Pharmaceutical Institute,
Tohoku University School of Medicine
Sendai

TOSHIO NAMBARA
MITSUTERU NUMAZAWA
HIROI TAKAHASHI

Received March 14, 1968

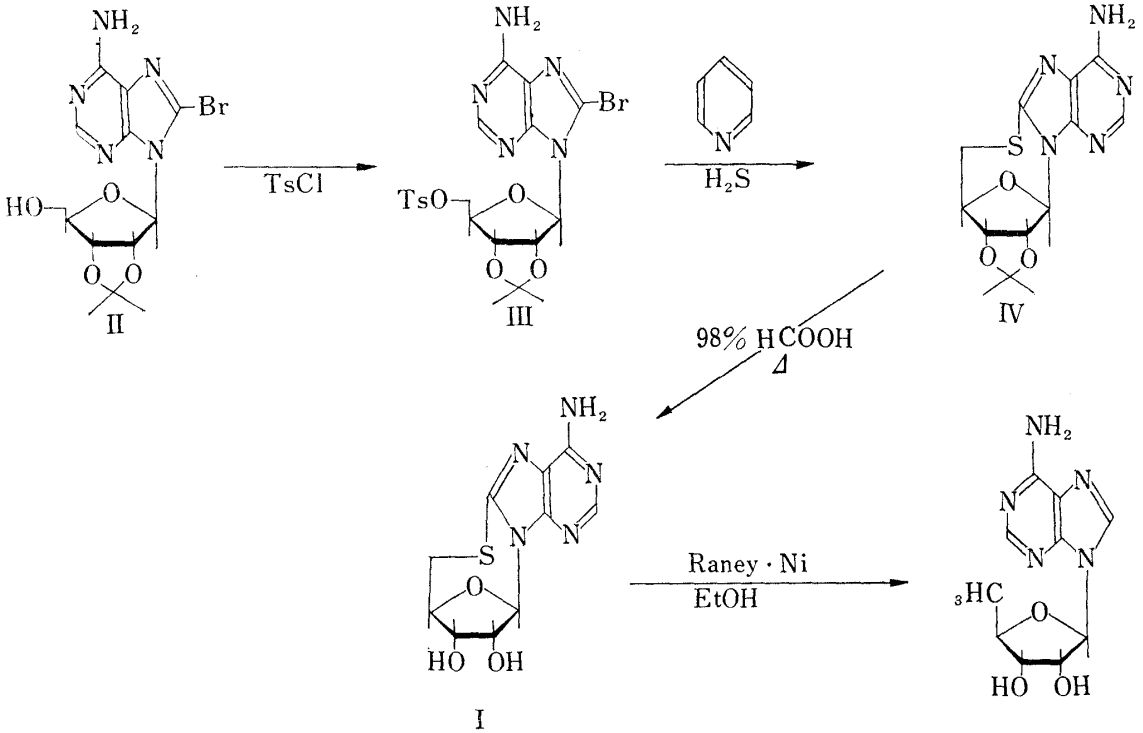
[Chem. Pharm. Bull. 16(6)1151—1153(1968)]

UDC 547.857.7.07

Synthesis of 8,5′-Anhydro-8-mercaptoadenosine

Since the first purine cyclonucleoside has been reported from our laboratory,[1] the possible cyclonucleosides derived from adenosine, *e.g.* 8,2–,[2] 8,3′–[3] and 8,5′–O–,[4] as well as 8,2′–[5] and 8,3′–S–[5] cyclonucleosides were synthesized and characterized in their chemical and physical nature. Especially in optical rotatory dispersion study,[6] these cyclonucleosides have been shown to have large positive Cotton curves around major absorption band.

Now, we wish to report on the synthesis of 8,5′–anhydro–8–mercaptoadenosine (I), which is the last possible cyclonucleoside derivable from adenosine.[7] In the study of 5′–

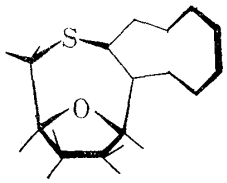


1) M. Ikehara and H. Tada, *J. Am. Chem. Soc.*, **85**, 2344 (1963); *ibid.*, **87**, 606 (1965).
2) M. Ikehara, H. Tada, K. Muneyama, and M. Kaneko, *J. Am. Chem. Soc.*, **88**, 3165 (1966).
3) M. Ikehara and M. Kaneko, *Chem. Pharm. Bull.* (Tokyo), **15**, 1261 (1967).
4) M. Ikehara and M. Kaneko, *J. Am. Chem. Soc.*, **90**, 497 (1968).
5) M. Ikehara and H. Tada, *Chem. Pharm. Bull.* (Tokyo), **15**, 94 (1967).
6) M. Ikehara, M. Kaneko, K. Muneyama, and H. Tanaka, *Tetrahedron Letters*, **1967**, 3977.
7) Although cyclonucleoside bearing 8,3′–O–linkage had been synthesized from 2′–deoxyadenosine[3] 8,3′–O–cyclization in adenosine was recently achieved in our laboratory.[8]
8) M. Kaneko and K. Tominoto, unpublished experiments.

