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Studies of Nucleosides and Nucleotides. LXVI.*,[1] Purine Cyclonucleosides 29. N-Oxides of Adenine Cyclonucleosides

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N^1-Oxides of 8,2′-, 8,3′- and 8,5′-S-cycloadenosine were synthesized by the oxidation using monoperphthalic acid. The structure of these N-oxides was confirmed by unambiguous synthesis from 2′- or 3′-O-triisopropylbenzenesulfonyl-8-bromoadenosine, which were oxidized at N^1-atom and cyclized with NaSH to give 2′- or 3′-S-cyclonucleoside N-oxide. For 5′-isomer, 2′,3′-ethoxymethylidene-5′-tosyl-8-bromoadenosine was converted to 8-mercapto N^1-oxide by the successive treatment with monoperphthalic acid and NaSH. Cyclization with sodium acetate in dimethylformamide and removal of ethoxymethylidene group with acetic acid gave 8,5′-S-cycloadenosine N^1-oxide. Ultraviolet and nuclear magnetic resonance spectral properties of these N-oxides were investigated.

In recent years, we have synthesized a number of purine cyclonucleosides and investigated their physical and biological properties.[3] While treatment of adenine S-cyclonucleosides with oxidizing reagent such as N-bromosuccinimide or *t*-butyl hypochlorite gave sulfoxides,[4] treatment with performic acid gave either sulfoxides and/or N-oxides depending on the reaction conditions. This paper describes the synthetic method and some properties of N-oxide of 8,2′-, 8,3′-, and 8,5′-S-cycloadenosine.

When 8,2′-anhydro-8-mercapto-9-β-D-arabinofuranosyladenine (I)[5] was oxidized with one equivalent of monoperphthalic acid in methanol or dioxane, for 1.5 hr at room temperature, an N-oxide (II) was obtained in a yield of 36%. This compound had ultraviolet (UV) absorption maxima at 246 and 280 nm (see Table II) suggesting the structure of N-oxide of adenine derivatives.[6] In order to confirm the structure of II, we attempted to synthesize it by an unambiguous route as shown in the chart. 8-Bromoadenosine (III) was first oxidized with H_2O_2 in acetic acid or monoperphthalic acid to give an N-oxide (IV), which was idential with a sample obtained by the usual bromination[7] of adenosine N-oxide (V), proving that the position of N-oxide had been on N-1. 8-Bromo-2′-O-(2,4,6-triisopopylbenzenesulfonyl)-adenosine[7] (VI) was then treated with monoperphthalic acid in dioxane. N-oxide (VII) having UV absorption spectra similar to those of V was obtained in a yield of 77%. Cyclization of compound VII with 40% NaSH in dimethylformamide (DMF)–water solution[8] gave 8,2′-S-cycloadenosine N^1-oxide (II) in a yield of 69%. This sample was identical with that obtained by the direct oxidation of compound I as above. The structure of 8,2′-S-cycloadenosine N^1-oxide (II) was thus confirmed.

When the oxidation reaction of I was conducted with two equivalents of monoperphthalic acid, a compound (VIII) having UV absorption maxima at 233.5 and 262 nm was obtained in

* Dedicated to the memory of Prof. Eiji Ochiai.

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addition to II. The UV absorption properties of VIII were similar to those of 2′,3′-O-isopropylidene-8,5′-O-cycloadenosine N¹-oxide (X), which was obtained by the oxidation of isopropylidene-8,5′-O-cycloadenosine (IX).[9] This indicated that the compound VIII may be formed by the hyperoxidation of II to 8-sulfoxide followed by the intramolecular rearrangement.[4]

