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# Studies of Nucleosides and Nucleotides. LX.[1] Purine Cyclonucleosides. (22). Synthesis of 8,5′-Anhydro-8-mercapto-9-β-D-arabinofuranosyladenine and 8,5′-Anhydro-8-mercapto-9-β-D-xylofuranosyladenine by the Rearrangement of O-Cyclonucleosides

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8.2-Anhydro-9-β-D-arabinofuranosyladenine (I) was converted to 5′-tosyl derivative (II) in a yield of 75%. When Compound (II) was heated with sodium hydrogen sulfide in dimethylformamide (DMF) 8,5′-S-cyclonucleoside having arabinosyl configuration (IV) was obtained in a yield of 46%. From the ditosyl derivative (III) analogously a cyclonucleoside having 3′-tosyl group (VII) was obtained. 8,3′-Anhydro-9-β-D-xylofuranosyladenine (VIII) was converted to 5′-tosyl derivative (IX) and heated with sodium hydrogensulfide in DMF. In addition to a 8,5-S-cyclonucleoside of xylofuranosyl configuration (X), two compounds, 8,3′-anhydro-8-oxy-9-(5′-deoxy-5′-mercapto-β-D-xylofuranosyl) adenine disulfide (XI) and 5′-deoxy-5′-mercapto-8-oxy-9-β-D-xylofuranosyladenine (XII) was obtained. Compound (XII) was also obtained from X by the treatment with 0.01N sodium hydroxide.

Thus, the OH group of xylo configuration in the sugar moiety of 8,5′-S-cyclonucleoside was found to be able to cleave the S-hydro linkage even in a mild condition.

We have previously reported[3] the interconversion between 8,2′-O-cycloadenosine and 8-oxy-arabinofuranosyladenine or 8,3′-O-cycloadenosine and 8-oxy-xylofuranosyladenine by the treatment with dilute aqueous alkali. Since this rearrangement would be caused by the closest sterical arrangement of hydroxyls of the carbohydrate moiety and C-8 atom of the adenine moiety, we can expect to utilize this reaction in the synthesis of 8,5′-S-cyclonucleosides of arabino- or xylo-configuration. Resulting 8,5′-S-cyclonucleosides may be interesting in comparing their physico-chemical properties with ribo counterpart.

8,2′-Anhydro-9-β-D-arabinofuranosyladenine[4] (1) was treated with 1.5 equivalent of tosyl chloride in pyridine at 0—5°. Monotosylated compound (II) was obtained in a yield of 75%. The position of the tosylation should be 5′, because 3′-tosyl group was found to be inert in the following reactions. When the condition of the tosylation reaction changed to 10—15° using 2.5 equivalents of tosyl chloride, 3′,5′-di-O-tosyl compound (III) was obtained.

Compound II was then heated in anhydrous DMF containing NaSH at 60° for 6 hr in nitrogen atmosphere. An S-cyclo-nucleoside (IV), mp 189—191°, was obtained in a yield of 46%. From ultraviolet (UV) absorption properties (see experimental) which closely resembled those of 8,5′-S-cycloadenosine[5] and elemental analysis, together with other physical data discussed below, the structure of IV was assigned to be 8,5′-anhydro-8-mercapto-9-β-D-arabinofuranosyladenine.[6] Although the pathway of this reaction could not be determined whether *via* 8-mercapto-5′-tosyl (V) or 5′-deoxy 5′-mercapto (VI) intermediate, the pathway through VI would be more plausible because the direct attack of SH-should occur on both

1) Part XLIX: M. Ikehara and T. Tezuka, *J. Carbohyd., Nucleosides, Nucleotides*, **1**, 67 (1974).
2) Location; *6-1-1, Toneyama, Toyonaka, Osaka.*
3) M. Ikehara, M. Kaneko and Y. Ogiso, *Tetrahed. Letters*, **1970**, 4673.
4) M. Ikehara and Y. Ogiso, *Tetrahedron*, **28**, 3695 (1972).
5) M. Ikehara, M. Kaneko and M. Sagai, *Tetrahedron*, **26**, 5757 (1970).
6) Recently this compound was described by Mizuno, *et al.*,[7] but elemental analysis value and detailed physical properties were not reported.

