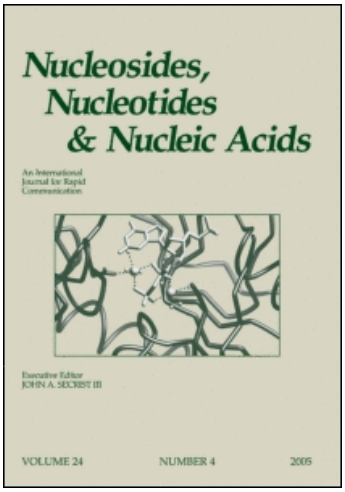

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Studies on the Chemical Synthesis of Potential Antimetabolites. 35.[1] Synthesis of 2-Chloro-1-deazaadenosine and 2-Chloro-1-deazainosine as Candidate Inhibitors for S-Adenosylhomocysteinases and Methyltransferases

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STUDIES ON THE CHEMICAL SYNTHESIS OF POTENTIAL ANTIMETABOLITES. 35.[1] SYNTHESIS OF 2-CHLORO-1-DEAZAADENOSINE AND 2-CHLORO-1-DEAZAINOSINE AS CANDIDATE INHIBITORS FOR S-ADENOSYLHOMOCYSTEINASES AND METHYLTRANSFERASES

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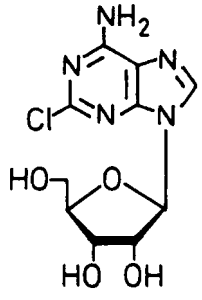
Abstract: The syntheses of 2-chloro-1-deazaadenosine (2) and 2-chloro-1-deazainosine (3) are described. Conversion of 7-ribosylated 6-chloro-1-deazapurine 3-oxide to the desired 2,6-disubstituted 9-ribosyl-1-deazapurines was effected by a series of reactions involving "deoxygenative chlorination" and transglycosylation in satisfactory yields.

As part of an ongoing program for the design and biological evaluation of novel deazapurine nucleosides of biochemical and biomedical interest, we have previously reported on the synthesis of a number of 1-deazapurine[2] and 3-deazapurine nucleosides[3]. Among these, 3-deazaadenosine and some derivatives thereof were found to possess potent antiviral activities and to inhibit S-adenosylmethionine (SAM)-dependent biological methylation[4]. These activities may be due to the inhi-



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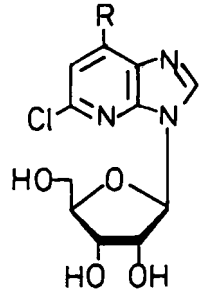
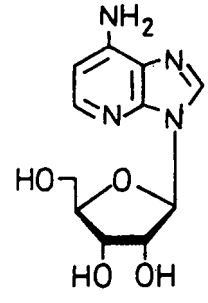


2, R = NH_2
3, R = OH



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bition of S-adenosylhomocysteinases (SAHase, EC 3.3.1.1) caused by the nucleosides[4]. These findings, coupled with the fact that 2-chloroadenosine (1) acts as a potent inactivator against SAHases[5] as well as an effector for adenylate cyclases[6], prompted us to undertake the synthesis of 2,6-disubstituted 1-deazapurine nucleosides.

This paper deals with the new syntheses of 2-chloro-1-deazaadenosine (2) and 2-chloro-1-deazainosine (3) and related subjects.

In our previous synthesis of 1-deazaadenosine (4)[2c], we have utilized some recent advances in both aromatic amine oxide and nucleoside chemistry. Thus, deoxygenative chlorination reaction of 7-glycosyl-7H-1-deazapurine 3-oxide (5) gave rise to 6-chloro-7-(2,3,5-tri-O-acetyl-ß-D-ribofuranosyl)-7H-1-deazapurine (6). A transglycosylation reaction of 6 catalyzed with $HgBr_2$, followed by treatment with hydrazine-Raney nickel afforded 4 in a satisfactory overall yield. The same methodology has been applied to the present synthesis.

