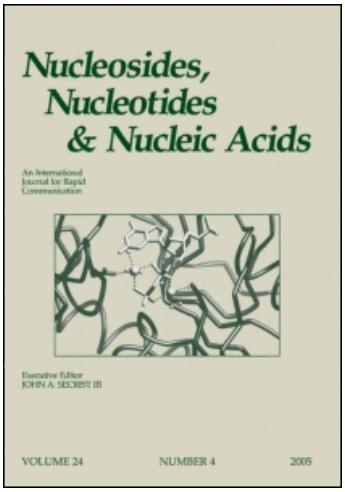

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Toyoaki Ishikura[a]; Sumiyo Oue[a]; Tokuo Itoh[a]; Akihiko Nomura[a]; Tohru Ueda[a]; Yoshihisa Mizuno[a]
[a] Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

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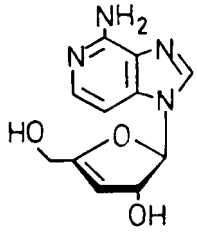
STUDIES ON THE CHEMICAL SYNTHESIS OF POTENTIAL ANTIMETABOLITES. 37[1]. SYNTHESIS OF 3-DEAZAADENINE NUCLEOSIDES MODIFIED AT THE SUGAR MOIETY

Toyoaki Ishikura, Sumiyo Oue, Tokuo Itoh*, Akihiko Nomura, Tohru Ueda, and Yoshihisa Mizuno

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

Abstract——Several types of 3-deazaadenine pentofuranosides, represented by 9-(3-deoxy-β-D-glycero-pent-3-enofuranosyl)-3-deazaadenine (1), 9-(5-deoxy-β-D-erythro-pent-4-enofuranosyl)-3-deazaadenine (2) and 9-β-D-xylofuranosyl-3-deazaadenine (3), were prepared starting from 6-chloro-9-β-D-ribofuranosyl-3-deazaadenine (4).

In view of the current interest in chemotherapeutic and biochemical properties of adenosine analogues, a variety of 3-deazaadenine nucleosides have been prevously prepared by us[2] and others[3]. Out of these, 3-deazaadenosine and some derivatives thereof (viz. 3-deaza-SIBA and 3-deaza-SAH) have been shown to exhibit potent antiviral activities[4]. Recently, neplanocin A, a nucleosidic antibiotic bearing an unsaturated carbocyclic polyol, was found to possess potent antileukemic[5] and antiviral[6] activities. These findings coupled with the facts that these nucleosides may act as potent inhibitors and/or inactivators against S-adenosylhomocysteine hydrolase (SAHase)[4,6,7] prompted us to prepare several 3-deazaadenine pentofuranosides bearing a double bond at the sugar moiety (1 and 2) and 9-β-D-xylofuranosyl-3-deazaadenine (3).



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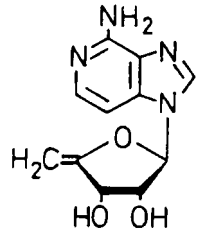

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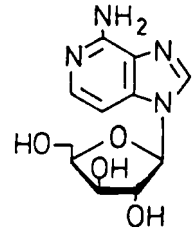

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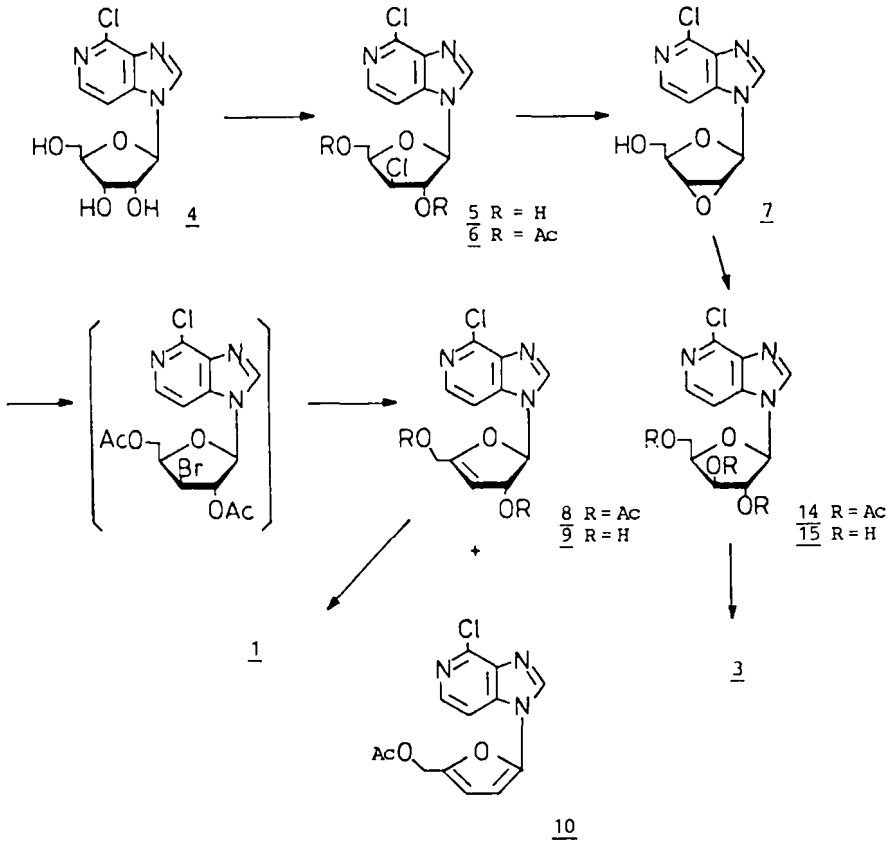