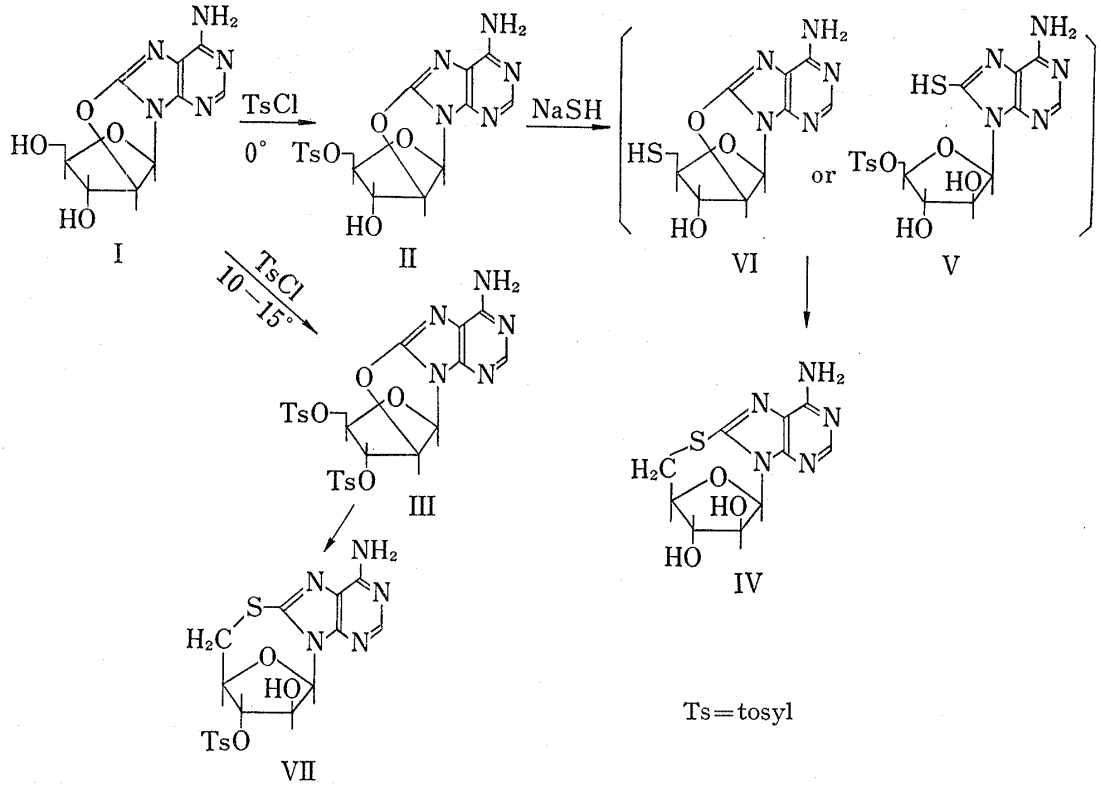



Chart 1

C-2′ and C-8[4] as experienced earlier. The analogous reaction of ditosylate (III) with NaSH afforded 8,5′-anhydro-8-mercapto-9-β-D-3′-O-tosylarabinofuranosyladenine (VII) in a yield of 32%. Nuclear magnetic resonance (NMR) signal of H-3′ (5.13 δ) shifted significantly towards the low field relative to compound IV. Circular dichroism (CD) spectrum of 8,5′-S-cycloarabinosyladenine (IV) was compared with that of the ribose counterpart[5] (Fig. 1). Although the whole spectra resembled each other, the positive band at 287 nm was significantly smaller in magnitude than that of ribosyl derivative. As discussed previously,[8] the magnitude of the Cotton band in B-region reflects the torsion angle ($\phi_{CN}$)[9] of the base. If this supposition were valid also for the present case, the torsion angle of the arabino-(IV) and the ribo-cyclonucleoside may be different in certain degree. This point may be clarified by the X-ray crystallographical analysis.