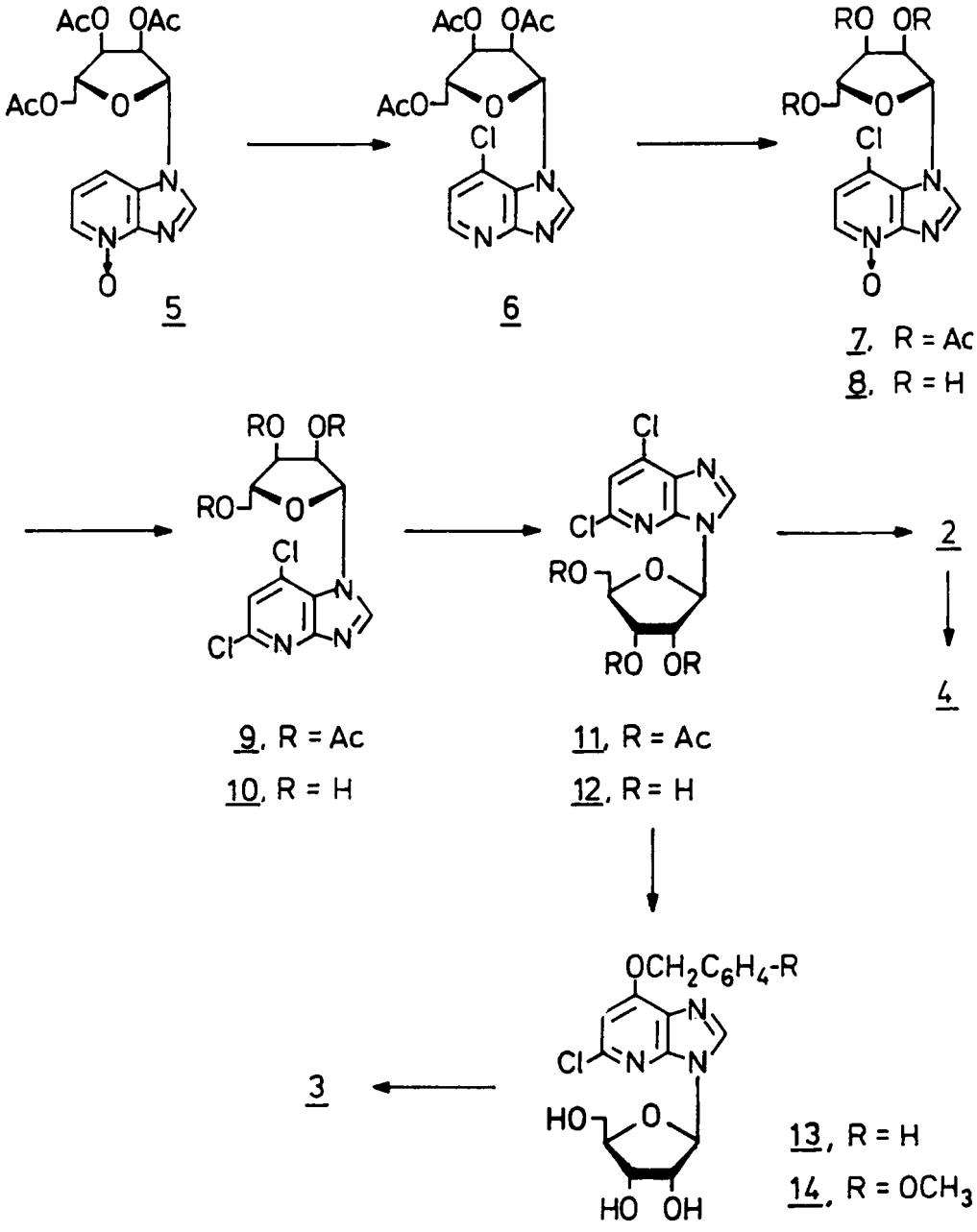
Compound 6 was oxidized with m-chloroperbenzoic acid to give the corresponding 3-oxide (7) in 82.2 % yield. Treatment of 7 with a Vilsmeier reagent ($POCl_3$ + DMF) gave 2,6-dichloro-7-(2,3,5-tri-O-acetyl-ß-D-ribofuranosyl)-7H-1-deazapurine (9) in 76 % yield. The structural assignment is consistent with the absence of the H-2 signal in the pmr and the presence of molecular ion peak cluster in the mass spectrum of 9.

The blocked nucleosides, 7 and 9, were treated with methanolic triethylamine to give the corresponding free nucleosides, 8 and 10, respectively, whose structure were confirmed by elemental analysis, pmr, and mass spectrometry.

Mercuric bromide catalyzed transglycosylation involving 9 smoothly proceeded to afford 2,6-dichloro-9-(2,3,5-tri-O-acetyl-ß-D-ribofuranosyl)-9H-1-deazapurine (11) in 76.7 % yield, which in turn was treated with methanolic triethylamine to give a deblocked nucleoside (12) in 83.7 % yield. Synthesis of the same nucleoside by a condensation procedure was also reported[7]. Physical properties of 12 were virtually identical with the reported values.

