/_2H_2SO_4$, 996-19-0; 2,6-$(Me)_2C_6H_3OH$, 576-26-1; 3,5-$(Me)_2$-4-OH-1-$(CHO)C_6H_2$, 2233-18-3; 2,6-$(Me)_2$-4-OMe-1-$(CHO)C_6H_2$, 19447-00-8; o-MeC_6H_4CHO, 529-20-4; 2,6-$(Me)_2C_6H_3Ac$, 2142-76-9; mesitaldehyde, 487-68-3; 1-naphthaldehyde, 66-77-3; 2-naphthaldehyde, 66-99-9; 4-quinolinecarboxaldehyde, 4363-93-3; 2-hydrazine-2-imidazoline hydrobromide, 55959-84-7; α-tetralone, 529-34-0; 1-indanone, 83-33-0; 7-methoxytetralone, 6836-19-7; 6-methoxytetralone, 1078-19-9; 5-methoxytetralone, 33892-75-0; 2-methyltetralone, 1590-08-5.

Supplementary Material Available: Spectroscopic data (NMR, IR) on target compounds, single-crystal X-ray data on **29**, including unit cell dimensions, space group, and atomic coordinates with their estimated precision, and structures and figures (energy vs rotation graphs) for computational chemistry on **17**, **18**, and **29** (12 pages). Ordering information is given on any current masthead page.

Effect of Acyclic Pyrimidines Related to 9-[(1,3-Dihydroxy-2-propoxy)methyl]guanine on Herpesviruses

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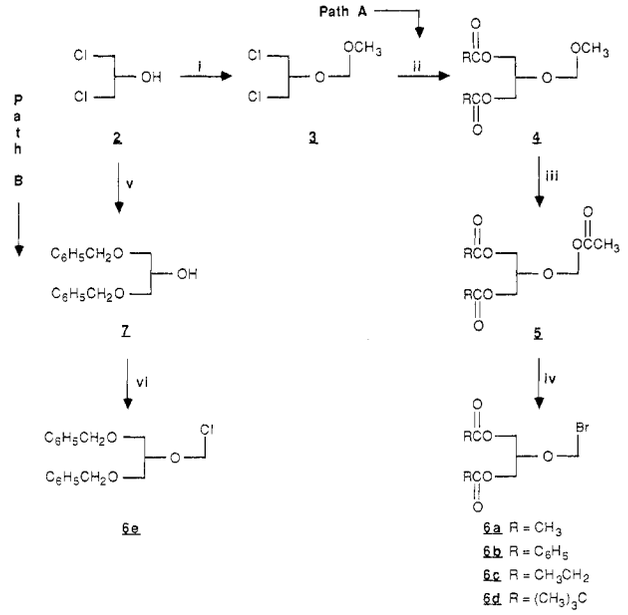
A series of pyrimidines related to the potent antiherpetic agent 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (**1**, BW B759U), all containing the same acyclic chain, have been synthesized. Some of the compounds were derivatives of the naturally occurring bases, cytosine, uracil, and thymine; others included compounds in which the 5-position of the cytosine and uracil moieties were substituted by bromo, iodo, fluoro, methyl, and amino groups. Other variations of the cytosine derivatives were the 5-aza, 2-mercapto, 4-methylamino, 4-dimethylamino, and isocytosine congeners. A 4-aminopyrimidine adduct was also made. Antiviral testing showed that 1-[(1,3-dihydroxy-2-propoxy)methyl]cytosine (**18**, BW A1117U) was equivalent to the guanine analogue in potency against human cytomegalovirus and Epstein Barr virus. Other compounds in the series were largely inactive in antiviral screening against the herpesviruses.

The acyclic nucleoside 9-[(1,3-dihydroxy-2-propoxy)-methyl]guanine (**1**, BW B759U, ganciclovir) is undergoing clinical trials for the treatment of cytomegalovirus (CMV) infections in immunocompromised and AIDS patients. This compound, which has been independently reported by us[1] and others,[2] exhibits a broad spectrum of activity against the family of herpesviruses, similarly to the parent, 9-[(2-hydroxyethoxy)methyl]guanine, acyclovir (ACV, Zovirax).[3] However, **1** is a much more potent anti-CMV agent (IC_{50} = 2–10 μM vs 90–200 μM for ACV). Both compounds are members of a heterocyclic series possessing open acyclic chain functions that mimic the closed sugar groups of naturally occurring nucleosides.

As part of an ongoing program of evaluating acyclic nucleosides in these laboratories, we have synthesized pyrimidines alkylated with acyclic chains similar to that of acyclovir, but none have shown any significant antiviral activity.[4] We now report the results of the syntheses and the in vitro virological testing of pyrimidines bearing the (1,3-dihydroxy-2-propoxy)methyl substituent.

Chemistry. Our principal targets in the series were derivatives of cytosine, uracil, and thymine. Scheme I illustrates the sequence used to synthesize the requisite acyclic chain, all commencing with 1,3-dichloro-2-propanol (**2**). The choice of protecting groups for the hydroxy termini was governed by well-known difficulties in the

Scheme I



[a] (i) $CH_3OCH_2OCH_3$, P_2O_5/room temperature; (ii) MOOCR, DMF/reflux (M = Na or K); (iii) Ac_2O, BF_3·Et_2O/0 °C; (iv) $(CH_3)_3SiBr$, CH_2Cl_2/reflux; (v) $C_6H_5CH_2ONa$, DMF/reflux; (vi) HCl, $(CH_2O)_3$, CH_2Cl_2/0 °C.