Since methods for modification of ribonucleosides at the sugar portion have been extensively explored, 6-chloro-9-β-D-ribofuranosyl-3-deazapurine (4)[2a] was the starting material of choice for the present syntheses.

Preparation of 9-(3-Deoxy-β-D-glycero-pent-3-enofuranosyl)-3-deazaadenine (1)

Synthesis of adenine nucleosides of the pent-3-enofuranosyl type has been accomplished through 2',5'-di-O-protected 3'-deoxy-3'-halogeno-xylofuranosyladenines by an elimination reaction[8]. A similar methodology was adopted for the preparation of 1.

The reaction of the riboside (4) with o-acetoxybenzoyl chloride in acetonitrile[9], followed by the treatment with methanolic triethylamine, gave 6-chloro-9-(3-chloro-3-deoxy-β-D-xylofuranosyl)-3-deazapurine (5, 60 %), which was treated with Dowex 1 x 2 (OH^- form) to afford the epoxide (7, 92 %). The treatment of 7 with tetraethylammonium bromide in the presence of acetic anhydride in DMF gave rise to 6-chloro-9-(3-deoxy-2,5-di-

O-acetyl-β-D-glycero-pent-3-enofuranosyl)-3-deazapurine (8) and a furan derivative (10) in varying amounts depending on the reaction conditions. Heating the reaction mixture at 70° for 30 h may be the condition of choice for the maximal formation of 8 (88 %). Under more vigorous conditions 10 was produced to a higher extent (for example, at 120° for 30 h, 10 was obtained as a major product). No formation of a double bond across $C_{3'}$ and $C_{4'}$ was observed in the absence of acetic anhydride or when 6-chloro-9-(3-chloro-3-deoxy-2,5-di-O-acetyl-β-D-xylofuranosyl)-3-deazapurine (6) was used in place of 7.

The structure of 8 was elucidated by mass and pmr spectrometry. Thus, the mass spectrum of 8 showed the molecular ion peaks at m/z 351/353 and furthermore peaks at m/z 291/293 which suggested facile elimination of acetic acid to the furan derivative (10). The pmr spectrum assigned to the H-5' appeared at δ 4.80 as a singlet and there was no peak due to the H-4'.

Deacetylation of 8 with methanolic triethylamine gave 9 (98 %), which was subjected to hydrazinolysis, followed by Raney nickel reduction, to afford the desired nucleoside 1 (31 % based on 9). The pmr chemical shifts due to the sugar protons were in good accordance with those of the adenine counterpart[8] with the exception of the H-2' signal[10].

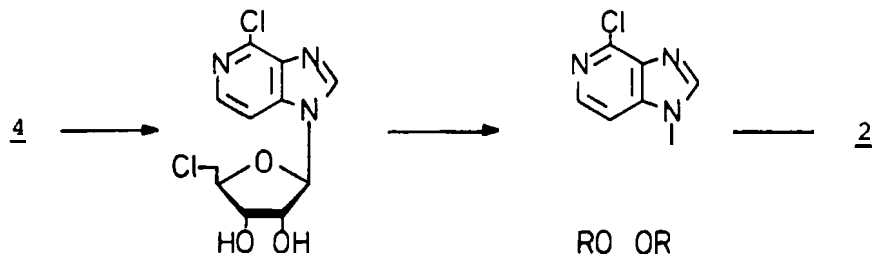
Preparation of 9-(5-Deoxy-β-D-erythro-pent-4-enofuranosyl)-3-deazaadenine (2)

The introduction of the exocyclic $C_{4'}$-$C_{5'}$ double bond in the sugar moiety of adenosine has been extensively investigated in view of the total synthesis of angustmycin and nucleocidin. These procedures involve an elimination reaction of an intermediate bearing a good leaving group (p-TsO, MsO, ArSe(O), I, or Br) at the $C_{5'}$-position[11]. In the present synthesis we used a 5'-chloro-5'-deoxy-derivative (11) as a key intermediate.

