Long-Bridged Cyclonucleosides. 2. A Synthetic Study Aimed at Cyclization between the C_8 and $C_{3'}$ of Some Purine Nucleosides Using a Methylhydrazo Bridge

Tadashi Sasaki,* Katsumaro Minamoto, Shunsuke Yamashita, and Yasumi Fujiki

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Japan

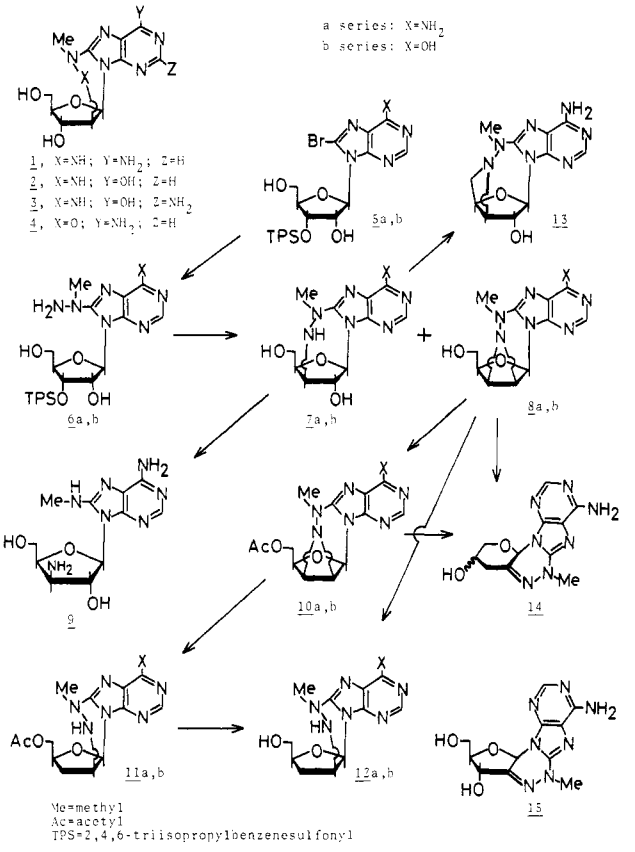
Received April 20, 1982

For expansion of the range of the model conformations of cyclonucleosides, synthesis of some new long-bridged purine cyclonucleosides has been achieved. Thus, 8-bromo-3′-*O*-[(2,4,6-triisopropylphenyl)sulfonyl]adenosine (**5a**) and its hypoxanthine analogue **5b** with methylhydrazine gave the corresponding 8-(N^{α}-methylhydrazino) analogues **6a,b**. The base-catalyzed cyclization of **6a,b** at high temperatures gave 8,3′-(N^{α}-methylhydrazo)-9-(3′-deoxy-β-D-xylofuranosyl) purines **7a,b** and 9-[2′,3′-[(methylamino)epimino]-2′,3′-dideoxy-β-D-lyxofuranosyl]purine 8,*N*-cyclonucleosides **8a,b**. **7a** was hydrogenolyzed to 3′-amino-8-(methylamino)-9-(3′-deoxy-β-D-xylofuranosyl)adenine (**9**). **8a,b** were converted to 5′-acetyl analogues **10a,b**, which were reduced to 5′-*O*-acetyl-8,2′-(N^{α}-methylhydrazo)-9-(2′,3′-dideoxy-β-D-arabinofuranosyl)purines **11a,b** with $NaBH_4$. Deacetylation of **11a,b** gave the corresponding parent compounds **12a,b**. **12a** was also obtained directly from **8a** by catalytic hydrogenolysis. Acidic hydrolysis of **8a** or **10a** gave 2′,N^{β}-didehydro-8,2′-(N^{α}-methylhydrazo)-9-(2′,3′-dideoxypyranosyl)adenine (**14**). Treatment of **7a** with diphenyl carbonate yielded 9-[3′,5′-[*N*-(methylamino)azetidino]-3′,5′-dideoxy-β-D-xylofuranosyl]adenine 8,*N*-cyclonucleoside (**13**).

As part of our recent program to expand the range of the model conformations of cyclonucleosides, the synthesis of some long-bridged purine cyclonucleosides with a diatomic bridge between C_8 and $C_{2'}$ (**1–4**) has been reported.[1] Some of this sort of cyclonucleosides have also proved to be useful as a new type of synthetic intermediate for bifunctionalization at the base and sugar moieties. This paper describes the results of a synthetic study for cyclization between the C_8 and $C_{3'}$ of adenosine as well as inosine by using methylhydrazine as a diatomic bridge component.

8-Bromo-3′-*O*-[(2,4,6-triisopropylphenyl)sulfonyl]inosine (**5b**) as a starting material was synthesized by the usual deamination of its adenine analogue (**5a**).[2] Reaction of **5a** with excess methylhydrazine under conditions similar to those for the one-step synthesis[1] of 8,2′-(N^{α}-methylhydrazo)-9-(2′-deoxy-β-D-arabinofuranosyl)adenine (**1**) and its analogues **2–4** gave 8-(N^{α}-methylhydrazino)-3′-*O*-[(2,4,6-triisopropylphenyl)sulfonyl]adenosine (**6a**) almost quantitatively (Scheme I), no other products being observed in terms of TLC. The structure of this compound is based upon the general spectroscopic data (Tables I and II and analyses). The bonding of the N^{α} of methylhydrazine to C_8 is clear from the broad two-proton signal at 4.80 ppm for the hydrazino NH_2 group in the ^1H NMR spectrum (Table II). Analogously, **5b** was converted to 8-(N^{α}-methylhydrazino)-3′-*O*-[(2,4,6-triisopropylphenyl)-sulfonyl]inosine (**6b**) which resisted crystallization. Heating **6a** at 135–140 °C under basic conditions gave two products, which were successfully separated by a combination of fractional crystallization and preparative TLC. The more polar product (25%) proved to be a methanolate of the expected 8,3′-(N^{α}-methylhydrazo)-9-(3′-deoxy-β-D-xylofuranosyl)adenine (**7a**) which absorbs at 275 nm. The proton resonances in the ^1H NMR spectrum were reasonably assigned on the basis of the spin-decoupling experiments (Table II).[3] Surprisingly, another less polar product (33%) proved to be 9-[2′,3′-[(methylamino)-epimino]-2′,3′-dideoxy-β-D-lyxofuranosyl]adenine 8,*N*-cyclonucleoside (**8a**) which showed an extensive bathochromic shift (299 nm) of the major UV absorption, suggesting extension of the chromophore. The ^1H NMR spectrum of this compound displayed a set of doublet of doublets at 2.65 and 3.06 ppm for two sugar protons which interacted with each other with a very large coupling constant (15.2 Hz), suggesting a cis orientation for these protons.[4] In this case, a chemical shift at as high as 2.65 or 3.06 ppm should be ascribed to a small-ring proton. The

