0.35 g (36.8% yield, as calculated for the hemihydrate); mp 167-168 °C.

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Registry No. 1, 79410-34-7; 2, 79410-36-9; 3, 79410-38-1; 4, 79410-40-5; 5, 79410-42-7; 6, 79410-44-9; 7, 79410-45-0; 8, 79410-46-1; 9, 79410-47-2; 10, 79464-63-4; 11, 79410-49-4; L-Leu, 61-90-5; L-Phe, 63-91-2; L-Glu, 56-86-0; DL-Met, 59-51-8; L-Trp, 73-22-3; LL-Ala-Phe, 3061-90-3; L-Tyr-Gly, 673-08-5; L-Phe-Oet, 3081-24-1; L-Ala-Oet, 3082-75-5; L-Leu-Oet, 2743-60-4; L-Asn, 70-47-3; triflyl azide, 3855-45-6.

Long-Bridged Cyclonucleosides. 1. Synthesis and Reactions of Some Purine 8,2′-(N^{α}-Methylhydrazino) and 8,2′-(N^{α}-Methyloxamido) Cyclonucleosides

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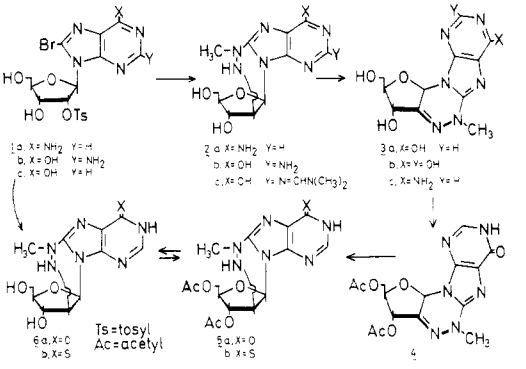
For expansion of the range of the model conformations of cyclonucleosides, synthesis of some long-bridged purine cyclonucleosides has been achieved. Thus, 8-bromo-2′-*O*-tosyladenosine (**1a**) and its guanine analogue (**1b**) with methylhydrazine gave the corresponding 8,2′-(N^{α}-methylhydrazino) cyclonucleosides **2a,b**. Treatment of **2a** and **2b** with nitrous acid yielded another type of long-bridged cyclonucleoside, 2′,N^{β}-didehydro-8,2′-(N^{α}-methylhydrazino)cycloinosine (**3a**) and its xanthine analogue (**3b**), respectively. Oxidation of **2a** with $NaIO_4$ or MCPBA gave the analogous cycloadenosine **3c**. Acetylation of **3a** followed by $NaBH_4$ reduction gave 3′,5′-di-*O*-acetyl-8,2′-(N^{α}-methylhydrazino)cycloinosine (**5a**), which was thiated to its thioinosine analogue **5b**. Deacetylation of **5a,b** afforded the corresponding parent 8,2′-(N^{α}-methylhydrazino) cyclonucleosides **6a,b**. Acidic hydrolysis of **2a** gave a new cyclonucleoside having the glycosidic bond to N_7. Catalytic hydrogenolysis of **2a** yielded the amino sugar nucleoside **8**. Compound **1a** with *N*-methylhydroxylamine gave 8-[(methylamino)-oxy]-9-(2′-*O*-tosyl-β-D-ribofuranosyl)adenine (**9**), 8,2′-(N^{α}-methyloxamido) cyclonucleoside **10**, and 8-(methylamino)-9-(β-D-arabinofuranosyl)adenine (**11**). Reduction of **10** with Zn/AcOH yielded 8-(methylamino)adenine which was isolated as hydrochloride **12**.

Among the hitherto known, large number of pyrimidine and purine cyclonucleosides,[1] notably missing members are those having a base–sugar bridge constructed by multiple atoms. In view of the numerous theoretically possible base–sugar conformations in natural nucleosidic or nucleotidic materials, it seems to be important to try to expand the presently limited bounds of the model conformations by bonding the base and sugar moieties with a reasonably longer chain. This type of cyclonucleoside might also be useful as a new type of synthetic intermediate for bifunctionalization at the base and sugar moieties, depending upon the chemical property of the bridge. We herein describe the syntheses and reactions of some purine 8,2′-cyclonucleosides containing an $N(CH_3)NH$, $N(CH_3)$-$N=$, or $N(CH_3)O$ bridge using bifunctional methylhydrazine and *N*-methylhydroxylamine as powerful synthetic tools.

Heating 8-bromo-2′-*O*-tosyladenosine (**1a**)[2] with excess methylhydrazine in methanol gave 8,2′-(N^{α}-methylhydrazino)-9-(2′-deoxy-β-D-arabinofuranosyl)adenine (**2a**) in 85% isolated yield (Scheme I). Similarly, **1b** with methylhydrazine provided 8,2′-(N^{α}-methylhydrazino)-9-(2′-deoxy-β-D-arabinofuranosyl)guanine (**2b**). Compound **2b** was sparingly soluble in most organic solvents and hence was converted to the N_2-[(dimethylamino)-methylene] derivative **2c** by treatment with DMF dimethyl acetal for spectroscopic measurements.[3] The UV and ^1H NMR spectra of these compounds are given in Tables I and II.

Scheme I



As the first step of base transformations, **2a** was treated with excess sodium nitrite in 80% acetic acid at 0 °C to afford another type of cyclonucleoside, 2′,N^{β}-didehydro-8,2′-(N^{α}-methylhydrazino)-9-(2′-deoxy-β-D-arabinofuranosyl)hypoxanthine (**3a**), in excellent yield. Similar treatment of **2b** with nitrous acid gave the corresponding xanthine analogue **3b** in a moderate yield.[4] The structures

(1) For reviews see: Ts'o, P. O. P., Ed. "Basic Principles in Nucleic Acid Chemistry"; Academic Press: New York, 1974; Vol. 1, p 170. (b) Ikehara, M. *Acc. Chem. Res.* **1969**, *2*, 47.

(2) Ikehara, M.; Maruyama, T. *Tetrahedron* **1975**, *31*, 1369.

