

SYNTHESIS AND STRUCTURE ASSIGNMENT OF 1-[(2-HYDROXY-ETHOXY)METHYL]- AND 1-[(1,3-DIHYDROXY-2-PROPOXY)METHYL]- 6-AZAISOCYTOSINE

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**Abstract-** 1-[(2-Acetoxyethoxy)methyl]-6-azaisocytosine and 1-[(1,3-dibenzyloxy-2-propoxy)methyl]-6-azaisocytosine have been prepared, and their unambiguous assignment of <sup>1</sup>H and <sup>13</sup>C peaks through the <sup>1</sup>H-<sup>13</sup>C heteronuclear correlation (HETCOR) nmr experiments is described. The X-ray crystallographic analysis reveals unambiguously the site of glycosylation at N<sub>1</sub>. Deprotection of both acyclonucleosides provided 1-[(2-hydroxyethoxy)methyl]-6-azaisocytosine and 1-[(1,3-dihydroxy-2-propoxy)methyl]-6-azaisocytosine, respectively.

### Introduction

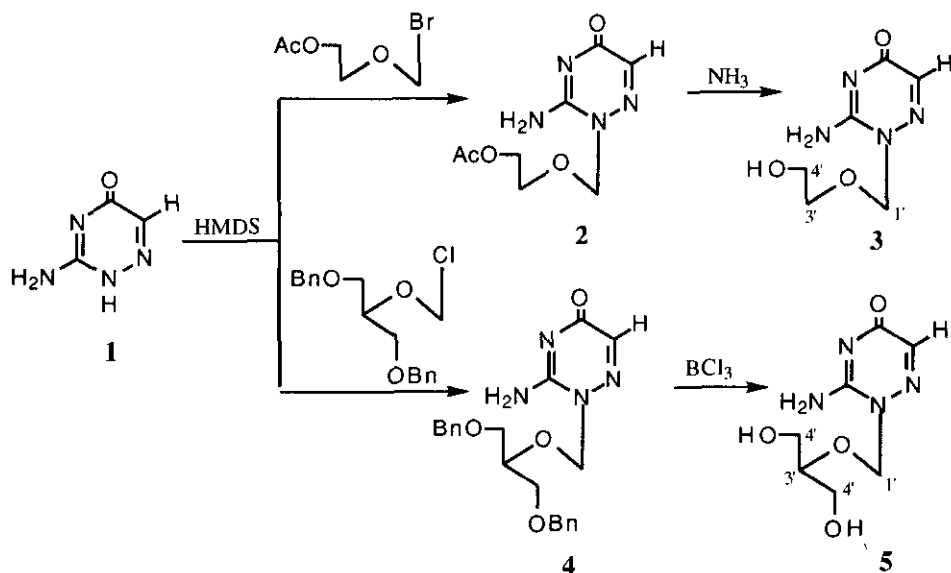
Previous studies revealed that 6-azapyrimidines (6-azauracil and 6-azacytosine) display a range of biological effects which include antiviral,<sup>1,2</sup> antitumor,<sup>3,4</sup> and antifungal<sup>5</sup> activities. 6-Azauridine and 6-azacytidine exhibit carcinostatic activity against a number of experimental tumors.<sup>6</sup> It was also found that 6-azacytidine which possesses a pronounced cancerostatic activity is deaminated *in vivo* to give 6-azauridine<sup>7</sup> and that cytosine arabinoside (Cytarabine) which is highly active against both mouse and human leukemias, is rather readily deaminated to the inactive uracil arabinoside by cytidine deaminase.<sup>8</sup> 6-Azaisocytosine, the isosteric isomer of 6-azauracil and 6-azacytosine, is of interest in both chemical and biological aspects due to its resistance to the deaminase. Synthesis of 6-azaisocytosine riboside (6-azaisocytidine)<sup>9</sup> and 6-azauracil acyclonucleosides<sup>10-14</sup> had