Scheme I



(1) Sasaki, T.; Minamoto, K.; Yamashita, S.; Yamaguchi, K.; Miyake, K. *J. Org. Chem.* **1981**, *46*, 5176.
(2) Ikehara, M.; Maruyama, T. *Tetrahedron* **1975**, *31*, 1369.
(3) All the 200-MHz ^1H NMR spectra were recorded on a Varian XL-200 FT NMR spectrometer in the laboratory of the Daiichi Pharmaceutical Co., Ltd. All the signal assignments are based upon the spin-decoupling data.
(4) Bhacca, N. S.; Williams, D. H. "Application of NMR Spectroscopy in Organic Chemistry"; Holden-Day: San Francisco, London, Amsterdam, 1964; p 49.

0022-3263/82/1947-4465$01.25/0

Table I. Ultraviolet Absorptions of 5b, 6a,b, 7a,b, 8a,b, 9, 10a,b, 11a, 12a,b, 13, and 14 in Methanol

compd	λ_{max}, nm (ϵ)
5b	254 (17 600)
6a	276 (21 000)
6b	265 (16 100)
7a	275 (20 900)
7b	264 (15 500), 292 (2000)[a]
8a	256 (5960),[a] 299 (17 800)
8b	254 (9200), 296 (13 400)
9	277 (15 200)
10a	258 (6260),[a] 299 (17 400)
10b	254 (7800), 297.5 (12 800)
11a	276.5 (18 700)
12a	278 (20 200)
12b	266 (16 700)
13	271 (17 700)
14	252 (3400), 303 (21 200)

[a] Shoulder.

resonance of 5′-OH as a triplet at a reasonable field substantiated the presence of the intact furanose ring (not pyranose). The presence of a long-range coupling analogous to allylic coupling between H_2, and H_4, is also in accord with this structure. These considerations and subsequent chemical transformations led to the proposed structure of **8a**. In recent years, a small number of nucleosides with a 2′,3′-aziridine ring were synthesized by Robins and co-workers[5] as well as by us.[6] The former authors synthesized 9-(2,3-epimino-2,3-dideoxy-β-D-ribofuranosyl)adenine and its lyxofuranosyl isomer principally from a biological interest by analogy with natural products having a fused aziridine ring such as mitomycin C. The ^{1}H NMR chemical shift data of a 5′-protected form of the latter 2,3-epimino adenine nucleoside are especially informative to us: both $H_{2'}$ and $H_{3'}$ in this compound resonate at 3.10 ppm, which is close to the corresponding chemical shifts of **8a**.

Compound **6b** was similarly converted to 8,3′-(N^{α}-methylhydrazo)-9-(3′-deoxy-β-D-xylofuranosyl)hypoxanthine (**7b**) and 9-[2′,3′-[(methylamino)epimino]-2′,3′-dideoxy-β-D-lyxofuranosyl]hypoxanthine 8,*N*-cyclonucleoside (**8b**) in 21% and 35% yields, respectively. The structures of these compounds followed from the close resemblances with the adenine series in the general spectral behavior (Tables I and II).

Assuming that compounds **8a,b** were derived from **7** by the action of the released 2,4,6-triisopropylbenzenesulfonic acid under the basic conditions[7] used, we carried out some simulating experiments using the methanolate of **7a** and an equimolar amount of anhydrous *p*-toluenesulfonic acid under the same conditions, yielding no positive data.[8] On the other hand, compound **7a** (methanolate) with excess diphenyl carbonate allowed the synthesis of another new tricyclic cyclonucleoside, 9-[3′,5′-[*N*-(methylamino)azetidino]-3′,5′-dideoxy-β-D-xylofuranosyl]adenine 8,*N*-cyclonucleoside (**13**). The hypsochromic shift of 4–5 nm of the UV absorption of **13** (Table I) as compared to that of **7a** or **6a** seems to stem from an enhanced skeletal rigidity which might lessen the contribution by the N^{β} lone pair to conjugation. In the ^{1}H NMR spectrum of **13**, the geminal 5′-protons resonated at appreciably high fields, 3.04 and 3.16 ppm, underlining the $C_{5'}$–N^{β} bonding according to our previous experiences with purine 8,5′-imino cyclonucleosides.[9] The other proton resonances were also reasonably assigned (Table II).

Hydrogenolysis of **7a** gave 3′-amino-8-(methylamino)-9-(3′-deoxy-β-D-xylofuranosyl)adenine (**9**), whose structure is clear on the basis of the spectroscopic data. 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.[10] This transformation and the previous synthesis of the arabinofuranosyl isomer of **9**[1] suggest the versatile utility of such a hydrazo or substituted hydrazo bridge for synthesizing a variety of amino sugar purine nucleosides.