(3) For compounds **2**, alternative structures in which the 1-nitrogen atom of methylhydrazine is attached to the $C_{2'}$ or its 2-nitrogen is attached to both $C_{2'}$ and C_8 were eliminated by conversion of **2** to **3** and also by X-ray analysis of **2a**.

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Table I. Ultraviolet Absorptions of 1c, 2a-c, 3a-c, 4, 5a,b, 6a,b, and 7-12 in Methanol

compd	λ_{max}, nm (ϵ)
1c	253 (19 000)
2a	278 (18 800)
2b	262 (10 100), 293 (5700)
2c	241 (19 500), 293 (16 400),[a] 319 (20 800)
3a	253 (1600), 297 (9470)
3b	242 (8100), 314 (10 900)
3c	255 (6400), 307 (16 700)
4	251 (5400), 302 (14 400)
5a	263 (15 600), 294 (13 000)[a]
5b	314 (16 100), 337 (15 800)
6a	266 (12 200), 293 (7900)[a]
6b	315 (15 100), 338 (16 000)
7	232 (19 300), 282 (11 700)
8	276 (15 060)
9	275 (16 700)
10	272 (13 000)
11	278 (16 500)
12	260 (5900)

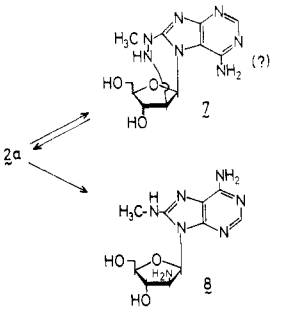
[a] Shoulder.

of **3a,b** were deduced from the extensive bathochromic shifts of the major UV absorptions as compared to those of 8-amino- and 8-(substituted amino)inosines[5] and of 8-amino- and 8-(substituted amino)xanthosines[5,6] as well as from the analysis of the ^{1}H NMR spectra of **3b** and **4**,[7] the diacetylated analogue of **3a** [absence of the hydrazino $N^{\beta}H$ signal and the resonance of $H_{1'}$ as a singlet; the significant deshielding of the $H_{1'}$ and *N*-methyl signals are to be noted for this class of compounds (Table II)]. On the other hand, compound **2a** proved to be smoothly oxidized with sodium metaperiodate or *m*-chloroperbenzoic acid (MCPBA) to yield the corresponding adenine analogue **3c**.[8]

After most of this series of work was finished, we discovered that compounds **2a** and **3c** had been synthesized by Reese et al. in 1978.[8] They obtained **3c** by oxidizing **2a** with mercury(II) acetate. In their short communication most of the proton resonances are not assigned, and hence we subjected **2a** to a couple of decoupling experiments.[9] On irradiation of the 3.97-ppm signal ($H_{3'}$), the doublet at 5.63 ppm (3'-OH) became a sharp singlet, and the broad singletlike multiplet at 3.75 ppm became rather sharpend,[10] while irradiation at 5.83 ppm ($H_{1'}$) caused the broad multiplet at 3.53 ppm to be a rather ill-resolved doublet of doublets, the others remaining unchanged. Hence, it became clear that the signals of $H_{3'}$ and $H_{4'}$ as well as of 3'-OH are assignable as shown in Table II and that the signal of $H_{2'}$ overlies on that of $H_{5'}$. The small discrepancies between their ^{1}H NMR chemical shift data and ours could be explained in terms of instrumental differences.

Compound **3a** was converted to 3',5'-di-*O*-acetyl-2',N^{β}-didehydro-8,2'-(N^{α}-methylhydrazino)-9-(2'-deoxy-β-D-arabinofuranosyl)hypoxanthine (**4**), which was reduced to 3',5'-di-*O*-acetyl-8,2'-(N^{α}-methylhydrazino)-9-(2'-deoxy-β-D-arabinofuranosyl)hypoxanthine (**5a**). The assignments of the ^{1}H NMR signals of **5a** are also based on the spin-decoupling experiments.[11] Treatment of **5a** with a mixture of methanol and concentrated ammonia (3:1) gave 8,2'-(N^{α}-methylhydrazino)-9-(2'-deoxy-β-D-arabinofuranosyl)hypoxanthine (**6a**).[12] Compound **6a** can be more economically obtained by an alternative, direct method. Thus, **1a** with excess nitrous acid afforded 8-bromo-2'-*O*-tosylinosine (**1c**) in high yield. Reaction of **1c** with methylhydrazine proceeded rapidly to give a 86% yield of **6a** which can be acetylated to **5a**.[13] Thiation of **5a** with excess phosphorus pentasulfide in pyridine gave the corresponding thioinosine analogue **5b** which was deacetylated to 8,2'-(N^{α}-methylhydrazino)-9-(2'-deoxy-β-D-arabinofuranosyl)-6-thiohypoxanthine (**6b**) by treatment with sodium methoxide in methanol.

Scheme II



The high-yield synthesis of **2a** spurred us to examine further chemical transformations. The methylhydrazino bridge should intrinsically be stable under hydrolysis conditions, and hence we aimed to cleave the glycosidic bond for further recombination transformations. Thus, the prolonged heating of **2a** in a 5:1 mixture of methanol and concentrated hydrochloric acid gave an equilibrium mixture of **2a** (in terms of TLC analysis) and a new, slightly more polar substance, **7** (Scheme II), the latter being isolated in 20% yield and found to absorb at 232 and 282 nm (Table I). There are no appropriately described specimens for direct UV spectral comparison with **7**, but, as far as 8-unsubstituted compounds are concerned, 7-glycosyladenines are known to absorb at wave lengths higher than 9-glycosylated analogues.[14] The ^{1}H NMR spectrum of this compound displayed a resonance pattern similar to that of **2a** except that the $H_{2'}$ and $H_{5'}$ signals were separated and the 6-amino signal shifted significantly upfield (0.46 ppm). This upfield shift of the 6-amino signal is particularly notable when compared with those of all the other compounds in Table II carrying a 6-amino group. A model study[15] has shown that in such a 8,2'-cyclonucleoside, bonding the $C_{1'}$ with either nitrogen in the

(4) Compound **3b** appears to be very labile to acid since a couple of overnight reactions did not allow the isolation of **3b** nor of any decomposition product.

