Chem. Pharm. Bull.
28(3) 876—881 (1980)

Synthesis of 5′-Hydroxyalkyl-5′-deoxy-8,5′(*R* and *S*)-cycloadenosines (Nucleosides and Nucleotides. XXXI[1])

Akira Matsuda, Kaori Niizuma, and Tohru Ueda

Faculty of Pharmaceutical Sciences, Hokkaido University[2]

(Received September 10, 1979)

Treatment of 2′,3′-*O*-isopropylidene-5′-oxo-8,5′-cycloadenosine with dimethyloxosulfonium methylide followed by hydrogenation afforded the diastereomeric pairs of 5′-methyl-5′-deoxy-8,5′-cycloadenosine and 5′-hydroxymethyl-5′-deoxy-8,5′-cycloadenosine. The configurations at the 5′-positions of these 8,5′-cycloadenosines were determined by nuclear magnetic resonance (NMR) measurements. The Wittig reactions of the 5′-oxo-8,5′-cycloadenosine with methoxymethylenetriphenylphosphorane, methylthiomethylenetriphenylphosphorane, and ethyl(dimethylsulfuranylidene)acetate afforded the corresponding 5′-substituted derivatives.

The action of ethoxycarbonylmethylenetriphenylphosphorane with the 5′-oxo-8,5′-cycloadenosine afforded the 5′-ethoxycarbonylmethylene-8,5′-cycloadenosine, which was converted to 5′-hydroxyethyl-5′-deoxy-8,5′-cycloadenosine by reduction with $LiBH_4$ followed by deacetonation. The 5′(*R*)- and 5′(*S*)-diastereomers of the 5′-hydroxyethyl derivative were separated and identified by NMR analysis. The circular dichroism (CD) spectra of the 5′-substituted-8,5′-cycloadenosines showed that the diastereomers having the substituent at the *trans-gauche* position around the C_4'–C_5' bond gave strong negative CD bonds, whereas the diastereomers with the 5′-substitutent at the *gauche-trans* position exhibited positive bands.

Keywords——adenosine; cyclonucleosides; Wittig reaction; conformation; NMR; CD

We have recently synthesized conformationally fixed analogs of purine nucleosides and nucleotides, such as 5′-deoxy-8,5′-cyclo-adenosine and -inosine,[3] 8,5′-(*R* and *S*)-cycloadenosines,[4,5] and 5′-deoxy-8,5′-cycloguanosine 2′,3′-cyclic phosphate.[6] The latter compound was utilized as a substrate in a study of the substrate specificity of ribonuclease T_1.[6] For the preparation of analogs of 5′-adenylate fixed in an "anti" conformation around the glycosylic linkage, the introduction of a primary hydroxyl group at the 5′-position of 5′-deoxy-8,5′-cycloadenosine is necessary. We describe here the synthesis of the 5′(*R* and *S*)-hydroxymethyl and 5′(*R* and *S*)-hydroxyethyl derivatives of 5′-deoxy-8,5′-cycloadenosine as models of "anti"-fixed adenosine.

2′,3′-*O*-Isopropylidene-5′-oxo-8,5′-cycloadenosine (**1**) was chosen as the starting material; it was readily prepared from 5′-deoxy-8,5′-cycloadenosine.[5] Treatment of **1** with dimethyloxosulfonium methylide in dimethylformamide (DMF) and dimethylsulfoxide (DMSO) gave the 5′,6′-epoxide (**2**) as an amorphous material in 60% yield. The nuclear magnetic resonance (NMR) spectra of **2** showed a set of doublets at 3.67 and 3.30 ppm due to the methylene group on the spiro epoxide. The epoxide connected to the adenine ring is assumed to be a benzyl ether system, so the reduction of **2** would be expected to give selectively the 5′-hydroxy-

---

[1] Part XXX, A. Yamane, H. Inoue, and T. Ueda, *Chem. Pharm. Bull.*, **28**, 157 (1980).
[2] Location: *Kita-12, Nishi-6, Kita-ku, Sapporo, 060, Japan.*
[3] A. Matsuda, K. Muneyama, T. Nishida, T. Sato, and T. Ueda, *Nucleic Acids Res.*, **3**, 3349 (1976).
[4] A. Matsuda, M. Tezuka, and T. Ueda, *Tetrahedron*, **34**, 2449 (1978).
[5] A. Matsuda, M. Tezuka, K. Niizuma, E. Sugiyama, and T. Ueda, *Tetrahedron*, **34**, 2633 (1978).
[6] T. Ueda, A. Matsuda, T. Asano, and H. Inoue, "Chemistry and Biology of Nucleosides and Nucleotides," R.E. Harmon, R.K. Robins, and L.B. Townsend (Eds.), Academic Press, N.Y., 1978, p. 397.

methyl derivative. Catalytic hydrogenation of **2** with Raney Ni in aqueous ethanol for two days afforded a mixture of products.