When 8,3′-anhydro-9-β-D-xylofuranosyladenine[5] (XI) was similarly oxidized with an equivalent amount of monoperphthalic acid, two compounds corresponding to N-oxide (XII) and S-oxide (XIII)[4] were obtained in the ratio of 1 : 9. Several attempts to obtain only XII failed. The structure of XII was confirmed by similar UV absorption properties with II, elemental analysis, and synthesis as follows. 8-Bromo-3′-O-triisopropylbenzenesulfonyladenosine (XIV)[7] was converted to N¹-oxide (XV) as in the case of 2′-(2,4,6-triisopropylbenzenesulfonyl) (TPS) compound. Compound XV was allowed to react with NaSH to give 8-SH compound (XVI) and cyclized by heating with sodium acetate in DMF to give 8,3′-S-cycloadenosine N¹-oxide (XII). This sample was identical with N-oxide (XII) obtained by the direct oxidation of XI. The reason of the prefered oxidation of S prior to N-atom in the 8,3′-S-cyclonucleoside but not in 8,2′- and 8,5′-counterpart is not clear.

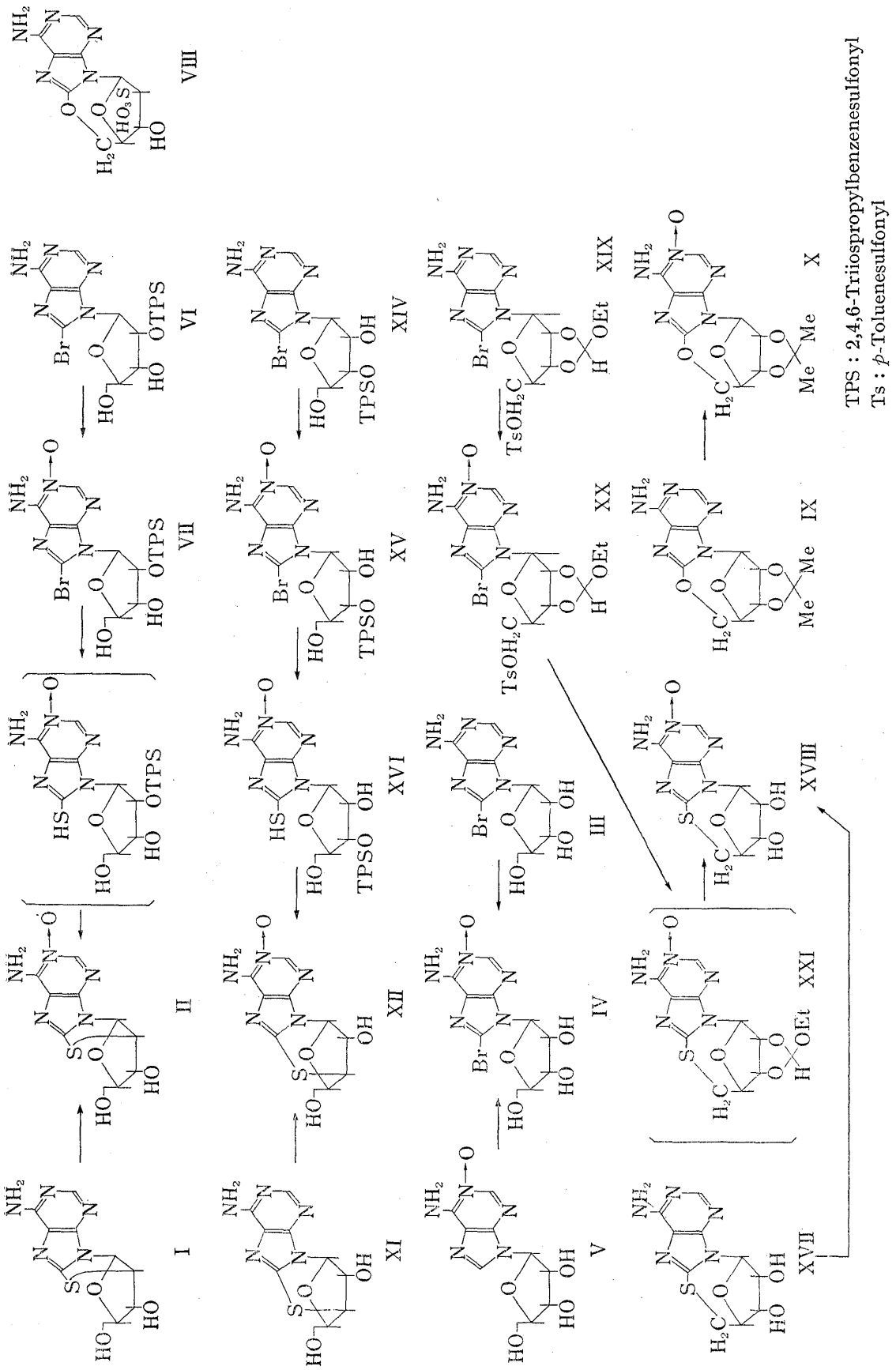
As to 8,5′-anhydro-8-mercaptoadenosine (XVII),[10] the oxidation with monoperphthalic acid proceeded preferentially to give N¹-oxide (XVIII), which was obtained in a yield of 94%. The structure of XVIII was confirmed by UV absorption properties, elemental analysis, and comparison with the sample sunthesized as follows. 8-Bromo-2′,3′-O-ethoxymethylidene-5′-O-tosyladenosine (XIX)[10] was first oxidized to N-oxide (XX) and treated with NaSH in DMF under N_2 atmosphere to yield 2′,3′-ethoxymethylidene 8,5′-S-cycloadenosine N-oxide (XXI). Treatment with 80% acetic acid gave unprotected N-oxide (VIII) together with deoxygenated cyclonucleoside (XVII). Separation by preparative thin-layer chromatography