(5) Long, R. A.; Robins, R. K.; Townsend, L. B. *J. Org. Chem.* **1967**, *32*, 2751.

(6) Saneyoshi, M. *Chem. Pharm. Bull.* **1968**, *16*, 1616.

(7) Compound **3a** is not sufficiently soluble in Me_2SO-d_6 for NMR measurement.

(8) Chattopadhyaya, J. B.; Reese, C. B. *J. Chem. Soc., Chem. Commun.* **1978**, 86.

(9) All the 200-MHz ^{1}H NMR spectra involving that of **2a** were recorded on a Varian XL-200 FT NMR spectrometer in the laboratory of the Daiichi Pharmaceutical Co., Ltd.

(10) Influence of the $H_{2'}$ signal overlapping that of the 5'-methylene was not conspicuous, especially due to disturbance by the H_2O signal.

(11) On irradiating the three-proton multiplet at 4.16 ppm (5'-CH_2 and $H_{2'}$) the two doublet peaks at 5.96 ($H_{1'}$) and 5.75 ppm (NH) and the triplet at 5.23 ppm ($H_{3'}$) collapsed into singlets, while irradiation at 4.04 ppm ($H_{4'}$) changed the multiplet at 4.16 ppm into an ill-resolved quartet (or dd), the $H_{3'}$ signal remaining essentially unchanged. These results indicate that the $H_{2'}$ signal overlies that of $H_{5'}$ and that $H_{3'}$–$H_{4'}$ coupling, if any, is negligible.

(12) The assignments of the ^{1}H NMR signals of **6a** and **6b** essentially followed from those of **2a**. In the 200-MHz spectrum of **6a**, irradiation at 3.97 ppm ($H_{3'}$) caused the doublet at 5.85 ppm (3'-OH) to collapse into a singlet. The signal envelope of $H_{5'}$ and $H_{2'}$ partially merged with that of H_2O.

(13) Leaving a mixture of **6a** (1 mmol) and acetic anhydride (10 mmol) in pyridine (4 mL) at room temperature overnight gave **5a** quantitatively after the usual workup.

(14) Montgomery, J. A.; Thomas, H, J. *J. Am. Chem. Soc.* **1963**, *85*, 2672.

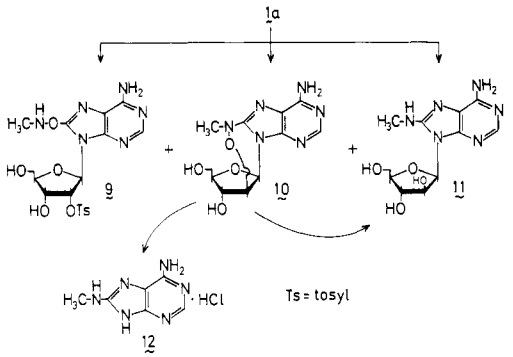
(15) An HGS flexible molecular model set (Maruzen Co., Ltd.) was used.

Table II. ^{1}H NMR Resonances of 1c, 2a,c, 3b,c, 4, 5a,b, 6a,b, 7–11 in Me_2SO-d_6 [a]

compd	$C_5'H$	$C_4'H$	$C_3'H$	$C_2'H$	$C_1'H$	C_2H	bridge NH [or 2'-NH_2]	bridge NMe [or 8-NHMe]	others
1c	3.57 (m)	4.03 (m)	4.37 (m)	5.78 (dd, $J_{1',2'}$ = 8.0, $J_{2',3'}$ = 5.0)	5.94 (d, $J_{1',2'}$ = 8.0)	7.97 (s)			12.0 (br s, N_1H)
2a [b]	3.53 (3 H, m)	3.75 (m)	3.97 (m)	c	5.83 (d, $J_{1',2'}$ = 4.8)	8.0 (s)	5.48 (d, J = 10)	3.14 (s)	6.71 (s, NH_2), 5.63 (d, J = 4.9, 3'-OH)
2c	3.52 (3 H, m)	3.69 (m)	3.98 (m)	c	5.64 (d, $J_{1',2'}$ = 5.6)		5.30 (d, J = 4.5)	3.15 (s)	3.00 (s, N-Me_2)
3b	3.76 (m)	3.96 (m)	4.42 (m)		6.03 (s)			3.44 (s)	9.93, 10.20 (br s, N_1H and N_3H)
3c	3.10–3.50 (m)	3.90–4.20 (m) (m)	4.49 (dd, $J_{3',3'\text{-OH}}$ = 4.5, $J_{3',4'}$ = 2.0)		6.22 (s)	8.05 (s)		3.58 (s)	6.92 (br s, NH_2)
4	4.20 (d, $J_{4',5'}$ = 4.0)	4.57 (m)	5.85 (br s)		6;40 (s)	8.00 (s)		3.62 (s)	2.11, 1.86 (s, 2MeCOO), 12.37 (br s, N_1H)
5a [b]	4.16 (3 H, m)	4.04 (m)	5.23 (t, J = 4.8)	c	5.96 (d, $J_{1',2'}$ = 6.5)	7.92 (s)	5.75 (d, J = 6.0)	3.07 (s)	2.10, 1.86 (s, 2MeCOO), 12.25 (br s, N_1H)
5b	4.20 (3 H, m)	4.08 (m)	5.18 (t, J = 5.0)	c	5.93 (d, $J_{1',2'}$ = 5.0)	8.03 (s)	5.80 (d, J = 4.5)	3.15 (s)	2.10, 1.82 (s, 2MeCOO), 13.60 (br s, N_1H)
6a [b]	3.50 (3 H, m)	3.74 (m)	3.97 (m)	c	5.81 (d, $J_{1',2'}$ = 4.5)	7.90 (s)	5.44 (d, J = 8.0)	3.08 (s)	12.14 (br s, N_1H), 5.85 (d, J = 4.8, 3'-OH)
6b	3.50 (3 H, m)	3.75 (m)	3.93 (m)	c	5.77 (d, $J_{1',2'}$ = 4.5)	7.98 (s)	5.70 (m)	3.14 (s)	13.05 (br s, N_1H)
7 [b]	3.55 (m)	3.90 (2 H, m)		3.40 (dd, $J_{1',2'}$ = 4.8, $J_{2',3'}$ = 11.6)	5.90 (d, $J_{1',2'}$ = 4.8)	8.08 (s)	5.65 (d, J = 8.9)	3.18 (s)	4.95 (t, J = 5.0, 5'-OH), 5.70 (d, J = 4.9, 3'-OH), 6.25 (s, NH_2)
8 [b]	3.69 (3 H, m)		4.12 (br s; t, J = 6.8, on D_2O addition)	3.47 (dd, $J_{1',2'}$ = 7.5, $J_{2',3'}$ = 6.8)	6.18 (d, $J_{1',2'}$ = 7.5)	7.92 (s)	[1.2–1.9 (br s)]	[2.86 (d, J = 4.8; s on D_2O addition]	5.45 (2 H, br s, 5'-OH), 6.87 (d, J = 4.8, NHMe), 5.65 (br, 3'-OH)
9	3.60 (m)	4.00 (m)	4.30 (m)	5.40 (dd, $J_{1',2'}$ = 7.0, $J_{2',3'}$ = 5.0)	5.97 (d, $J_{1',2'}$ = 7.0)	7.30 (s)			2.80 (d, J = 5.0, NHMe), 6.53 (br s, NH_2), 6.90 (br d, J = 5.0, NHMe)
10 [b]	3.50 (m)	3.75 (br d, $J_{4',3'}$ = 5.4)	4.18 (m; dd, $J_{2',3'}$ = 2.0 $J_{3',4'}$ = 5.4, on D_2O addition)	4.70 (dd, $J_{1',2'}$ = 4.0, $J_{2',3'}$ = 2.0)	5.97 (d, $J_{1',2'}$ = 4.0)	8.09 (s)		3.24 (s)	6.97 (br s, NH_2), 4.83 (t, J = 5.5, 5'-OH), 5.79 (d, J = 6.4, 3'-OH)
11 [b]	3.72 (3 H, br s)		4.20 (2 H, br s)		6.20 (d, $J_{1',2'}$ = 5.0)	7.91 (s)		[2.88 (d, J = 5.2)]	6.46 (br s, 6-NH_2), 6.67 (d, J = 5.2, NHMe), 5.50 (d, J = 4.8 Hz, 2'- or 3'-OH), 5.60 (br t, J = 4.5, 5'-OH and 3'- or 2'-OH)