Compound **8** appeared to be a precursor for the synthesis of the 2′- or 3′-deoxy analogues of **7** or **1** and **2** under controlled hydrogenolytic conditions. The epimino compounds **8a,b** were acetylated to 5′-*O*-acetyl-9-[2′,3′-[(methylamino)epimino]-2′,3′-dideoxy-β-D-lyxofuranosyl]-adenine 8,*N*-cyclonucleoside (**10a**) and its hypoxanthine analogue (**10b**) in high yields. The ^{1}H NMR spectra of **10** revealed a deshielding influence by the acetyl on $H_{5'}$, $H_{4'}$, and $H_{3'}$ in this decreasing order. The similarity of the coupling patterns of the sugar protons in **10** with those in **8** confirmed that the aziridine ring was retained intact in **10**. After a couple of trial experiments, the aziridine ring in **10a** was found to be susceptible to reduction with sodium borohydride rather specifically. Thus, the treatment of **10a** with a 3-fold excess sodium borohydride gave 5′-*O*-acetyl-8,2′-(N^{α}-methylhydrazo)-9-(2′,3′-dideoxy-β-D-arabinofuranosyl)adenine (**11a**) in 51% yield. The structure of **11a** was established after deacetylation. Thus, treatment of **11a** with methanolic ammonia afforded 8,2′-(N^{α}-methylhydrazo)-9-(2′,3′-dideoxy-β-D-arabinofuranosyl)adenine (**12a**) in 80% isolated yield (Experimental Section, method B). In the ^{1}H NMR spectrum of **12a** (Table II), the anomeric proton signal appeared at 5.64 ppm as a doublet (J = 3.6 Hz) after D_2O addition, which collapsed into a singlet when the multiplet at 3.75 ppm was irradiated. At the same time, the complex signals at 1.65 and 2.40 ppm changed into a pair of well-resolved doublet of doublets with J_{gem} = 14.0 Hz plus J = 7.0 and 8.0 Hz, respectively. Hence, the 3.75-ppm signal should be assigned to $H_{2'}$ and the latter two to the geminal $C_{3'}$ protons. The other signal assignments are also based upon the spin-decoupling experiments. The skeletal structure of the sugar moiety was shown by the triplet resonance of the 5′-hydroxyl.[11] Catalytic hydrogenolysis of **8a** also gave **12a** with a very minor dihydro isomer, whose structural elucidation was abandoned owing to its paucity (method A).

Analogously, compound **10b** was reduced with a two-fold excess sodium borohydride to give 5′-*O*-acetyl-8,2′-(N^{α}-methylhydrazo)-9-(2′,3′-dideoxy-β-D-arabinofuranosyl)-hypoxanthine (**11b**), which resisted crystallization and accordingly was treated with methanolic ammonia to give 8,2′-(N^{α}-methylhydrazo)-9-(2′,3′-dideoxy-β-D-arabinofuranosyl)hypoxanthine (**12b**) as crystals in 70% yield.

(5) Robins, M. J.; Hawrelak, S. D.; Kanai, T.; Siefert, J.-M.; Mengel, R. *J. Org. Chem.* **1979**, *44*, 1317.

(6) Sasaki, T.; Minamoto, K.; Sugiura, T.; Niwa, M. *J. Org. Chem.* **1976**, *41*, 3138.

(7) We postulated the reaction of the released sulfonic acid with the 2′-hydroxyl group followed by cyclization or direct dehydration of it at the high temperatures.

(8) A couple of trials to obtain **8a** from **1a** and anhydrous *p*-toluenesulfonic acid or diphenyl carbonate were also unsuccessful.

(9) (a) Sasaki, T.; Minamoto, K.; Itoh, H. *J. Org. Chem.* **1978**, *43*, 2320. (b) Sasaki, T.; Minamoto, K.; Itoh, H. *Tetrahedron* **1980**, *36*, 3509.

(10) The signals of the 3′- and 6-amino groups also disappeared on D_2O addition.

(11) It may be rather strange to note that $H_{2'}$ adjacent to the NH group in **12a** resonates at lower field (3.75 ppm) than $H_{5'}$ next to the OH group (3.37 ppm). This is in contrast with the spectral behavior of compound **1**, in which the $H_{2'}$ signal overlapped the signal of the 5′-methylene.[1] However, this assignment is further reinforced by the fact that D_2O exchange or irradiation at 5.45 ppm (NH) caused the 3.75-ppm peak to narrow and that irradiation at 5.64 ppm ($H_{1'}$) changed the 3.75-ppm multiplet into a dd (J = 8.0, 4.0 Hz) without influencing the other protons.

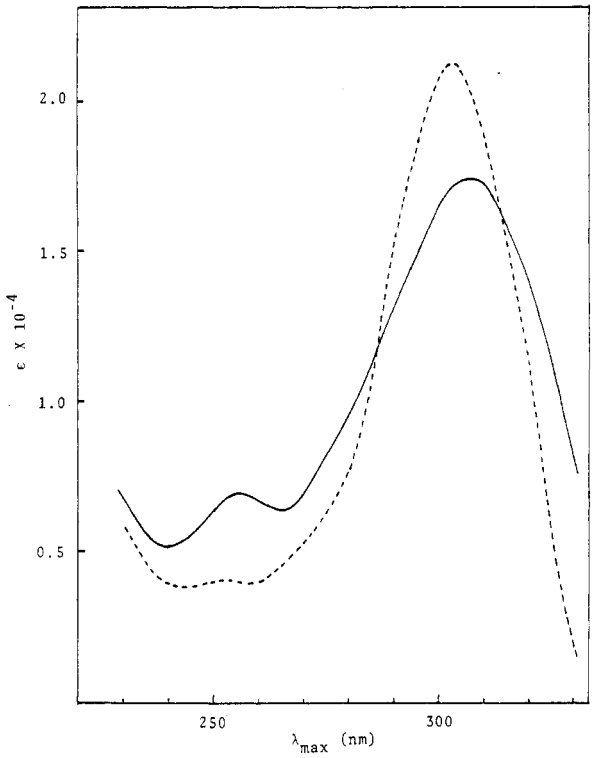


Figure 1. Ultraviolet spectra of **15** (—) and **14** (---) in methanol.

The general spectroscopic data are in harmony with the structure of **12b**. The rather specific reductive cleavage of the N^{β}–$C_{3'}$ bond in **10** is reminiscent of the known reactivity of the 2',3'-anhydro (oxirane) function of a variety of nucleosides with nucleophiles.[12] We are not aware of any other example of such reductive fission of an aziridine with sodium borohydride.