Compound 4 was treated with $SOCl_2$/HMPA[12] to give 11 (73 %). An elimination reaction in the presence of sodium iodide and DBU smoothly proceeded to afford 13, which was purified as the acetyl derivative (12, 48 %). Compound 13 was converted into one of the targets (2, 29 %) by treatment with hydrazine hydrate, followed by Raney nickel reduction. The pmr spectra of 2 and 13 showed the presence of two signals due to the H-5' with a geminal coupling and no signal due to H-4'. The mass spectra of 2 and 13 showed molecular ion peaks at m/z 248 and 267/269, respectively, providing the evidence for the desired structure.

Preparation of 9-β-D-Xylofuranosyl-3-deazaadenine (3)

Nucleophilic attack of acetate anion to the epoxide (7) in the presence of acetic anhydride predominantly occurred at the 3'-position to give



11

12 R = Ac
13 R = H

an acetylated xyloside (14, 76 %) which was subjected to deacetylation to afford 6-chloro-9-β-D-xylofuranosyl-3-deazapurine (15, 98 %). Conversion of 15 into 3 was performed the treatment with hydrazine hydrate followed by Raney nickel reduction. The structure of 3 was confirmed by instrumental analyses. Compound 3 was readily distinguished from the corresponding riboside[2a] and arabinoside[2c] by electrophoretical and pmr analysis.

Biological and biochemical studies of the nucleosides, herein described, are under investigation. The results will be the subject of forthcoming papers.

EXPERIMENTAL

All melting points were determined on a Yamato melting point apparatus, MP-1, and are uncorrected. UV absorption spectra were taken on a Hitachi 323 recording spectrometer. Pmr spectra were recorded with JEOL FX-100 and FX-200 spectrometer. Chemical shifts and coupling constants of the nucleosides, herein described, are summarized in Table 1 and signals are designated as s (singlet), d (doublet), t (triplet), m (multiplet), and b (broad). Mass spectra (MS) were taken on a JEOL JMS D-300 spectrometer.

6-Chloro-9-(3-chloro-3-deoxy-β-D-xylofuranosyl)-3-deazapurine (5)

To a suspension of 4[2] (2.16 g, 7.68 mmol) in acetonitrile (21 ml) was added o-acetoxybenzoyl chloride (6.08 g, 30.6 mmol) and the mixture was stirred at 40° for 2 d. The solvent was evaporated in vacuo to give a residue, which was triturated with ether several times. The insoluble material was dissolved in chloroform (200 ml) and the solution was washed with 5 % $NaHCO_3$ solution (100 ml x 3) and with water (100 ml). The organic layer was dried over Na_2SO_4. Concentration of the dried solution gave

Table 1 Pmr Chemical Shifts (δ in ppm) and Coupling Constants (J in Hz) of Prepared Nucleosides