[a] s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet. Chemical shifts are given in parts per million and J values in hertz. [b] 200-MHz spectra; see also footnotes 9, 11, 12, 19, and 21. [c] Overlapped the signal of H_5'.

Scheme III



pyrimidine part of the adenine ring is absolutely excluded, irrespective of the sugar species (furanose or pyranose). Furthermore, geminal protons ($H_{5'a}$ and $H_{5'b}$) in pyranose nucleosides are known to resonate at lower fields (usually 4–4.5 ppm) than those of **2a** or **7**.[16] However, it has proved to be rather difficult to deduce the configuration at $C_{3'}$ on the basis of the $H_{2'}$–$H_{3'}$ coupling constant and the model study.[17] From the above considerations, we tentatively assign the structure of **7** as an 8,2′-(N^{α}-methylhydrazino)-7-furanosyladenine with unknown configuration at $C_{3'}$ and $C_{4'}$.

A separate, similar hydrolysis experiment using a small amount of **7** as starting material gave again a similar equilibrium mixture, from which **2a** was isolated and was identical, IR as well as UV spectroscopically, with an authentic sample. However, it is uncertain at present whether the hydrolysis products **2a** and **7** are optically homogeneous or not.[18]

On the other hand, catalytic hydrogenolysis of **2a** afforded 2′-amino-8-(methylamino)-9-(2′-deoxy-β-D-arabinofuranosyl)adenine (**8**), whose structure is clear on the basis of the general spectroscopic data on Table I and II. In the ^{1}H NMR spectrum of this compound, the doublet signal of the methyl group collapsed into a sharp singlet on D_2O addition.[19]

We next attempted to construct an *N*-methyloxamido bridge between the C_8 and $C_{2'}$ of adenosine. The experiments using **1a** and *N*-methylhydroxylamine were focussed on the complete consumption of the first-formed apolar product, since we knew by experience from a preliminary, small-scale experiment that the apolar product retained the 2′-*O*-tosyl group. However, the TLC-controlled pursuit of the reaction indicated that the second, slower moving product gradually transformed to another more polar product prior to the disappearance of the apolar product. In this paper a typical experiment in such a situation is given (method A in the Experimental Section) in which 8-[(methylamino)oxy]-9-(2′-*O*-tosyl-β-D-ribofuranosyl)-adenine (**9**), 8,2′-(N^{α}-methyloxamido)-9-(2′-deoxy-β-D-arabinofuranosyl)adenine (**10**), and 8-(methylamino)-9-(β-D-arabinofuranosyl)adenine (**11**) were isolated in 18%, 14%, and 18% yields, respectively (Scheme III). In the ^{1}H NMR spectrum of **9**, the *N*-methyl group coupled with the adjacent imino proton with J = 5.0 Hz (collapsed into a singlet on D_2O addition), establishing the structure with a 8-[(methylamino)oxy] function (Table II). The conclusive structural elusidation of **10** followed from its chemical transformations. Compound **10** was quantitatively reduced to **11** by prolonged heating with excess *N*-methylhydroxylamine,[20] while the attempted reduction with a zinc–acetic acid system invariably resulted in the concomitant cleavage of the glycosidic bond to afford 8-(methylamino)adenine that was isolated as the hydrochloride **12**. The direct bonding of C_8 with nitrogen was hence established for **10** and, accordingly, for **11**. The spectroscopic data are also in accord with the structures **10** and **11**.[21] A separate cyclization experiment using **9** under similar conditions (100 °C, in methanol containing triethylamine in a pressure tube) was unsuccessful, and, accordingly, we consider the initially formed apolar product to be a mixture of two tightly running 8-substituted derivatives, one of which is cyclized to **10**. It must be noted that another short-time reaction of **1a** with *N*-methylhydroxylamine followed by a simpler workup gave **10** in 64% yield with minor amount of **9**.

