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Synthesis of 8-Alkyladenosines, 8,2′-Anhydro-8-hydroxymethyl-9-(β-D-arabinofuranosyl)adenine and Related Compounds (Nucleosides and Nucleotides. LVIII[1])

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Synthesis of 8-alkyladenosines and related nucleosides is described. Treatment of 5′-*O*-acetyl-2′,3′-*O*-isopropylidene-8-methylsulfonyladenosine with ethyl sodioacetoacetate gave the 8-ethoxycarbonylmethyl derivative (**1**). Hydrolytic decarboxylation of **1** followed by deacetonation afforded 8-methyladenosine (**2**) in high yield. Alkylation of **1** with methyl or ethyl iodide followed by hydrolytic decarboxylation afforded 8-ethyl- and 8-propyladenosines, respectively. Attempts at dimethylation of the 8-methylene group of **1** resulted in the formation of the N^6-dimethyladenosine derivative. Selective dimethylation of the amino groups of 2′-deoxyadenosine and 2′-deoxycytidine has been accomplished by using a combination of methyl iodide and sodium hydride without methylation of the sugar hydroxyl groups of these nucleosides. 8,2′-Anhydro-9-β-D-arabinofuranosyl-8-hydroxymethyladenine was prepared from a 8-cyanoadenosine derivative by the procedure involving anhydro-bond formation by base treatment of 8-hydroxymethyl-2′-*O*-tosyladenosine. The circular dichroism spectral characteristics of 8-alkyladenosines are discussed.

Keywords——adenosine; 8-alkyladenosine; anhydroadenosine; N^6,N^6-dimethyl-2′-deoxyadenosine; N^4,N^4-dimethyl-2′-deoxycytidine; nucleoside conformation; NMR; CD

For investigation of the structure activity relationship of enzymes utilizing adenosine derivatives, such as adenosine deaminase, adenosine kinase, and S-adenosylhomocysteinase, 8-substituted adenosines may serve as probes of the influence of conformation around the glycosyl bonds, since the 8-substituents tend to force the usual *anti* form of adenosine to adopt the *syn*-conformation as a result of the steric effect. Among various substituents, alkyl groups have least electronic effect on the adenine nucleus, which is essential for binding to the recognition site of enzymes utilizing adenosine. There seems to be no general method for the introduction of alkyl groups into the 8-position of adenosine. A radical alkylation of adenosine at the C-8 position by the use of *tert*-butyl hydroperoxide and ferrous sulfate[2] is restricted to methylation, and the reaction also takes place at the 2-position. Therefore, 2-methylthioinosine was methylated with this system to afford the 8-methyl derivative, which was eventually converted to 8-methyladenosine.[3] We have already reported the usefulness of the methylsulfonyl group as a leaving group in displacement with carbon nucleophiles such as cyanide and acetoacetate at the C-6 position of purine nucleosides,[4] and cyanide at the 8-position of adenosine.[5]

This paper describes a general method for the introduction of alkyl groups at the 8-position of adenosines by the use of properly protected 8-methylsulfonyladenosines. The synthesis of a cycloadenosine, 8,2′-anhydro-9-β-D-arabinofuranosyl-8-hydroxymethyladenine is also described. A preliminary account of this work has appeared.[6] After the completion of our work, reports on 8-alkylation by the use of purine 8-lithio compounds were published.[7,8] A synthesis of 8,2′-anhydro-8-(α-hydroxyisopropyl)-9-(β-D-arabinofuranosyl)adenine, similar to that of the anhydroadenosine to be described, has also been reported recently.[9]

Treatment of 5′-*O*-acetyl-2′,3′-*O*-isopropylidene-8-methylsulfonyladenosine (**1**), previously prepared in our laboratory,[5] with the sodium salt of ethyl acetoacetate in tetrahydrofuran (THF) under reflux afforded the 8-ethoxycarbonylmethyl derivative (**2**) as a syrup in near quantitative yield. Saponification of **2** with sodium hydroxide in 50% ethanol followed by heating of the product at pH 4 resulted in decarboxylation of the presumably formed adenosine 8-acetic acid with concomitant deacetylation at the 5′-position to give 2′,3′-*O*-isopropylidene-8-methyladenosine (**3**). The physical data of **3** were consistent with those reported by Ikehara and co-workers,[3] except for the melting point. Deacetonation of **3** gave 8-methyladenosine (**4**) in high yield.