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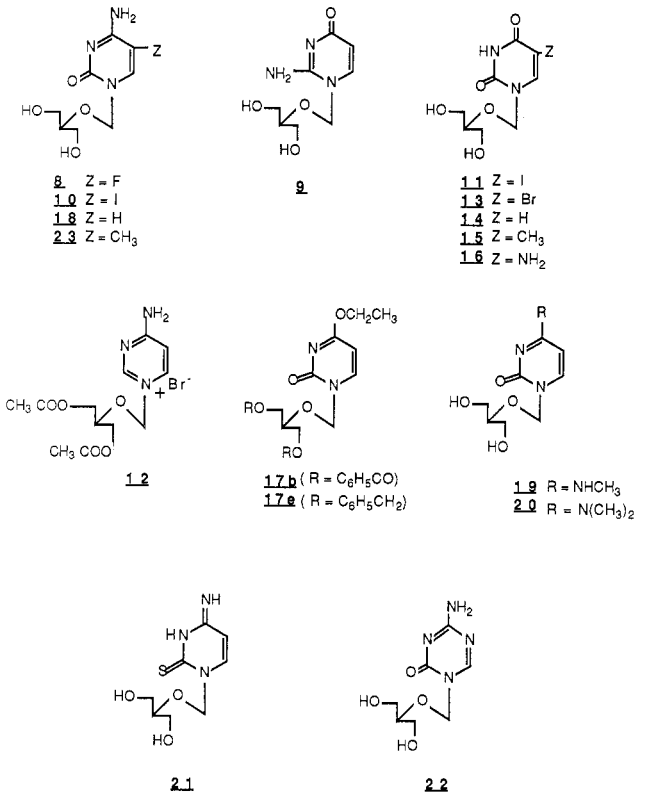
0022-2623/88/1831-0144$01.50/0

Chart I



removal of benzyloxy functions, which are the most commonly used blocking groups for glycerol derivatives. Deprotection by catalytic reduction, the usual debenzylation method, is particularly problematic with cytosine nucleosides due to their propensity for cleavage to the parent base during hydrogenolysis. Thus, in the cytosine series, ester blocking groups were used in the acyclic chain (path A, Scheme I), allowing the employment of mild deprotecting agents. The function of the methoxymethylene substituent in the 2-position of **3** served a dual purpose. It protected that position from transacylation by the neighboring 1- and 3-ester moieties that might have occurred under the subsequent reaction conditions. It also furnished the backbone methyleneoxy unit, whose terminus could be converted to the most suitable leaving group for the alkylation of the nucleoside bases. We have found that the bromomethyl ethers **6a–d** usually provide more favorable yields of pyrimidine acyclic compounds than the acetoxymethyl ethers **5**. Thus, the synthetic sequence leading to the requisite acyclic chain consisted of an exchange reaction of the appropriately halogenated alcohol with dimethoxymethane using an acidic catalyst, phosphorus pentoxide. The resultant methoxymethyl ether **3** was treated with the desired acid salt in refluxing dimethylformamide to give good yields of the disubstituted ester **4**. Acetolysis at 0 °C smoothly converted the methoxymethylene terminus to the acetoxymethyl moiety, and finally, treatment of **5** with bromotrimethylsilane produced the bromomethyl ether **6**, usually in quantitative yields.

One of the procedures for making the cytosine derivatives is illustrated in the Experimental Section by the synthesis of the 5-fluorocytosine analogue **8** (Chart I). Alkylation of the silylated base, formed in situ after a method of Vorbruggen and Bennua,[5] with the bromomethyl ether **6b**, produced the precursor ester derivative, which was subsequently deprotected with 40% aqueous methylamine at room temperature to yield the target **8**. (The temperature of this reaction and its workup is critical; higher temperatures lead to transamination at the 4-position of the pyrimidine.) Alternate syntheses of this compound have been published by Ogilvie et al.[6] and Martin and co-workers;[7] each group used different methods and reported different melting points (135–136 °C and 165–166 °C, respectively). Our data are generally in agreement with the latter and are supported by extensive spectroscopic analyses. The isocytosine derivative **9** was made by treatment of the base with **6b** and sodium hydride in DMF, followed by hydrolysis of the ester termini with aqueous methylamine in an overall yield of 8.8%. A more circuitous route was used by Martin to prepare the same analogue.[7] The 5-iodo compounds **10** and **11** were made similarly to the preparation of **8**, i.e., by alkylation of the silylated 5-iodo bases.

The 4-aminopyrimidine adduct **12**, produced by simple addition of **6a** to the pyrimidine base, was synthesized to explore the possibility of enzymatic hydroxylation of the 2-position of the heterocycle, analogous to the conversion of 2-aminopurine compounds to guanine derivatives by xanthine oxidase.[8] The site of alkylation in **12** was determined to be the N-1 position rather than N-3 by comparison of the ^{13}C NMR spectrum of the compound with that of the 4-aminopyrimidine base. The shift values of the peaks for C-4 and C-5 in the latter were the same as those in the spectrum of **12**, while the C-2 and C-6 values were different, indicating the influence of an N-1 substituent. No attemp was made to deprotect the ester groups.

A few uracil congeners were prepared by the Hilbert Johnson reaction, exemplified in the Experimental Section by the synthesis of the 5-bromouracil analogue **13**.[9] Compounds **14**, the uracil, and **15**, the thymine analogues, were made by utilizing [1,3-bis(benzyloxy)-2-propoxy]-methyl chloride (**6e**), prepared by the standard method of chloromethylation of 1,3-di-*O*-benzylglycerol (**7**) (Aldrich) with paraformaldehyde and gaseous hydrogen chloride[10] (path B). These uracil derivatives were deprotected by hydrogenolysis using 5% palladium–carbon catalyst at room temperature. The reductions required prolonged reaction times to effect the conversions.

The 5-aminouracil derivative **16**, was obtained by amination of **13**, subsequent to protection of the hydroxy

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Table I. Physical Properties of Analogues Not Listed in Experimental Section

no.	meth	yield[a]	alkyl ch/depr agt[b,c]	mp, °C	recrystn solv
21	A	39/57	5b/M	175–177	H_2O–hexane
10	A	55/55	5b/M	176–178	MeOH, acetone, hexane
22	A	59/38	5b/M	185–188	MeOH, acetone, hexane
11	A	39/31	5b/N	140–142	MeOH
19	B	63/28	5c/M	158–162	EtOH–EtOAc

[a] Alkylation/deprotection. [b] Chain used and deprotecting agent at room temperature. [c] Chain code: b = benzoate, c = pivalate. Deprotecting code: N = NH_3/MeOH, M = 40% aqueous CH_3NH_2.

groups by acetolysis. An alternate method, reduction of a 5-nitrouracil analogue, was used by Ogilvie.[9] Alkylation of 2,4-diethoxypyrimidine with **6b** by the Hilbert Johnson method provided the versatile intermediate **17b**, which was converted to cytosine **18**, 4-methylamino **19**, and 4-dimethylamino **20**, congeners by reaction with ammonia or the appropriate amine, with concomitant deprotection of the ester groups.