The strong CD extrema near the major UV absorptions of **2a**, **2b**, **6a**, and **10** reflect their high anti conformations in solution.[22] Particularly interesting to us is the chemical conversion of **2a** to **8** or of **10** to **11**, which exemplifies the importance of such cyclonucleosides with a breakable diatomic bridge in terms of epimerizing bifunctionalization. The formation of **7** could also allow one to envisage a new facet of chemical modification through such cyclonucleosides.[24] Similar diatomic bridging between the C_8 and $C_{3'}$ of adenosine has also been achieved in this laboratory.[25]

Experimental Section[26]

8-Bromo-2′-*O*-tosylinosine (1c). To a stirred solution of 8-bromo-2′-*O*-tosyladenosine (**1a**; 500 mg, 1 mmol) in 80% acetic acid (16 mL) was added at 0 °C sodium nitrite (690 mg, 10 mmol). After being stirred for 30 min, the mixture was left at 0 °C for 2 days, evaporated, and repeatedly coevaporated with methanol to remove residual acetic acid. The residue was digested with ice–water (10 mL), and the sparingly soluble remaining **1a** was recovered (160 mg, 0.3 mmol). The aqueous phase was extracted with $CHCl_3$(10 × 15 mL). The $CHCl_3$ extract was recrystallized from ethanol to give 290 mg (85%) of **1c**: mp 169–171 °C dec; IR (KBr) 1180 cm^{-1} (covalent sulfonate).

Anal. Calcd for $C_{17}H_{17}N_4O_7BrS$: C, 40.73; H, 3.42; N, 11.19. Found: C, 40.51; H, 3.58; N, 10.98.

8,2′-(N^{α}-Methylhydrazino)-9-(2′-deoxy-β-D-arabinofuranosyl)adenine (2a). A mixture of **1a** (1.0 g, 2.0 mmol) and methylhydrazine (1.05 mL, 20 mmol) in methanol (50 mL) in a pressure tube was heated at 90–95 °C for 4 h under argon. After cooling, the mixture was evaporated and repeatedly coevaporated

(16) For example see: (a) Leutzinger, E. E.; Bowles, W. A.; Robins, R. K.; Townsend, L. B. *J. Am. Chem. Soc.* **1968**, *90*, 127. (b) Fisher, L. V.; Lee, W. W.; Goodman, L. *J. Heterocycl. Chem.* **1969**, *6*, 949.

(17) In compounds **7** and **2**, the bonds in the bicyclic partial structure containing the furanose ring and the bridge are rather flexible, and hence the H_2–H_3 dihedral angle is also variable within ca. 70–80°.

(18) The possibility of racemization cannot be excluded.

(19) The very shallow two-proton signal of the 2′-amino group centered at 1.5 ppm and all the other signals for the labile protons disappeared on D_2O addition.

(20) Reduction of *o*-dinitrosobenzene with hydroxylamine is described: Boyer, J. H.; Schoen, W. *J. Am. Chem. Soc.* **1956**, *78*, 423.

(21) On irradiation at 6.67 (NH) or 2.85 ppm (CH_3), either doublet became a singlet, while irradiation at 4.20 ppm ($H_{2'}$ and $H_{3'}$) caused the doublet at 6.20 ppm ($H_{1'}$) to become a singlet.

(22) The X-ray analysis of **2a**, conducted by the research group of the Takeda Chemical Industries Co., Ltd., has disclosed a glycosidic torion angle χ (C_8–N_9–$C_{1'}$–$O_{1'}$) of 105°, corresponding to a high anti conformation, shown also by 8,2′-*O*-cycloadenosine having χ = 107°.[23]

(23) Neidel, S.; Taylor, G. L.; Cowling, P. C. *Acta Crystallogr., Sect. B* **1979**, *B35*, 708.

(24) We are actually exploiting the scope of chemical transformations involving fission and recombination at the anomeric position, utilizing another model compound.

(25) Given orally at the 43rd Annual Meeting of the Chemical Society of Japan, 1981, Tokyo.

(26) The general methods used are similar to those described earlier.[27] The CD spectra were recorded on a JASCO Model ORD/UV-5 spectrometer in the laboratory of the Takeda Chemical Industries Co., Ltd., for which we are grateful.

(27) Sasaki, T.; Minamoto, K.; Suzuki, T.; Sugiura, T. *J. Org. Chem.* **1979**, *44*, 1424.

with methanol to give a gum, which gave crystals on being allowed to stand in methanol (10 mL). After the crystals were collected, the filtrate was evaporated, and the residue was left with ethanol (10 mL) in a refrigerator to afford a second crop. Recrystallization from MeOH gave 500 mg (85%) of **2a**: mp 244.5–246 °C; CD (MeOH) [θ] +21 820 (278 nm).

Anal. Calcd for $C_{11}H_{15}N_7O_3$: C, 45.04; H, 5.16; N, 33.43. Found: C, 45.01; H, 5.21; N, 33.48.

8,2′-(N^{α}-Methylhydrazino)-9-(2′-deoxy-β-D-arabinofuranosyl)guanine (2b). To a solution of **1b** (1.14 g, 2.2 mmol) in MeOH (70 mL) was added methylhydrazine (1.16 mL, 22 mmol), and the mixture was heated at reflux for 40 h under argon bubbling. The mixture was evaporated and coevaporated wtih ethanol, and the residue was digested with a small volume of MeOH to give TLC-homogeneous solid, which was collected and recrystallized from water to give 370 mg (55%) of **2b**: mp above 300 °C; CD (MeOH) [θ] +12 260 (258 nm).