been previously described. Recently, we described the preparation of 1-[(2-acetoxyethoxy)methyl]-5-chloro-6-azauracil and its unambiguous assignment of  $^1\text{H}$  and  $^{13}\text{C}$  peaks through the  $^1\text{H}$ - $^{13}\text{C}$  heteronuclear correlation (HETCOR) nmr experiments.<sup>15</sup> The isosteric 1-[(2-acetoxyethoxy)methyl]-5-bromo-6-azaisocytosine was also prepared for the X-ray crystallographic analysis to determine the site of N-glycosylation. The present study describes the synthesis, the antiviral evaluation, and the structure assignment of 1-[(2-hydroxyethoxy)methyl]-6-azaisocytosine and 1-[(1,3-dihydroxy-2-propoxy)methyl]-6-azaisocytosine.

## Results and Discussion

6-Azaisocytosine (**1**) was persilylated with hexamethyldisilazane (HMDS) and then alkylated with (2-acetoxyethoxy)methyl bromide<sup>4</sup> in dry acetonitrile to furnish 1-[(2-acetoxyethoxy)methyl]-6-azaisocytosine (**2**), as shown in Scheme 1. The  $^1\text{H}$  nmr spectrum of **2** showed four singlets at  $\delta$  7.41, 7.30, 5.29, and 1.99 ppm

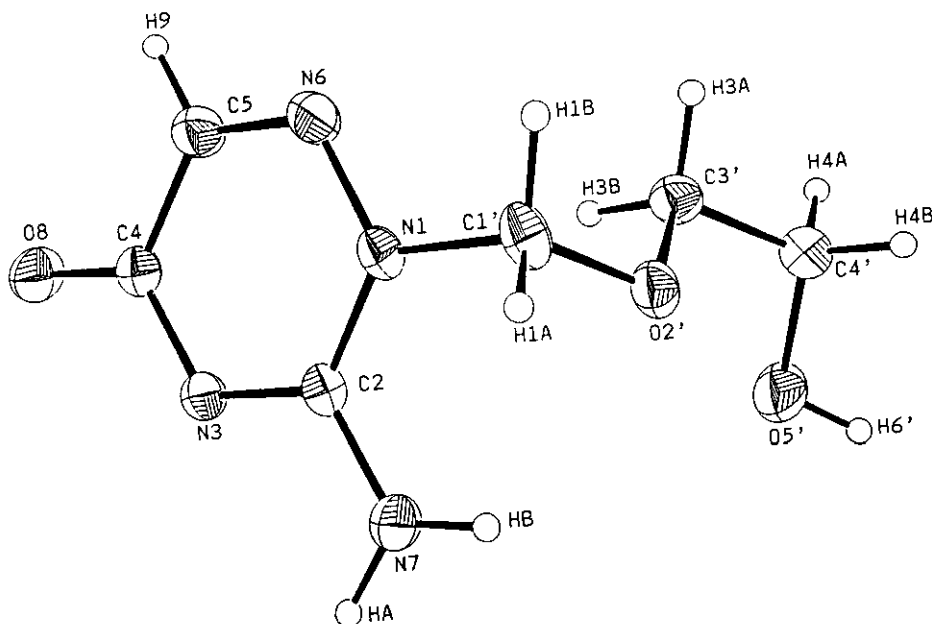
Scheme 1



corresponding to  $\text{NH}_2$ , H-5,  $1'\text{-CH}_2$ , and  $\text{CH}_3$ , respectively. The remaining two triplets which couple to each other ( $\text{A}_2\text{B}_2$  type,  $J = 2.9$  Hz) at  $\delta$  4.11 and 3.73 ppm were attributed to the resonances of two methylene protons. The proton-decoupled  $^{13}\text{C}$ -nmr and DEPT spectra of **2** indicated eight resonances which include one methyl ( $\delta$  at 20.25 ppm), three methylene ( $\delta$  at 81.49, 66.18 and 62.61 ppm), and four quaternary ( $\delta$  at 170.42, 162.88, 155.37 and 139.34 ppm) carbons. In order to assign specific resonances within each carbon type, standard and long-range  $^1\text{H}$ - $^{13}\text{C}$  heteronuclear correlation (HETCOR) nmr experiments were carried out.