An aziridine is generally known to be labile to acid: protonation at the nitrogen atom is usually followed by ring opening with introduction of a nucleophile.[13] Treatment of **8a** with 1 N hydrochloric acid in methanol afforded two polar products, the major of which was isolated and characterized as 2',N^{β}-didehydro-8,2'-(N^{α}-methylhydrazo)-9-(2',3'-dideoxypyranosyl)adenine (**14**). The configuration of 4'-hydroxyl is uncertain at present. The ultraviolet absorption spectrum of **14** resembles that of 2',N^{β}-didehydro-8,2'-(N^{α}-methylhydrazo)-9-(2'-deoxy-β-D-arabinofuranosyl)adenine (**15**;[1] Figure 1). The ^{1}H NMR spectrum of **14** exhibited the signals of the methyl group and anomeric proton at 3.58 and 6.25 ppm. These chemical shifts coincide with the corresponding values, 3.58 as well as 6.22 ppm, found for **15**.[1] However, the sharp doublet signal for the secondary hydroxyl group supported the pyranose structure. Furthermore, the resonances of the 5'-methylene protons at rather lower fields (3.88 and 4.11 ppm) are sufficiently indicative of a 5'-methylene group in a pyranose nucleoside[14] and in sharp contrast with the 5'-methylene group in **15** resonating at 3.10–3.50 ppm.[1] In this sense, the corresponding proton signals of **7a,b** at as low as 3.87 and 3.90 ppm are unusual and probably stem from anisotropy by the purine ring. We subjected **10a** to the same hydrolytic conditions to exclude participation by the 5'-hydroxyl group, resulting in the same results owing to the preceeding deacetylation. The net result of the conversion of **8a** into **14** is the fission and recombination of the anomeric bond with skeletal rearrangement involving hydrogen transfer from $C_{2'}$ to $C_{3'}$. A similar acid-catalyzed ketimine formation from a fused aziridine with skeletal rearrangement is described.[15,16] Anyway, such a furanose to pyranose conversion has not yet been described in the field of cyclonucleoside chemistry and would provide a feasible route to various aminopyranose nucleosides.[17]

Thus, cyclization between the C_8 and $C_{3'}$ of purine nucleosides with a diatomic bridge proved to require much more drastic conditions than in the case of 8,2'-cyclization. The newly introduced tricyclic cyclonucleosides **8** and **13** allow us to envisage a variety of transformations, and studies along this line are under way.

Experimental Section[18]

8-Bromo-3'-*O*-[(2,4,6-triisopropylphenyl)sulfonyl]inosine (5b). To a stirred solution of **5a** (1.5 g, 2.5 mmol) in 85% acetic acid (65 mL) was added sodium nitrite (2.6 g, 15 × 2.5 mmol) at 0 °C. After being stirred for 30 min, the mixture was left at 0 °C for 2 days and evaporated. After repeated coevaporation with MeOH, the residue was digested with ice–water and the insoluble material collected by suction. The filter cake was thoroughly dried in vacuo, dissolved in MeOH, and treated with Norit to give 1.44 g (95%) of **5b** as a practically homogeneous foam after evaporation of the solvent and drying in vacuo at 90–100 °C. A part was again purified by preparative TLC [silica gel, $CHCl_3$/MeOH (9:1)] for analysis; IR (KBr) 1180 cm^{-1} (covalent sulfonate).

Anal. Calcd for $C_{25}H_{33}O_7N_4BrS$: C, 48.94; H, 5.42; N, 9.13. Found: C, 48.96; H, 5.40; N, 9.13.

8-(N^{α}-Methylhydrazino)-3'-*O*-[(2,4,6-triisopropylphenyl)sulfonyl]adenosine (6a). A mixture of **5a** (1.15 g, 1.9 mmol) and methylhydrazine (1.74 g, 20 × 1.9 mmol) in MeOH (50 mL) was heated at 90–100 °C in an argon atmosphere in a pressure tube for 1 h. The solvent was evaporated off and the residue repeatedly coevaporated with MeOH to remove the residual methylhydrazine. The residue was digested with ice–water (10 mL) and the insoluble solid collected and dried. Recrystallization from MeOH at room temperature gave 983 mg (90%) of **6a** as crystals, mp 168–170 °C.

Anal. Calcd for $C_{26}H_{39}N_7O_6S$: C, 54.06; H, 6.80; N, 16.97. Found: C, 54.11; H, 6.83; N, 16.89.

8-(N^{α}-Methylhydrazino)-3'-*O*-[(2,4,6-triisopropylphenyl)sulfonyl]inosine (6b). A mixture of **5b** (1.44 g, 2.35 mmol) and methylhydrazine (1.24 mL, 10 × 2.35 mmol) in MeOH (30 mL) was heated at 90–100 °C under argon in a pressure tube

(12) (a) Codington, J. F.; Fecher, R.; Fox, J. J. *J. Org. Chem.* **1962**, *27*, 163. (b) Lee, W. W.; Benitez, A.; Goodman, L.; Baker, B. R. *J. Am. Chem. Soc.* **1960**, *82*, 2648. (c) Martinez, A. P.; Lee, W. W.; Goodman, L. *J. Org. Chem.* **1966**, *31*, 3263. (d) Lee, W. W.; Martinez, A. P. *Ibid.* **1967**, *32*, 2538. (e) Hirata, M. *Chem. Pharm. Bull.* **1968**, *16*, 291. (f) Sasaki, T.; Minamoto, K.; Kidokoro, N. *Org. Prep. Proced. Int.* **1973**, *5* (2), 75.

(13) Dermer, O. C.; Ham, G. E. "Ethylenimine and Other Aziridines"; Academic Press: New York, 1969; p 205.

(14) (a) Zorbach, W. W.; Tipson, R. S. "Synthetic Procedures in Nucleic Acid Chemistry"; Wiley-Interscience: New York, 1973; Vol. 2, pp 366–367. (b) Leutzinger, E. E.; Bowles, W. A.; Robins, R. K.; Townsent, L. B. *J. Am. Chem. Soc.* **1968**, *90*, 127. (c) Fisher, L. V.; Lee, W. W.; Goodman, L. *J. Heterocycl. Chem.* **1969**, *6*, 949.

(15) Reference 13, p 279.