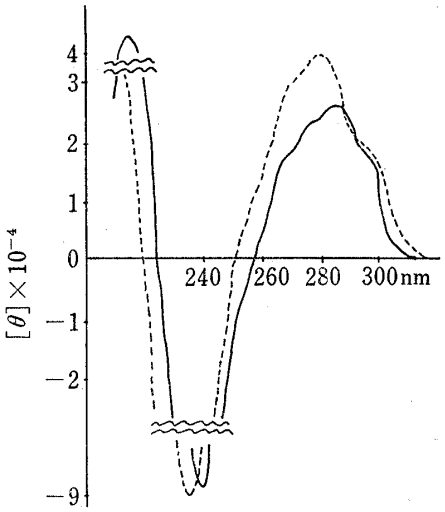
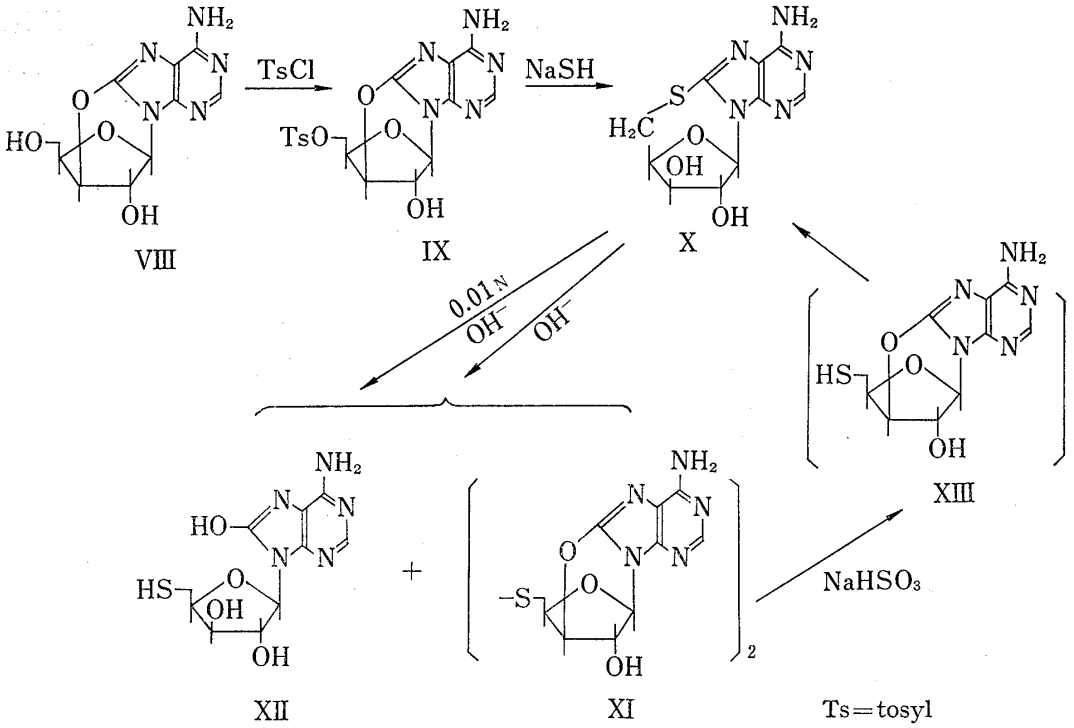



Fig. 1
----: ribofuranose
——: arabinofuranose

8,3′-Anhydro-9-β-D-xylofuranosyladenine[4] (VIII) was next treated with 1.5 equivalent of tosyl chloride in pyridine at 0—5° for 18 hr. A monotosylated compound (IX) was obtained in a yield of 52%. When compound (IX) was heated in dimethyl formamide (DMF) with NaSH at 60° for 6 hr in nitrogen atmosphere, the starting material converted completely

7) Y. Mizuno, C. Kaneko and Y. Okawa, *J. Org. Chem.*, **39**, 1440 (1974).
8) M. Ikehara, M. Kaneko, Y. Nakahara, S. Yamada and S. Uesugi, *Chem. Pharm. Bull.* (Tokyo), **19**, 1381 (1971).
9) J. Donohue and K.N. Trueblood, *J. Mol. Biol.*, **2**, 363 (1960).