Through the standard HETCOR experiment, which was performed to reveal the direct attachment between protons and carbons, it is clear that C-1' ( $\delta$  81.49) is coupled to H-1' ( $\delta$  5.29), C-5 ( $\delta$  139.34) is coupled to H-5 ( $\delta$  7.30) and the more downfield methylene carbon ( $\delta$  66.18) is coupled to the more upfield methylene protons ( $\delta$  3.73) while the more upfield methylene carbon ( $\delta$  62.61) is coupled to the more downfield methylene protons ( $\delta$  4.11). Through the long-range HETCOR experiment, which reveals two-, and three- bond  $^1\text{H}$ - $^{13}\text{C}$  connectivities, the methyl protons ( $\delta$  1.99) were found to couple to the most downfield carbonyl carbon ( $\delta$  170.42), and the H-1' methylene protons were coupled to carbons with resonances of  $\delta$  155.37 and 66.18 ppm corresponding to C-2 and C-3', respectively. The remaining carbon resonances at  $\delta$  162.88 and 62.61 ppm which did not couple to H-1' can be unambiguously assigned to C-4 and C-4', respectively. Therefore, the two triplets of proton resonances at  $\delta$  4.11 and 3.73 ppm were attributed to the 4'-CH<sub>2</sub> and 3'-CH<sub>2</sub>, respectively. Deacetylation of **2** with methanolic ammonia afforded 1-[(2-hydroxyethoxy)methyl]-6-azaisocytosine (**3**) in good overall yield. A view of a single molecule of **3** is given in Figure 1. As can be seen in the Figure, the glycosylation occurs at N1. The crystal data and the atomic parameters of all non-hydrogen atoms are listed in

Figure 1 ORTEP drawing of **3**



Tables 1 and 2, respectively. Bond lengths and bond angles are presented in Table 3. Glycosylation of persilylated derivatives of **1** with one molarequivalent of 1,3-dibenzyloxy-2-chloromethoxypropane in a non-polar solvent (dry toluene or dry dichloromethane) gave the desired 1-[(1,3-dibenzyloxy-2-propoxy)methyl]-6-azaisocytosine (**4**) in 53% yield. Debenylation of **4** with either boron trichloride in dichloromethane or by hydrogenation in the presence of palladium oxide in the mixed solvent of absolute alcohol and cyclohexene afforded 1-[(1,3-dihydroxy-2-propoxy)methyl]-6-azaisocytosine (**5**).

**Table 1** Crystal data of 1-[(2-hydroxyethoxy)methyl]-6-azaisocytosine (**3**)

Formula	C <sub>6</sub> H <sub>10</sub> N <sub>4</sub> O <sub>3</sub>
Molecular weight	186.17
Diffractionmeter used	CAD4
Space group	P $\bar{1}$
<i>a</i> , Å	5.738 (2)
<i>b</i> , Å	8.1943 (6)
<i>c</i> , Å	9.272 (3)
$\alpha$ , °	72.72 (2)
$\beta$ , °	77.32 (3)
$\gamma$ , °	85.52 (2)
<i>V</i> , Å <sup>3</sup>	406.1 (2)
<i>Z</i>	2
<i>D</i> (calc), g·cm <sup>-3</sup>	1.523
$\lambda$ (Mo <i>K</i> $\alpha$ ), Å	0.71069
<i>F</i> (000)	196
unit cell detn; #; 2 $\theta$ range	25, (20.80-28.54)
scan type	$\omega/2\theta$
2 $\theta$ scan width, deg	2 (0.7 + 0.35 tan $\theta$ )
2 $\theta$ max, deg	50°
$\mu$ (Mo <i>K</i> $\alpha$ ), cm <sup>-1</sup>	1.158
Crystal size, mm	0.45 x 0.50 x 0.70
Temperature, K	298
No. of unique reflns	1426
No. of obs reflns ( <i>I</i> > 2 $\sigma$ ( <i>I</i> ))	1228
<i>R</i> , <i>R</i> <sub>w</sub> *	0.031, 0.029
GoF	1.37
Minimized function	$\sum w  F_o - F_c ^2$