Anal. Calcd for $C_{11}H_{15}N_7O_4$: C, 42.71; H, 4.89; N, 31.70. Found: C, 42.80; H, 4.90; N, 31.49.

8,2′-(N^{α}-Methylhydrazino)-9-(2′-deoxy-β-D-arabinofuranosyl)-N^2-[(dimethylamino)methylene]guanine (2c). To a solution of **2b** (70 mg, 0.23 mmol) in DMF (0.8 mL) was added DMF dimethyl acetal (0.24 mL, 2.3 mmol), and the mixture was stirred at room temperature for 3 days. After evaporation of the solvent and the excess of the reagent, the residue was triturated with a small volume of EtOH to give a crystalline solid, which was collected and recrystallized from MeOH to give 45 mg (54%) of **3c** as colorless needles, mp >300 °C.

Anal. Calcd for $C_{14}H_{20}N_8O_4$: C, 46.15; H, 5.52; N, 30.76. Found: C, 46.43; H, 5.56; N, 30.53.

2′,N^{β}-Didehydro-8,2′-(N^{α}-methylhydrazino)-9-(2′-deoxy-β-D-arabinofuranosyl)hypoxanthine (3a). To a stirred solution of **2a** (200 mg, 0.68 mmol) in 80% acetic acid (8 mL) was added at 0 °C sodium nitrite (235 mg, 5 × 0.68 mmol). After being stirred at 0 °C for 30 min, the mixture was left at this temperature overnight. TLC with an aliquot of the reaction mixture indicated no starting material. The mixture was evaporated and repeatedly coevaporated with MeOH to remove the residual AcOH. Treatment of the residue with water (2 mL) gave a solid, which was collected, dried, and recrystallized from MeOH to afford 165 mg (83%) of **3a**, mp 293–294 °C dec. This product was not sufficiently soluble in Me_2SO-d_6 for NMR measurement.

Anal. Calcd for $C_{11}H_{12}N_6O_4$: C, 45.20; H, 4.14; N, 28.76. Found: C, 45.25; H, 4.35; N, 28.51.

2′,N^{β}-Didehydro-8,2′-(N^{α}-methylhydrazino)-9-(2′-deoxy-β-D-arabinofuranosyl)xanthine (3b). To a stirred solution of **2b** (520 mg, 1.67 mmol) in 80% AcOH (20 mL) was added at 0 °C sodium nitrite (464 mg, 4 × 1.67 mmol). The solution gradually became a gellike mixture and then a more mobile suspension. After a total of 4 h at 0 °C, the mixture was evaporated below 30 °C and repeatedly coevaporated with EtOH. The residue was digested with a small volume of water and the insoluble solid collected. Recrystallization from MeOH gave 260 mg (50.3%) of **3b** as crystals, which became brown above 250 °C but did not melt below 300 °C.

Anal. Calcd for $C_{11}H_{12}N_6O_5 \cdot H_2O$: C, 40.60; H, 4.09; N, 25.89. Found: C, 40.66; H, 4.10; N, 25.93.

2′,N^{β}-Didehydro-8,2′-(N^{α}-methylhydrazino)-9-(2′-deoxy-β-D-arabinofuranosyl)adenine (3c). Method A. A mixture of **2a** (400 mg, 1.36 mmol) and sodium metaperiodate (350 mg, 1.2 × 1.36 mmol) in MeOH (40 mL) was stirred at room temperature for 3 h. The solvent was evaporated and the residue digested with ice–water (25 mL). The solid precipitate was collected, dried, and recrystallized from MeOH to give 160 mg (40%) of **3c**, mp 248–249.5 °C.

Anal. Calcd for $C_{11}H_{13}N_7O_3$: C, 45.36; H, 4.50; N, 33.66. Found: C, 45.36; H, 4.56; N, 33.59.

Method B. To a stirred solution of **2a** (100 mg, 0.34 mmol) in AcOH (3.5 mL) was added MCPBA (80% pure, 78 mg, 0.363 mmol), and the solution was left at room temperature for 4 h. The mixture was evaporated and coevaporated with MeOH. The residue was thoroughly digested with ether (10 mL) and the insoluble solid collected. The solid was again washed with ether (10 mL) and then recrystallized from MeOH to give 65 mg (78%) of **3c**, identical with the product in procedure A in terms of mixture melting point and IR spectroscopy.

3′,5′-Di-O-acetyl-2′,N^{β}-didehydro-8,2′-(N^{α}-methylhydrazino)-9-(2′-deoxy-β-D-arabinofuranosyl)hypoxanthine (4). A mixture of **3a** (67 mg, 0.23 mmol) and acetic anhydride (0.22 mL, 2.3 mmol) in pyridine (1 mL) was stirred at room temperature overnight. The mixture was treated with MeOH (1 mL) at room temperature for 1 h, evaporated, and repeatedly coevaporated with MeOH. The residue was left with EtOH (3 mL) in a refrigerator and the collected solid recrystallized from MeOH to give 78 mg (90%) of **4** as crystals, mp 254–257 °C dec.

Anal. Calcd for $C_{15}H_{16}N_6O_6$: C, 47.87; H, 4.29; N, 22.33. Found: C, 47.91; H, 4.42; N, 22.12.

3′,5′-Di-O-acetyl-8,2′-(N^{α}-methylhydrazino)-9-(2′-deoxy-β-D-arabinofuranosyl)hypoxanthine (5a). $NaBH_4$ (38 mg, 1.0 mmol) was added to a solution of **4** (380 mg, 1.0 mmol) in DMF (4 mL) and the mixture stirred at room temperature for 24 h. After being neutralized with AcOH, the mixture was evaporated and dissolved in water (10 mL), and the pH of this solution was adjusted to 7 with a mixture of MeOH and concentrated ammonia (3:1 v/v). Extraction of this solution with $CHCl_3$ (10 × 20 mL) and subsequent workup with the chloroform solution gave a paste, which was applied on a silica gel column (2.8 × 20 cm). Elution with $CHCl_3$/MeOH (9:1) gave a solid, which was recrystallized from acetone to afford 190 mg (50%) of **5a**, mp 252–254 °C.