(16) One of the referees has suggested that "the conversion of **10a,b** to **14**, if proceeding via the mechanism suggested by the authors, should afford the α configuration of the 4'-hydroxyl of the furanose". However, in this paper we only denote the net result but no deepseated mechanism. The formal skeletal rearrangement may have occurred either by a concerted (or concerted-like) or a stepwise mechanism. If we assume, for example, an intermediate in which both the N^9–$C_{1'}$ and O–$C_{1'}$ (furanose ether) bonds are broken (with or without a $C_{2'}$,N^{β} double bond), the two two-carbon group, HO–$C_{5'}H_2$–$C_{4'}$H–OH, may be able to rotate around the $C_{3'}$–$C_{4'}$ bond axis in both directions for recondensation with the CHO group (anomeric carbon). Therefore, the configuration of the 4'-hydroxyl in **14** cannot be mechanistically foreseen. We further add that deacetylation of **10a** to **8a** prior to the product formation in this hydrolytic condition was confirmed by TLC in a small-scale experiment.

(17) We have recently found that compound **15** also transforms into a couple of pyranosyl isomers under acidic conditions. A part of this series of work has been given at the 45th Annual Meeting of the Chemical Society of Japan, 1982, Tokyo.

(18) The general methods used are similar to those described earlier.[19]

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

Table II. ^{1}H NMR Resonances of 6a, 7a,b, 8a,b, 9, 10a,b, 12a,b, and 13 in Me_2SO-d_6 [a,b]

	carbon								
compd	$C_5'H$	$C_4'H$	$C_3'H$	$C_2'H$	$C_1'H$	C_2H	bridge NH [or 3'-NH_2]	bridge NMe [or 8-NHMe]	others
6a	3.50 (3 H, m)		5.10 (2 H, m)		6.52 (d, $J_{1',2'}$ = 6.0)	7.91 (s)		[3.07 (s)]	1.20, 1.30 (each s, 18 H, isopropyl Me, 4.80 (br s, hydrazino NH_2), 6.92 (s, NH_2)
7a	3.87 (d, $J_{5',4'}$ = 5.3)	4.47 (dd, $J_{4',3'}$ = 5.0, $J_{4',5'}$ = 5.3)	3.50 (d, $J_{3',4'}$ = 5.0)	4.20 (d, J = 3.3)	6.04 (s)	8.03 (s)	5.59 (br s)	3.06 (s)	4.70 (t, J = 5.0, 5'-OH), 5.87 (d, 2'-OH), 6.48 (br s, NH_2)
7b	3.90 (d, $J_{4',5'}$ = 5.0)	4.47 (dd, $J_{4',3'}$ = 4.0, $J_{4',5'}$ = 5.0)	3.52 (d, $J_{3',4'}$ = 4.0)	4.24 (s)	5.99 (s)	7.98 (s)	5.65 (s)	3.00 (s)	4.82 (br s, 5'-OH), 5.99 (br s, 2'-OH)
8a	3.44 (dd, $J_{5',4'}$ = 4.4, $J_{5',5'}$-OH = 5.6)	4.41 (m, $J_{4',5'}$ = 4.4, $J_{4',3'}$ = 8.8, $J_{4',2'}$ = 4.4)	3.06 (dd, $J_{3',2'}$ = 15.2, $J_{3',4'}$ = 8.8)	2.65 (dd, $J_{2',3'}$ = 15.2, $J_{2',4'}$ = 4.4)	6.09 (s)	8.05 (s)		3.65 (s)	4.92 (t, J = 5.6, 5'-OH), 6.93 (s, NH_2)
8b	3.42 (dd, $J_{5',4'}$ = 4.0, $J_{5',5'}$-OH = 6.0)	4.41 (m, $J_{4',5'}$ = 4.0, $J_{4',3'}$ = 9.0, $J_{4',2'}$ = 4.0)	3.07 (dd, $J_{3',2'}$ = 15.0, $J_{3',4'}$ = 9.0)	2.65 (dd, $J_{2',3'}$ = 15.0, $J_{2',4'}$ = 4.0)	6.10 (s)	7.94 (s)		3.52 (s)	4.90 (t, J = 6.0, 5'-OH), 12.40 (br s, N_1H)
9	3.5–3.7 (3 H, m)		4.10 (m)	4.25 (d, $J_{2',1'}$ = 5.0)	5.79 (d, $J_{1',2'}$ = 5.0)	7.91 (s)	[1.1–1.4 (br s)]	[2.92 (d, J = 2.0; s on D_2O-addition]	4.0–4.4 (br s, 5'-OH), 7.9–8.1 (br s, NHMe), 5.6–5.9 (br s, 2'-OH), 6.49 (br s, NH_2)
10a	4.08 (d, $J_{5',4'}$ = 4.0)	4.66 (m, $J_{4',5'}$ = 4.0, $J_{4',3'}$ = 9.0, $J_{4',2'}$ = 5.0)	3.20 (dd, $J_{3',2'}$ = 16.0, $J_{3',4'}$ = 9.0)	2.65 (dd, $J_{2',3'}$ = 16.0, $J_{2',4'}$ = 5.0)	6.14 (s)	8.06 (s)		3.58 (s)	1.98 (s, acetyl), 6.94 (s, NH_2)
10b	4.09 (d, $J_{5',4'}$ = 4.0)	4.67 (m, $J_{4',5'}$ = 4.0, $J_{4',3'}$ = 9.0, $J_{4',2'}$ = 4.0)	3.22 (dd, $J_{3',2'}$ = 16.0, $J_{3',4'}$ = 9.0)	2.64 (dd, $J_{2',3'}$ = 16.0, $J_{2',4'}$ = 4.0)	6.15 (s)	7.95 (s)		3.53 (s)	1.83 (s, acetyl), 12.40 (br s, N_1H)
12a	3.37 (dd, J_{gem} = 12.0, $J_{5'a,4'}$ = 4.0, $H_{5'a}$), 3.50 (dd, J_{gem} = 12.0, $J_{5'b,4'}$ = 3.5, $H_{5'b}$)	4.10 (br m, $J_{4',3'a}$ = 7.0, $J_{4',3'b}$ = 8.0, $J_{4',5'a}$ = 4.0, $J_{4',5'b}$ = 3.5)	1.65 (ddd, J_{gem} = 14.0, $J_{3'a,4'}$ = 7.0, $J_{3'a,2'}$ = 4.4, $H_{3'a}$), 2.40 (dt, J_{gem} = 14.0, $J_{3'b,4'}$ = 8.0, $J_{3'b,2'}$ = 8.0, $H_{3'b}$)	3.75 (m, $J_{2',3'b}$ = 8.0, $J_{2',3'a}$ = 4.4 $J_{2',1'}$ = 3.6)	5.64 (d, $J_{1',2'}$ = 3.6)	7.99 (s)	5.45 (d, J = 10.3)	3.14 (s)	4.96 (t, J = ~4, 5'-OH), 6.69 (s, NH_2)
12b	3.36 (dd, J_{gem} = 12.0, $J_{5'a,4'}$ = 4.0, $H_{5'a}$), 3.49 (dd, J_{gem} = 12.0, $J_{5'b,4'}$ = 4.0, $H_{5'b}$)	4.08 (br m, $J_{4',3'a}$ = 7.0, $J_{4',3'b}$ = 8.0, $J_{4',5'a}$ = $J_{4',5'b}$ = 4.0)	1.72 (ddd, J_{gem} = 13.0, $J_{3'a,4'}$ = 7.0 $J_{3'a,2'}$ = 4.0, $H_{3'a}$), 2.39 (dt, J_{gem} = 13.0, $J_{3'b,4'}$ = $J_{3'b,2'}$ = 8.0, $H_{3'b}$)	3.75 (m, $J_{2',3'b}$ = 8.0, $J_{2',3'a}$ = 4.0, $J_{2',1'}$ = 4.0)	5.64 (d, $J_{1',2'}$ = 4.0)	7.90 (s)	5.41 (d, J = 10.3)	3.09 (s)	4.98 (shallow peak, 5'-OH)