Weighting scheme	$1/\sigma^2 (F_o)$
$g$ (second.ext.coeff.) $\times 10^4$	0.524 (7)
$(\Delta/\sigma)$ max	0.0197
$(\Delta\rho)$ max, min $\text{\AA}^{-3}$	0.15, -0.16
Computation program	NRCVAX16

$$*R = [\sum |F_o - F_c| / F_o]$$

$$R_w = [\sum w(|F_o - F_c|^2) / \sum w(|F_o|^2)]^{1/2}; \sigma^2 (F_o) \text{ from counting statistics}$$

**Table 2** Atomic Parameters  $x, y, z$  and  $B_{eq}$  of **3**

	$x$	$y$	$z$	$B_{eq}$
N1	0.39381(24)	0.34386(17)	0.25658(14)	2.75(6)
C2	0.2252(3)	0.40273(19)	0.16956(17)	2.55(7)
N3	0.23101(23)	0.36404(17)	0.03947(15)	2.73(6)
C4	0.4072(3)	0.25991(20)	-0.00535(18)	2.72(7)
C5	0.5804(3)	0.19731(22)	0.09280(20)	3.29(8)
N6	0.5750(3)	0.23682(18)	0.21732(16)	3.25(6)
N7	0.0514(3)	0.50450(19)	0.21446(16)	3.47(7)
O8	0.42032(23)	0.21965(17)	-0.12575(14)	4.01(6)
C1'	0.3995(3)	0.39212(22)	0.39636(18)	3.26(8)
O2'	0.20189(21)	0.33229(13)	0.51447(12)	3.06(5)
C3'	0.1961(3)	0.14875(20)	0.57060(19)	3.01(7)
C4'	-0.0083(3)	0.09737(22)	0.70410(20)	3.41(8)
O5'	-0.22459(23)	0.15027(21)	0.65359(16)	5.01(8)
HA	-0.052(3)	0.5511(23)	0.1473(21)	4.5(4)
HB	0.030(3)	0.5248(23)	0.3016(21)	4.4(4)
H1A	0.393(3)	0.5147(21)	0.3709(19)	3.7(4)
H1B	0.551(3)	0.3424(22)	0.4277(20)	3.7(4)
H3A	0.344(3)	0.1052(22)	0.6065(20)	3.8(4)
H3B	0.172(3)	0.1016(21)	0.4856(19)	3.6(4)
H4A	-0.002(3)	-0.0277(21)	0.7460(19)	3.7(4)
H4B	0.007(3)	0.1458(21)	0.7899(19)	3.3(4)
H9	0.704(3)	0.1203(23)	0.0655(21)	4.2(4)
H6'	-0.331(4)	0.158(3)	0.730(3)	7.5(6)

Estimated standard errors refer to the last digit printed.