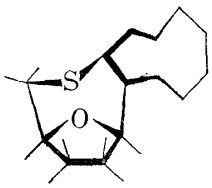
NII-Electronic Library Service

tosylation of adenosine, Jahn[9] showed that the N^3,5′-cyclization could be inhibited by introduction of acyl group in 6-NH_2 group. We investigated, therefore, partial acylation of 2′,3′-O-isopropylidene-8-bromoadenosine (II). However, inspite of many efforts, N^6-acyl compound could not easily be obtained.

We started then with direct tosylation of II. Using a low temperature tosylation at −20°, 5′-tosyl-2′,3′-isopropylidene-8-bromoadenosine (III) (*Anal.* Calcd. for $C_{20}H_{22}O_6N_5BrS$: C, 44.48; H, 4.11; N, 12.97. Found: C, 44.57; H, 4.13; N, 12.74. UV: $\lambda_{max}^{H^+}$ 263 mμ, $\nu_{max}^{H_2O}$ 265 mμ, $\lambda_{max}^{OH^-}$ 265 mμ. IR: ν_{max}^{KBr} 1175—1185 cm^{-1} (covalent tosylate). Paper chromatography: *Rf* 0.85 (isopropanol–ammonia–water, 7:1:2), *Rf* 0.92 (*n*-butanol–acetic acid–water, 5:2:3)) was obtained in the yield of 80%. When compound III was dissolved in pyridine and hydrogen sulfide was bubbled into this solution at room temperature for 5 min, 8,5′-anhydro-2′,3′-isopropylidene-8-mercaptoadenosine (IV) (*Anal.* Calcd. for $C_{13}H_{15}O_3N_5S$: C, 48.64; H, 4.71; N, 21.82. Found: C, 48.57; H, 4.90; N, 21.70. UV: $\lambda_{max}^{H^+}$ 284, 276 (shoulder), 294 mμ (shoulder); $\lambda_{max}^{H_2O}$ 286, 277 (shoulder), 296 mμ (shoulder); $\lambda_{max}^{OH^-}$ 286, 277 (shoulder), 296 mμ

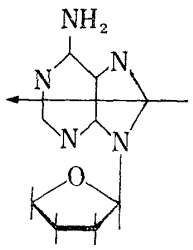


exo Type



endo Type

Fig. 1. Schematic Representation of Configuration of 8,5′-Anhydro-8-mercaptoadenosine