13	3.04 (d, J_{gem} = 16.0, $J_{5'a,4'}$ < 1.5, $H_{5'}$a), 3.16 (dd, J_{gem} = 16.0, $J_{5'b,4'}$ = 5.0, $H_{5'}$b)	5.23 (dd, $J_{4',3'}$ = 3.0, $J_{4',5'b}$ = 5.0)	4.31 (d, $J_{3',4'}$ = 3.0)	4.48 (d, $J_{2',2'\text{-OH}}$ = 4.0)	5.84 (s)	8.08 (s)	3.33 (s)	6.33 (d, 2'-OH), 7.14 (s, NH_2)
14	3.88 (d, J_{gem} = 13.0, $H_{5'}$a), 4.11 (d, J_{gem} = 13.0, H $H_{5'}$b)	4.08 (br s)	2.50 (dd, J_{gem} = 13.0, $J_{3',4'}$ = 2.0, $H_{3'}$a), 2.85 (dd, J_{gem} = 13.0, $J_{3'b,4'}$ = 4.0, $H_{3'}$b)		6.25 (s)	8.06 (s)	3.58 (s)	5.10 (d, J = 4.0, 4'-OH), 6.95 (s, NH_2)

[a] s = singlet, d = doublet, dd = doublet of doublets, t = triplet, ddd = doublet of dd, dt = doublet of triplets, and m = multiplet. Chemical shifts are given in parts per million and J values in hertz. [b] All the spectra except that of **6a** (60 MHz) were measured at 200 MHz, and most of the sugar proton resonances are recorded from spin-decoupling experiments after D_2O addition.

for 2 h and worked up as in the case of **6a**. The finally obtained foamy product (**6b**; 1.26 g, 93%) was sufficiently pure for the next transformation. A part was purified by preparative TLC [silica, EtOAc/MeOH (95:5 v/v)] for analysis; IR (KBr) 1180 cm^{-1} (covalent sulfonate).

Anal. Calcd for $C_{26}H_{38}O_7N_6S$: C, 53.96; H, 6.62; N, 14.52. Found: C, 54.20; H, 6.60; N, 14.26.

8,3'-(N^{α}-Methylhydrazo)-9-(3'-deoxy-β-D-xylofuranosyl)-adenine (7a) and 9-[2',3'-[(Methylamino)epimino]-2',3'-dideoxy-β-D-lyxofuranosyl]adenine 8,*N*-Cyclonucleoside (8a). A mixture of **6a** (430 mg, 0.74 mmol) and triethylamine (0.2 mL, 2 × 0.74 mmol) in dry DMF (8 mL) was heated at 135–140 °C under argon in a pressure tube for 3 h. TLC at this stage showed the complete consumption of **6a** and formation of two products. After evaporation of the solvent, the residue was dissolved in EtOH (10 mL) and left in a refrigerator overnight to give crystals of the more polar product (**7a**) which was collected. The filtrate was concentrated and subjected to preparative TLC [silica, 20 × 20 cm; $CHCl_3$/MeOH (8:2), twice developed] to afford another crop of **7a** and another product, **8a**, after each band was eluted with MeOH. The more polar fraction was repeatedly recrystallized from MeOH to give 60 mg (25%) of a methanolate of **7a**, which softened above 160 °C and gradually melted up to 175 °C. The analysis sample was dried at 70–80 °C for 3 h under high vacuum.

Anal. Calcd for $C_{11}H_{15}O_3N_7 \cdot CH_3OH$: C, 44.30; H, 5.89; N, 30.14. Found: C, 44.26; H, 5.80; N, 30.09.

The faster moving fraction was recrystallized from MeOH to give **8a**: 67 mg (33%); mp 248–250 °C.

Anal. Calcd for $C_{11}H_{13}O_2N_7$: C, 48.00; H, 4.76; N, 35.62. Found: C, 48.15; H, 4.80; N, 35.42.