$$B_{eq} = 8/3 p^2 \sum_{i,j} U_{ij} a_i a_j^* a_j^* a_i^*$$

**Table 3** Bond Lengths (Å) and Bond Angles (degree) in **3**

N1-C2	1.3629(20)	C5-N6	1.2822(22)	C3'-C4'	1.488(3)
N1-N6	1.3653(19)	C5-H9	0.955(18)	C3'-H3a	0.977(17)
N1-C1'	1.4706(20)	N7-Ha	0.935(18)	C3'-H3b	1.013(17)
C2-N3	1.3284(20)	N7-Hb	0.853(18)	C4'-O5'	1.4133(22)
C2-N7	1.3260(21)	C1'-O2'	1.3959(22)	C4'-H4a	0.983(17)
N3-C4	1.3471(21)	C1'-H1a	0.982(17)	C4'-H4b	1.011(16)
C4-C5	1.4553(24)	C1'-H1b	0.996(17)	O5'-H6'	0.840(23)
C4-O8	1.2406(19)	O2'-C3'	1.4384(19)		
C2-N1-N6	121.73(13)	N1-N6-C5	116.36(14)	O2'-C3'-H3b	109.0(10)
C2-N1-C1'	123.47(14)	C2-N7-Ha	116.8(11)	C4'-C3'-H3a	108.5(10)
N6-N1-C1'	114.79(13)	C2-N7-Hb	122.6(12)	C4'-C3'-H3b	109.0(10)
N1-C2-N3	122.28(14)	Ha-N7-Hb	120.6(16)	H3a-C3'-H3b	111.6(14)
N1-C2-N7	119.10(14)	N1-C1'-O2'	112.24(13)	C3'-C4'-O5'	109.31(14)
N3-C2-N7	118.61(14)	N1-C1'-H1a	108.4(10)	C3'-C4'-H4a	107.8(10)
C2-N3-C4	118.43(13)	N1-C1'-H1b	105.7(10)	C3'-C4'-H4b	111.0(9)
N3-C4-C5	117.37(14)	O2'-C1'-H1a	106.4(10)	O5'-C4'-H4a	110.5(10)
N3-C4-O8	120.94(15)	O2'-C1'-H1b	111.2(10)	O5'-C4'-H4b	111.6(9)
C5-C4-O8	121.69(15)	H1a-C1'-H1b	112.9(14)	H4a-C4'-H4b	106.5(13)
C4-C5-N6	123.80(15)	C1'-O2'-C3'	112.77(12)	C4'-O5'-H6'	108.8(16)
C4-C5-H9	119.1(11)	O2'-C3'-C4'	108.92(13)		
N6-C5-H9	117.1(11)	O2'-C3'-H3a	109.7(10)		

### Antiviral Studies

Antiviral and cytotoxicity assays of the new acyclic nucleosides against HSV-1 and HSV-2 in Human Foreskin Fibroblast (HFF) cells were performed by the cytopathic effect (CPE) inhibition assay.<sup>17</sup> None of the compounds were active against HSV-1 and HSV-2 or exhibited toxic effects in uninfected HFF cells when tested up to 100  $\mu$ M.

### EXPERIMENTAL

Melting points were determined on a YANACO micromelting point apparatus and are uncorrected. The uv absorption spectra were obtained on a Beckman UV-Visible spectrophotometer. Ir spectra were recorded on a Hitachi 260-30 spectrophotometer. Nmr (<sup>1</sup>H and <sup>13</sup>C)spectra were obtained with a Varian Gemini-200 spectrometer. Chemical shifts are expressed in ppm ( $\delta$ ) with tetramethylsilane as an internal standard. Tlc was

run on precoated (0.2 mm) silica gel 60 F-254 plates manufactured by EM Laboratories, Inc., and short-wave uv light (254 nm) was used to detect the uv absorbing spots. Elemental analyses were carried out on a Heraeus CHN-O-Rapid elemental analyzer.