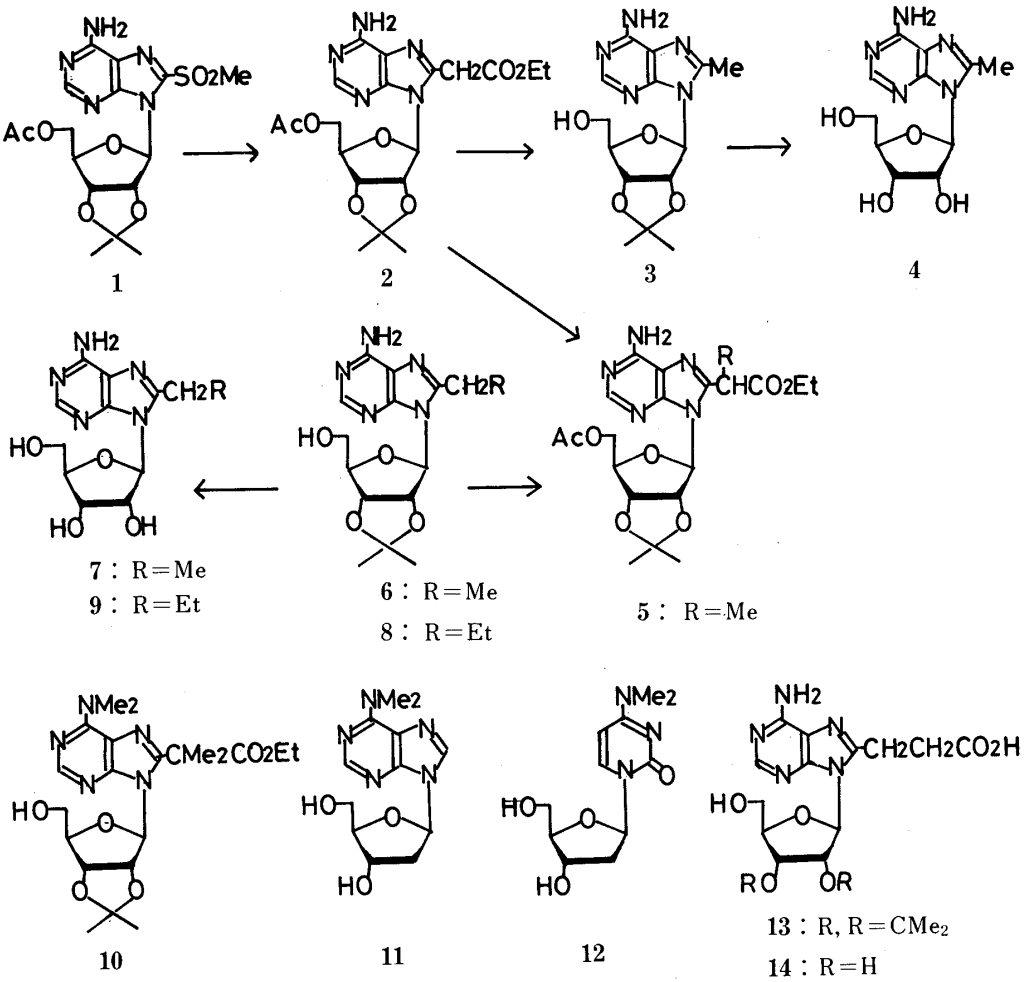
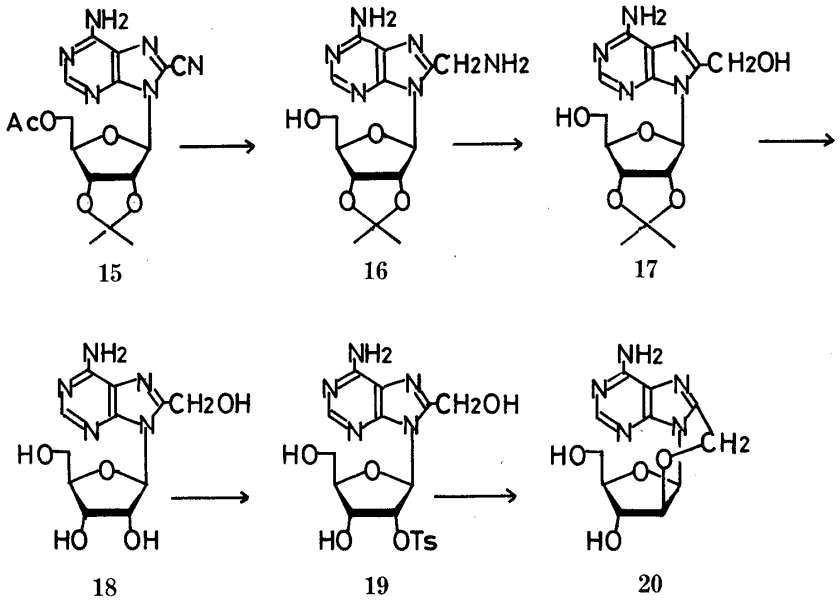


Chart 1

For the synthesis of 8-alkyladenosines other than the methyl compound, alkylation at the 8-methylene group of **2** was attempted. Treatment of **2** with a small excess of sodium hydride and methyl iodide in dimethylformamide (DMF) afforded the 8-(α-ethoxycarbonyl)ethyl derivative (**5**). The nuclear magnetic resonance (NMR) spectra of **5** showed a set of methyl doublet signals at around 1.7 ppm, indicating that the compound is an epimeric mixture. Saponification followed by decarboxylation of **5** afforded 2′,3′-*O*-isopropylidene-8-ethyladenosine (**6**), which was converted to 8-ethyladenosine (**7**) by successive deacetonation. Treatment of **2** with ethyl iodide and similar work-up gave 2′,3′-*O*-isopropylidene-8-*n*-propyladenosine (**8**) and its free nucleoside (**9**). Treatment of **2** with an excess of methyl iodide and sodium hydride to accomplish dimethylation at the 8-methylene position resulted in the formation of the N^6-dimethylderivative (**10**) with deacetylation at the 5′-position. It should be

noted that treatment of 2′-deoxyadenosine and 2′-deoxycytidine with an excess of sodium hydride and methyl iodide gave N^6,N^6-dimethyl-2′-deoxyadenosine[10] (**11**) and N^4,N^4-dimethyl-2′-deoxycytidine[11] (**12**), respectively, without any methylation of the sugar hydroxyls, in rather good yields as compared to the reported multi-step conversion for the preparation of these nucleosides. A recent report on C-8 and N^6 methylation of N^6-methyl-2′,3′-*O*-isopropylideneadenosine by treatment with butyllithium and methyl iodide is noteworthy.[12] It is clear that sodium hydride is basic enough to dissociate the amino protons of adenosines and cytidines to be alkylated but not the C-8 proton of adenosine or the C-6 proton of cytidine.

For the conformational studies of 8-alkyl-substituted adenosines, 8-alkyladenosine fixed in an anti conformation would be required for comparison. We have already reported such conformationally fixed adenosines as carbon-bridged 8,5′-cycloadenosines.[13] We attempted here the preparation of cyclonucleoside through the use of an oxyalkyl function. For this purpose, the synthesis of adenosine 8-propionic acid was undertaken. Compound **2** was treated with sodium hydride and ethyl bromoacetate to give the adenosine 8-succinate derivative, which was saponified and then decarboxylated to furnish 2′,3′-*O*-isopropylideneadenosine 8-propionic acid (**13**) and its deacetonated derivative (**14**). Compound **14** migrated as a monoanion on paper electrophoresis. Several attempts to lactonize **13** or **14** between the 5′(or 2′)-hydroxyl and the propionic acid functions, however, were unsuccessful, probably due to the steric hindrance often encountered in the formation of a medium-sized ring.