The 2-mercaptopyrimidine acyclic **21** was made by the treatment of the silylated base with **6b**, then deprotected in the usual manner. Of interest in the ^1H NMR spectrum of **21** was the existence of two singlets, at 7.72 and 7.59, each integrating for one hydrogen, for the 4-amino group, indicating that this structure exists in the imino form.

The 5-azacytosine **22**[6] and the 5-methylcytosine analogue **23** were prepared similarly.

Table I lists the pertinent synthetic data for all the compounds not described in the Experimental Section.

Biological Results and Discussion

Results of antiviral testing by the plaque reduction assay[11,12] of each series are listed in Table II. Since the activity of the purine acyclic congener, acyclovir, has been demonstrated to result initially from its phosphorylation to the monophosphate form by the herpes thymidine kinase,[13] which is subsequently converted to the triphosphate by cellular kinases,[14] similar mechanisms were assumed to exist for any positive testing pyrimidine compound. However, the activities of the parent compound 1-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]cytosine (**18**, BW A1117U) against the herpesviruses that have been shown to induce a viral thymidine kinase range from very poor for herpes simplex virus (HSV) types 1 and 2 to moderate for varicella zoster virus (VZV). In contrast, the potency of its inhibition of cytomegalovirus, which is not known to code for a viral TK, is striking, being comparable to other strong inhibitors such as ganciclovir and 2′-deoxy-2′-fluoro-5-iodo-1-β-D-arabinofuranosylcytosine, FIAC (the IC_{50}'s for the latter two are 3.4 and 3.2 μM, respectively, against the AD 169 strain). Of the other compounds in the three groups, only the cytosine analogues, 5-fluoro **8** and 5-aza **24**, showed an antiviral effect against HCMV. Interestingly, activity in the cytosine series is somewhat dependent on the cell line used in the assay. For example, **18** has IC_{50}'s of 2.6 μM in the HFF (human foreskin fibroblast) cell line and 11.2 μM in MRC-5 (human lung fibroblast), both against the AD 169 viral strain. This phenomenon of cell variability has not been encountered in the purine acyclic series in cytomegalovirus testing. As is the case with the acyclovir chain series, i.e., pyrimidines with the 1-(2-hydroxyethoxy)methyl substituent, the thymine derivative **17**, which would be expected to display some antiviral effect on the enzyme whose natural substrate is the cyclic counterpart, has scarcely any antiviral activity at all. Compound **12**, the 4-aminopyrimidine adduct, was not active against HSV, VZV, or HCMV. In evaluation with xanthine oxidase, in vitro, it did not show any conversion to **18** in spite of the fact that esters of 2-aminopurine acyclic congeners are also good substrates of this enzyme.

Testing against Epstein Barr virus (EBV) was performed by a nucleic acid hybridization assay in which virus-producing cells (P3HR-1) were exposed to the test compound for 14 days, and the number of viral genome copies per treated cell was determined by hybridization with an EBV-specific cRNA probe.[15] The activity against EBV of cytosine **18** (IC_{50} = 0.05–0.09 μM) compares favorably with that of **1** (IC_{50} = 0.05 μM) and ACV (IC_{50} = 6 μM), which was run as a control. The cytosine congeners **8**, **10**, and **22** were also strongly inhibitory. Uracil derivatives **11** and **13** were similarly potent, while variations on positions 2 and 4 on the ring decreased or eliminated the activity.

In the absence of an animal model for human cytomegalovirus, it was of special interest to evaluate the effect of 1-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]cytosine on cell cultures. In an assay measuring the effect of the test compound on the growth of tumor cells, it showed no cytotoxicity on mouse L cells or Detroit 98 cells at a concentration of 10^{-5} M. In MRC-5 cells (human lung fibroblast), the IC_{50} was greater than 1 mM. When CD-1 male mice were used, the LD_{50} was determined to be greater than 250 mg/kg ip. Acute toxicological studies in rats and dogs at doses of 65 and 60 mg/kg, respectively, given iv, every 24 h for 14 days, did not uncover any deleterious effects.

Experiments on the mechanism of action of **18** in HCMV infections and results of testing in vivo against animal cytomegaloviruses will be the subjects of forthcoming papers.[16,17]

Experimental Section

Melting points were obtained with a hot stage or a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs or the Analytical Services Section of Burroughs Wellcome Co. and were within 0.4% of the theoretical values. Proton nuclear magnetic resonance spectra (^1H NMR) were recorded at ambient temperature on either a Varian XL-100 spectrophotometer, a Hitachi Perkin-Elmer R-24A spectrophotometer, or a Varian FT-80A spectrophotometer in $CDCl_3$ or Me_2SO-d_6 with Me_4Si as the internal standard. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained with a Varian CFT-20 spectrometer in $CDCl_3$ or Me_2SO-d_6 with reference to internal Me_4Si. Ultraviolet spectra (UV) were recorded on a Norelco Unicam SP-820 or a Varian Super Scan 3 spectrophotometer. Mass spectra (MS) were obtained with a Varian MAT 731 instrument using either EI or CI techniques. Thin-layer chromatography was performed on silica gel plates purchased from Analtech, and silica gel 60 (230–400 mesh) obtained from Brinkmann Instruments was used in column chromatography. HPLC studies employed a Waters Model 600A