Separation of the products by silica gel column chromatography followed by preparative thin layer chromatography afforded four compounds. The products (**3** and **4**) having *Rf* 0.77 and 0.72 (solvent: $CHCl_3$–EtOH, 10: 1) showed the same absorption maximum at 264 nm in their ultraviolet (UV) absorption spectra. The mass spectra of both compounds showed a molecular ion peak at *m/e* 303. The NMR spectrum of the former showed a doublet at 1.58 ppm due to a methyl group and a doublet at 4.63 ppm due to a 4'-proton, while those of the latter showed a doublet due to a methyl group and a singlet due to the 4'-proton at 1.58 and 4.52 ppm, respectively. These result led to the identification of **3** and **4** as 5'-methyl-5'-deoxy-8,5'-cycloadenosines, the former having the *S*-configuration at the 5'-position (the methyl group being situated in the *trans-gauche* (*tg*) position with respect to the lactol ring oxygen and the 3'-carbon, respectively, around the C_4'—C_5' bond).

The products (**5** and **6**) having *Rf* 0.38 and 0.29 gave the same molecular ion peak at *m/e* 319 in their mass spectra, which indicated the introduction of a hydroxyl group into **3** or **4**. Deacetonation of **5** and **6** afforded the corresponding free cyclonucleosides (**7** and **8**) as hygroscopic crystals. The NMR spectrum of **7** showed a doublet at 4.68 ppm due to the 4'-proton while that of **8** showed a singlet at 4.69 ppm. Methyl protons were not detected in either compound. Therefore, **7** was assigned as 5'-hydroxymethyl-5'-deoxy-8,5'(*R*)-cycloadenosine (the hydroxymethyl group being situated in the *tg* position around the C_4'—C_5' bond) and **8** as the *S*-diastereomer. These findings showed the original epoxide (**2**) to be a diastereomeric mixture. The yields of the products **3**, **4**, **5** and **6** (18.5, 14.6, 22, and 15%, respectively) showed that the hydrogenation of **2** proceeded without regioselectivity.

Introduction of a one-carbon substituent into the 5'-position of **1** by an alternative route was next attempted. Treatment of **1** with methoxymethylenetriphenylphosphorane, methylthiomethylenetriphenylphosphorane, and ethyl (dimethylsulfuranyllidene) acetate gave the corresponding 5'-substituted derivatives of 8,5'-cycloadenosine (**9**, **10**, **11**) in high yields. However, attempts to convert these derivatives to the 5'-formyl derivatives were

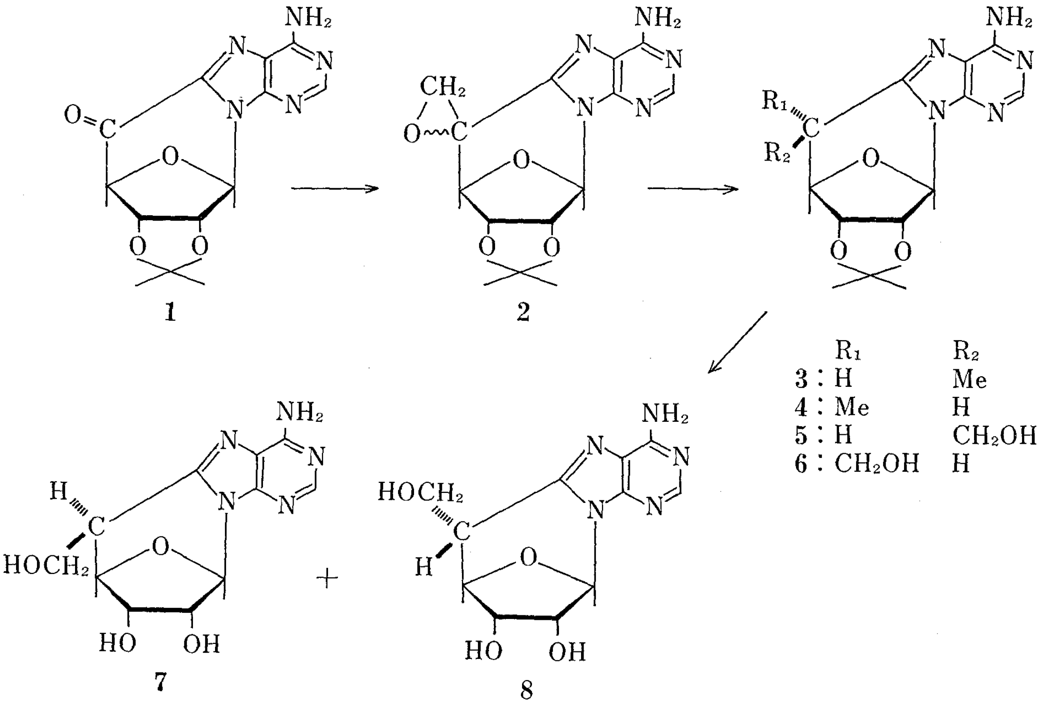
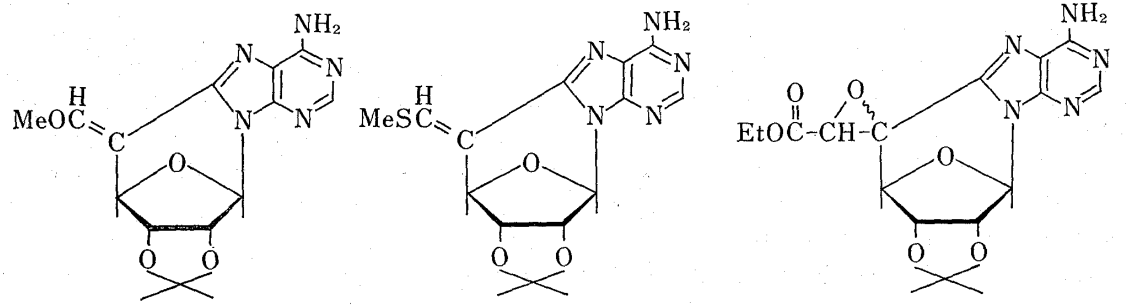