2-Chloro-1-deazaadenosine (2) was prepared by treatment of 12 with liquid ammonia in 72.8 % yield. Catalytic hydrogenation of 2 gave rise to 4 in a high yield, showing that the 6-chloro- rather than the 2-chloro-group in 12 had been replaced with an amino function[2c,d].

Nucleophilic substitution of the 6-chloro-group in 12 with alkoxide anions also took place to give 6-benzyloxy- (13) and 6-(p-methoxy-



benzyloxy)-2-chloro-1-deazapurine nucleosides (14) in 64 and 58 % yields, respectively. Removal of the benzyl group in 13 by a catalytic hydrogenation with 10 % Pd-C gave 2-chloro-1-deazainosine (3) in 68 % yield, whose structure was confirmed by its mass spectrum and elemental analysis. The p-methoxybenzyl group in 14 , however, failed to be removed even with DDQ treatment[8].

It was anticipated that the nucleosides, 13 and 3, would be useful precursors for the preparation of 1-deazaguanosine. It turned out, however, that the chlorine function was too inert to be replaced by such nitrogen nucleophiles as hydrazine or azide.

Pmr chemical shifts and coupling constants of the nucleosides, herein described, are summarized in TABLE 1 and TABLE 2.

The nucleosides, 2 and 3, were preliminarily tested for their activity to inhibit S-adenosylhomocysteinase. Neither compound showed remarkable activity against the yellow lupin enzyme.[9]

EXPERIMENTAL

Melting points were determinated with a Yamato melting point apparatus, type MP-1, and are uncorrected. Ultraviolet absorption spectra were taken on a Hitachi 323 recording spectrometer. Pmr spectra were obtained on a JEOL FX 200 spectrometer. Mass spectra (MS) were taken on a JEOL JMS D-300 mass spectrometer.

6-Chloro-7-(2,3,5-tri-O-acetyl-ß-D-ribofuranosyl)-7H-1-deazapurine 3-oxide (7)

To a solution of 6-chloro-7-(2,3,5-tri-O-acetyl-ß-D-ribofuranosyl)-7H-1-deazapurine (6, 2.00 g, 4.86 mmol) in glacial acetic acid (5 ml) was added m-chloroperbenzoic acid (2.00 g, 11.6 mmol) and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo to give a white residue, to which was added satd. sodium bicarbonate solution (100 ml) and the mixture was extracted with three 200-ml portions of chloroform. Concentration of the dried ($MgSO_4$) organic solution gave a glassy residue, which was chromatographed over a silica-gel column (ϕ 1.8 cm x 34 cm) with chloroform-ethanol as an eluent to give the desired oxide (7, 1.70 g, 82.1 %) as a white foam. Uv $\lambda_{max}^{H_2O}$: nm (pH 7 and 12) 228, 302; (pH 1) 228, 301. MS: m/z 427 (M^+), 411/413 (M-O), 352/354 (M-O-OAc), 259 (M-B), 169/171 (B+H), 153/155 (M+B-O).

6-Chloro-7-ß-D-ribofuranosyl-7H-1-deazapurine 3-oxide (8)

A solution of 7 (100 mg, 0.23 mmol) in absolute methanol (5 ml) and triethylamine (0.5 ml) was allowed to stand for 24 h at room temperature. The reaction mixture was concentrated in vacuo to give a white residue, which was crystallized from methanol to afford 8 (37 mg,

TABLE 1 Pmr Chemical Shifts and Coupling Constants of Acetylated Nucleosides in $CDCl_3$*

Compd.	H-1	H-2	H-8	H-1'	H-2'	H-3'	H-4'	H-5'	Acetyl protons		
6	7.32d	8.51d	8.65s	6.75d	5.65q	5.43t	4.52m	4.44m	2.20s	2.13s	
	$J_{1,2}$ = 5.4 Hz			$J_{1',2'}$ = 4.2 Hz							
7	7.18d	8.30d	8.55s	6.73d	5.65q	5.42t	4.48m	4.45m	2.16s	2.12s	2.01s
	$J_{1,2}$ = 6.8 Hz			$J_{1',2'}$ = 3.9 Hz							
9	7.33s		8.57s	6.68d	5.62t	5.42t	4.48m	4.42m	2.18s	2.13s	
				$J_{1',2'}$ = 4.4 Hz							
11	7.37s		8.42s	6.24d	5.86t	5.66t	4.43m		2.16s	2.14s	2.09s
				$J_{1',2'}$ = 5.4 Hz							

*Signals are designated as s (singlet), d (doublet), t (triplet or pseudo-triplet), q (quartet or double doublet), and m (multiplet).