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Table II. Antiherpetic Activity of Pyrimidine Acyclic Nucleosides

no.	subst	IC_{50}, μM HSV-1	HSV-2	VZV	HCMV[a]	EBV[b]
			Cytosine Derivatives			
18	5-H	140	50–100	17.1	1.9–14	0.05–0.09 (46/273 at 10 μM)
8	5-F	–	–	–	14 (HFF) 100 (MRC-5)	22/206
10	5-I	–	–	>100	>100	43/577/35
23	5-Me	–	–	>100	>100	*c*
22	5-aza	–	>100	±	>25 (HFF) 100 (MRC-5)	22/206
12	2-H	–	–	–	>100	161/577/35
			Uracil Derivatives			
14	5-H	–	–	>100	>250	
11	5-I	>100	–	>100	>100[e]	27/464/44
13	5-Br	–	–	>100	>100	33/610/35
15	5-Me	–	–	>100	>250	100/206
16	5-NH_2	–	–	>100	nd[d]	nd
			Miscellaneous			
9	2-NH_2-4-OH	–	–	–	>100	*c*
19	2-OH-4-NHMe	–	–	–	>100	178/464/44
20	2-OH-4-NMe_2	>100	nd	>100	>100	436/464/44
21	2-SH-4-NH_2	–	–	–	>100	164/464/44
1	B759	0.1	0.1	2.8	3.4	0.05 (30/380)

[a] Cell lines: Vero (HSV-1, HSV-2, VZV); human foreskin fibroblast (HFF) except where otherwise noted, human lung fibroblast (MRC-5)[HCMV]; P3HR1 (EBV). [b] Number of viral genome copies per cell/control value/ACV value (when run) at 50 μM. [c] Stimulated EBV induction by 70% at 50 μM. [d] Not done. [e] Detroit cells.

delivery solvent system with an ultraviolet detector. The HPLC reagents Pic A (0.005 M aqueous tetrabutylammonium phosphate) and Pic B (0.005 M aqueous 1-heptanesulfonic acid) were purchased from Waters Associates.

1,3-Dichloro-2-(methoxymethoxy)propane (3). To a solution of 500 g (3.88 mol) of 1,3-dichloro-2-propanol (**2**), 780 mL of chloroform, and 780 mL of dimethoxymethane was added 330 g (2.32 mol) of phosphorus pentoxide, portionwise, with vigorous stirring, with the temperature maintained at 40–45 °C. The mixture was then stirred at ambient temperature for 18 h. The supernatant was decanted and washed once with water, once with 10% aqueous sodium bicarbonate, and once more with water. The organic layer was dried (sodium sulfate) and evaporated in vacuo to give 569 g (85%) of a pale amber liquid, **3**, which was of sufficient purity for use: ^{1}H NMR ($CDCl_3$) δ 4.78 (s, 2 H, OCH_2O), 3.7 (m, 5 H, CH, CH_2), 3.4 (s, 3 H, OMe).

2-(Methoxymethoxy)-1,3-propanediyl Dibenzoate (4b). A mixture of 181.1 g (1.04 mol) of 3453.0 g (3.14 mol) of sodium benzoate, 20 mL (0.1 mol) of 15-crown-5 ether, and 2.5 L of dimethylformamide was refluxed with stirring for 2 days. The cooled reaction mixture was filtered and the precipitate washed with ether. The combined washings and filtrate were flash evaporated, and the residue was triturated with ether. The ethereal extracts were washed with water, dried (sodium sulfate), and evaporated to yield 341 g (95%) of a dark brown oil, **4b**: ^{1}H NMR ($CDCl_3$) δ 8.1–7.1 (m, 10 H, C_6H_5), 4.7 (s, 2 H, OCH_2O), 4.3 (br s, 5 H, CH, CH_2), 3.25 (s, 3 H, OMe); ^{13}C NMR ($CDCl_3$) δ 166.34 (CO), 133.28 (aromatic C-4), 129.93, 129.81, 128.56 (aromatic C-1, C-2,6, C-3,5), 96.22 (OCH_2O), 73.03 (CH), 64.28 (CH_2OCO), 55.69 (Me).

2-(Acetoxymethoxy)-1,3-propanediyl Dibenzoate (5b). A solution of 143 g (0.415 mol) of **4b** in 55 mL (0.581 mol) of acetic anhydride and 14.3 mL (0.12 mol) of boron trifluoride etherate was stirred at 0 °C for 2 h. The solution was poured into 800 mL of ice and water containing 60 g of sodium bicarbonate. The oily mixture was extracted with three 600-mL portions of ether. The ethereal extracts were washed once with 10% aqueous sodium bicarbonate solution and twice with water and dried over sodium sulfate. The solvent was removed in vacuo to give 154 g (99%) of **5b**, which was of sufficient purity for further use: ^{1}H NMR ($CDCl_3$) δ 8.1–7.1 (m, 10 H, C_6H_5), 5.3 (s, 2 H, OCH_2O), 4.38 (br s, 5 H, CH, CH_2), 1.8 (s, 3 H, MeCO).

2-(Bromomethoxy)-1,3-propanediyl Dibenzoate (6b). A mixture of 15 g (0.04 mol) of **5b**, 70 mL of dry dichloromethane, and 17 mL of bromotrimethylsilane was gently refluxed for 18 h. The solution was evaporated in vacuo to give the target compound, **6b**, as a light amber oil in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 8.1–7.1 (m, 10 H, C_6H_5), 5.75 (s, 2 H, OCH_2O), 4.5 (br s, 5 H, CH, CH_2).