VIII IX X XIII XII XI

Chart 2

to a compound (X) having UV absorption resembling that of 8,5′-S-cyclonucleoside IV. However, after work-up procedure other compounds XI having UV absorption of 8,3′-O-cyclonucleoside and XII having 8-oxyadenosine chromophore were obtained in addition to X. Preparative thin-layer chromatography (TLC) of the reaction mixture gave 8,5′-anhydro-8-mercapto-9-β-D-xylofuranosyladenine (X) in a poor yield (8.9%). The structure of X was confirmed by elemental analysis and UV absorption spectra having maximum around 286 nm, together with physical properties to be discussed below.[10] The second product (XI) could be obtained from the mother liquor of X by a triethyl amino ethyl (TEAE)-cellulose column chromatography. Compound (XI) had UV absorption similar to that of 8,3′-O-cycloadenosine, but migrated very slowly in TLC or paper chromatography. When XI was heated in sodium bisulfite solution, it converted to 8,5′-S-cyclo-xylosyladenine (X) *via* 5′-SH compound (XIII). These facts suggested that compound XI might be disulfide of 5′-deoxy-5′-mercapto-8,3′-anhydro-8-oxy-9-β-D-xylofuranosyladenine. Another product XII was also isolated from the mother liquor of X. This compound could be obtained easily from X by heating in 0.01N NaOH at 60—70° for 3 hr. Therefore, compound (XII) may be originated from X during isolation procedure by the catalysis of basic TEAE-allulose. The UV absorption properties resembling those of 8-oxyadenosine[11] and migration distance 0.63 relative to 8-oxyadenosine in a borate paper electrophoresis suggested the structure of 8-oxy-9-(5′-deoxy-5′-mercapto-β-D-xylofuranosyl)adenine for compound (XII). Comparative hydrolysis of arabino cyclonucleoside IV by this condition brought about no reaction.

Thus it was concluded that when an up hydroxyl group in the carbohydrate moiety situated sterically close to the anhydro linkage as was expected in X, even the sulfide bond could easily be cleaved. This fact reflects that the distance between OH groups of arabino and xylonucleosides and the C-8 atom of the base may be different. In the latter nucleoside (X) an entropically favored reaction which involved the attack of xylo-OH to the nearby situated 8-C atom occurred and gave rise to compounds (X) and (XI).

10) This compound was described by Mizuno, *et al.*,[7] but detailed chemical and physical properties were not reported.

11) M. Ikehara, H. Tada and M. Kaneko, *Tetrahedron*, **24**, 3489 (1968).

Table I. NMR Signals of 8,5′-Cycloadenosines (ppm)

| Compound | 2-H | 6-$NH_2$ | 1′-H | 2′-H | 3′-H | 4′-H | 5′-H | 2′-OH | 3′-OH |
|---|---|---|---|---|---|---|---|---|---|
| S-ribo | 8.12 (S) | 7.27 (S) | 6.17 (d) $J1'$-2′= 1.5 | 4.71 (m) $J2'$-3′= 6.0 | 4.36 (m) | 4.80 (t) $J4'$-5′= 2.5 | 3.15 (q) | 5.61 (d) $J2'$-2′OH= 7.0 | 5.27 (d) $J3'$-3′OH= 4.5 |
| S-arabo | 8.06 (S) | 7.17 (S) | 6.46 (d) $J1'$-2′= 2.0 | 4.5[a] | | 4.78 (t) $J4'$-5′= 2.0 | A, 3.32(q) B, 3.14(q) $J4'$-5′B= 4.0 $J_{A\text{-}B}$= 14.5 | 5.56 (d)[a] $J2'$-2′OH= 5.0 | |
| S-xylo | 8.10 (S) | 7.25 (S) | 5.99 (d) $J1'$-2′= 2.0 | | | | | | |
| O-ribo | 8.10 (S) | 6.99 (S) | 5.97 (S) | 4.54 (d) | 4.50 (d) $J3'$-4′= 6.0 | 4.25 (m) $J4'$-5′A =2.0 | A, 4.58(q) B, 4.08(q) $J4'$-5′B =1.5 $J4$-B= 13.0 | 5.59 (d) $J2'$-2′OH =6.0 | 5.29 (d) $J3'$-3′OH =5.0 |
| O-arabo | 8.06 (S) | 6.85 (S) | 6.30 (d) $J1'$-2′= 6.0 | 4.4[a] | | 4.20 (d) | A, 4.52(q) B, 4.11(d) $J_{A\text{-}B}$= 13.0 | 5.62 (d) $J2'$-2′OH =6.0 | 5.50 (d) $J3'$-3OH =4.0 |
| O-xylo | 8.06 (S) | 6.96 (S) | 5.76 (S) | | | | | | |

a) This signal could not be assigned definitely to each proton.