Chart 1

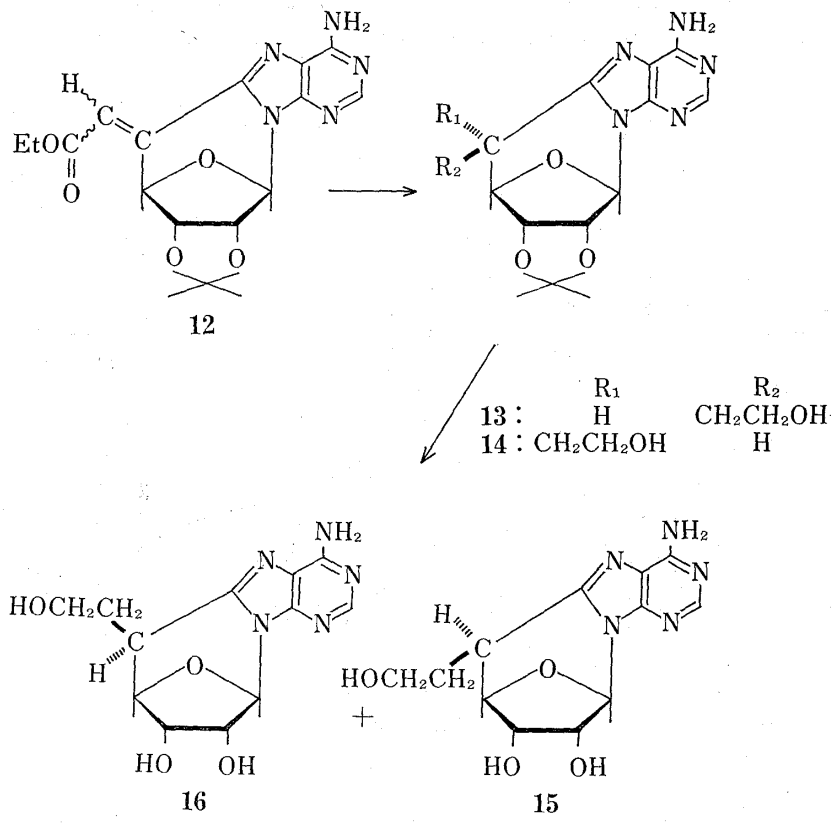
unsuccessful. For the introduction of a hydroxyethyl group to the 5′-position of **1**, a Wittig reaction was also attempted.

Treatment of **1** with ethoxycarbonylmethylenetriphenylphosphorane afforded 5′-ethoxycarbonylmethylene-2′,3′-*O*-isopropylidene-5′-deoxy-8,5′-cycloadenosine (**12**). The NMR spectrum of **12** showed two singlets due to 6′-vinylic proton at 6.86 and 6.84 ppm in a ratio of 4: 1, which suggests the presence of an *E*/*Z*-mixture of **12**. Treatment of **12** with sodium borohydride and lithium chloride in ethanol for three days afforded two products (**13** and **14**), which were separated by silica gel chromatography. Deacetonation of **13** and **14** gave the corresponding 5′-hydroxyethyl-5′-deoxy-8,5′-cycloadenosines (**15** and **16**). The NMR spectra of **15** and **16** were consistent with these structures. The 4′-proton of **15** was detected at 4.55 ppm as a doublet while that of **16** gave a singlet at 4.47 ppm, allowing the assignment of the 5′(*S*)-configuration for **15** and the 5′(*R*)-configuration for **16**.