Direction of Arrow

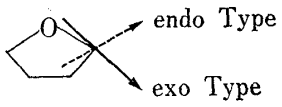


Fig. 3. Schematic Representation of the Angle of Base Plane on Furanose Ring

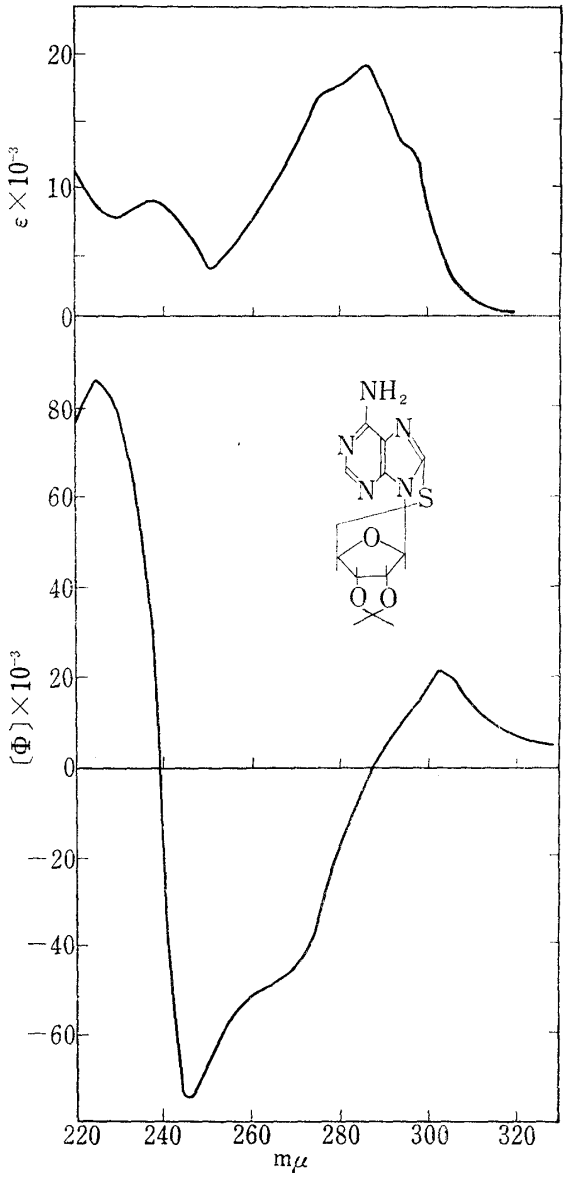


Fig. 2. Optical Rotatory Dispersion Curve of 8,5′-Anhydro-2′,3′-O-isopropylideneadenosine

9) R. Kuhn and W. Jahn, *Chem. Ber.*, **98**, 1699 (1965).

NII-Electronic Library Service

(shoulder). IR: no tosylate band at 1175—1185 cm^{-1}. Paper chromatography: *Rf* 0.72 (isopropanol–ammonia–water, 7:1:2), *Rf* 0.83 (*n*–butanol–acetic acid–water, 5:2:3)) was obtained.

From the inspection of molecular model, 8,5′–cyclonucleoside could be in two forms, namely "exo," in which bridge S atom situates in the side of sugar lactol O (see Fig. 1), and "endo," in which bridge S situates in the side of 2′ and 3′–H. Although final configuration should be elucidated by X-ray diffraction studies, we tentatively assigned "exo" type to the compound IV deduced from the following evidences. Optical rotatory dispersion curve (Fig. 2) of compound IV has extensively large ([Φ]+96000) positive Cotton effect around 280 mμ. This might suggest that the base plane is in the position shown by the arrow[6] of solid line (Fig. 3) and not in the dashed line, because 8,3′S–cycloadenosine having base plane fixed in the position of the dashed arrow has Cotton effect of magnitude +30600, which is much smaller than that of IV. As summarized in Table I, magnitude of Cotton effect increases as the plane of base rotates from 8,2′– to 8,5′–direction both in S– and O–cyclonucleosides. This is in accordance with the postulation of Miles, *et al.*[10]

Table I. Amplitude of Cotton Effect of Adenine Cyclonucleosides

	S–Cyclonucleosides	O–Cyclonucleosides
8,2′	$+249\times10^2$	$+158\times10^2$
8,3′	$+306\times10^2$	$+284\times10^2$ a)
8,5′	$+960\times10^2$	$+472\times10^2$

a) Value obtained in 2′–deoxyadenosine

Nuclear magnetic resonance spectra of IV showed the low field shift of H_4, and H_1, peaks in 0.18 ppm as compared to those of 8,5′–O–cyclonucleoside, while H_2, and H_3, were not shifted. This may caused by the magnetic deshielding effect of nearby situated S atom to H_4, and H_1, and not to H_2, and H_3. This situation could be satisfied only in the "exo" configuration.

Acidic removal of isopropylidene group from IV was carried out by 98% formic acid at 50—60° for 15 hr. 8,5′–Anhydro–8–mercaptoadenosine (*Anal.* Calcd. for $C_{10}H_{11}O_3N_5S\cdot0.5H_2O$: C, 41.41; H, 4.17. Found: C, 41.40, H, 4.32. UV: $\lambda_{max}^{H^+}$ 284, 276 (shoulder), 294 mμ (shoulder); $\lambda_{max}^{H_2O}$ 286, 277 (shoulder), 296 mμ (shoulder); $\lambda_{max}^{H^+}$ 286, 277 (shoulder), 296 mμ (shoulder). Paper chromatography: *Rf* 0.27 (isopropanol–ammonia–water, 7:1:2), *Rf* 0.54 (*n*–butanol–acetic acid–water, 5:2:3)) was obtained. Desulfurization of I with Raney nickel afforded 5′–deoxyadenosine, which had properties identical with those reported by Baker.[11]

Faculty of Pharmaceutical Sciences,
Hokkaido University
Sapporo

Morio Ikehara
Masakatsu Kaneko
Masaru Sagai

Received March 15, 1968

10) D.W. Miles, R.K. Robins, and H. Eyring, *J. Phys. Chem.*, 71, 3931 (1967).
11) H.M. Kissman and B.R. Baker, *J. Am. Chem. Soc.*, 79, 5534 (1957).

NII-Electronic Library Service