15 16 17

18 19 20

Chart 2

Next, we attempted the preparation of an 8,2′-cyclonucleoside. Treatment of 5′-*O*-acetyl-8-cyano-2′,3′-*O*-isopropylideneadenosine (**15**)[5] with lithium aluminum hydride in THF afforded 8-aminomethyl-2′,3′-*O*-isopropylideneadenosine (**16**), which was deaminated by treatment with nitrous acid to give the 8-hydroxymethyladenosine (**17**). In this reaction an unidentified by-product was also obtained. Deacetonation of **17** gave 8-hydroxymethyladenosine (**18**), which was tosylated by treatement with di-*n*-butyltin oxide and tosyl chloride[14] to furnish the 2′-*O*-tosylate (**19**). Treatment of **19** with potassium *tert*-butoxide in *tert*-butanol–DMF furnished 8,2′-anhydro-8-hydroxymethyl-9-(β-D-arabinofuranosyl)adenine (**20**). The NMR spectra of **20** showed the bridge methylene protons as a pair of doublets with

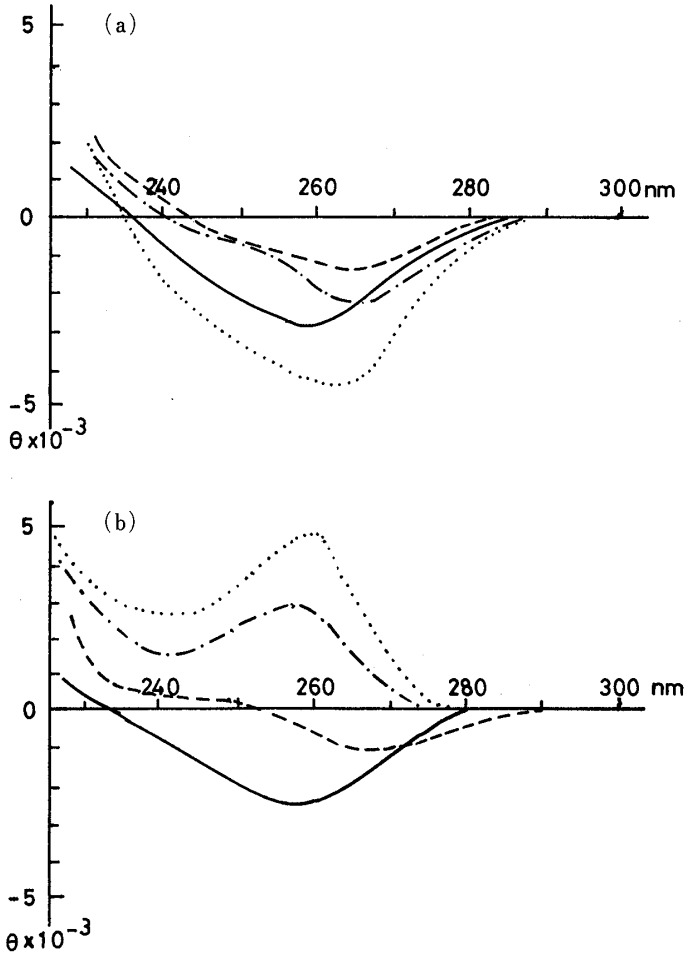


Fig. 1. CD Spectra of 8-Alkyladenosines (a) and Their 2′,3′-*O*-Isopropylidene Derivatives (b)

CD Spectra were taken in H_2O at room temperature. The molar ellipticities were based on the ε values reported in the experimental section or published data (see text). The ε values used for **7** and **9** were of their 2′,3′-*O*-isopropylidene derivatives. (a) ——, adenosine; – – –, Me (**4**); –·–·–, Et (**7**); ------, Pr (**9**). (b) ——, adenosine; – – –, Me (**3**); –·–·–, Et (**6**); ------, Pr (**8**).

geminal coupling ($J=14$ Hz) at 4.98 and 4.76 ppm, respectively. Taking into account the coupling constants of the 1′, 2′, and 3′ protons, the ring conformation including the oxymethylene bridge can be assumed to take the *exo* form in terms of the ring puckering. The mass spectra (MS) of **20** showed a relatively strong molecular ion peak, characteristic of the cyclo structure, at *m/z* 279.

The circular dichroism spectra (CD) of 8-alkyladenosines, **4**, **7**, and **9** (Fig. 1a), showed negative bands at their main absorption regions, resembling that of adenosine. However, their 2′,3′-*O*-isopropylidene derivatives, **3**, **6**, and **8**, tended to show decreased negative ellipticities with increasing bulkiness of the 8-substituents, and show the positive bands in the cases of 6 and **8** (Fig. 1b). This would suggest that, although the unprotected nucleosides still have rather free rotations around the glycosyl bonds, possessing preferred anti conformations as does adenosine, their 2′,3′-*O*-isopropylidene derivatives are in preferred *syn*-conformation as the 8-substituent becomes bulkier, probably due to the change of the sugar puckering from the *endo–exo* pucker of C-2′,3′ to the *O*-1′. However, the relative preponderance of *syn–anti* conformation cannot be simply determined by the sign of the CD bands until the molar ellipticities of conformationally fixed cyclonucleosides are known. The 8,2′-anhydroadenosine (**20**) showed a weak positive CD band (Fig. 2), which is very similar to that of 2′-deoxy-8,2′-ethano-cycloadenosine,[15] a recently prepared carbon-bridged cycloadenosine, in accordance with the similarity of their glycosyl torsion angles, and these two compounds are rather fixed in the *syn*-region. Since we have already noted the reversal of the sign of CD bands, from negative to positive, at glycosyl torsion angles between those of 8,5′-cyclo-5′-deoxyadenosines[13] and 8,6′-cyclo-9-(5′-*O*-acetyl-6′-deoxy-2′,3′-*O*-isopropylidene-β-D-allo-