	solvent	H-1'	H-2'	H-3'	H-4'	H-5'	H-2	H-3	H-8	OH or CH_3CO	NH_2
5	DMSO-d_6	6.00d $J_{1';2'}$=3.4	4.8	4.1m		3.80m	8.22d $J_{2,3}$=5.7	7.83d	8.64s	6.55d 5.18t	-
7	DMSO-d_6	6.39s	3.45-3.27m		4.62d $J_{4';5'}$=2.4	4.22m	8.18d $J_{2,3}$=5.8	7.82d	8.67s	4.99t	-
8	$CDCl_3$	6.41d $J_{1';2'}$=2.1	5.46m	5.86m	-	4.80s	8.26d $J_{2,3}$=5.6	7.37d	8.18s	2.16s 2.12s	-
9	DMSO-d_6	6.51d $J_{1';2'}$=2.5	5.08m	5.34m	-	4.07bd	8.20d $J_{2,3}$=5.6	7.63d	8.63s	5.86d 5.4m	-
1	DMSO-d_6	6.48d $J_{1';2'}$=2.8	5.02m	5.32d	-	4.06m	7.66d $J_{2,3}$=5.6	6.89d	8.58s	5.97bd 5.4m	6.20s
11	DMSO-d_6	5.99d $J_{1';2'}$=6.1	4.52m	4.3-4.1m		3.97m	8.20d $J_{2,3}$=5.6	7.80d	8.68s	5.9-5.4bm	-
13	DMSO-d_6	6.35d $J_{1';2'}$=4.5	4.6-4.4m		-	4.46d 4.35d	8.22d $J_{2,3}$=5.6	7.69d	8.74s	5.9-5.6bm	-
12	$CDCl_3$	6.31d $J_{1';2'}$=6.1	5.55dd $J_{2';3'}$=5.1	5.86dd	-	4.87dd 4.67dd	8.28d $J_{2,3}$=5.6	7.43d	8.11s	2.19s 2.10s	-
2	DMSO-d_6	6.11d $J_{1';2'}$=5.6	4.6-4.4		-	4.38d 4.27d	7.68d $J_{2,3}$=5.6	6.71d	8.27s	5.72bs	6.25s
14	$CDCl_3$	6.00d $J_{1';2'}$=1.4	5.21dd $J_{2';3'}$=1.2	5.45dd	4.71m $J_{3';4'}$=3.4	4.46m	8.25d $J_{2,3}$=5.6	7.58d	8.23s	2.22s 2.12s 2.03s	
15	DMSO-d_6	5.92d $J_{1';2'}$=1.7	4.25-4.15m		4.08m	3.73m	8.17d $J_{2,3}$=5.6	7.89d	8.53s	6.00d 5.61d 4.79t	
3	DMSO-d_6	5.92d $J_{1';2'}$=4.0	5.72d $J_{2';3'}$=2.2	5.44m	4.10m $J_{3';4'}$=3.9	3.74m	7.68d $J_{2,3}$=5.9	6.91d	8.17s	6.15d 4.72t	6.27s

a yellow foam, which was dissolved in methanol containing triethylamine (6 ml). After being allowed to stand overnight, the mixture was concentrated to leave a gray solid, which was crystallized from water to afford 5 (1.38 g, 60 %): mp 195-196°. MS m/z: 303/305/307 (M^+), 182/184 (B + 30), 166/168 (B + 14), 153/155 (B + H).

Anal. Calcd for $C_{11}H_{11}N_3O_3Cl_2$: C, 43.44; H, 3.65; N, 13.82; Cl, 23.32. Found: C, 43.58; H, 3.63; N, 13.83; Cl, 23.07.

9-(2,3-Anhydro-β-D-ribofuranosyl)-6-chloro-3-deazapurine (7)

A solution of 5 (1.06 g, 3.49 mmol) in methanol (40 ml) was stirred with Dowex 1 x 8 (OH^- form, ca 10 ml) for 2.5 h at room temperature. The resin was filtered off and washed with methanol several times. The methanol solution was concentrated in vacuo to give 7 (858 mg, 92 %) as needles: mp 232°. MS m/z: 267/269 (M^+), 166/168 (B + 14), 154/156 (B + 2H), 153/155 (B + H), 115 (sugar portion).

Anal. Calcd for $C_{11}H_{10}N_3O_3Cl$: C, 49.36; H, 3.77; N, 15.70; Cl, 13.25. Found: C, 49.46; H, 3.77; N, 15.76; Cl, 13.21.

6-Chloro-9-(3-deoxy-2,5-di-O-acetyl-β-D-glycero-pent-3-enofuranosyl)-3-deazapurine (8)

A solution of 7 (140 mg, 0.52 mmol), tetraethylammonium bromide (250 mg, 1.19 mmol), acetic anhydride (0.25 ml, 2.5 mmol), and a catalytic amount of N,N-dimethylaminopyridine in DMF (2 ml) was stirred at 70° for 30 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo to afford a thick syrup, which was partitioned between chloroform (30 ml) and 5 % $NaHCO_3$ solution (30 ml). The organic layer was washed with water (30 ml) and dried over Na_2SO_4. Concentration of the dried extract gave a colorless residue, which was chromatographed over a silica gel column with ethanol-chloroform (1 : 19) as an eluent to leave 8 (163 mg, 88 %) as a foam. MS m/z: 351/353 (M^+), 291/293 (M - 60).