Anal. Calcd for $C_{15}H_{18}N_6O_6$: C, 47.62; H, 4.80; N, 22.72. Found: C, 47.76; H, 4.92; N, 22.95.

3′,5′-Di-O-acetyl-8,2′-(N^{α}-methylhydrazino)-9-(2′-deoxy-β-D-arabinofuranosyl)-6-thiohypoxanthine (5b). A mixture of **5a** (300 mg, 0.78 mmol) and phosphorus pentasulfide (1.4 g, 2.34 mmol) in dry pyridine (20 mL) was heated to reflux for 7 h. The mixture was evaporated, coevaporated with MeOH to remove residual pyridine, and then stirred with warm water (20 mL) for 1 h. After the mixture cooled, the insoluble material was filtered off, and the aqueous phase extracted with $CHCl_3$ (15 × 30 mL). After the usual workup, the obtained product mixture was dissolved in $CHCl_3$ (5 mL) and applied on a silica gel column (1.8 × 20 cm). Elution with $CHCl_3$/MeOH (9:1) gave a colorless solid as a main fraction, which was recrystallized from EtOH to give 160 mg (52%) of **5b**, mp 155–157 °C.

Anal. Calcd for $C_{15}H_{18}N_6O_5S$: C, 45.68; H, 4.60; N, 21.31. Found: C, 45.45; H, 4.41; N, 21.14.

8,2′-(N^{α}-Methylhydrazino)-9-(2′-deoxy-β-D-arabinofuranosyl)hypoxanthine (6a). Method A. To a solution of **5a** (70 mg, 0.19 mmol) in MeOH (4 mL) was added concentrated ammonia (1.3 mL), and the mixture was left at room temperature overnight. After evaporation of the solvent, the residue was digested with ice–water (1-2 mL) and the solid collected by suction. Recrystallization from MeOH gave 45 mg (80%) of **6a**: mp >300 °C; CD (MeOH) [θ] +15 128 (261 nm).

Anal. Calcd for $C_{11}H_{14}N_6O_4$: C, 44.90; H, 4.79; N, 28.56. Found: C, 45.11; H, 4.81; N, 28.33.

Method B. Compound **1c** (250 mg, 0.5 mmol) and methylhydrazine (0.27 mL, 5 mmol) in MeOH (5 mL) were combined in a pressure tube, and the mixture was stirred at 90 °C for 2.5 h under argon. After cooling, the mixture was evaporated and repeatedly coevaporated with MeOH. The residue was triturated with EtOH (5 mL) to give 125 mg (85%) of TLC-homogeneous crystals, identical with the product prepared by method A.

8,2′-(N^{α}-Methylhydrazino)-9-(2′-deoxy-β-D-arabinofuranosyl)-6-thiohypoxanthine (6b). To a solution of **5b** (50 mg, 0.2 mmol) in MeOH (10 mL) was added sodium methoxide (43 mg, 4 × 0.2 mmol), and the mixture was stirred at room temperature for 1 h under an argon stream. The solution was neutralized with a 1:1 mixture of MeOH and AcOH and then evaporated. After coevaporation with MeOH, the residue in acetone (20 mL) was heated at reflux for 30 min. The insoluble material was filtered off and the filtrate evaporated. Digestion of the residue with EtOH (2 mL) gave crystals, which were collected and recrystallized from EtOH to give 25 mg (64%) of **6b**, mp 263–265 °C.

Anal. Calcd for $C_{11}H_{14}N_6O_3S$: C, 42.57; H, 4.55; N, 27.08. Found: C, 42.30; H, 4.77; N, 26.88.

8,2′-(N^{α}-Methylhydrazino)-7-(2′-deoxy-β-D-arabinofuranosyl)adenine (7). Compound **2a** (200 mg, 0.67 mmol) in a mixture of MeOH and concentrated hydrochloric acid (5:1 v/v, 20 mL) was heated to reflux for 30 h under an argon stream. TLC (silica gel; $CHCl_3$/MeOH, 85:15) with an aliquot of the reaction

mixture indicated the presence of two tightly running substances in approximately equal amounts, the faster running one being the starting material. The mixture was evaporated and coevaporated with MeOH several times, and the residue was dissolved in MeOH (10 mL). After neutralization with triethylamine, the mixture was evaporated and again dissolved in MeOH (1 mL). The insoluble material was filtered off and the filtrate subjected to preparative TLC [20 × 20 cm, $CHCl_3$/MeOH (8:2), developed three times]. The desired band was eluted with MeOH, and the obtained product was repeatedly recrystallized from MeOH to give 40 mg (20%) of **7**, mp 265–267 °C.

Anal. Calcd for $C_{11}H_{15}N_7O_3$: C, 45.04; H, 5.16; N, 33.43. Found: C, 45.31; H, 5.42; N, 33.18.

Acidic Hydrolysis of 7. Compound **7** (50 mg, 0.17 mmol) was treated with a mixture of MeOH and concentrated hydrochloric acid (5:1) under the same reaction conditions as for the above hydrolysis of **2a** and the mixture worked up similarly. The analogous preparative TLC gave 13 mg (26%) of a faster moving material, which was identical with **2a** in terms of mobility in TLC and IR and UV spectroscopy.

2′-Amino-8-(methylamino)-9-(2′-deoxy-β-D-arabinofuranosyl)adenine (8). A solution of **2a** (293 mg, 1.0 mmol) in EtOH (20 mL) containing Raney Ni (W-5, 4.5 mL) was deoxygenated by argon bubbling and then put under a hydrogen stream at atmospheric pressure. The mixture was stirred at 50 °C for 24 h and then cooled to room temperature. After removal of the catalyst by decantation and filtration, the solution was concentrated and subjected to preparative TLC [20 × 20 cm, twice developed with $CHCl_3$/MeOH (7:3)]. After the usual workup, 95 mg of the starting material was recovered. The slightly slower moving band was eluted with MeOH and the obtained solid recrystallized from MeOH to give 90 mg (45% on the basis of the consumed starting material) of **8**, mp 230–231.5 °C.