8,3'-(N^{α}-Methylhydrazo)-9-(3'-deoxy-β-D-xylofuranosyl)-hypoxanthine (7b) and 9-[2',3'-[(Methylamino)epimino]-2',3'-dideoxy-β-D-lyxofuranosyl]hypoxanthine 8,*N*-Cyclonucleoside (8b). A mixture of **6b** (1.26 g, 2.19 mmol) and triethylamine (0.61 mL, 2 × 2.19 mmol) in DMF (25 mL) was heated at 135–140 °C for 5 h under argon in a pressure tube. TLC [silica, $CHCl_3$/MeOH (85:15)] with an aliquot of the mixture revealed the presence of of two products, whose comparative mobilities are similar to those of **7a** and **8a**. The mixture was thoroughly evaporated, and the residue in MeOH (30 mL) was left in a refrigerator to afford first crystals of the faster moving product (**8a**), which were collected. The filtrate was concentrated and subjected to preparative TLC [silica gel, 20 × 20 cm; $CHCl_3$/MeOH (85:15), developed three times], and the respective band was eluted with MeOH. Recrystallization of the faster moving fraction from MeOH gave 225 mg (35%) of **8b** as powderlike crystals which did not melt below 300 °C.

Anal. Calcd for $C_{11}H_{12}O_3N_6$: C, 47.82; H, 4.38; N, 30.42. Found: C, 47.69; H, 4.34; N, 30.57.

The slower running fraction was treated with Norit in MeOH as usual. On concentration and cooling to room temperature, the solution became a gel, which gave flocky crystals (**7b**) very slowly (in 1–2 weeks): mp 216–128 °C; yield 124 mg (20.6%).

Anal. Calcd for $C_{11}H_{14}O_4N_6$: C, 44.89; H, 4.80; N, 28.56. Found: C, 45.13; H, 4.91; N, 28.27.

3'-Amino-8-(methylamino)-9-(3'-deoxy-β-D-xylofuranosyl)adenine (9). A solution of **7a** (methanolate; 150 mg, 0.46 mmol) in MeOH (10 mL) containing Raney Ni (W-5, 2.5 mL) was deoxygenated by argon bubbling and then put under a hydrogen stream at atmospheric pressure. The mixture was stirred at 50 °C for 1 week and then cooled to room temperature. After removal of the catalyst by decantation and filtration, the solution was concentrated and subjected to preparative TLC [silica gel, 20 × 20 cm, $CHCl_3$/MeOH (7:3)]. After the usual workup, 65 mg of the starting material was recovered. The slower moving band was eluted with MeOH and the obtained solid recrystallized from MeOH to give 36 mg (46% on the basis of the consumed starting material) of **9**, mp 273.5–275 °C dec.

Anal. Calcd for $C_{11}H_{17}O_3N_7$: C, 44.74; H, 5.80; N, 33.20. Found: C, 44.61; H, 5.99; N, 32.96.

5'-*O*-Acetyl-9-[2',3'-[(methylamino)epimino]-2',3'-dideoxy-β-D-lyxofuranosyl]adenine 8,*N*-Cyclonucleoside (10a). A solution of **8a** (90 mg, 0.33 mmol) and acetic anhydride (0.095 mL, 3 × 0.33 mmol) in dry pyridine (2 mL) was left at room temperature overnight. TLC with an aliquot of the reaction indicated the presence of one main product with slight amounts

of two side products. The mixture was treated with MeOH (1 mL) at room temperature for 30 min, evaporated, and repeatedly coevaporated with MeOH to give a solid precipitate, which was collected with a small volume of EtOH and recrystallized from MeOH to afford 75 mg (72%) of **10a**, mp 200–202 °C.

Anal. Calcd for $C_{13}H_{15}O_3N_7$: C, 49.20; H, 4.77; N, 30.90. Found: C, 49.08; H, 4.92; N, 30.80.

5′-*O*-Acetyl-9-[2′,3′-[(methylamino)epimino]-2′,3′-dideoxy-β-D-lyxofuranosyl]hypoxanthine 8,*N*-Cyclonucleoside (10b). A mixture of **8b** (235 mg, 0.85 mmol) and acetic anhydride (0.24 mL, 3 × 0.85 mmol) in pyridine (5.1 mL) was stirred at room temperature for 5 h and then left for 1 h after addition of MeOH (2 mL). After removal of the solvents, the residue was repeatedly coevaporated with MeOH and the precipitating solid collected with a small volume of EtOH. Recrystallization from MeOH gave 223 mg (82%) of **10b**, mp 234–236 °C.

Anal. Calcd for $C_{13}H_{14}O_4N_6$: C, 49.05; H, 4.43; N, 26.41. Found: C, 49.05; H, 4.42; N, 26.42.

5′-*O*-Acetyl-8,2′-(*N*$^{\alpha}$-methylhydrazo)-9-(2′,3′-dideoxy-β-D-arabinofuranosyl)adenine (11a). A mixture of **10a** (165 mg, 0.52 mmol) and sodium borohydride (60 mg, 3 × 0.52 mmol) in dry DMF (2.6 mL) was stirred in a stoppered vessel for 2 days. TLC [silica gel, $CHCl_3$/MeOH (85:15)] with an aliquot of the reaction mixture indicated the presence of a slower moving product and another substance which corresponded to the starting material in mobility. The mixture was neutralized with acetic acid and thoroughly evaporated. The residue was digested with a small volume of MeOH and the sparingly soluble inorganic material removed by filtration. The filtrate was concentrated and subjected to preparative TLC [silica gel, 20 × 20 cm; $CHCl_3$/MeOH (85;15), twice developed]. The slower running band was eluted with MeOH and the obtained solid repeatedly recrystallized from MeOH to give 85 mg (51%) of **11a**, mp 258–261 °C (after drying in vacuo at room temperature).

Anal. Calcd for $C_{13}H_{17}O_3N_7$: C, 48.99; H, 5.37; N, 30.71. Found: C, 49.10; H, 5.38; N, 30.74.

8,2′-(*N*$^{\alpha}$-Methylhydrazo)-9-(2′,3′-dideoxy-β-D-arabinofuranosyl)adenine (12a). Method A. A solution of **8a** (90 mg, 0.32 mmol) in MeOH (5 mL) containing Raney Ni (W-5, 2.5 mL) was deoxygenated by argon bubbling and treated with a hydrogen stream for 2.5 h as in the synthesis of **9**. TLC [silica, $CHCl_3$/MeOH (7:3)] at this stage indicated a small amount of the starting material and two slower moving products, the minor of which was extremely polar. After removal of the catalyst, the solution was concentrated, applied on a silica gel plate (20 × 20 cm), and developed with $CHCl_3$/MeOH (7:3). The faster moving product was recrystallized from a small volume of MeOH to give 20 mg (22%) of **12a**, mp 244–245 °C (after drying in vacuo at 90 °C).