6-Chloro-9-(5-acetoxymethylfuran-2-yl)-3-deazapurine (10)

The preceding reaction was performed at 120° in 20 mg-scale. After work-up as described above, 10 was isolated as a colorless syrup (90 %). MS m/z: 291/293 (M^+). Pmr in $CDCl_3$ δ: 8.33 (d, 1H, H-2, $J_{2,3}$= 5.6 Hz), 8.27 (s, 1H, H-8), 7.51 (d, 1H, H-3, $J_{2,3}$= 5.6 Hz), 6.64 (d, 1H, H-2', $J_{2',3'}$= 3.4 Hz), 6.43 (d, 1H, H-3', $J_{2',3'}$= 3.4 Hz), 5.12 (s, 2H, H-5'), 2.13 (s, 3H, CH_3CO).

6-Chloro-9-(3-deoxy-β-D-glycero-pent-3-enofuranosyl)-3-deazapurine (9)

A solution of 8 (157 mg, 0.45 mmol) in methanol (10 ml) containing triethylamine (6 drops) was allowed to stand overnight at room temperature. Concentration of the reaction mixture in vacuo left 9 (117 mg, 98 %) as a white foam.

9-(3-Deoxy-β-D-glycero-pent-3-enofuranosyl)-3-deazaadenine (1)

A solution of 9 (60 mg, 0.22 mmol) in hydrazine hydrate (4 ml) was stirred at 100° for 1 h under a nitrogen atmosphere. After cooling, the mixture was concentrated in vacuo and a trace of hydrazine was coevaporated twice with oxygen-free warer to give a hydrazino-derivative, which, without further purification, was treated with Raney nickel (W-2, ca 50 mg) in oxygen-free water (2 ml). The mixture was refluxed for 1 h under a nitrogen atmosphere. After decolorization with Norit, concentration of the reaction mixture gave a crude sample of 1 (HCl salt[13], 49 mg, 78 %) as a white solid, which was chromatographed over a Dowex 1 x 8 (OH^- form) column with 50 % methanol as an eluent to afford 1 (17 mg, 31 %). Crystallization from water gave a pure sample as needles: mp 195°. UV $\lambda_{max}^{H_2O}$(nm): (pH 2.39) 263.5 (ε9,920), 270sh(ε9,100); (pH 11.7) 266.5 (ε9,700). MS m/z: 248 (M^+), 230 (M - H_2O), 135 (B + 2H), 134 (B + H). HR-MS Calcd for $M^+(C_{11}H_{12}N_4O_3)$: 248.09106. Found: 248.09199.

6-Chloro-9-(5-chloro-5-deoxy-β-D-ribofuranosyl)-3-deazapurine (11)

To a suspension of 4 (2.85g, 10 mmol) in HMPA (16 ml) was added $SOCl_2$ (4 ml, 55 mmol) under cooling with ice-water and the mixture was stirred overnight at room temperature. The reaction mixture was poured on ice-water and the solution was made alkaline with concentrated ammonia. Ammonium chloride, precipitated, was filtered off and the filtrate was chromatographed over a Dowex column (1 x 8, OH^- form) with 50 % methanol as an eluent to give 11 (2.23 g, 73 %) as a white solid: mp 83-134° and 187° (dec). MS m/z: 303/305/307 (M^+), 153/155 (B + H).

Anal. Calcd for $C_{11}H_{11}N_3O_3Cl_2$: C, 43.44; H, 3.65; N, 13.82; Cl, 23.31. Found: C, 43.24; H, 3.57; N, 13.76; Cl, 23.14.

6-Chloro-9-(5-deoxy-2,3-di-O-acetyl-β-D-erythro-pent-4-enofuranosyl)-3-deazapurine (12)

A mixture of 11 (660 mg, 2.17 mmol), sodium iodide (450 mg, 3.00 mmol), and DBU (0.4 ml, 2.60 mmol) in acetonitrile (16 ml) was refluxed for 1.5 d. After addition of acetic anhydride (1 ml, 10 mmol), the solution was stirred for 2 h at room temperature. Concentration of the re-

action mixture gave a syrup, which was partitioned between chloroform (50 ml) and water (50 ml). The organic layer was washed with saturated $Na_2S_2O_3$ solution (50 ml x 3) and dried over Na_2SO_4. Concentration of the dried solution left an oily substance, which was chromatographed over a silica gel column with ethanol-chloroform (1 : 19) as an eluent to give 12 as a white foam (280 mg, 48 %).