Method A. 1-[[2-Hydroxy-1-(hydroxymethyl)ethoxy]methyl]-5-methylcytosine (23). A mixture of 5 g (30.9 mmol) of 5-methylcytosine, 0.094 g (0.71 mmol) of ammonium sulfate, and 309 mL of hexamethyldisilazane was refluxed under nitrogen for 4 h. The clear solution was evaporated in vacuo, combined with 40.3 mmol of **6b**, 9.0 mL of triethylamine, 20 mL of dichloromethane, and 50 mL of toluene, and refluxed for 18 h. The solvents were removed by flash evaporation, and the residual oil was refluxed with 95% ethanol for 30 min. The ethanol was removed in vacuo, the oil was dissolved in dichloromethane and washed three times with water, and the organic extracts were evaporated. Recrystallization from dichloromethane and hexane yielded 5.284 g (39%) of 1-[[2-(benzoyloxy)-1-[(benzoyloxy)methyl]ethoxy]methyl]-5-methylcytosine: ^{1}H NMR (Me_2SO-d_6) δ 7.7 (m, 13 H, C_6H_5, NH_2), 7.1 (s, 1 H, H-6), 5.38 (s, 2 H, NCH_2O), 4.55 (s, 5 H, CH, CH_2), 1.75 (s, 3 H, Me), also a trace amount of EtOH. A solution of 1.33 g of the dibenzoate ester in 60 mL of 40% aqueous methylamine was stirred at room temperature for 1 h. The solution was concentrated to half-volume and extracted with benzene. The aqueous phase was evaporated and recrystallized twice from water–hexane to produce 0.394 g (57%) of **23**: mp 188–189 °C; UV λ_{max} (0.1 N HCl) 283 (ε 12729), (MeOH) 276 (8015), 235 (sh, 10608), (0.1 N NaOH) 276 (8015), 235 (sh, 10608); ^{1}H NMR (Me_2SO-d_6) δ 7.45 (s, 1 H, H-6), 7.0 (br s, 2.5 H, NH_2), 5.12 (s, 2 H, NCH_2O), 4.6 (br s, 2 H, OH), 3.46 (m, 6.7 H, CH, CH_2), 1.83 (s, 3 H, Me); ^{13}C NMR (Me_2SO-d_6) δ 165.76 (C-4), 155.76 (C-2), 142.54 (C-6), 101.04 (C-5), 79.72 (CH), 76.56 (NCH_2O), 60.81 (CH_2OH), 12.96 (5-Me). Anal. ($C_9H_{15}N_3O_4 \cdot {}^7/_{20}H_2O$) C, H, N.

Method B. 2-[(4-Ethoxy-1,2-dihydro-2-oxo-1-pyrimidinyl)methoxy]-1,3-propanediyl Dibenzoate (17b). A mixture of 2.2 g (13.08 mmol) of 2,4-diethoxypyrimidine, 1.98 g (14.33 mmol) of potassium carbonate, 26 mL of dichloromethane, and 5.1 g (0.013 mol) of **6b** was stirred at room temperature overnight. The mixture was filtered, the precipitate washed with benzene, and the mother liquor evaporated in vacuo. The resulting clear yellow oil was purified by flash chromatography, eluting successively with 40:1 and 1:1 dichloromethane–ether. Evaporation of the latter gave 4.8 g (81%) of **17b** as a golden oil: ^{1}H NMR ($CDCl_3$) δ 8.0, 7.97 (d, J = 7.1 Hz, 1 H, H-6), 7.45 (m, 10 H, C_6H_5), 5.71, 5.67 (d, J = 7.2 Hz, 1 H, H-5), 5.43 (s, 2 H, NCH_2O), 4.45 (m, 7 H, CH_2, CH, CH_2-ethyl), 1.32 (t, 3 H, Me-ethyl); ^{13}C NMR ($CDCl_3$) δ 171.53 (CO), 166.05 (C-4), 156.68 (C-2), 145.60 (C-6),

133.23 (C-4 phenyl), 129.66, 129.47, 128.4 (aromatic C-1, C-2,6, C-3,5), 96.94 (C-5), 76.47 (NCH_2O), 75.37 (CH), 63.78 (CH_2OCO), 63.39 (CH_2-ethyl), 14.20 (Me-ethyl).

1-[[2-Hydroxy-1-(hydroxymethyl)ethoxy]methyl]cytosine (18). A mixture of 5.5 g (12.16 mmol) of **17b** and 80 mL of methanolic ammonia was heated for 18 h in a bomb at 95 °C. The solution was evaporated in vacuo and purified by flash chromatography. Elution with 5% and 10% methanol–dichloromethane eluted the *N*-methylbenzamide byproduct and the target compound, respectively. On recrystallization from ethanol–acetonitrile, the latter gave 1.75 g (67%) of **18**, mp 145–148 °C (lit.[6] mp 140–141 °C, lit.[7] mp 147–148 °C); UV λ_{max} (0.1 N HCl) 277.5 (ϵ 12 380), (H_2O) 268 (7750), 230 (sh, 7540), (0.1 N NaOH) 268 (8070), 230 (sh, 8070); ^{1}H NMR (Me_2SO-d_6) δ 7.61 (d, J = 4.57 Hz, 1 H, H-6), 7.15 (br s, 2 H, NH_2), 5.68 (d, J = 4.88 Hz, 1 H, H-5), 5.15 (s, 2 H, NCH_2O), 4.57 (t, 2 H, OH), 3.35 (m, 5 H, CH, CH_2); ^{13}C NMR (Me_2SO-d_6) δ 166.17 (C-4), 155.94 (C-2), 145.33 (C-6), 94.03 (C-5), 79.89 (CH), 76.8 (NCH_2O), 60.85 (CH_2OH). Anal. ($C_8H_{13}N_3O_4$) C, H, N.