NMR signals of 8,5′-cyclonucleosides, having, ribo-, arabino- and xyloconfigurations were listed in Table I. The base plane of the 8,5′-S-ribocyclonucleoside was found to be in endo conformation by X-ray crystallography.[12] The NMR data of the coupling constant $J4'$—5′ or $J4'$—5″ were 2.5 Hz and supported this endo conformation held also in the solution (see Fig. 2). Also 8,5′-O-ribocyclonucleoside showed coupling constants 1.5—2.0 Hz. However, in the case of 8,5′-O- and S-arabinonucleosides coupling constants of two 5′-Hs differ in the range of 2.0 Hz and suggested a conformation other than the pure endo form. Considering a sterical repulsion between up OH and S- or O-atom of the anhydro linkage, we may predict a conformation somewhat twisted toward the exo direction. This point may be clarified by the X-ray crystallography. In the xylocyclonucleosides, signals of 2′ and 5′-H could not be assigned certainly due to poorly resolved peaks.

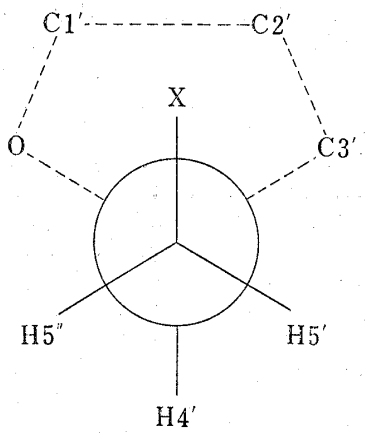


Fig. 2

Table II. Prinincipal Peaks in Mass Spectra of 8,5′-Cyclonucleosides (%)

| Compound | $M^+$ | B[a] | B+1 | Others |
|---|---|---|---|---|
| O-araA | 265 (100) | 151 (69) | 152 (88) | 167 (69) |
| S-araA | 281 (100) | 167 (73) | 168 (33) | 192 (19) |
| S-xyloA | 281 (38) | 167 (100) | 168 (41) | 185 (41) |

a) peaks corresponding to either 8-oxyadenine or 8-mercaptoadenine

12) K. Tomita, T. Nishida, T. Fuziwara and M. Ikehara, *Biochem. Biophis Res. Commun.*, **41**, 1043 (1970).

Mass spectra of the 8,5′-cyclonucleosides were listed in Table II. All these compounds gave the molecular ion peak and the peaks corresponding to 8-OH or SH-adenine as reported previously on other cyclonucleosides.[13] This fact supported the structure of these compounds to be correct.

## Experimental[14]

**8,2′-Anhydro-8-oxy-9-(5′-O-*p*-toluensulfonyl-β-D-arabinofuranosyl)adenine (II)**——8,2′-Anhydro-8-oxy-9-β-D-arabinofuranosyladenine (I) (260 mg, 1.0 mmole) was dissolved in anhydrous pyridine (50 ml) and concentrated to 25 ml *in vacuo*. The solution was cooled to 0° and tosyl chloride (290 mg, 1.5 mmole) was added. The mixture was kept at 0—5° for 18 hr under exclusion of the moisture. Water was added under cooling with acetone-dry ice and the solvent was evaporated. To the residue was added ethanol (2 ml) and the solution was dropped into water. Powder was collected by centrifugation, washed with water, and recrystallized from ethanol–water. 5′-Tosyl derivative was obtained in a yield of 311 mg (75%). UV $\lambda_{max}^{50\%\ EtOH}$ (nm) 261; $\lambda_{max}^{H^+}$ 229, 258; $\lambda_{max}^{OH^-}$ 260, PPC: *Rf* (A) 0.50.