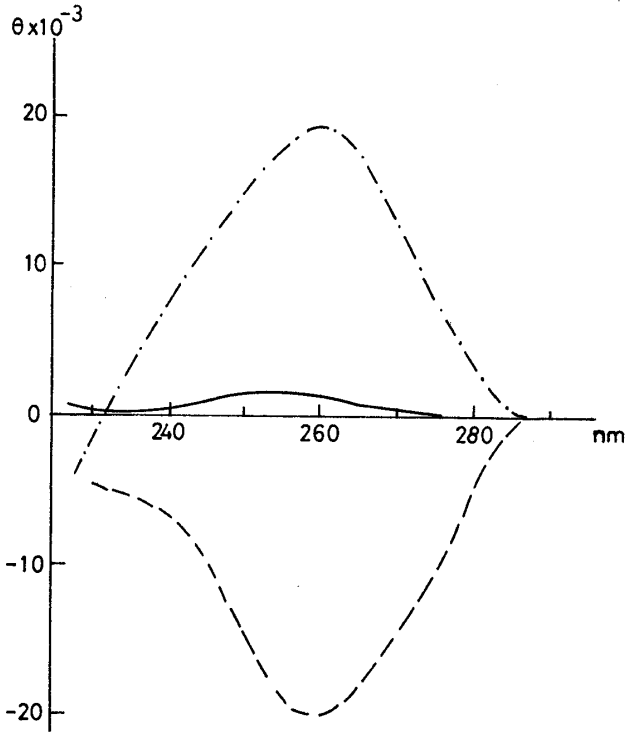


Fig. 2. CD Spectra of Adenosine 8-Cyclonucleosides

CD Spectra were taken in H_2O at room temperature.8,5′-Cyclo represents 8,5′-cyclo-5′-deoxyadenosine; this spectrum was taken from ref. 13*b*. 8,6′-Cyclo represents 8,6′-cyclo-9-(5′-*O*-acetyl-6′-deoxy-2′,3′-*O*-isopropylidene-β-allofuranosyl)adenine; this spectrum was taken from ref. 16. The molar ellipticity of **20** was calculated by assuming the ε value to be 15000 at 263 nm. ----, 8,5′-cyclo; -·-·-, 8,6′-cyclo; ——, (**20**).

furanosyl)adenine[16] (Fig. 2), it follows that there is a transient torsional angle for the reversal of the sign within the *anti* region, as already found in the case of carbon-bridged pyrimidine cyclonucleosides.[17]

Therefore, the above statement on the *syn–anti* preference of the unprotected or 2′,3′-*O*-isopropylidene 8-alkyladenosines is tentative, and should be regarded referring to the preference under conditions of *syn–anti* equilibrium.

However, an extensive proton nuclear magnetic resonance (^{1}H-NMR) study of the *syn–anti* dynamic equilibrium in adenosines and their 8-substituted derivatives has been reported by Shugar and co-workers[9] in which they have drawn a similar conclusion on the existence of *syn–anti* equilibrium for 8-methyladenosine and a *syn*-preference of the 2′,3′-*O*-isopropylidene purine ribonucleosides.

Experimental

Melting points were determined with a Yanaco MP-3 melting point apparatus and are uncorrected. Ultraviolet (UV) spectra were recorded on a Shimadzu UV-300 recording spectrophotometer. NMR spectra were taken with a JEOL JNM-FX 100FT NMR spectrometer in DMSO-d_6 unless otherwise noted. Chemical shifts are reported in ppm (δ), and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). All exchangeable protons were confirmed by addition of D_2O. MS were taken with a JEOL JMS-D 300 spectrometer. CD spectra were recorded on a JASCO J-40 spectropolarimeter with a data processor (8 accumulations) at room temperature. Silica gel for column chromatography and preparative thin layer chromatography (pTLC) was Wakogel C-200. Thin layer chromatography (TLC) was performed on Merck TLC plates (60 F_{254}, precoated).

5′-*O*-Acetyl-8-ethoxycarbonylmethyl-2′,3′-*O*-isopropylideneadenosine (2)——EtOAc (44 ml, 420 mmol) in 50 ml of THF was treated with 1.92 g (40 mmol) of 50% NaH. After the evolution of hydrogen had ceased, 5′-*O*-acetyl-2′,3′-*O*-isopropylidene-8-methylsulfonyladenosine[5] (4.27 g, 10 mmol) was added to the solution. After being refluxed overnight, the mixture was neutralized by the addition of 1 N HCl and the solvent was evaporated off *in vacuo*. The residue was dissolved in $CHCl_3$ and applied to a column of silica gel (150 g) and the column was eluted with 4% EtOH–$CHCl_3$. Evaporation of the solvent gave 3.93 g (93%) of **2** as a foam. NMR: 8.14 (1H, s, H-2), 7.32 (2H, br, NH_2), 6.14 (1H, d, H-1′), 5.57 (1H, dd, H-2′). 5.14 (1H, dd, H-3′), 4.17 (7H, m, H-4′,5′, $CH_2 \times 2$), 1.94 (3H, s, Ac), 1.55, 1.33 (3H each, s, Me_2C), 1.18 (3H, t, CH_3). UV $\lambda_{max}^{H_2O}$ nm: 260, 210; λ_{min} nm: 228. $\lambda_{max}^{0.1\ N\ HCl}$: 258 nm; λ_{min}: 238 nm. MS *m/z*: 435 (M^+).