5-Fluoro-1-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]cytosine (8). A mixture of 1.0 g (7.74 mmol) of 5-fluorocytosine, 2.88 g (7.74 mmol) of **6b**, 1.16 mL of hexamethyldisilazane, 4.58 mL of trimethylchlorosilane, 6.28 g (25.5 mmol) of potassium nonaflate, and 50 mL of acetonitrile was refluxed for 6 h. The reaction mixture, which had remained heterogeneous, was cooled and filtered, giving 1.913 g (56%) of the intermediate 4-amino-5-fluoro-1-[[2-(benzoyloxy)-1-[(benzoyloxy)methyl]ethoxy]methyl]cytosine. The mother liquors were evaporated in vacuo, dissolved in dichloromethane, and washed with H_2O. The aqueous extract was washed twice with dichloromethane and once with ether. The organic phases were dried (Na_2SO_4), concentrated, and filtered to give more of the intermediate. Most of the first crop (1.8 g) was stirred in 40 mL of 40% aqueous methylamine for 30 min at room temperature. The excess reagent was removed in vacuo at 35 °C and the residue triturated with acetone. The solid was dissolved in methanol and purified by flash column chromatography, eluting the target compound with 40% methanol–ethyl acetate. Recrystallization from water–acetone gave 0.276 g of **8**: mp 160–161 °C (lit.[6] mp 134–135 °C, lit.[7] mp 165–166 °C); UV λ_{max} (0.1 N HCl) 285 (ϵ 9933), 250 (sh, 1943), (MeOH) 238 (7774), (0.1 N NaOH) 278 (6694), 237 (sh); CI mass spectrum, m/e 234 ($M^+ + 1$); ^{1}H NMR (Me_2SO-d_6) δ 7.79 (d, J = 6 Hz, 1 H, H-6), 7.42 (br s, 2 H, NH_2), 5.1 (s, 2 H, NCH_2O), 4.4 (t, 2 H, OH), 3.39 (m, 8 H, CH_2, CH, MeOH); ^{13}C NMR (Me_2SO-d_6) δ 157.88 (d, $^2J_{CF}$ = 13.3, C-4), 154.22 (C-2), 129.33 (d, $^2J_{CF}$ = 30.8, C-6), 135.75 (d, $^1J_{CF}$ = 242, C-5), 80.14 (CH), 76.8 (NCH_2O), 60.85 (CH_2OH). Anal. ($C_8H_{12}FN_3O_4 \cdot {}^1/_4H_2O$) C, H, N.

1-[[2-Hydroxy-1-(hydroxymethyl)ethoxy]methyl]isocytosine (9). A mixture of 2.555 g (23.0 mmol) of isocytosine, 0.6 g (25.0 mmol) of 50% sodium hydride–mineral oil dispersion previously washed with hexane, and 80 mL of dry dimethylformamide was stirred at room temperature for 20 min. To the suspension was added 9.045 g (23 mmol) of **6b**, and the mixture was stirred at ambient temperature for 2 days. The reaction mixture was diluted with 200 mL of dichloromethane and the excess sodium hydride decomposed with water. The decanted solution was washed twice with water, dried (Na_2SO_4), and evaporated in vacuo to a dark yellow oil. Purification by flash chromatography using, successively, dichloromethane, ether, acetone, and ethanol was done twice. The desired intermediate, 1-[[2-(benzoyloxy)-1-[(benzoyloxy)methyl]ethoxy]methyl]isocytosine, was obtained from the acetone and ethanol eluates, 1.18 g (13%). Hydrolysis of 0.94 g (2.22 mmol) of the latter material with 30 mL of 40% aqueous methylamine produced, after extraction of the concentrated residue with benzene to remove the *N*-methylbenzamide, evaporation, and recrystallization from methanol–ethyl acetate–hexane, 0.35 g (68%) of **9**: mp 189–191 °C (lit.[7] mp 182–184 °C); UV λ_{max} (0.1 N HCl) 218 (ϵ 9254), 254 (7424), (water) 208 (17 432), 225 (sh, 11 729), 249 (sh, 5380), (0.1 N NaOH) 219 (17 863), 250 (sh, 4950); ^{1}H NMR (Me_2SO-d_6) δ 7.43 (d, J = 7.5 Hz, 1 H, H-6), 6.85 (br s, 2 H, NH_2), 5.53 (d, J = 7.5 Hz, 1 H, H-5), 5.18 (s, 2 H, NCH_2O), 4.83 (t, 2 H, OH), 3.43 (m, 5 H, CH, CH_2); ^{13}C NMR (Me_2SO-d_6) δ 170.04 (C-4), 155.32 (C-2), 142.32 (C-6), 106.10 (C-5), 79.30 (NCH_2O), 79.22 (CH), 60.82 (CH_2). Anal. ($C_8H_{13}N_3O_4$) C, H, N.

1-[[2-Acetoxy-1-(acetoxymethyl)ethoxy]methyl]-4-aminopyrimidinium Bromide (12). A solution of 0.2 g (2.1 mmol) of 4-aminopyrimidine, 5 mL of dry DMF, and 0.58 g (2.16 mmol) of **6a** was stirred at room temperature for 18 h. TLC on silica gel in 5% MeOH–CH_2Cl_2 showed that the starting material (pyrimidine) was consumed. The solution was diluted with acetone, ethyl acetate, and ether and chilled for 18 h. The oily deposit was separated by decantation, dissolved in methanol, and diluted with acetone and ether until turbidity occurred. After standing at room temperature for 5 days, the crystals formed were collected to give 0.456 g (60%) of **12**: mp 110–113 °C; HPLC on C-18 reverse phase in 1:1 Pic A–Pic B gave a single tailing peak; UV λ_{max} (H_2O) 252 (ϵ 17 490); ^{1}H NMR (Me_2SO-d_6) δ 9.30 (s, 1 H, NH), 9.24 (s, 1 H, NH), 8.96 (d, $J_{2,NH}$ = 1.56 Hz, 1 H, H-2), 8.35 (dd, $J_{6,5}$ = 7.5 Hz, $J_{6,NH}$ = 1.9 Hz, 1 H, H-6), 6.85 (d, J = 7.5 Hz, 1 H, H-5), 5.54 (s, 2 H, NCH_2O), 4.15 (m, 5 H, CH, CH_2), 1.95 (s, 3 H, MeCO); ^{13}C NMR (DMSO-d_6) δ 169.96 (CO), 164.17 (C-4), 153.79 (C-2), 144.98 (C-6), 105.03 (C-5), 81.77 (NCH_2O), 74.73 (CH), 62.72 (CH_2O), 20.45 (Me). Anal. ($C_{12}H_{18}N_3O_5Br$) C, H, N, Br.