**8,5′-Anhydro-8-mercapto-9-β-D-arabinofuranosyladenine (IV)**——Into a solution of DMF (20 ml) containing NaSH (2 mmoles, prepared from NaH and dry $H_2S$) was added 5′-tosyl-cyclonucleoside (II) (300 mg). The mixture was heated at 60° for 6 hr in a sealed tube. The reaction mixture was neutralized with 1N HCl, $H_2S$ was chased off with $N_2$ gas, and the solvent was evaporated *in vacuo*. Water (1 ml) was added and the precipitating powder was collected by filtration. The powder was washed with a small amount of water and recrystallized from methanol to give 94 mg (46%) of cyclonucleoside (IV), mp 189—191°. *Anal.* Calcd. for $C_{10}H_{11}O_3N_5\ S\cdot 1.5\ H_2O$: C, 41.81; H, 4.00: N, 24.38: S, 11.16. Found: C, 41.79; H, 4.16: N, 24.30; S, 11.04. UV: nm (ε) $\lambda_{max}^{H^+}$ 285.5 (21500), 294 (shoulder, 16800); $\lambda_{max}^{H_2O}$ 236 (8800) 278 (shoulder, 17700), 286 (19700), 296 (shoulder, 13200); $\lambda_{max}^{OH^-}$ 278 (shoulder, 17700), 286 (19700), 296 (shoulder, 13200). PPC: *Rf* (A) 0.31. TLC ($CHCl_3$–EtOH, 9: 1) *Rf* 0.15.

**8,5′-Anhydro-8-mercapto-9-(3′-O-*p*-toluenesulfonyl-β-D-arabinofuranosyl)adenine (VII)**——8,2′-Anhydro-8-oxy-9-β-D-arabinofuranosyladenine (I) (260 mg, 1.0 mmole) was dissolved in anhydrous pyridine (50 ml) and evaporated *in vacuo* to 25 ml. The solution was cooled to −5—10° and tosyl chloride (470 mg) was added. The mixture was kept at 10—15° for 24 hr under exclusion of the moisture. Into the mixture was added water with dry ice-acetone cooling and the solvent was removed by vacuum distillation. The residue was taken up in water (1 ml) and undissolved powder was collected by filtration. After drying, the powder was dissolved in DMF (20 ml) and NaSH (2 mmoles) was added. The mixture was heated at 60° for 6 hr in a sealed tube. Neutralization with 1N HCl, bubbling through with $N_2$ gas, and evaporation of the solvent gave a residue. After washing with water (1 ml), the residue was recrystallized from methanol to give 140 mg (32.6%) of compound VII, mp 217—220°. *Anal.* Calcd. for $C_{17}H_{17}O_5N_5\ S\cdot 1.5\ H_2O$, C, 45.95, H, 4.08; N, 15.76; S, 14.40. Found: C, 46.2, 1; H, 4.29; N, 15.38, S, 14.10. TLC ($CHCl_3$–EtOH, 9: 1) *Rf* 0.24. UV: (nm) $\lambda_{max}^{H^+}$ 285.5, 294 (shoulder); $\lambda_{max}^{H_2O}$ 236, 278 (shoulder), 286, 296 (shoulder); $\lambda_{max}^{OH^-}$ 278 (shoulder, 286, 296 shoulder). NMR (δ) 8.03 (S, H-2), 7.19 (S, $NH_2$-6), 6.49 (d, H-1, *J*H1′–H2′=7.5 Hz), 4.85 (m, H-2′), 5.13 (d, H-3′), 4.79 (t, H-4), 5.98 (d, 2′-OH, *J*H2′–HO2′=6.5 Hz) 7.84 (d, Ts–Ha), 7.45 (d, Ts–Hb, *J*Ha–Hb=8.0 Hz), 2.41 (s, Ts–$CH_3$).

**8,3′-Anhydro-8-oxy-9-(5′-O-*p*-toluenesulfonyl-β-D-xylofuranosyl) adenine (IX)**——8,3′-Anhydro-8-oxy-9-β-D-xylofuranosyladenine (III) (980 mg, 3.8 mmoles) was dissolved in anhydrous phyridine (250 ml) and tosyl chloride (1.05 g, 5.5 mmoles) was added. The mixture was kept at 0—5° for 18 hr under exclusion of the moisture. Water was added under cooling with dry ice-acetone to decompose tosyl chloride, solvent was evaporated in vacuo, and the residue was dissolved in EtOH–water. 5′-Tosyl derivative (IX) was obtained in a yield of 500 mg (52.3%). UV $\lambda_{max}^{H^+}$ (nm) 263, $\lambda_{max}^{50\%\ EtOH}$ 229, 263; $\lambda_{max}^{OH^-}$ 262, PPC: *Rf* (A) 0.48.