Table I. Principal Signals in NMR Spectra of Adenine Cyclonucleoside N-Oxides

Compound	2-H	6-NH_2	1′-H	2′-H	3′-H	4′-H	5′-H	2′-OH	3′-OH	5′-OH
8,2′-S-Cycloadenosine	8.04 (s)	7.03 (s)	6.49 (d) $J_{1'H-2'H}$ =7	4.86 (q) $J_{2'H-3'H}$ =2.5	4.38 (q) $J_{3'H-4'H}$ =3.5	3.99 (q)	3.43 (m)	—	5.86 (d)	4.85
8,2′-S-Cycloadnosine N-oxide	8.51 (s)	8.12 (s)	6.53 (d) $J_{1'H-2'H}$ =7	4.88 (q) $J_{2'H-3'H}$ =2.5	4.32 (t)	4.03 (q)	3.41 (m)	—	5.96 (br)	4.9 (br)
8,3′-S-Cycloadenosine	8.05 (s)	7.07 (s)	5.81 (s)	4.87 (d) $J_{2'H-2'OH}$ =3.5	3.92 (d) $J_{3'H-4'H}$ =4	4.63 (q) $J_{4'H-5'H}$ =5.5	3.67 (t)	6.36 (d)	—	4.89
8,3′-S-Cycloadenosine N-oxide	8.53 (s)	8.10 (br)	5.78 (s)	4.89 (s)	3.96 (d) $J_{3'H-4'H}$ =4	4.60 (q) $J_{4'H-5'H}$ =6	3.72	6.48	—	4.90
8,5′-S-Cycloadenosine	8.12 (s)	7.27 (s)	6.17 (d) $J_{1'H-2'H}$ =1.5	4.71 (m)	4.39 (m)	4.80 (t) $J_{4'H-5'H}$ =2.5	3.15 (q)	5.61 (d) $J_{2'H-2'OH}$ =7	5.27 (d) $J_{3'H-3'OH}$ =4.5	—
8,5′-S-Cycloadenosine N-oxide	8.56 (s)	8.10 (br)	6.09 (d) $J_{1'H-2'H}$ =1	4.66 (q) $J_{2'H-3'H}$ =6	4.37 (q) $J_{3'H-4'H}$ =2	4.79 (m)				

Chemical shift from tetramethylsilane was given in ppm. Coupling constants were given in Hz. Abbreviation br means broad.

9) M. Ikehara, M. Kaneko, and R. Okano, *Tetrahedron*, **26**, 5675 (1970).
10) M. Ikehara, M. Kaneko, and M. Sagai, *Tetrahedron*, **26**, 5757 (1970).