6-Chloro-9-(5-deoxy-β-D-erythro-pent-4-enofuranosyl)-3-deazapurine (13)

A solution of 12 (250 mg, 0.71 mmol) in methanol (20 ml) containing triethylamine (1 ml) was allowed to stand for 8 h at room temperature. Concentration of the reaction mixture in vacuo gave a white foam (174 mg, 99 %), which was crystallized from water to afford 13 as a colorless solid: mp 55°(sintered) and 180 - 181°(dec). MS m/z: 267/269 (M^+), 195/197 (B + 43), 180/182, 166/168 (B + 14), 154/156 (B + 2H), 153/155 (B + H), 118 (B + H - Cl).

9-(5-Deoxy-β-D-erythro-pent-4-enofuranosyl)-3-deazaadenine (2)

A solution of 13 (100 mg, 0.37 mmol) in hydrazine hydrate (3 ml) was refluxed for 1 h under a nitrogen atmosphere. Excess hydrazine was evaporated in vacuo and coevaporated with oxygen-free water to give a light green solid, 6-hydrazino-intermediate. To a solution of the substance in oxygen-free water (3 ml) was added Raney nickel (W-2, ca 50 mg) and the mixture was refluxed for 1 h under a nitrogen atmosphere. A small amount of insoluble material was removed by filtration and the filtrate was concentrated in vacuo to give a brown residue, which was chromatographed over a Dowex column (1 x 8, OH^- form) with 50 % methanol as an eluent to afford a white solid. Crystallization from water gave 2 (27 mg, 29 %) as needles; mp 102-103° and 180-181°. MS m/z: 248 (M^+), 214, 176 (B + 43), 147 (B + 14), 135 (B + 2H), 134 (B + 2H). UV $\lambda_{max}^{H_2O}$ (nm): (pH 2.20) 262.5 (ε10,100), 268 (ε9,260); (pH 11.7) 266 (ε9,920).

Anal. Calcd for $C_{11}H_{14}N_4O_3 \cdot H_2O$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.33; H, 5.28; N, 20.62.

6-Chloro-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-3-deazapurine (14)

To a solution of the epoxide (7, 1.36 g, 5.07 mmol) in DMF (16 ml) was added anhydrous sodium acetate (0.81 g, 9.9 mmol) and acetic anhydride (7.5 ml, 79 mmol) and the mixture was stirred at 100° for 27 h. Concentration of the mixture in vacuo gave a thick syrup, which was dissolved in chloroform (40 ml). The organic layer was washed with saturated $NaHCO_3$ solution (40 ml) and water (40 ml). After being dried with Na_2SO_4, the solvent was evaporated in vacuo to give a residue, which was chromato-

graphed over a silica gel column with ethanol-chloroform (1 : 19) as an eluent to afford 14 (1.59 g, 76 %) as a white foam. MS m/z: 411/413 (M^+), 259 (M -B), 153/155 (B + H).

6-Chloro-9-β-D-xylofuranosyl-3-deazapurine (15)

Compound 14 (320 mg, 0.778 ml) was deacetylated by the procedure described in the preparation of 9 to give 15 (219 mg, 98 %) as a white foam. Crystallization from water gave an analytically pure sample: mp 134-135°. MS m/z: 285/287 (M^+), 166/168 (B + 14), 153/155 (B + H).

9-β-D-Xylofuranosyl-3-deazaadenine (3)

A solution of 15 (126 mg, 0.44 mmol) in hydrazine hydrate (3 ml) was refluxed for 1 h under a nitrogen atmosphere. The reaction mixture was concentrated in vacuo to give a light violet gum, which was reduced in deoxygenated water (3 ml) with Raney nickel (W-2, ca 50mg) at 100°. The catalyst was filtered off and the filtrate was decolored with Norit. Concentration of the solution gave the hydrochloride salt of 3 (74 mg, 56 %) as leaflets: mp 173-174°. UV $\lambda_{max}^{H_2O}$ (nm): (pH 2.21) 262.5 (ε9,590), 267.5sh (ε8,980); (pH 11.7) 266 (ε9,610).

Anal. Calcd for $C_{11}H_{14}N_4O_4 \cdot HCl$: C, 43.64; H, 5.00; N, 18.51; Cl, 11.71. Found: C, 43.40; H, 4.93; N, 18.38; Cl, 11.97.

A part of the hydrochloride was chromatographed over a Dowex 1 x 8 (OH^- form) with 40 % methanol as an eluent to give an HCl-free sample of 3, which was subjected to the instrumental analyses. MS m/z: 266 (M^+), 147 (B + 14), 134 (B + H).

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