TABLE 2 Pmr Chemical Shifts and Coupling Constants of OH-Free Nucleosides in Dimethylsulfoxide-d_6*

Compd.	H-1	H-2	H-8	H-1'	H-2'	H-3'	H-4'	H-5'	OH (Sugar)	Other protons
8	7.38d	8.20d	8.91s	6.38d	4.39q	4.13m	4.04m	3.70m	5.64d 5.2m	
	$J_{1,2}$ = 6.8 Hz			$J_{1',2'}$= 3.4 Hz						
10	7.63s		9.06s	6.34d	4.38m	4.12m	3.98m	3.65m	5.61d 5.2m	
				$J_{1',2'}$= 3.9 Hz						
12	7.68s		8.84s	5.98d	4.54q	4.13q	3.94q	3.66m	5.53d 5.24d 5.03t	
				$J_{1',2'}$= 5.3 Hz						
2	6.37s		8.30s	5.82d	4.54q	4.10q	3.91m	3.57m	5.38d 5.14d 5.10t	6.80s (NH_2)
				$J_{1',2'}$= 6.4 Hz						
13	7.09s		8.56s	5.92d	4.54m	4.13m	3.92m	3.60m	5.46d 5.20d 5.02t	7.5 7.3m (Phenyl) 5.51s (CH_2)
				$J_{1',2'}$= 5.9 Hz						
14	7.09s		8.57s	5.94d	4.54m	4.14m	3.95m	3.61m	5.47d 5.23d 5.05t	7.44d 6.97d (Phenyl) 5.44s 3.77s (CH_2) (CH_3)
				$J_{1',2'}$= 5.9 Hz						
3	6.55s		8.35s	5.87d	4.49m	4.14m	3.95m	3.61m	5.40bs 4.58t	7.30s (OH)
				$J_{1',2'}$= 5.9 Hz						

*Signals are designated as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet).

70.2 %), mp 143° (dec.). Uv $\lambda_{max}^{H_2O}$: nm (pH 7 and 12) 227, 302; (pH 1) 226.5, 300.5. MS: m/z 169/171 (B + H), 153/155 (B + H - O).

Anal. Calcd for $C_{11}H_{12}N_3O_5Cl \cdot 1/2\ CH_3OH$: C, 43.47; H, 4.41; N, 13.22; Cl, 11.16. Found: C, 43.40; H, 4.39; N, 13.22; Cl, 10.89.

2,6-Dichloro-7-(2,3,5-tri-O-acetyl-ß-D-ribofuranosyl)-7H-1-deazapurine (9)

To a solution of 7 (1.50 g, 3.51 mmol) in chloroform (10 ml) was added a Vilsmeier reagent, prepared from $POCl_3$ (0.7 ml, 7.51 mmol) and DMF (0.6 ml, 7.76 mmol), and the mixture was stirred for 3 h at room temperature. The reaction mixture was poured into satd. sodium bicarbonate solution (100 ml). The solution was extracted with three 100-ml portions of chloroform. Concentration of the dried ($MgSO_4$) extract gave a syrup, which was chromatographed over a silica gel column (ϕ 2.2 cm x 36 cm) with chloroform as an eluent to afford 9 (1.19 g, 76.1 %) as a colorless syrup. Uv $\lambda_{max}^{H_2O}$: nm (pH 7 and 12) 261.5, 291; (pH 1) 258, 291. MS: m/z 445/447 (M^+), 259 (M - B), 187/189/191 (B + H).

2,6-Dichloro-7-ß-D-ribofuranosyl-7H-1-deazapurine (10)

Compound 9 (80 mg, 0.18 mmol) was deacetylated as described in the synthesis of 8. Recrystallization from methanol gave 10 (38 mg, 66.2 %) as needles, mp 116 - 117°. Uv $\lambda_{max}^{H_2O}$: nm (pH 7 and 12) 261.5, 290; (pH 1) 258, 291. MS: m/z 319/321/323 (M^+), 230/232/234 (B + 44), 216/218/220 (B + 30), 187/189/191 (B + H).

Anal. Calcd for $C_{11}H_{11}N_3O_4Cl_2 \cdot CH_3OH$: C, 40.92; H, 4.30; N, 11.93; Cl, 20.14. Found: C, 40.86; H, 4.32; N, 11.63; Cl, 19.96.