1-[[2-Hydroxy-1-(hydroxymethyl)ethoxy]methyl]uracil (14). A mixture of 112.56 g (0.67 mol) of 2,4-diethoxypyrimidine and 209.4 g (0.65 mol) of **6e** was combined at 0 °C and then stirred at room temperature under 30-mm pressure for 4 days. The resulting oil, 1-[[2-(benzyloxy)-1-[(benzyloxy)methyl]ethoxy]methyl]-4-ethoxy-2-pyrimidinone, was dissolved in methanol and 700 mL of 1.0 N HCl and stirred at room temperature for 4 days. The solution was extracted with chloroform, and the organic extracts were evaporated to yield a thick orange oil, **17e**. Sixty grams of the latter in 500 mL of methanol and 7 g of 5% palladium on carbon were shaken in a Parr apparatus for 7 h, during which time the theoretical amount of hydrogen was consumed. The mixture was filtered through a pad of Celite and the cake washed with methanol. The filtrate was evaporated, and the residue was recrystallized from methanol and ether. A second run using 490 g was run similarly, to give a total of 53 g of **14** (38%) from the two runs: mp 110–112 °C (lit.[10] mp 120–122 °C); UV λ_{max} (ethanol) 259 (ϵ 7500); ^{1}H NMR (Me_2SO-d_6) δ 11.276 (s, 1 H, CONH), 7.67 (d, J = 7.8 Hz, 1 H, H-6), 5.58 (d, J = 7.9 Hz, 1 H, H-5), 5.15 (s, 2 H, NCH_2O), 4.62 (t, 2 H, OH), 3.4 (m, 9 H, CH, CH_2OH, H_2O). Anal. ($C_8H_{12}N_2O_5$) C, H, N.

2-[(5-Bromo-1,2,3,4-tetrahydro-2,4-dioxo-1-pyrimidinyl)methoxy]-1,3-propanediyl Diacetate (13a). A suspension of **14** in 30 mL of acetic anhydride was heated on a steam bath to effect solution (20 min). To the ice-cooled solution was added a solution of 3.8 g of bromine in 3.0 mL of acetic acid at a rate to maintain the temperature at 20 °C (10 min). The flask was wrapped in aluminum foil and stirred at ambient temperature for 2.5 h. The pale yellow solution was evaporated in vacuo and stored in a desiccator over potassium hydroxide for 18 h at 1.0 mm. The oil was dissolved in methanol, reevaporated, and dissolved in benzene. The solution was purified by column chromatography, eluting with chloroform and 5% and 10% methanol–chloroform. The chloroform eluates were pooled, evaporated, and recrystallized from benzene to yield 1.85 g (22%) of **13a**: mp 94–95 °C (lit.[7] mp 92–94 °C); UV λ_{max} (ethanol) 276 (ϵ 8500). Anal. ($C_{12}H_{15}N_2O_7Br$) C, H, N.

5-Bromo-1-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]uracil (13). A mixture of 1.6 g (4.2 mmol) of **13a** in 40 mL of 10% ammonia in methanol was stirred in a bomb at room temperature for 2 days. The solution was evaporated in vacuo at 22 °C and the residual oil recrystallized once from methanol–chloroform and twice from methanol to give **13**, as pale yellow crystals: 0.35 g (41%); mp 144–145 °C (lit.[7,10] mp 145–147 °C); *light sensitive*; UV λ_{max} (95% ethanol) 276 (ϵ 8630); ^{1}H NMR (Me_2SO-d_6) δ 11.59 (s, 1 H, CONH), 8.21 (s, 1 H, H-6), 5.18 (s, 2 H, NCH_2O), 3.4 (m, 6 H, CH, CH_2, OH); ^{13}C NMR (Me_2SO-d_6) δ 159.91 (C-4) 150.45 (C-2), 144.59 (C-6), 95.13 (C-5), 80.97 (CH), 76.17 (NCH_2O), 60.92 (CH_2OH). Anal. ($C_8H_{11}BrN_2O_5$) C, H, N.

5-Amino-1-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]uracil Hydrochloride (16). A mixture of 3.0 g (7.91 mmol) of **13** in 100 mL of liquid ammonia was heated in a bomb at 60 °C for 18 h. The solution was evaporated in vacuo and the residue stored in a desiccator over sulfuric acid overnight. The grayish oil was dissolved in 200 in mL of 0.1 N HCl and added to a column of Dowex 50 (hydrogen ion form). The column was

washed with 700 mL of water and then with 1.4 L of 0.1 N HCl. The acidic eluates were pooled and concentrated. A white precipitate formed, which was separated and discarded. The mother liquors were evaporated and triturated with ethanol twice, the ethanol insolubles being discarded each time. The residue obtained from the evaporation of the last ethanol extract was recrystallized from ethanol and ethyl acetate to give 0.4 g (19%) of **16**:[10] mp 175–176 °C (eff); UV λ_{max} (ethanol) 230 (sh, ϵ 6400), 263 (6500); ^{1}H NMR (Me_2SO-d_6) δ 11.78 (br s, 1 H, CONH), 8.22 (s, 1 H, H-6), 5.19 (s, 2 H, NCH_2O), 4.65 (s, 2 H, NH_2), 3.34 (m, 6.4 H, CH, CH_2, OH); ^{13}C NMR (Me_2SO-d_6) δ 159.56 (C-4), 150.38 (C-2), 144.59 (C-6), 95.08 (C-5), 80.96 (CH), 76.16 (NCH_2O), 60.91 (CH_2OH). Anal. ($C_8H_{14}N_3O_5Cl$) C, H, N.