9 **10** **11**

Chart 2



12

	R_1	R_2
13 :	H	CH_2CH_2OH
14 :	CH_2CH_2OH	H

16 **15**

Chart 3

In order to confirm the configurations at the 5′-position in these 8,5′-cyclonucleosides the circular dichroic (CD) spectra of the pairs of diastereomers were measured. As we have already reported,[6] the CD spectrum of 8,5′(*S*)-cycloadenosine showed a strong negative CD band in the 260 nm region, whereas the *R*-diastereomer showed a positive band with weaker amplitude.

The CD spectra of the 5′-substituted-8,5′-cycloadenosines synthesized in the present work are shown in Fig. 1.

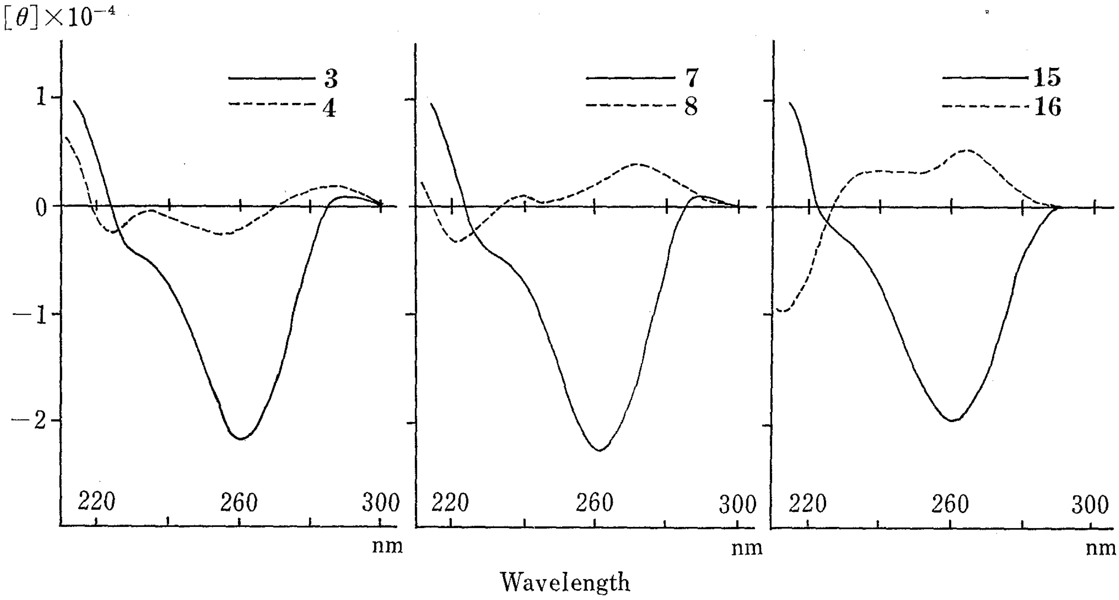


Fig. 1. CD Spectra of Diastereomeric Pairs of 8,5′ (*R* and *S*)-Cycloadenosines in Water

Compounds **3**, **7**, and **15** (the 5′-substituents being situated on the front-side, or the *tg* position, as depicted) showed strong negative bands around their main absorption regions. Compounds **8** and **16** showed weak positive bands in the same regions. Although the 5′-(*R*) methyl derivative (**4**) showed a negative band its magnitude was very weak. Since the CD bands in these compounds reflect the chiralities of both the C–1′ and C–5′ positions connected to the "anti"-fixed purine chromophore, and since the contribution of the anomeric carbon in this 8,5′-cyclo- system to the sign of the CD band is towards the negative side (as is evident from the CD spectra of 5′-deoxy-8,5′-cycloadenosine[6]), the patterns of the CD bands of these three pairs of diastereomers reflect the chiralities of the 5′-position in that a 5′-substituent located on the front-side exerts a negative contribution and the substituent on the back-side exerts a positive contribution. Assignments of the configurations at the 5′-position based on the CD spectra are in good accordance with those based on the NMR measurements, as described earlier.

The synthesis of mono- and tri-phosphate esters of **7**, **8**, **15** and **16**, and studies with various enzymes utilizing adenylates are in progress, and the results will be reported elsewhere.

Experimental

Melting points were determined with a Yanaco MP-3 melting points apparatus and are uncorrected. UV spectra were recorded on a Shimadzu UV-300 recording spectrophotometer. NMR spectra were recorded on a Hitachi R-20B (60 MHz) or JEOL JNM-FX 100Ft NMR spectrometer using tetramethylsilane as an internal standard. The abbreviations used to describe the splittings are as follows: s (singlet), d (doublet), t (triplet), m (multiplet), and b (broad). CD spectra were recorded on a JASCO J-40 spectropolarimeter with a data processor (8 accumulations) at room temperature. Infrared (IR) spectra were recorded on a Hitachi 215 spectrophotometer.