TPS : 2,4,6-Triiospropylbenzenesulfonyl
Ts : *p*-Toluenesulfonyl

(TLC) gave the pure compound XVIII in a yield of 15.6%. This sample is identical with that obtained above. Thus N^1-oxide of 8,2′-, 8,3′-, and 8,5′-S-cyclonucleosides were unambiguously synthesized.

Signals in nuclear magnetic resonance (NMR) spectra of three cyclonucleoside N-oxides were listed in Table I. As expected from the introduction of O atom into N^1-position, H-2 signals were shifted *ca.* 0.5 ppm from the original cyclonucleosides. Also 6-NH_2 signals were shifted around 0.1 ppm toward the low field. Essentially no big change in carbohydrate signals was observed. Coupling constants $J_{1H'-2H'}$ were equal to 7 Hz for 8,3′- and 0—1.5 Hz for 8,3′- and 8,5′-cyclonucleosides. This may indicate no alteration of the sugar puckering[3,11] by the introduction of the N^1-oxide function.

Reactions regarding to the N-oxide function of cyclonucleosides will be reported in subsequent papers.

Table II. UV Absorption Properties of Adenine S-Cyclonucleoside N-Oxides [nm(ε)]

Compound	λ_{max}(0.1N HCl)	λ_{max}(H_2O)	λ_{max}(0.1N NaOH)
8,2′-S-Cycloadenosine	226 (20100)	248 (40100)	248 (28000)
N-oxide	283 (18500)	285 (13800)	290 (9800)
8,3′-S-Cycloadenosine	227 (19300)	247 (33700)	249 (25000)
N-oxide	284 (18700)	286 (14000)	292 (9200)
8,5′-S-Cycloadenosine	285 (18500)	249 (19900)	227 (sh, 19900)
N-oxide		285 (13700)	249 (sh, 15400)
			289 (11100)
8,5′-O-Cycloadenosine	262 (7500)	235.5(22800)	236 (15400)
N-oxide		264 (5600)	269 (sh, 5400)

Abbreviation sh means shoulder.

Experimental[12]

8-Bromo-2′-O-triisopropylbenzenesulfonyladenosine N^1-Oxide (VII)——8-Bromo-2′-O-triisopropylbenzenesulfonyladenosine (607 mg, 1 mmole) was dissolved in anhyd. dioxane (100 ml). Into the solution was added monoperphthalic acid (ether solution, 1.5 equiv.). After keeping at room temperature for 6—7 hr the mixture was added dropwise to water containing 5% $NaHCO_3$. Precipitate was collected by filtration and dried over P_2O_5. Yield was 430 mg (77%). UV $\lambda_{max}^{H^+}$: 265 nm; $\lambda_{max}^{H_2O}$ 237, 272 nm; $\lambda_{max}^{OH^-}$: 237, 280 nm IR ν_{max}^{KBr}: 1170 cm^{-1} (N-oxide).

8,2′-Anhydro-8-mercapto-9-β-D-arabinofuranosyladenine N^1-Oxide (II)——i) Bromo-TPS-adenosine N-oxide (VII) (625 mg, 1 mmole) was dissolved in anhyd. DMF (10 ml). To the solution was added 40% NaSH aq. (2 equiv.) under N_2 bubbling. The tightly stoppered reaction mixture was kept at room temperature for 24 hr. The mixture was neutralized with 1N HCl, the solvent was evaporated, and the residue was recrystallized from water–methanol to give 8,2′-S-cycloadenosine N-oxide (205 mg, 69%). mp was 205—206°. *Anal.* Calcd. for $C_{10}H_{11}O_4N_5S$: C, 40.40; H, 3.70; N, 23.57. Found: C, 40.22, H, 3.79; N, 23.55. UV absorption properties are listed in Table II, PPC: *Rf* (solvent A) 0.66; *Rf* (B) 0.42.

ii) 8,2′-S-Cycloadenosine (140 mg, 0.5 mmole) was dissolved in anhyd. dioxane (60 ml) and monoperphthalic acid (1.5 equiv.) was added. After keeping the mixture at room temperature for 1.5 hr, white precipitates were collected by filtration and recrystallized from methanol-water. 8,2′-S-Cycloadenosine N-oxide was obtained in a yield of 36%. This sample was identical with that obtained by i) in criteria of mixed mp and UV absorption properties as listed in Table II.