Anal. Calcd for $C_{11}H_{17}N_7O_3$: C, 44.74; H, 5.80; N, 33.20. Found: C, 44.94; H, 5.89; N, 32.92.

Reaction of 8-Bromo-2′-*O*-tosyladenosine (1a) with *N*-Methylhydroxylamine. Synthesis of 9–11. Method A. A solution of *N*-methylhydroxylamine hydrochloride (2.5 g, 30 mmol) in MeOH (15 mL) was adjusted to pH 8–9 with 4 N KOH/MeOH and the inorganic precipitate was filtered off. The filtrate and **1a** (1.0 g, 2.0 mmol) were combined in a pressure tube, and the total volume was adjusted to 30 mL by adding further MeOH. The mixture was stirred at 100 °C for 140 h under argon and then evaporated. The residue was dissolved in EtOH (50 mL) and the insoluble, UV-transparent material filtered off. The filtrate was evaporated, and the residue was partitioned between water (20 mL) and EtOAc (80 mL). The EtOAc extract was subjected to preparative TLC [20 × 20 cm, $CHCl_3$/MeOH (85:15)], and three major bands were eluted with MeOH. The fastest running fraction was recrystallized from a small volume of acetone to give 135 mg (18%) of **9**: mp 203–206 °C; IR (KBr) 1180 cm^{-1} (covalent sulfonate).

Anal. Calcd for $C_{18}H_{22}N_6O_7S$: C, 46.35; H, 4.75; N, 18.02. Found: C, 46.61; H, 4.84; N, 18.27.

The second fraction crystallized on being allowed to stand with a small amount of EtOH. Recrystallization from MeOH gave 80 mg (14%) of **10**, which gradually became brown above 200 °C and melted between 216 and 220 °C with effervescence; CD (MeOH) [θ] +18 480 (265 nm).

Anal. Calcd for $C_{11}H_{14}N_6O_4$: C, 44.89; H, 4.80; N, 28.56. Found: C, 44.77; H, 5.05; N, 28.43.

The slowest moving fraction was recrystallized from a small volume of MeOH to give 110 mg (17.6%) of **11** as colorless crystals, which became colored above 240 °C and melted at 248–250 °C with effervescence.

Anal. Calcd for $C_{11}H_{16}N_6O_4$: C, 44.59; H, 5.44; N, 28.37. Found: C, 44.70; H, 5.53; N, 28.24.

Method B. A solution of CH_3NHOH·HCl (2.5 g, 30 mmol) in MeOH (15 mL) was neutralized with anion-exchange resin IRA-410 (OH form) and the resin filtered. The filtrate was adjusted to pH 8–9 with 4 N KOH/MeOH and the inorganic salt filtered off. The filtrate volume was adjusted to 30 mL by adding MeOH, and this solution was combined with **1a** (1.0 g, 2.0 mmol) in a pressure tube. The mixture was heated at 100 °C for 11 h under argon and thoroughly evaporated. The residue was left with EtOH (7–8 mL) in a refrigerator overnight to give a solid precipitate, which was collected and recrystallized from MeOH to give 376 mg (64%) of **10** after drying under high vacuum. The filtrate separated from most of the **10** was subjected to preparative TLC as in method A to give 50 mg of **9**.

Conversion of 10 into 11. A solution of CH_3NHOH·HCl (426 mg, 15 × 0.34 mmol) in MeOH (3 mL) was neutralized with anion-exchange resin IRA-410 (OH form) and filtered. The filtrate was adjusted to pH 8–9 with 4 N KOH/MeOH and again filtered to remove the inorganic salt. In each case, the filter cake was washed with a small volume of MeOH. The obtained solution of *N*-methylhydroxylamine and **10** (100 mg, 0.34 mmol) were combined in a pressure tube, and the mixture heated at 100 °C for 100 h under an argon atmosphere. After cooling, the mixture was evaporated and the residue triturated with EtOH (2 mL) to give a TLC-pure solid precipitate of **11** (98 mg, 97%), identical with an authentic sample of **11** as obtained above in all respects after one recrystallization.

8-(Methylamino)adenine Hydrochloride (12). To a solution of **10** (100 mg, 0.34 mmol) in AcOH (2 mL) was added zinc powder (111 mg, 5 × 0.34 mmol), and the mixture was stirred at room temperature for 8 h. After the inorganic material was filtered off, the residue was evaporated and coevaporated with MeOH. The residue was dissolved in MeOH (3 mL) and neutralized with IRA-410 (OH form). The mixture total was poured into a column and eluted with MeOH (100 mL). The eluant was concentrated and subjected to preparative TLC [10 × 20 cm, $CHCl_3$/MeOH (8:2), twice developed]. The main slower moving band gave a gum, which resisted crystallization. The gum was dissolved in MeOH (10 mL), acidified with saturated hydrogen chloride solution in dry dioxane, and rapidly evaporated below 30 °C. The residue was repeatedly coevaporated with dry MeOH and left with EtOH (1.5 mL) in a refrigerator to give crystals, which were recrystallized from EtOH at room temperature to yield 25 mg (37%) of **12**, mp >290 °C.

Anal. Calcd for $C_6H_8N_6$·HCl: C, 35.92; H, 4.52; N, 41.89. Found: C, 36.09; H, 4.68; N, 41.62.

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Registry No. **1a**, 16667-73-5; **1b**, 56845-07-9; **1c**, 79483-43-5; **2a**, 66642-58-8; **2b**, 79483-44-6; **2c**, 79483-45-7; **3a**, 79483-46-8; **3b**, 79483-47-9; **3c**, 66642-59-9; **4**, 79483-48-0; **5a**, 79483-49-1; **5b**, 79483-50-4; **6a**, 79483-51-5; **6b**, 79483-52-6; **7**, 79483-53-7; **8**, 79483-54-8; **9**, 79483-55-9; **10**, 79483-56-0; **11**, 64854-82-6; **12**, 79483-57-1.