Anal. Calcd for $C_{11}H_{15}O_2N_7$: C, 47.64; H, 5.45; N, 35.36. Found: C, 47.45; H, 5.32; N, 35.06.

Recrystallization of the slower moving fraction from a tiny amount of MeOH gave 8 mg (9%) of another dihydro compound of unknown structure as a monohydrate: mp 225–227 °C; UV (MeOH) λ_{max} 276 nm (ε 9200).

Anal. Calcd for $C_{11}H_{15}O_2N_7 \cdot H_2O$: C, 42.40; H, 5.46; N, 31.48. Found: C, 42.42; H, 5.58; N, 31.33.

Method B. Compound **11a** (40 mg, 0.125 mmol) in a mixture of concentrated ammonia and MeOH (1:5 v/v, 2 mL) was stirred at room temperature for 4 h and evaporated. Repeating coevaporation with MeOH gave a solid residue, which was recrystallized from a small volume of MeOH to afford 28 mg (80%) of **12a**, identical with the product obtained above in terms of mixture melting point and IR spectroscopy.

8,2′-(*N*$^{\alpha}$-Methylhydrazo)-9-(2′,3′-dideoxy-β-D-arabinofuranosyl)hypoxanthine (12b). A solution of **10b** (223 mg, 0.7 mmol) and sodium borohydride (53 mg, 1.4 mmol) in DMF (3.5 mL) was left at room temperature overnight. TLC [silica gel; $CHCl_3$/MeOH (85:15)] with an aliquot of the reaction revealed one main product with two very small amounts of side products. The mixture was neutralized with acetic acid, thoroughly evaporated, taken into a small volume of MeOH, and directly subjected to preparative TLC [silica, 20 × 20 cm; $CHCl_3$/MeOH (85:15), twice developed]. The major fraction gave a paste which resisted crystallization, and hence was dissolved in a 1:5 mixture (10 mL) of concentrated ammonia and MeOH. After 8 h, the mixture was evaporated and coevaporated with MeOH, and the residual solid was recrystallized from MeOH to give **12b**: 137 mg (70%); mp 265–268 °C.

Anal. Calcd for $C_{11}H_{14}O_3N_6$: C, 47.48; H, 5.07; N, 30.20. Found: C, 47.65; H, 5.21; N, 29.92.

9-[3′,5′-[(*N*-Methylamino)azetidino]-3′,5′-dideoxy-β-D-xylofuranosyl]adenine 8,*N*-Cyclonucleoside (13). A mixture of **7a** (monomethanolate; 90 mg, 0.28 mmol), diphenyl carbonate (90 mg, 1.5 × 0.28 mmol), and triethylamine (0.12 mL, 3 × 0.28 mmol) in DMF (1.8 mL) in a pressure tube was heated at 135–140 °C for 30 min under argon. After cooling, the mixture was evaporated and digested with $CHCl_3$ (5–6 mL), and the precipitating solid was collected. Recrystallization from a small volume of MeOH gave 48 mg (59%) of **13** as hemimethanolate, mp 260–262 °C dec (after drying in vacuo at 95–100 °C for a couple of hours).

Anal. Calcd for $C_{11}H_{13}O_2N_7 \cdot 0.5CH_3OH$: C, 47.41; H, 5.19; N, 33.66. Found: C, 47.12; H, 5.25; N, 33.90.

2′,*N*$^{\beta}$-Didehydro-8,2′-(*N*$^{\alpha}$-methylhydrazo)-9-(2′,3′-dideoxypyranosyl)adenine (14). Compound **8a** (180 mg, 0.66 mmol) was poured into 1 N HCl/MeOH (prepared from concentrated hydrochloric acid and MeOH). **8a** dissolved rapidly, and after a couple of hours powdery crystals began to deposit. TLC monitoring with an aliquot of the reaction mixture (after neutralization) was carried out every few hours. Formation of two slower moving main products was observed. After 38 h, the mixture was rapidly evaporated below 35 °C and repeatedly coevaporated with MeOH to remove the residual acid. The residue was dissolved in MeOH (20 mL) and neutralized with anion-exchange resin (IRA-410, OH form). The resin was filtered through a column and thoroughly washed with MeOH. The methanolic solution was concentrated, and the residue digested with a small volume of MeOH to give 55 mg of the less polar product. Preparative TLC [silica, 20 × 20 cm; $CHCl_3$/MeOH (85:15)] with the filtrate gave another crop. The combined product was recrystallized from MeOH to give 60 mg (34%) of fine needles (**14**): mp 261–262 °C dec; mass spectrum, *m/e* 275 (M^+, parent peak).

Anal. Calcd for $C_{11}H_{13}O_2N_7 \cdot 0.5H_2O$: C, 46.48; H, 4.93; N, 34.51. Found: C, 46.60; H, 4.88; N, 34.43.

Acknowledgment. We are grateful to the Daiichi Pharmaceutical Co., Ltd., and Nippon Ajinomoto Co., Ltd., for generous gifts of purine ribonucleosides. We are also particularly indebted to the former company for the measurements of so many 200-MHz ^1H NMR spectra.

Registry No. 5a, 29836-22-4; **5b**, 60076-61-1; **6a**, 82918-84-1; **6b**, 82918-85-2; **7a**, 82918-86-3; **7b**, 82918-87-4; **8a**, 82932-67-0; **8b**, 82918-88-5; **9**, 82918-89-6; **10a**, 82918-90-9; **10b**, 82918-91-0; **11a**, 82918-92-1; **11b**, 82918-97-6; **12a**, 82918-93-2; **12b**, 82918-94-3; **13**, 82918-95-4; **14**, 82918-96-5; methylhydrazine, 60-34-4.