11) M. Ikehara and H. Tada, The Purine-Theory and Experiment, B. Pullman Ed., The Jerusalem Symposia on Quantum Chemistry and Biochemistry, IV, p. 455, (1972).

12) UV absorption spectra were taken with a Hitachi EPS-3T spectrophotometer, infrared (IR) spectra were taken with a Hitachi EPI-L spectrophotometer, and NMR spectra were taken with a Hitachi R-22 (90 MC) and varian HA-100 (100 MC) spectrometer in d_6-DMSO (dimethyl sulfoxide) using tetramethylsilane as external standand. Circular dichroism (CD) spectra were taken with a JASCO ORD/UV-5 spectropolarimeter using 10 mm light path cell and *d*-10-camphorsulfonic acid was used for calibration. Paper chromatography was performed on Toyo filter paper No. 51A using solvent A (H_2O adjusted to pH 10 with conc. ammonia) or B (iso-propanol–conc. ammonia–water, 7:1:2).

8-Bromo-3′-triisopropylbenzenesulfonyladenosine N¹-Oxide (XV)——8-Bromo-3′-TPS-adenosine (1.2 g) was dissolved in dioxane (20 ml) and monoperphthalic acid (1.5 equiv.) was added. After keeping at room temperature for 3 hr, the mixture was added dropwise to 5% $NaHCO_3$ aq. Precipitates were collected by filtration and dried over P_2O_5. Yield was 845 mg (68%). UV $\lambda_{max}^{H^+}$: 266 nm; $\lambda_{max}^{H_2O}$: 237, 273 nm; $\lambda_{max}^{OH^-}$: 237, 280 nm. IR ν_{max}^{KBr}: 1170 cm^{-1} (N-oxide).

8-Mercapto-3′-triisopropylbenzenesulfonyladenosine N¹-Oxide (XVI)——8-Bromo-3′-TPS-adenosine N-oxide (628 mg) was dissolved in anhyd. DMF (30 ml). To the solution was added 40% NaSH aq. (2 equiv.) under bubbling of N_2 gas. The mixture was kept at room temperature for 24 hr and evaporated carefully. The residue was recrystallized from methanol to give 8-mercapto-TPS-adenosine N-oxide (407 mg, 70%). For analysis the sample was further recrystallized from ethanol. mp 213—215°. *Anal.* Calcd. for $C_{25}H_{35}O_7N_5S_2$: C, 51.63; H, 5.50; N, 12.04; S, 11.00. Found: C, 51.38; N, 12.10; S, 10.99. UV $\lambda_{max}^{H^+}$: 234, 311.5; $\lambda_{max}^{H_2O}$: 240 (shoulder), 257, 310 nm; $\lambda_{max}^{OH^-}$: 256, 310 nm. IR ν_{max}^{KBr}: 1170 cm^{-1} (N-oxide).

8,3′-Anhydro-8-mercapto-9-β-D-xylofuranosyladenine N¹-Oxide (XII)——i) 8-Mercapto-3′-TPS-adenosine N-oxide (855 mg, 1.47 mmoles) was dissolved in anhyd. DMF (20 ml) and anhyd. sodium acetate (1.4 g) was added. The mixture was heated at 90—100° for 2.5 hr with stirring. After cooling sodium acetate was filtered off and DMF was evaporated *in vacuo*. The residue was recrystallized from methanol to give 8,3′-S-cycloadenosine N-oxide (183 mg, 42%), mp 261°. *Anal.* Calcd. for $C_{10}H_{11}O_4N_5 \cdot 1/2, CH_3OH$: C, 40.25; H, 4.18; N, 22.36; S, 10.22. Found: C, 39.77; H, 4.09; N, 22.11; S, 10.23. UV absorption properties are listed in Table II. PPC: *Rf* (solvent A) 0.67, *Rf* (B) 0.44.