5′,6′-Epoxy-5′-hydroxymethyl-2′,3′-*O*-isopropylidene-8,5′(*R* and *S*)cycloadenosine (2)——Dimethyloxosulfoniummethylide was prepared by the reported method[7] from 360 mg of trimethyloxosulfonium chloride and 119 mg of 50% NaH in 4 ml of DMSO, and was suspended in 5 ml of THF at 0°. A solution of 500 mg of **1** in 20 ml of THF was added to the above suspension and stirred for 70 min at 0°. After addition of a small volume of acetone and ethanol to the suspension, the solvent was removed and the residue was partitioned with EtOAc and H_2O. The organic layer was dried (Na_2SO_4) and concentrated to leave a residue which was taken up in $CHCl_3$ and applied to a column of silica gel (2×10 cm). The eluate with 4% EtOH in $CHCl_3$ gave 316 mg (60%) of **2**, on removal of the solvent, as a homogeneous glass. MS *m/e*: 317 (M^+). UV $\lambda_{\max}^{H_2O}$: 268 nm. NMR ($CDCl_3$) δ: 8.39 (s, 1, 2-H), 6.47 (bs, 3, 1′-H and NH_2), 5.15 (d, 1, 2′ or 3′-H), 4.81 (d, 1, 3′ or 2′-H), 4.40 (s, 1, 4′-H), 3.67 (d, 1, 6′-CH_a), 3.30 (d, 1, 6′-H_b), 1.56, 1.32 (s, 3+3, CMe_2); $J_{2',3'}=6.0$ Hz, $J_{a,b}=6.0$ Hz.

Hydrogenation of 2 with Ni Catalyst——A solution of **2** (400 mg) in EtOH (50 ml) and H_2O (10 ml) was hydrogenated with Raney Ni catalyst (W-2, 600 mg wet wt) at room temperature at 4.5 kg/cm² for 2 days. The catalyst was filtered off and the filtrate was concentrated, then the residue was taken up in $CHCl_3$. The solution was applied to a column of silica gel (2×12 cm). The eluate with 4% EtOH in $CHCl_3$ contained **3** and **4**, and the eluate with 8% EtOH in $CHCl_3$ contained **5** and **6**. These mixtures were separated by preparative TLC.

2′,3′-*O*-Isopropylidene-5′-methyl-5′-deoxy-8,5′(*S*)-cycloadenosine (3)——The residue of the 4% eluate was charged on 3 plates (20×20 cm) of silica gel, which were developed several times with $CHCl_3$–EtOH (15: 1) until a satisfactory separation was accomplished. Two main bands were detected on each plate. The faster-migrating bands were excised and eluted with $CHCl_3$–EtOH (1: 1), and the eluate was evaporated to dryness to leave 70 mg (18%) of **3** as a homogeneous glass. MS *m/e*: 303 (M^+). UV $\lambda_{\max}^{H_2O}$: 264 nm (ε, 16000). NMR ($CDCl_3$) δ: 8.36 (s, 1, 2-H), 6.34 (s, 1, 1′-H), 5.93 (bs, 2, NH_2), 4.86 (d, 1, 2′ or 3′-H), 4.68 (d, 1, 3′ or 2′-H), 4.63 (d, 1, 4′-H), 3.67 (m, 1, 5′-H), 1.57, 1.30 (s, 3+3, CMe_2), 1.52 (s, 3, 5′-Me); $J_{2',3'}=6.0$ Hz, $J_{4',5'}=4.5$ Hz, $J_{5',6'}=7.0$ Hz. CD (H_2O): θ_{262} −22200, θ_{223} 0.

2′,3′-O-Isopropylidene-5′-methyl-5′-deoxy-8,5′(*R*)-cycloadenosine (4)——The slower-migrating band of the p-TLC described above was excised and eluted with the same solvent. Removal of the solvent gave 54 mg (14%) of **4** as a homogeneous glass. MS *m/e*: 303 (M^+). UV $\lambda_{\max}^{H_2O}$: 264 nm (ε, 13000). NMR ($CDCl_3$) δ: 8.37 (s, 1, 2-H), 6.35 (s, 1, 1′-H), 6.20 (bs, 2, NH_2), 4.68 (bs, 2, 2′, 3′-H), 4.52 (s, 1, 4′-H), 3.11 (q, 1, 5′-H), 1.58 (d, 3,5′-Me), 1.57, 1.30 (s, 3+3, CMe_2), $J_{5',6'}=7.0$ Hz. CD (H_2O): θ_{289} 1900, θ_{270} 0, θ_{256} −2700, θ_{233} −600, θ_{224} −3000, θ_{219} 0.