2′,3′-*O*-Isopropylidene-8-methyladenosine (3)——Compound **2** (1.79 g, 4.1 mmol) was dissolved in 50% EtOH (20 ml), then 5 ml of 5 N NaOH was added, and the solution was stirred for 30 min at room temperature. The solution was acidified to pH 4 by addition of 50% HCO_2H and then heated on a boiling water bath for 2 h. After neutralization of the solution with 1 N NaOH, the solution was partitioned between $CHCl_3$ and H_2O. The organic layer was separated, and dried over Na_2SO_4, then the solvent was removed *in vacuo*. The residue was crystallized from H_2O to give 828 mg (63%) of **3**, mp 249—251 °C (ref. 3, 240—243 °C). NMR: 8.09 (1H, s, H-2), 7.22 (2H, br, NH_2), 6.04 (1H, d, H-1′, $J_{1',2'}$ = 2.9 Hz), 5.57 (1H, dd, H-2′, $J_{2',3'}$ = 6.2 Hz), 5.24 (1H, t, HO-5′), 5.00 (1H, dd, H-3′, $J_{3',4'}$ = 3.1 Hz), 4.13 (1H, m, H-4′), 3.47 (2H, m, H-5′), 3.33 (3H, s, Me-8), 1.55, 1.33 (3H each, 6, Me_2C). UV $\lambda_{max}^{H_2O}$ nm: 260, 210; λ_{min} nm: 227. MS *m/z*: 321 (M^+), 149 (base peak, B^+).

8-Methyladenosine (4)——Compound **3** was treated with 90% trifluoroacetic acid as described in ref. 3, and the product was crystallized from H_2O to give pure **4**, mp 213—216 °C (sintered at 125 °C (125—130 or 130—133 °C)[3]). *Anal.* Calcd for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.62; H, 5.39; N, 24.69.

5′-*O*-Acetyl-2′,3′-*O*-isopropylidene-8-(α-ethoxycarbonylethyl)adenosine (5)——Compound **2** (1.30 g, 3.0 mmol) in 10 ml of DMF was treated with 50% NaH (163 mg, 3.4 mmol). After the evolution of hydrogen had ceased, CH_3I (0.22 ml, 3.6 mmol, in 2 ml of DMF) was added dropwise, and the solution was kept for 1 h at room temperature. The solution was neutralized by the addition of 1 N HCl and the solution was partitioned between AcOEt and H_2O. The organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was dissolved in a small volume of $CHCl_3$ and applied to a column of silica gel (30 g). The eluate with 2% MeOH–$CHCl_3$ was concentrated to give 928 mg (69%) of **5** as a foam. NMR ($CDCl_3$): 8.28 (1H, s, H-2), 6.15, 6.07 (0.5 each, d, H-1′), 5.79 (2H, br, NH_2), 5.63 (1H, m, H-2′), 5.21 (1H, m, H-3′), 4.32 (5H, m, H-5′, CH, CH_2), 2.03, 2.01 (3/2 each, s, Ac), 1.72, 1.71 (0.5 each, d, $CHC\underline{H}_3$), 1.61, 1.39 (3 each, s, Me_2C). UV $\lambda_{max}^{H_2O}$ nm: 262; λ_{min} nm: 228.

8-Ethyl-2′,3′-*O*-isopropylideneadenosine (6)——a) Compound **2** (211 mg, 0.49 mmol) in 5 ml of DMF was treated with 26 mg (0.55 mmol) of 50% NaH. After the evolution of hydrogen had ceased, CH_3I (0.037 ml, 0.60 mmol) in 2 ml of DMF was added and the mixture was kept for 1 h during which formation of **5** was completed. Water (5 ml) and 5 N NaOH (1 ml) were added to the solution and the mixture was stirred for 30 min at room temperature, then acidified with 50% HCO_2H to pH 4.0, and heated over a boiling water bath for 2 h. After neutralization, the solution was partitioned between AcOEt and H_2O. The organic layer was dried over Na_2SO_4, the solvent was removed *in vacuo*, and the residue was crystallized from H_2O to give 80 mg (49%) of **6**, mp 227—228 °C. NMR: 8.19 (1H, s, H-2), 7.21 (2H, br, NH_2), 6.00 (1H, d, H-1′, $J_{1',2'}$ = 3.2 Hz), 5.51 (1H, dd, H-2′, $J_{2',3'}$ = 6.1 Hz), 5.35 (1H, t, HO-5′), 5.01 (1H, dd, H-3′, $J_{3',4'}$ = 2.9 Hz), 4.21 (1H, m, H-4′), 3.55 (2H, m, H-5′), 2.93 (2H, q, Et), 1.57, 1.34 (3H each, s, Me_2C), 1.32 (3H, t, Et). UV $\lambda_{max}^{H_2O}$ nm (ε): 263 (16700), 213 (21700); λ_{min} nm (ε): 228 (2900). MS *m/z*: 335 (M^+).

b) The same compound was also obtained from **5** by similar work-up after decarboxylation and deacetylation.

8-Ethyladenosine (7)——Compound **6** (50 mg, 0.15 mmol) in 10 ml of 50% HCO_2H was stirred overnight at room temperature. Water (5 ml) was added to the solution and evaporated. Addition and evaporation with H_2O were repeated several times, and the final residue was crystallized from H_2O to give 24 mg (54%) of **7**, mp 251—252 °C. NMR: 8.07 (1H, s, H-2), 7.24 (2H, br, NH_2), 6.02 (1H, dd, HO), 5.78 (1H, d, H-1′, $J_{1',2'}$ = 7.1 Hz), 5.38 (1H, d, HO), 5.22 (1H, d, HO), 4.90 (1H, dd, H-2′, $J_{2',3'}$ = 5.4 Hz), 4.18 (1H, m, H-3′), 4.03 (1H, m, H-4′), 3.64 (2H, m, H-5′), 2.90 (2H, q, Et), 1.32 (3H, t, Et). UV $\lambda_{max}^{H_2O}$ nm: 263, 213. λ_{min} nm: 232. MS *m/z*: 295 (M^+).