2,6-Dichloro-9-(2,3,5-tri-O-acetyl-ß-D-ribofuranosyl)-9H-1-deazapurine (11)

To a solution of 9 (1.42 g, 3.19 mmol) in toluene (50 ml) were added 1,2,3,5-tetra-O-acetyl-ß-D-ribofuranose (1.00 g, 3.14 mmol) and $HgBr_2$ (1.15 g, 3.19 mmol). The mixture was refluxed for 3 h. The solvent was evaporated in vacuo to give a brown residue, which was dissolved in chloroform (100 ml). The solution was washed with two 100-ml portions of 25 % potassium iodide solution and then with water (100 ml). Concentration of the dried ($MgSO_4$) organic solution gave a syrup, which was chromatographed over a silica gel column (ϕ 2.2 cm x

36 cm) with chloroform as an eluent to afford 11 (1.09 g, 76.7 %) as a colorless syrup. Uv $\lambda_{max}^{H_2O}$: nm (pH 7 and 12) 260.5, 289; (pH 1) 256, 289. MS: m/z 445/447 (M^+), 187/189/191 (B + H).

2,6-Dichloro-9-ß-D-ribofuranosyl-9H-1-deazapurine (12)

Compound 11 (1.00 g, 2.24 mmol) was deacetylated as described in the preparation of 8. Recrystallization from water gave 12 (598 mg, 83.7 %), mp 137 - 138°. Uv $\lambda_{max}^{H_2O}$: (pH 7 and 12) 260.5, 289; (pH 1) 256, 289. MS: m/z 319/321/323 (M^+), 289/291/293 (M - 30), 216/218/220 (B + 30), 187/189/191 (B + H).

Anal. Calcd. for $C_{11}H_{11}N_3O_4Cl_2 \cdot H_2O$: C, 39.07; H, 3.87; N, 12.42; Cl, 20.96. Found: C, 38.98; H, 3.86; N, 12.32; Cl, 20.97.

2-Chloro-1-deazaadenosine (2)

A solution of 12 (200 mg, 0.63 mmol) in liquid ammonia (30 ml) was heated at 100° in a sealed tube for 40 h. After evaporation of ammonia, the residue was chromatographed over a silica gel column (ϕ 1.2 cm x 20 cm) with chloroform - ethanol (5 : 1) as an eluent to give a white foam, which was crystallized from water to afford 2 (137 mg, 72.8 %), mp 215° (dec.). Uv $\lambda_{max}^{H_2O}$: (pH 7 and 12) 227 (ε 20,500), 267.5 (ε 14,200), 276sh (ε 12,200); (pH 1) 227 (ε 20,000), 273 (ε 11,200), 283sh (ε 11,000). MS: m/z 300/302 (M^+), 270/272 (M - 30), 197/199 (B + 30), 168/170 (B + H).

Anal. Calcd. for $C_{11}H_{13}N_4O_4Cl$: C, 43.93; H, 4.35; N, 18.64; Cl, 11.79. Found: C, 43.81; H, 4.30; N, 18.46; N, 11.77.

1-Deazaadenosine (4)

Compound 2 (60 mg, 0.2 mmol) was hydrogenated over 10 % Pd-C in water (100 ml) for a day under hydrogen pressure (40 psi). The catalyst was filtered off and the filtrate was neutralized with a drop of conc. ammonia. Concentration of the solution gave rise to a white solid, which was recrystallized from water to afford 4 (43 mg, 63 %) in an analytically pure state, mp 250 - 252°. No depression was observed by admixture with an authentic sample[2c]. Uv and pmr spectra of the sample were superimposable with those of the reported[2c].

6-Benzyloxy-2-chloro-9-ß-D-ribofuranosyl-9H-1-deazapurine (13)

To a solution of 12 (416 mg, 1.30 mmol) in benzyl alcohol (10 ml) was added N-sodium benzylate solution, prepared from benzyl alcohol

(10 ml) and sodium (0.23 g, 10 mmol), and the mixture was stirred at 80° for 2h. After cooling, the reaction mixture was neutralized with 10 % acetic acid and concentrated in vacuo to give a solid, which was chromatographed over a silica gel column (ϕ 2.4 cm x 17 cm) with chloroform-ethanol (10 : 1) as an eluent to afford 13. Recrystallization from water gave an analytically pure sample of 13 (325 mg, 63.9 %), mp 168 - 169°. Uv $\lambda_{max}^{H_2O}$: nm (pH 7 and 12) 254sh, 259, 267sh; (pH 1) 259, 267sh. MS: m/z 391/393 (M^+), 361/363 (M - 30), 302/304 (M - 89), 288/290 (B + 30), 259/261 (B + H), 91 ($C_6H_5CH_2$-).