5′-Hydroxymethyl-2′,3′-*O*-isopropylidene-5′-deoxy-8,5′(*R*)-cycloadenosine (5)——The eluate with 8% EtOH in $CHCl_3$ of the above chromatography was charged on 3 plates for p-TLC and was developed several times with $CHCl_3$–EtOH (10: 1). From the faster-migrating band, 87 mg (22%) of **5** was obtained as a homogeneous glass. MS *m/e*: 319 (M^+). UV $\lambda_{\max}^{H_2O}$: 263 nm.

5′-Hydroxymethyl-2′,3′-*O*-isopropylidene-5′-deoxy-8,5′(*S*)-cycloadenosine (6)——From the slower-migrating band of the above p-TLC, 60 mg (15%) of **6** was obtained as a homogeneous glass. MS *m/e*: 319 (M^+). UV $\lambda_{\max}^{H_2O}$: 263 nm.

5′-Hydroxymethyl-5′-deoxy-8,5′(*R*)-cycloadenosine (7)——Compound **5** was dissolved in 7 ml of 0.1 N HCl and the solution was kept at 85—90° for 45 min. After neutralization of the solution with 2 N NH_4OH, the solution was concentrated and the residue was crystallized from hot H_2O to leave 56 mg (74%) of **7** as hygroscopic crystals, mp 242° (dec.). *Anal.* Calcd for $C_{11}H_{13}N_5O_4\cdot 1/3H_2O$: C, 46.32; H, 4.81; N, 24.56. Found: C, 46.37; H, 4.92; N, 24.29. MS *m/e*: 279 (M^+). UV $\lambda_{\max}^{H_2O}$: 263 nm (ε, 16400). $\lambda_{\max}^{0.1N\ HCl}$ 260 nm (ε, 16400). CD (H_2O): θ_{263} −16600, θ_{222} 0. NMR (DMSO-d_6+D_2O) δ: 8.11 (s, 1, 2-H), 6.01 (s, 1, 1′-H), 4.68 (d, 1, 4′-H), 4.43 (d, 1, 2′ or 3′-H), 4.21 (m, 2, 6′-H), 3.99 (d, 1, 3′ or 2′-H), 3.64 (m, 1, 5′-H); $J_{2',3'}=6.1$ Hz, $J_{4',5'}=4.6$ Hz.

5′-Hydroxymethyl-5′-deoxy-8,5′(*S*)-cycloadenosine (8)——Compound **6** (60 mg) was deacetonated in the manner described above and 18 mg (34%) of **8** was obtained as hygroscopic crystals from H_2O, mp 268° (dec.). *Anal.* Calcd for $C_{11}H_{13}N_5O_4\cdot 1/2H_2O$: C, 45.81; H, 4.90; N, 24.29. Found: C, 46.16; H, 4.88, N, 23.71. MS *m/e*: 279 (M^+). UV $\lambda_{\max}^{H_2O}$ 264.5 nm (ε, 14300), $\lambda_{\max}^{0.5N\ HCl}$ 260.5 nm (ε, 14100). CD (H_2O): $\theta_{288.5}$ +1100, θ_{282} +550, $\theta_{271.5}$ +1100, θ_{264} 0, $\theta_{253.5}$ −1300, θ_{233} −400, θ_{219} −4200, θ_{216} 0. NMR (DMSO-d_6+D_2O) δ: 8.13 (s, 1, 2-H), 6.02 (s, 1, 1′-H), 4.69 (d, 1, 4′-H), 4.22 (d, 1, 2′ or 3′-H), 4.06 (d, 1, 3′ or 2′-H), 3.56 (t, 2, 6′-H), 3.14 (m, 2, 5′-H); $J_{2',3'}=5.9$ Hz.

2′,3′-*O*-Isopropylidene-5′-methoxymethylene-5′-deoxy-8,5′-cycloadenosine (9)——Methoxymethylenetriphenylphosphorane was prepared from 599 mg of methoxymethyltriphenylphosphonium chloride and 84 mg of 50% NaH in 4.4 ml of DMSO. A solution of 100 mg of **1** in 4 ml of DMSO was added to the solution and the mixture was stirred for 1 hr at room temperature. The deep red solution was poured into 65 ml of H_2O. The mixture was extracted with $CHCl_3$ (20 ml×3) and the organic phase was dried over Na_2SO_4 then evaporated to dryness. The residue was taken up in $CHCl_3$ and the solution was charged on 2 plates of silica gel, which were developed with $CHCl_3$–EtOH (10: 1). The main band was excised and extracted with $CHCl_3$–

---

7) E.J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).