2′,3′-*O*-Isopropylidene-8-*n*-propyladenosine (8)——Compound **2** (218 mg, 0.50 mmol) in 5 ml of DMF was treated with 50% NaH (42 mg, 0.90 mmol). After the evolution of hydrogen had ceased, C_2H_5I (0.052 ml, 0.65 mmol) in 2 ml of DMF was dropwisely added. After 1 h, 5 N NaOH (3 ml) was added to the solution and the mixture was stirred for 2 h at room temperature, made acidic (pH 4) by addition of 50% HCO_2H, heated on a boiling water bath for 1 h, and neutralized. It was then partitioned between AcOEt and H_2O, and the organic layer was dried over Na_2SO_4. The solvent was evaporated off and the residue was crystallized from H_2O to give 66 mg (36%) of **8**, mp 210.5—212.5 °C. NMR: 8.11 (1H, s, H-2), 7.23 (2H, br, NH_2), 5.99 (1H, d, H-1′, $J_{1',2'}$ = 3.4 Hz), 5.53 (1H, dd, H-2′, $J_{2',3'}$ = 6.1 Hz), 5.40 (1H, t, HO-5′), 5.02 (1H, dd, H-3′, $J_{3',4'}$ = 2.4 Hz), 4.21 (1H, m, H-4′), 3.57 (2H, m, H-5′), 2.89 (2H, t, $C\underline{H}_2CH_2CH_3$), 1.78 (2H, m, $CH_2C\underline{H}_2CH_3$), 1.57, 1.34 (3H each, s, Me_2C), 0.98 (3H, t, $CH_2CH_2C\underline{H}_3$). UV $\lambda_{max}^{H_2O}$ nm (ε): 263 (15700); λ_{min} nm (ε): 212 (3000). MS *m/z*: 349 (M^+). *Anal.* Calcd for $C_{16}H_{23}N_5O_4$: C, 55.00; H, 6.64; N, 20.05. Found: C, 55.22; H, 6.68; N, 20.00.

8-*n*-Propyladenosine (9)——Compound **8** (60 mg, 0.17 mmol) in 10 ml of 50% HCO_2H was stirred overnight at room temperature. Water (5 ml) was added to the solution and the solvent was evaporated off. The addition and evaporation of H_2O were repeated several times and the residue was dissolved in 2 N NH_4OH (5 ml), and kept for 30 min at room temperature. The solvent was removed and the residue was dissolved in a small volume of MeOH. This solution was subjected to pTLC. After development of the plate with $CHCl_3$–EtOH (5 : 1), the appropriate band was eluted with MeOH. The solution was evaporated and the residue was crystallized from H_2O to give 47 mg (88%) of **9**, mp 179—181 °C. NMR: 8.05 (1H, s, H-2), 7.28 (2H, br, NH_2), 5.96 (1H, br, HO), 5.75 (1H, d, H-1′, $J_{1',2'}$ = 7.3 Hz), 6.36, 6.24 (1H each, br, HO), 4.90 (1H, dd, H-2′, $J_{2',3'}$ = 6.0 Hz), 4.16 (1H, dd, H-3′, $J_{3',4'}$ = 1.0 Hz), 4.01 (1H, d, H-4′), 3.64 (2H, m, H-5′), 2.85 (2H, t, $C\underline{H}_2CH_2CH_3$), 1.77 (2H, m, $CH_2C\underline{H}_2CH_3$), 0.98 (3H, t, $CH_2CH_2C\underline{H}_3$). UV $\lambda_{max}^{H_2O}$ nm: 263, 212; λ_{min} nm: 228. *Anal.* Calcd for $C_{13}H_{19}N_5O_4$: C, 50.47; H, 6.19; N, 22.65. Found: C, 50.24; H, 6.13; N, 22.47.

N^6,N^6-Dimethyl-8-(α-ethoxycarbonyl)isopropyl-2′,3′-*O*-isopropylideneadenosine (10)——Compound **2** (980 mg, 2.3 mmol) in 30 ml of DMF was treated with 50% NaH (432 mg, 9.0 mmol). After the evolution of hydrogen had ceased, CH_3I (0.56 ml, 9.0 mmol) was added and the solution was kept for 1 h at room temperature. The solution was neutralized with 2 N HCl, and partitioned between AcOEt–H_2O, then the organic layer was dried over Na_2SO_4. The solvent was removed and the residue was dissolved in $CHCl_3$; this solution was applied to a column of silica gel (30 g). The eluate with 0.5% EtOH–$CHCl_3$ was concentrated to leave 622 mg (69%) of **10** as a foam. NMR: 8.21 (1H, s, H-2), 6.95 (1H, br, HO-5′), 5.67 (1H, d, H-1′, $J_{1',2'}=5.1$ Hz), 5.38 (1H, dd, H-2′, $J_{2',3'}=6.1$ Hz), 5.11 (1H, d, H-3′), 4.41 (1H, s, H-4′), 4.21 (2H, m, C$\underline{H}_2$CH$_3$), 3.84 (2H, d, H-5′), 3.54 (6H, s, N(CH$_3$)$_2$), 1.63, 1.35 (3 each, s, Me$_2$C), 1.75, 1.71 (3 each, s, Me$_2$C-8), 1.21 (3H, t, CH$_2$C$\underline{H}_3$). MS *m/z*: 431 (M^+).