ii) 8,3′-S-Cycloadenosine (280 mg, 1 mmole) was dissolved in anhyd. methanol (30 ml) and monoperphthalic acid (1 mmole) was added. After keeping the mixture for 3 hr at room temperature, the solvent was evaporated. The residue was washed with water (1 ml × 2) to give 8,3′-S-cycloadenosine sulfoxide (100 mg, 34%), which was identified with an authentic sample.[4] The mother liquor was applied to a thick-layer silica gel plate and developed with $CHCl_3$–EtOH (7: 4 vol/vol). Band migrated at *Rf* 0.07 (cyclonucleoside 0.55, N-oxide 0.23) was extracted with 50% ethanol. 8,3′-S-Cycloadenosine N¹-oxide was obtained in a yield of 3.4%. This sample was identical with that obtained in i).

8-Bromo-2′,3′-O-ethoxymethylidene-5′-O-tosyladenosine N¹-Oxide (XX)——8-Bromo-2′,3′-O-ethoxymethylidene-5′-O-tosyladenosine (1.566 g, 2 mmoles) was dissolved in anhyd. DMF (20 ml) and monoperphthalic acid (1.5 equiv.) was added. After keeping the mixture at room temperature for 3 hr, it was added dropwise to 50% $NaHCO_3$ aq. Organic material was extracted with $CHCl_3$. After drying over $MgSO_4$, $CHCl_3$ was evaporated to give a caramel (1.103 g).

8,5′-Anhydro-8-mercaptoadenosine N¹-Oxide (XVIII)——i) 8-Bromo-2′,3′-O-ethoxymethylidene-5′-O-tosyladenosine N-oxide (1.103 g) was dissolved in DMF (30 ml). To the solution was added NaSH (2 equiv.) under bubbling of N_2. After keeping the reaction mixture for 24 hr at room temperature, it was evaporated. The residue was dissolved in 80% AcOH (60 ml) and kept at room temperature for 48 hr. Acetic acid was removed by evaporation *in vacuo*. The residue was applied to a preparative silica gel TLC in solvent A. The band migrated at *Rf* 0.55 was extracted with H_2O–MeOH (1: 1, vol/vol, 100 ml × 2) and the solvent was evaporated 8,5′-S-Cycloadenosine N¹-oxide was obtained in a yield of 93 mg (15.6%). *Anal.* Calcd. for $C_{10}H_{11}O_4N_5S \cdot 1/2CH_3OH \cdot 1/2H_2O$: C, 39.44; H, 4.38; N, 21.73. Found: C, 39.55; H, 4.68; N, 21.63. UV absorption properties are listed in Table II. PPC: *Rf*(A) 0.52, *Rf*(B), 0.33.

ii) 8,5′-S-Cycloadenosine (260 mg) was dissolved in dioxane (20 ml) and monoperphthalic acid (1 equiv.) was added. The mixture was kept at room temperature for 3 hr. White precipitates were collected by filtration. 8,5′-S-Cycloadenosine N-oxide was obtained in a yield of 279 mg (94%). This sample was identical with that obtained in i).

8,2′-Anhydro-2′,3′-isopropylidene-8-oxyadenosine N¹-Oxide (X)——2′,3′-Isopropylidene-8,5′-O-cycloadenosine (25 mg, 0.1 mmole) was dissolved in dioxane (2 ml) and monoperphthalic acid (1 equiv.) was added. After keeping the mixture for 12 hr, it was added dropwise in 5% $NaHCO_3$ aq. Organic material was extracted with $CHCl_3$ and evaporated. 2′,3′-Isopropylidene-8,5′-O-cycloadenosine N¹-oxide was obtained in 18 mg (64%). UV absorption properties are listed in Table II.

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