EtOH (1: 1). The solvent was removed and the residue was crystallized from aqueous EtOH to give 82 mg (75%) of **9** as hygroscopic crystals, mp 290° (dec.). *Anal.* Calcd for $C_{15}H_{17}N_5O_4 \cdot 1/4H_2O$: C, 53.65; H, 5.22; N, 20.86. Found: C, 53.93; H, 5.24; N, 20.56. MS *m/e*: 331 (M^+). UV $\lambda_{\max}^{H_2O}$ 324 nm (sh), 309 nm, 300 nm (sh). NMR (DMSO-d_6) δ: 8.10 (s, 1, 2-H), 7.19 (bd, 2, NH_2), 6.89 (s, 1, 6′-H), 6.12 (s, 1, 1′-H), 5.01 (s, 1, 4′-H), 4.68 (bs, 2, 2′, 3′-H).

2′,3′-*O*-Isopropylidene-5′-methylthiomethylene-5′-deoxy-8,5′-cycloadenosine (10)——A solution of methylthiomethylenetriphenylphosphorane was prepared from 142 mg of methylthiomethyltriphenylphosphonium chloride and *n*-BuLi (0.6 ml of 15% solution) in 10 ml of THF. Compound **1** (100 mg) was added to the solution and the mixture was stirred for 4 hr at room temperature. The solution was then neutralized with 1 N HCl and concentrated. The residue was partitioned with $CHCl_3$ and H_2O and the organic layer was concentrated. This was applied to 3 plates of silica gel and developed with $CHCl_3$–EtOH (14: 1). The main band was excised and extracted with $CHCl_3$–EtOH (1: 1). The solvent was removed and the residue was crystallized from MeOH to give 76 mg (66%) of **10**, mp 292° (dec.). *Anal.* Calcd for $C_{15}H_{17}N_5O_3S$: C, 51.87; H, 4.90; N, 20.17; S, 9.22. Found: C, 51.82; H, 4.89; N, 19.92; S, 8.98. MS *m/e*: 347 (M^+). UV $\lambda_{\max}^{H_2O}$ 332, 259 nm. NMR (DMSO-d_6) δ: 8.17 (s, 1, 2-H), 7.45 (s, 1, 6′-H), 7.23 (bs, 2, NH_2), 6.24 (s, 1, 1′-H), 5.20 (s, 1, 4′-H), 4.88 (d, 1, 2′ or 3′-H), 4.70 (d, 1, 3′ or 2′-H), 3.33 (s, 3, SMe), 1.46, 1.27 (s, 3+3, CMe_2); $J_{2',3'}=7.0$ Hz.

Ethyl 5′-(2′,3′-*O*-Isopropylidcne-8,5′-cycloadenosinyl)glycidate (11)——A mixture of ethyl(dimethylsulfuranylidene)acetate (293 mg) and **1** (330 mg) in 30 ml of $CHCl_3$ was stirred overnight at room temperature. The solution was washed with H_2O and the organic layer was concentrated to leave a residue. This was taken up in Et_2O containing a small amount of MeOH and kept overnight. The separated crystals were collected to give 367 mg (83%) of **11** as the monohydrate, mp 187—189°. *Anal.* Calcd for $C_{17}H_{19}N_5O_6 \cdot H_2O$: C, 50.10; H, 5.21; N, 17.19. Found: C, 49.94; H, 5.13; N, 17.19. MS *m/e*: 389 (M^+). UV $\lambda_{\max}^{H_2O}$ 275 nm. IR (nujol): 1740 cm^{-1}. NMR ($CDCl_3$) δ: 8.38 (s, 1, 2-H), 6.45 (bs, 3, 1′-H and NH_2), 5.20 (d, 1, 2′ or 3′-H), 4.83 (d, 2, 3′ or 2′-H and 4′-H), 4.40 (q, 2, $OC\underline{H}_2CH_3$), 4.36 (s, 1, 6′-H), 1.56, 1.35 (s, 3+3, CMe_2), 1.37 (t, 3, $OCH_2C\underline{H}_3$).