N^6,N^6-Dimethyl-2′-deoxyadenosine (11)——2′-Deoxyadenosine (125 mg, 0.5 mmol) was dissolved in 10 ml of DMF, and 60% NaH (100 mg, 2.5 mmol) was added to the solution. After the evolution of hydrogen had ceased, CH_3I (0.06 ml, 1.0 mmol in 2 ml of DMF) was added dropwise and the mixture was kept at room temperature for 1 h, neutralized with 50% HCO_2H and evaporated to dryness. The residue was taken up in EtOH, the insoluble material being filtered off, and the filtrate was subjected to pTLC. The plate was developed with $CHCl_3$–EtOH (10 : 1). The appropriate band was eluted with 50% $CHCl_3$–EtOH and the solvent was evaporated off to give 56 mg (40%) of **11**, mp 174—174.5 °C (177.5—179 °C[10]). NMR: 8.40 (1H, s, H-8), 8.27 (1H, s, H-2), 6.44 (1H, t, H-1′), 5.30 (2H, m, H-3′, HO-3′), 4.50 (1H, br, HO-5′), 3.96 (1H, m, H-4′), 3.69 (2H, d, H-5′), 3.49 (6H, s, N(CH$_3$)$_2$), 2.50 (2H, m, H-2′). UV $\lambda_{max}^{H_2O}$ nm (ε): 277 (17700), 217 (15300); λ_{min} nm (ε): 237 (1900). $\lambda_{max}^{0.1\,N\,HCl}$ nm (ε): 269 (16800); λ_{min} nm (ε): 234 (2300). MS *m/z*: 279 (M^+), 163 (B+1). *Anal.* Calcd for $C_{12}H_{17}N_5O_3$: C, 51.60; H, 6.15; N, 25.06. Found: C, 51.57; H, 6.11; N, 25.08.

N^4,N^4-Dimethyl-2′-deoxycytidine (12)——2′-Deoxycytidine (132 mg, 0.5 mmol) in 10 ml of DMF was treated with 60% NaH (160 mg, 4.0 mmol). After the evolution of hydrogen had ceased, CH_3I (0.12 ml, 2.0 mmol, in 2 ml of DMF) was added dropwise to the solution. After neutralization of the mixture with 1 N HCl, the solvent was removed *in vacuo* and the residue was taken up in EtOH–$CHCl_3$ (1 : 1, 5 ml). This solution was subjected to pTLC. The plate was developed with $CHCl_3$–EtOH (5 : 1) and the appropriate band was extracted with 50% EtOH–$CHCl_3$. Concentration of the solution gave crystalline **12** (83 mg, 65%), mp 183—187 °C (176—180 °C[11]). NMR: 7.97 (1H, d, H-6), 6.28 (1H, d, H-1′), 6.11 (1H, d, H-5), 5.00 (2H, br s, HO-3′,5′), 4.23 (1H, br H-3′), 3.60 (3H, m, H-4′,5′), 3.08 (6H, s, N(CH$_3$)$_2$), 2.10 (2H, m, H-2′). UV $\lambda_{max}^{H_2O}$ nm: 280; λ_{min} nm: 252. $\lambda_{max}^{0.1\,N\,HCl}$ nm: 285; λ_{min} nm 215. MS *m/z*: 255 (M^+), 138 (B^+).

3-(2′,3′-*O*-Isopropylideneadenosin-8-yl)propionic Acid (13)——Compound **2** (3.0 g, 6.9 mmol) in 15 ml of DMF was treated with 60% NaH (416 mg, 10.4 mmol) and after the evolution of hydrogen had ceased ethyl bromacetate (0.76 ml, 6.9 mmol, in 2 ml of DMF) was slowly added to the solution. At 5 min after the completion of the addition (the appearance of a spot of **13** on TLC was confirmed), 10 ml of 5 N NaOH was added and the solution was stirred for 90 min at room temperature. Then 50% formic acid was added to the solution, and the pH was adjusted to 4.0. The solution was warmed on a boiling water bath for 2 h. After cooling, the separated crystals were collected by filtration to give 1.67 g (64%) of **13**, mp 239.5—242.0 °C (dec.). NMR: 12.29 (1H, br s, CO_2H), 8.01 (1H, s, H-2), 7.21 (2H, br, NH_2), 6.07 (1H, d, H-1′), 5.61 (1H, dd, H-2′), 5.26 (1H, br s, HO-5′), 5.00 (1H, dd, H-3′), 4.17 (1H, m, H-4′), 3.46 (2H, br s, H-5′), 3.08 (2H, t, 8-C$\underline{H}_2$–), 2.83 (2H, t, –CH$_2$CO–), 1.55, 1.33 (3 each, s, Me$_2$C). UV $\lambda_{max}^{H_2O}$ nm (ε): 263 (16000); λ_{min} nm (ε): 229 (2800). *Anal.* Calcd for $C_{16}H_{21}N_5O_6$: C, 50.65; H, 5.58; N, 18.46. Found: C, 50.59; H, 5.61; N, 18.20.

3-(Adenosin-8-yl)propionic Acid (14)——Compound **13** (379 mg, 1.0 mmol) was dissolved in 10 ml of 50% HCO_2H and the solution was stirred overnight at room temperature. Water (5 ml) was added to the solution and the mixture was evaporated. Addition and evaporation of H_2O were repeated several times until the final concentrate began to crystallize. The crystals were collected to give 238 mg (70%) of **14**. NMR: 12.33 (1H, br s, CO_2H), 8.06 (1H, s, H-2), 7.25 (2H, br s, NH_2), 5.90 (1H, br s, HO), 5.79 (1H, d, H-1′), 5.48 (1H, br d, HO), 5.37 (1H, br d, HO), 4.88 (1H, m, H-2′), 4.12 (1H, br s, H-3′), 4.02 (2H, d, H-5′), 3.07 (2H, d, H-5′), 3.05 (2H, d, 8-C$\underline{H}_2$CH$_2$–), 2.83 (2H, d, CH$_2$C$\underline{H}_2$CO).