*1-[(2-Acetoxyethoxy)methyl]-6-azaisocytosine (2)*

6-Azaisocytosine (1.12 g, 10 mmol) was suspended in hexamethyldisilazane (HMDS; 25 ml, 118 mmol) and then a catalytic amount of ammonium sulfate (*ca.* 60 mg, 0.53 mmol) was added. The mixture was heated under reflux with the exclusion of moisture until a clear solution was obtained (*ca.* 4 h). The excess HMDS was removed under reduced pressure to give silylated intermediate as an oil, which was dissolved in dry acetonitrile (20 ml) and cooled to 0°C. To this stirred solution was added a solution of (2-acetoxyethoxy)methyl bromide (1.97g, 10 mmol) in dry acetonitrile (15 ml). The reaction mixture was stirred at room temperature for 24 h (monitored by tlc). The solvent was evaporated to afford crude product as an oil which was applied to a silica gel column. The column was eluted with a mixed solvent of CHCl<sub>3</sub> and MeOH (20:1) and the proper fractions were combined and evaporated. The residue thus obtained was crystallized from CH<sub>2</sub>Cl<sub>2</sub> and MeOH (1:1) to give **2** (1.17g, 52% yield). mp 198-199°C; uv: λ<sub>max</sub> (log ε) 252 (3.74) (0.1 N HCl); 248 (3.88) (H<sub>2</sub>O); 225 (4.26) (0.1 N NaOH); <sup>1</sup>H nmr (DMSO-*d*<sub>6</sub>): δ 1.99 (s, 3H, CH<sub>3</sub>), 3.73 (t, 2H, *J* = 2.8 Hz, 3'-CH<sub>2</sub>), 4.11 (t, 2H, *J* = 2.8 Hz, 4'-CH<sub>2</sub>), 5.29 (s, 2H, 1'-CH<sub>2</sub>), 7.30 (s, 1H, H-5), 7.41 (s, 2H, NH<sub>2</sub>); <sup>13</sup>C nmr (DMSO-*d*<sub>6</sub>): δ 20.25 (CH<sub>3</sub>), 62.61 (C-4'), 66.18 (C-3'), 81.49 (C-1'), 139.34 (C-5), 155.37 (C-2), 162.88 (C-4), 170.42 (CO); Ms, *m/z* 228 (M<sup>+</sup>). Anal. Calcd for C<sub>8</sub>H<sub>12</sub>N<sub>4</sub>O<sub>4</sub>: C, 42.11; H, 5.30; N, 24.55. Found: C, 42.08; H, 5.32; N, 24.52.

*1-[(2-Hydroxyethoxy)methyl]-6-azaisocytosine (3)*

A solution of **2** (0.57 g, 2.5 mmol) in methanolic ammonia (previously saturated at 0°C; 100 ml) was stirred at room temperature in a sealed flask for 24 h. The solvent was then evaporated to give a residual solid as the crude product, which was purified by silica gel chromatography using CHCl<sub>3</sub>-MeOH (5:1) as an eluent. The proper fractions were combined and evaporated. The residue thus obtained was crystallized from ethanol to provide **3** (0.42 g, 89% yield). mp 206 - 207°C; uv: λ<sub>max</sub> (log ε) 253 (3.71) (0.1 N HCl); 250 (3.79) (H<sub>2</sub>O); 225 (4.14) (0.1 N NaOH); <sup>1</sup>H nmr (DMSO-*d*<sub>6</sub>): δ 3.53 (m, 4H, OCH<sub>2</sub>CH<sub>2</sub>O), 4.68 (br s, 1H, 4'-OH), 5.28 (s, 2H, 1'-CH<sub>2</sub>), 7.29 (s, 1H, 5-H), 7.38 (s, 2H, NH<sub>2</sub>); <sup>13</sup>C nmr (DMSO-*d*<sub>6</sub>): δ 59.92 (C-4'), 70.21 (C-3'), 82.06 (C-1'), 139.31 (C-5), 155.47 (C-2), 162.84 (C-4); Ms, *m/z* 186 (M<sup>+</sup>). Anal. Calcd for C<sub>6</sub>H<sub>10</sub>N<sub>4</sub>O<sub>3</sub>: C, 38.71; H, 5.41; N, 30.09. Found: C, 38.79; H, 5.45; N, 30.04.