**8,5′-Anhydro-8-mercapto-9-β-D-xylofuranosyladenine (X), 8,3′-Anhydro-8-oxy-9-(5′-deoxy-5′-mercapto-β-D-xylofuranosyl)adenine Disulfide (XI) and 8-Oxy-9-(5′-deoxy-5′-mercapto-β-D-xylofuranosyl) adenine (XII)**——i) Sodium hydrogensulfide (2 mmoles) was dissolved in anhydrous DMF (10 ml). Into the solution was added 5′-tosyl-8,3′-O-cyclonucleoside (IX) (100 mg) under atmosphere of $N_2$ gas. Tightly stoppered solution was heated at 60° for 6 hr. TLC ($CHCl_3$–EtOH, 7: 3) examination of the reaction mixture at this stage showed only one spot corresponding to 8,5′-S-cyclo-arabinonucleoside (X). The mixture was neutralized with 1N HCl, bubbled through with nitrogen gas, and the solvent was evaporated *in vacuo*. The residue was applied to the preparative TLC ($CHCl_3$–EtOH, 15.5) and bands were extracted with $CHCl_3$–methanol (1: 1) mixture. Recrystallization of the extract from methanol gave 6 mg (8.9%) of X. The mother liquor contained X and XII and the latter compound increased in due time. X: *Anal.* Calcd. for $C_{10}H_{11}O_3N_5S$: C, 42.70; H, 3.94; N, 24.90; S, 11.40. Found: C, 42.26; H, 4.01; N, 24.71; S, 11.70. UV

13) M. Ikeda, Y. Tamura and M. Ikehara, *T. Heterocycl. Chem*, 7, 1377 (1970).

14) Experimental conditions were as described in previous paper[4] except for solvent of paper chromatograpy: A, water adjusted to pH 10 with conc. ammonia.

(nm) $\lambda_{max}^{H^+}$ 285.5, 294 (shoulder); $\lambda_{max}^{H_2O}$ 236, 278 (shoulder), 286, 296 (shoulder); $\lambda_{max}^{OH^-}$ 278, 286, 296 (shoulder). PPC; *Rf* (A) 0.30. XII: UV: (nm) $\lambda_{max}^{H^+}$ 264, 285 (shoulder), $\lambda_{max}^{H_2O}$ 271; $\lambda_{max}^{OH^-}$ 281. PPC: *Rf* (A) 0.17. PEP: (pH 7.5) $R_{8\text{-SH-adenosine}}$ 0.56, (borate); $R_{8\text{-OH-adenosine}}$ 0.63.

ii) Sodium hydrogensulfide (4 mmoles) was dissolved in anhydrous DMF (60 ml) and compound IX (830 mg, 2 mmoles) was added with bubbling through of $N_2$. The sealed solution was heated at 60° for 6 hr and worked up as described in i). In order to remove compound XII first, the products were dissolved in 80% EtOH and applied to a column of TEAE-cellulose (200 ml), which was eluted with 80% EtOH. Eluants had UV max at 260—265 nm. Solvent was evaporated and the residue was recrystallized from methanol to give a mixture of X and XI (173 mg, the ratio of X: XI as estimated from NMR peaks was 1: 3). Separation of this mixture with TLC gave XI: UV: (nm) $\lambda_{max}^{H^+}$ 264, $\lambda_{max}^{H_2O}$ 264.5, $\lambda_{max}^{OH^-}$ 265. NMR: ($\delta$) 8.01 (s, H-2), 6.84 (s, $NH_2$-6), 5.80 (s, H-1′).

iii) 8,5′-S-Cyclonucleoside (X, 1 mg) was dissolved in 0.01N NaOH and heated at 60—70° for 3 hr. Checking with PEP showed only a spot corresponding to compound XII ($R_{8\text{-SH-adenosine}}$ 0.56).

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