Anal. Calcd for $C_{18}H_{18}N_3O_5Cl$: C, 55.17; H, 4.63; N, 10.72; Cl, 9.06. Found: C, 55.23; H, 4.61; N, 10.55; Cl, 8.88.

2-Chloro-6-(p-methoxybenzyloxy)-9-β-D-ribofuranosyl-9H-1-deazapurine (14)

To a mixture of p-methoxybenzyl alcohol (433 mg, 3.13 mmol), sodium hydride (60 % purity, 125 mg, 3.13 mmol), and dioxane (5 ml) was added 12 (200 mg, 0.63 mmol) and the suspension was stirred at room temperature for 3h. The reaction mixture was neutralized with 10 % acetic acid and was concentrated in vacuo to give a gray residue, which was acetylated with acetic anhydride (5 ml) and a catalytic amount of dimethylaminopyridine in dioxane (5 ml) for 1 h at room temperature. The mixture was concentrated in vacuo and chromatographed over a silica gel column (ϕ 1.4 cm x 11 cm) with chloroform as an eluent to give a tri-O-acetyl derivative of 14 (207 mg) as a foam. Uv $\lambda_{max}^{H_2O}$: nm (pH 7 and 12) 225sh, 258, 267sh, 277sh, 291sh; (pH 1) 225sh, 258.5, 266sh, 291sh. MS: m/z 547/549 (M^+), 289/291 (B + H), 259 (M - B), 121 ($CH_3OC_6H_4CH_2$-). Pmr in $CDCl_3$: δ 8.06 (1H, s, H-8), 7.40 (2H, d, J = 8.7 Hz, Ph), 6.90 (2H, d, J = 8.7 Hz, Ph), 6.78 (1H, s, H-1), 6.25 (1H, d, J = 5.4 Hz, H-1'), 5.85 (1H, t, H-2'), 5.66 (1H, q, H-3'), 5.47 (2H, s, $-CH_2Ph$), 4.42 (3H, m, H-4' and H-5'), 3.81 (3H, s, OCH_3), 2.15 (3H, s, $COCH_3$), 2.14 (3H, s, $COCH_3$), 2.08 (3H, s, $COCH_3$).

The acetyl derivative (80 mg, 0.15 mmol) was treated with methanolic triethylamine as described in the preparation of 8. Recrystallization from ethanol gave pure 14 (31 mg, 44 %), mp 126 - 127°. Uv $\lambda_{max}^{H_2O}$: nm (pH 7 and 12) 225sh, 258, 267sh, 277sh, 291sh; (pH 1) 225sh, 258.5, 266sh. 291sh. MS: m/z 301/303 (M^+), 271/273 (M - 30), 269/271 (M - 42), 212/214 (M - 89), 170/172 (B + 2H), 169/171 (B + H).

Anal. Calcd for $C_{11}H_{12}N_3O_5Cl$: C, 43.79; H, 4.01; N, 13.93; Cl, 11.75. Found: C, 43.49; H, 4.09; N, 13.77; Cl, 11.60.

2-Chloro-1-deazainosine (3)

A solution of 14 (280 mg, 0.80 mmol) was hydrogenated over 10 % Pd-C in methanol (20 ml) for 3 h under hydrogen pressure (30 psi). The catalyst was filtered off and washed with methanol (10 ml). Concentration of the combined filtrate and washing gave 3 as a foam (163 mg, 68 %), which was crystallized from water, mp 175-178°. Uv $\lambda_{max}^{H_2O}$: nm (pH 7) 257 (ε 7,290), 263 (ε 7,000), 275 (ε 5,050); (pH 12) 262.5 (ε 8,430), 276 (ε 6,710); (pH 1) 261 (ε 6,860). MS: m/z 301/303 (M^+), 271/273 (M-30), 212/214 (B+44), 198/200 (B+30), 170/172 (B+2H), 169/171 (B+H).

Anal. Calcd for $C_{11}H_{12}N_3O_5Cl$: C, 43.78; H, 4.01; N, 13.93; Cl, 11.75. Found: C, 43.60; H, 4.11; N, 13.77; Cl, 11.51.

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