*1-[(1,3-Dibenzyloxy-2-propoxy)methyl]-6-azaisocytosine (4)*

6-Azaisocytosine (1.12 g, 10 mmol), HMDS (25 ml, 118 mmol), and ammonium sulfate (0.1 g, 0.88 mmol) were heated under reflux with the exclusion of moisture until a clear solution was obtained. The excess HMDS was removed *in vacuo* and the residual oil dissolved in dry dichloromethane (30 ml). To this solution was added 1,3-dibenzyloxy-2-chloromethoxypropane (3.21 g, 10 mmol) in dry dichloromethane (15 ml) and the resulting mixture was allowed to stir at room temperature for 24 h (monitored by tlc). The organic solvent was evaporated to give a residual oil as a crude product, which was purified by silica gel chromatography using a mixed solvent of  $\text{CHCl}_3$  : MeOH (60 : 1). The proper fractions were combined and evaporated to give a solid residue, which was crystallized from  $\text{CH}_2\text{Cl}_2$  and MeOH (1:1) to afford **4** (2.1 g; 53%). mp 94-96°C; uv:  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 254 (3.72) (0.1 N HCl); 252 (3.65) ( $\text{H}_2\text{O}$ ); 218 (4.18) (0.1 N NaOH);  $^1\text{H}$  nmr (DMSO- $d_6$ ):  $\delta$  3.49 (m, 4H, 4'- $\text{CH}_2$ ), 4.00 (m, 1H, 3'-CH), 4.45 (s, 4H, Ar- $\text{CH}_2$ ), 5.40 (s, 2H, 1'- $\text{CH}_2$ ), 7.29 (s, 1H, 5-H), 7.30 (m, 10H, Ar), 7.36 (s, 2H,  $\text{NH}_2$ );  $^{13}\text{C}$  nmr (DMSO- $d_6$ ):  $\delta$  69.34 (C-4'), 72.07 (Ar-C), 76.03 (C-3'), 81.41 (C-1'), 139.26 (C-5), 155.48 (C-2), 163.00 (C-4); Ms,  $m/z$  397 ( $\text{M}^++1$ ). Anal. Calcd for  $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_4$ : C, 63.62; H, 6.10; N, 14.13. Found: C, 63.66; H, 6.12; N, 14.23.

*1-[(1,3-Dihydroxy-2-propoxy)methyl]-6-azaisocytosine (5)*

To an ice-salt cooled solution of **4** (1.19 g, 3 mmol) in dry dichloromethane (30 ml) was added boron trichloride in dichloromethane (5 ml, 1 M solution, 5 mmol). The mixture was stirred at the same temperature (-8°C) for 30 min (monitored by tlc to ensure the reaction was complete). A solution (40 ml) of methanol and dichloromethane (1:1) was then added and the resulting mixture was allowed to warm to room temperature. The solvents were evaporated under reduced pressure to give a solid residue, which was crystallized from ethanol to obtain **5** (0.53 g, 82%). mp 137-138°C; uv:  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 254 (3.90) (0.1 N HCl); 249 (3.82) ( $\text{H}_2\text{O}$ ); 225 (4.24) (0.1 N NaOH);  $^1\text{H}$  nmr (DMSO- $d_6$ ):  $\delta$  3.41 (m, 4H, 4'- $\text{CH}_2$ ), 3.60 (m, 1H, 3'-CH), 4.29 (br s, 2H, OH), 5.43 (s, 2H, 1'- $\text{CH}_2$ ), 7.56 (s, 1H, 5-H), 8.21 (s, 2H,  $\text{NH}_2$ );  $^{13}\text{C}$  nmr (DMSO- $d_6$ ):  $\delta$  61.09 (C-4'), 80.92 (C-3'), 82.55 (C-1'), 139.84 (C-5), 153.45 (C-2), 157.17 (C-4); Ms,  $m/z$  217 ( $\text{M}^++1$ ). Anal. Calcd for  $\text{C}_7\text{H}_{12}\text{N}_4\text{O}_4$ : C, 38.89; H, 5.59; N, 25.91. Found: C, 38.85; H, 5.65; N, 25.60.

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