1-[[2-Hydroxy-1-(hydroxymethyl)ethoxy]methyl]thymine (15). To 0.151 mol of 5-methyl-2,4-bis[(trimethylsilyl)oxy]pyrimidine in 150 mL of dry toluene were added 10 mL of dry triethylamine and 4.85 g (0.0151 mol) of **6e**. The solution was refluxed under nitrogen for 48 h and then evaporated in vacuo to a brown oil. The oil was treated four times with 150 mL of 95% ethanol and the solvent evaporated off each time. The residue was purified by column chromatography twice, eluting initially with ethyl acetate and then with 1:1 ethyl acetate–hexane to yield, after evaporation, 2.5 g (40%) of a yellow oil, which solidified on standing. An analytical sample was prepared by recrystallization of 700 mg from benzene–cyclohexane, giving a white solid, 1-[[2-(benzyloxy)-1-[(benzyloxy)methyl]ethoxy]-methyl]thymine (**15e**): mp 92–94 °C; ^{1}H NMR ($CDCl_3$) δ 7.28 (s, 10 H, C_6H_5), 5.25 (s, 2 H, NCH_2O), 4.5 (s, 4 H, OCH_2), 4.1 (m, 1 H, CH), 3.6 (d, J = 6 Hz, 4 H, CH_2), 1.85 (s, 3 H, Me). Anal. ($C_{23}H_{26}N_2O_5$) C, H, N. A solution of 1.7 g (4.14 mM) of **15e** and 950 mg of 5% palladium on charcoal in 150 mL of 15% ethanol in methanol was shaken under hydrogen in a Parr apparatus for 6 h. The mixture was filtered, evaporated in vacuo, and redissolved in 160 mL of methanol. The solution was recharged with 400 mg of catalyst and shaken for 20 h under hydrogen (50 psi). After a similar workup, the material was charged a third time with 500 mg of fresh catalyst and shaken under hydrogen for 3 days. The mixture was filtered through a pad of Celite, that was washed with methanol, and the combined washings and filtrate were evaporated in vacuo. The residue was recrystallized thrice from ethyl acetate–hexane to give 0.22 g (23%) of **15** as white needles: mp 155–156.5 °C (lit.[10] mp 155–156 °C); UV λ_{max} (0.1 N HCl) 265 (ϵ 9200), (H_2O) 265 (8700), (0.1 N NaOH) 265 (6200); ^{1}H NMR (Me_2SO-d_6) δ 7.55 (s, 1 H, C-6 H), 5.14 (s, 2 H, NCH_2O), 6.55 (br s, 2 H, OH), 3.42 (m, 7 H, CH, CH_2, H_2O), 1.77 (s, 3 H, Me). Anal. ($C_9H_{14}N_2O_5$) C, H, N.

4-Amino-1-[[2-hydroxy-1-(hydroxymethyl)ethoxy]-methyl]-2(1*H*)-pyrimidinethione (21). A mixture of 2.5 g (0.019 mol) of thiocytosine, 40 mL of hexamethyldisilazane, 0.4 mL of trimethylsilyl chloride, and 40 mL of dry dioxane was refluxed with stirring for 5 days and at room temperature for 7 days. The solution was evaporated in vacuo and the oil combined with 7.47 g (0.019 mol) of **6b** in dry acetonitrile. The mixture was stirred at room temperature overnight and then refluxed with stirring for 18 h. After an additional 18 h at ambient temperature, the reaction mixture was filtered, the solid was washed with acetonitrile, and the combined filtrate and washings were evaporated in vacuo. The residue was stirred in methanol at room temperature and filtered to give 866 mg of a white solid. The solid (831 mg) was stirred with a saturated solution of methanolic ammonia for 3 days at ambient temperature. The solution was evaporated and the residue recrystallized twice from 5% methanol in ethanol with decolorizing carbon to yield **21**: 86 mg (20%); mp 175–177 °C; UV λ_{max} (0.1 N HCl) 228 (ϵ 15650), 278 (17730), (H_2O) 250 (21200), 273 (sh, 15880), (0.1 N NaOH) 250 (2100), 273 (sh, 15880); ^{1}H NMR (Me_2SO-d_6) δ 7.89 (d, J = 7 Hz, 1 H, C_6 H), 7.73 (s, 1 H, 3-NH), 7.59 (s, 1 H, 4-NH), 6.47 (d, 1 H, C_5 H), 5.7 (s, 2 H, NCH_2O), 4.65 (t, J = 5.5 Hz, 2 H, OH), 3.58 (m, 1 H, CH), 3.4 (m, 17 H, CH_2, H_2O); ^{13}C NMR (Me_2SO-d_6) δ 180.42 (C-4), 160.55 (C-2), 144.82 (C-6), 97.63 (C-5), 81.02 (NCH_2O), 80.49 (CH), 60.66 (CH_2OH). Anal. ($C_8H_{13}N_3O_3S$) C, H, N.

4-(Dimethylamino)-1-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]-2(1*H*)-pyrimidinone (20). A mixture of 2.232 g (4.93 mmol) of **17b** and 20 mL of 40% aqueous dimethylamine solution was heated in a bomb at 35 °C for 18 h and then at 55 °C for 18 h. The cooled mixture was evaporated in vacuo and partitioned between water and dichloromethane three times. The aqueous phases were evaporated and purified by column chromatography, eluting initially with 2% methanol in dichloromethane and then with 10% methanol in dichloromethane. The latter yielded, after evaporation, 1.2 g of a product whose ^{1}H NMR spectrum indicated that it was a mixture of the desired product and its monobenzoate ester. The material was recharged with dimethylamine solution and heated at 55 °C for 18 h. After a similar workup, 1.1 g of an oil was obtained with a satisfactory proton NMR spectrum. The oil was dissolved in ethanol after azeotropically drying and ethereal HCl added to bring the pH to 3.0. A sticky precipitate formed, which was separated quickly, dissolved in methanol, and evaporated in vacuo at room temperature. Recrystallization from methanol, acetone, and ether gave 445 mg (31%) of **20** as the hydrochloride salt: mp 162–167 °C; UV λ_{max} (water) 276 (13935); ^{1}H NMR (Me_2SO-d_6) δ 8.09 (d, J = 8.0 Hz, 1 H, C_6-H), 6.4 (d, J = 8.0 Hz, 1 H, C_5-H), 5.28 (s, 2 H, NCH_2O), 4.35 (br s, 7.6 H, OH, H_2O), 3.57 (m, 1 H, CH), 3.3 (m, 4 H, CH_2), 3.22 (s, 6 H, NMe_2). Anal. ($C_{10}H_{18}ClN_3O_4 \cdot 0.5H_2O$) C, H, N.

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