5′-Ethoxycarbonylmethylene-2′, 3′-*O*-isopropylidene-5′-deoxy-8, 5′-cycloadenosine (12)——A mixture of 454 mg of **1** and 574 mg of ethoxycarbonylmethylenetriphenylphosphorane in 50 ml of $CHCl_3$ was stirred overnight at room temperature. The reaction mixture was concentrated to half the original volume and applied to a column of silica gel (2.3 × 20 cm). After elution of triphenylphosphine oxide with 0—2% EtOH in $CHCl_3$ the product was eluted with 4% EtOH in $CHCl_3$. Removal of the solvent gave 548 mg (98%) of **12** as a yellow powder. *Anal.* Calcd for $C_{17}H_{19}N_5O_5$: C, 54.66; H, 5.14; N, 18.76. Found: C, 54.65; H, 5.28; N, 18.84. MS *m/e*: 373 (M^+). UV $\lambda_{\max}^{H_2O}$ 328 nm (ε, 11900), 285 nm (sh, ε, 6500) 239.5 nm (ε, 22050). min 267 nm (ε, 5300). IR (nujol): 1705 cm^{-1}. NMR (DMSO-d_6) δ: 8.26 (s, 1, 2-H), 7.60 (bs, 2, NH_2), 6.86 and 6.84 (s, total 1, 6′-H), 6.37 (s, 1, 1′-H), 6.17 (s, 1, 4′-H), 5.89 (bs, 2, 2′, 3′-H), 4.27 (q, 2, $OC\underline{H}_2CH_3$),1.50, 1.29 (s, 3+3, CMe_2), 1.29 (t, 3, $OCH_2C\underline{H}_3$). CD (H_2O): θ_{335} −3530, θ_{301} −1500, θ_{282} −4640, θ_{268} 0, θ_{265} +560, θ_{263} 0, θ_{245} −18200, θ_{232} 0, θ_{215} +21000.

Reduction of 12 with $NaBH_4$ in the Presence of LiCl——A solution of **12** (541 mg) in EtOH (50 ml) was treated with LiCl (308 mg) and $NaBH_4$ (274 mg), and the mixture was stirred at room temperature for 3 days. After filtration of the insoluble material the filtrate was evaporated to dryness and the residue was taken up in $CHCl_3$. This solution was applied to a column of silica gel (2.5 × 25 cm). The column was eluted with 8% EtOH in $CHCl_3$. Concentration of the initial eluate provided 5′-hydroxyethyl-2′,3′-O-isopropylidene-5′-deoxy-8,5′(*S*)-cycloadenosine (**13**, 120 mg, 23%) as a homogeneous glass. MS *m/e*: 333 (M^+). From the second fraction, a mixture of **13** and the *R*-diastereomer (133 mg, 26%) was obtained. The final fraction, on removal of the solvent, gave 121 mg (23%) of the (*R*)-isomer (**14**), MS *m/e*: 333 (M^+).

5′-Hydroxyethyl-5′-deoxy-8,5′(*S*)-cycloadenosine (15)——A solution of **13** (120 mg) in 20 ml of 0.1 N HCl was kept at 85—90° for 75 min. After neutralization with 2 N NH_4OH the solution was concentrated and the residue was crystallized from H_2O to give 75 mg (70%) of **15**, mp 279° (dec.). *Anal.* Calcd for $C_{12}H_{15}N_5O_4$: C, 49.14; H, 5.16; N, 23.88. Found: C, 49.36; H, 5.16; N, 23.71. MS *m/e*: 293 (M^+). UV $\lambda_{\max}^{H_2O}$ 264 nm (ε, 16100), $\lambda_{\max}^{0.5N\ HCl}$ 261 nm (ε, 16000). CD (H_2O): θ_{262} −20400, θ_{223} 0, θ_{204} +30300. NMR (DMSO-d_6) δ: 8.11 (s, 1, 2-H), 6.01 (s, 1, 1′-H), 4.55 (d, 1, 4′-H), 4.27 (d, 1, 2′ or 3′-H), 4.00 (d, 3′ or 2′-H), 3.74 (m, 2, 7′-H), 3.52 (m, 1, 5′-H), 1.78 (m, 2, 6′-H); $J_{2',3'}=5.2$ Hz, $J_{4',5'}=6.1$ Hz.

5′-Hydroxyethyl-5′-deoxy-8,5′(*R*)-cycloadenosine (16)——Compound **14** (120 mg) was deacetonated in the manner described above and **16** was crystallized from H_2O to give 67 mg (63%), mp 267—269°. *Anal.* Calcd for $C_{12}H_{15}N_5O_4$: C, 49.14; H, 5.16; N, 23.88. Found: C, 48.83; H, 5.12; N, 23.46. MS *m/e*: 293 (M^+). UV $\lambda_{\max}^{H_2O}$ 264.5 nm (ε, 16400), $\lambda_{\max}^{0.5N\ HCl}$ 261.5 nm (ε, 16200). CD (H_2O): θ_{265} +5300, θ_{226} 0, θ_{212} −9400. NMR (DMSO-d_6) δ: 8.11 (s, 1, 2-H), 6.00 (s, 1, 1′-H), 4.47 (s, 1, 4′-H), 4.15 (d, 1, 2′ or 3′-H), 3.99 (d, 1, 3′ or 2′-H), 3.64 (m, 2, 7′-H), 3.16 (t, 1, 5′-H), 1.90 (m, 2, 6′-H); $J_{2',3'}=6.1$ Hz.

Acknowledgement This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, and the Ministry of Welfare, Japan. The mass, NMR, and elemental analyses were performed by the staff of the Central Analytical Room of this faculty, to whom our thanks are due.