8-Aminomethyl-2′,3′-*O*-isopropylideneadenosine (16)——5′-*O*-Acetyl-8-cyano-2′,3′-*O*-isopropylideneadenosine[4] (1.12 g, 3.0 mmol) was dissolved in 50 ml of THF, and $LiAlH_4$ (342 mg, 9.0 mmol) was added to the solution. After 30 min, H_2O was added until the cloudy suspension became clear. The precipitate was filtered off and the filtrate was absorbed on 3.5 g of silica gel, which was then dried under a vacuum. This was suspended in $CHCl_3$ and applied on the top of a column of silica gel (20 g). The eluate with 8—25% EtOH–$CHCl_3$ was collected and concentrated to leave 660 mg (65%) of **16** as a foam. NMR: 8.03 (1H, s, H-2), 7.19 (2H, br s, 6NH_2), 6.24 (1H, d, H-1′), 5.48 (1H, dd, H-2′), 4.19 (1H, dd, H-3′), 4.06 (1H, m, H-4′), 3.89 (2H, s, 8-CH_2), 3.38 (2H, m, H-5′), 1.47, 124 (3 each, s, Me$_2$C). The signals of the 8-amino and 5′-hydroxyl protons were masked by that of H_2O around 3.3 ppm. Ninhydrin test of **16**: positive.

8-Hydroxymethyl-2′,3′-*O*-isopropylideneadenonine (17)——Compound **16** (548 mg, 1.63 mmol) in 20 ml of DMF was treated with 0.5 ml of iso-AmONO and 0.2 ml of CF_3CO_2H for 30 min at room temperature. The solution was neutralized with 2 N NH_4OH and the solvent was removed *in vacuo*. The residue was dissolved in $CHCl_3$ and applied to a column of silica gel (20 g). The eluate with 4% EtOH–$CHCl_3$ was concentrated to give 77 mg of an unidentified

product, mp 135—142 °C (dec.). From the eluate with 8% EtOH–$CHCl_3$, **17** was obtained after evaporation of the solvent; 292 mg (53%), mp 211.5—213.5 °C. NMR: 8.13 (1H, s, H-2), 7.34 (2H, br s, NH_2), 6.29 (1H, d, H-1′), 5.80 (1H, t, CH_2OH), 5.55 (1H, dd, H-2′), 5.26 (1H, t, HO-5′), 5.00 (1H, dd, H-3′), 4.68 (2H, d, 8-CH_2), 4.16 (1H, m, H-4′), 3.50 (2H, m, H-5′), 1.55, 1.32 (3 each, s, Me_2C). UV $\lambda_{max}^{H_2O}$ nm: 262; λ_{min} nm: 230. MS *m/z*: 337 (M^+), 148 (adenine + CH_2).

8-Hydroxymethyladenosine (18)——Compound **17** (60 mg, 0.18 mmol) was dissolved in 5 ml of 50% HCO_2H and the solution was kept overnight at room temperature. Water was added and evaporated *in vacuo*. The addition and evaporation of H_2O were repeated several times, then the residue was dissolved in 2 N NH_4OH (5 ml) and kept for 30 min. The solvent was evaporated off and the residue was subjected to preparative TLC developed with $CHCl_3$–EtOH (4 : 1). The main band was extracted with $CHCl_3$–EtOH (1 : 1) and concentrated to leave 45 mg (84%) of **18** as a foam. NMR: 8.08 (1H, s, H-2), 7.39 (2H, br s, NH_2), 6.03 (1H, d, H-1′, $J_{1',2'}$ = 6.8 Hz), 4.82 (1H, dd, H-2′), 4.66 (2H, m, 8-CH_2), 4.17 (1H, m, H-3′), 3.98 (1H, m, H-4′), 3.63 (m, H-5′, H_2O). UV $\lambda_{max}^{H_2O}$ nm: 262; λ_{min} nm: 230.

8.2′-Anhydro-9-β-D-arabinofuranosyl-8-hydroxymethyladenine (20)——Compound **18** (207 mg, 0.70 mmol) was suspended in 10 ml of MeOH, and Bu_2SnO (174 mg, 0.70 mmol) was added. The mixture was refluxed for 2 h, then cooled to room temperature. TsCl (2.0 g) and Et_3N (4 ml) were added, and the whole was stirred for 30 min. Silica gel (7 g) was added to the mixture and then dried *in vacuo*. The dried gel was applied on top of a silica gel column (100 g). The eluate with 12% EtOH–$CHCl_3$ was concentrated and the residue was crystallized from EtOH to give 75 mg (24%) of the 2′-*O*-tosylate (**19**). Compound **19** (75 mg, 0.17 mmol) was dissolved in a mixture of DMF (2 ml) and *tert*-BuOH (2 ml). *tert*-BuOK (32 mg, 0.34 mmol) was added to the solution and the mixture was stirred at room temperature for 3 h. The solution was neutralized with 1 N HCl, then concentrated to dryness, and the residue was dissolved in MeOH. This solution was subjected to preparative TLC developed with $CHCl_3$–MeOH (4 : 1). The main band was extracted with the same solvent and the solution was evaporated. The residue was crystallized from EtOH to give 51 mg (98%) of **20**. NMR: 8.12 (1H, s, H-2), 7.21 (2H, br s, NH_2), 5.86 (1H, d, H-1′, $J_{1',2'}$ = 2.7 Hz), 5.72 (1H, d, HO-3′), 4.98 (1H, d, 8-CH_a), 4.76 (1H, d, 8-CH_b, $J_{a,b}$ = 14 Hz), 4.85 (1H, t, HO-5′), 4.29 (1H, d, H-2′), 4.07 (1H, m, H-3′), 3.84 (1H, m, H-4′), 3.48 (2H, m, H-5′, partially overlapped with the signals of H_2O contained in the solvent). UV $\lambda_{max}^{H_2O}$ nm: 263; λ_{min} nm: 235. *Anal.* Calcd for $C_{11}H_{13}N_5O_4$: C, 47.31; H, 4.69; N, 25.08. Found: C, 47.15; H, 4.69; N, 24.91.

References and Notes

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