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PHOTOCHEMICAL CYCLISATION OF 2',3'-O-ISOPROPYLIDENE-8-PHENYLTHIOADENOSINE TO THE 8,5'(*R*)- AND 8,5'(*S*)-CYCLOADENOSINES (NUCLEOSIDES AND NUCLEOTIDES—XVIII)[1]

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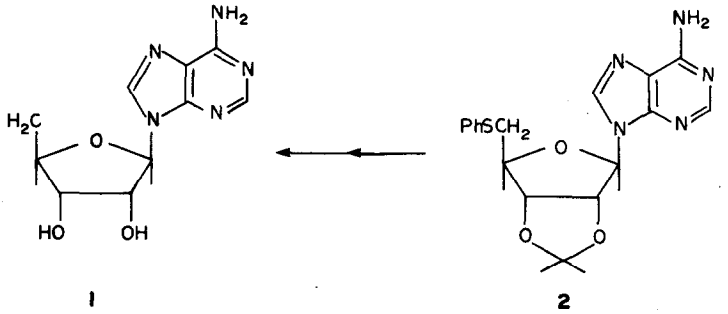
Abstract—Photo-irradiation of 2',3-O-isopropylidene-8-phenylthioadenosine in the presence of the peroxides afforded the 8,5'-cyclonucleosides, which, after deacetonation, gave 8,5'(*S*)- and 8,5'(*R*)-cycloadenosine, the anti-type fixed model of adenosine. The absolute configurations of the 5'-carbon in these nucleosides were determined by NMR measurements.

One of the interesting subjects of the conformational studies of nucleosides and nucleotides is concerned with the orientation of the base moiety to the sugar moiety around the glycosylic bond.[2] Recently several C–C bridged cyclonecleosides have been prepared[3] and some of them were utilized as the conformationally fixed nucleosides or nucleotides in some enzymatic reactions.[4] We have also undertaken the synthesis of the anti-type fixed purine nucleosides. In a recent report[3a] we described a photochemical synthesis of 5'-deoxy-8,5'-cycloadenosine(1) from a 5'-deoxy-5'-phenylthio derivative(2) of adenosine, which was an identical product obtained by the anaerobic photolysis of 5'-deoxyadenosyl-cobalamine.[5] However, compound 1 lacks the 5'-OH group to be required as the conformationally fixed model of adenosine. Thus, the synthesis of 8,5'-cycloadenosine, the least modified anti-conformer of adenosine, was undertaken as described in this paper.[6]

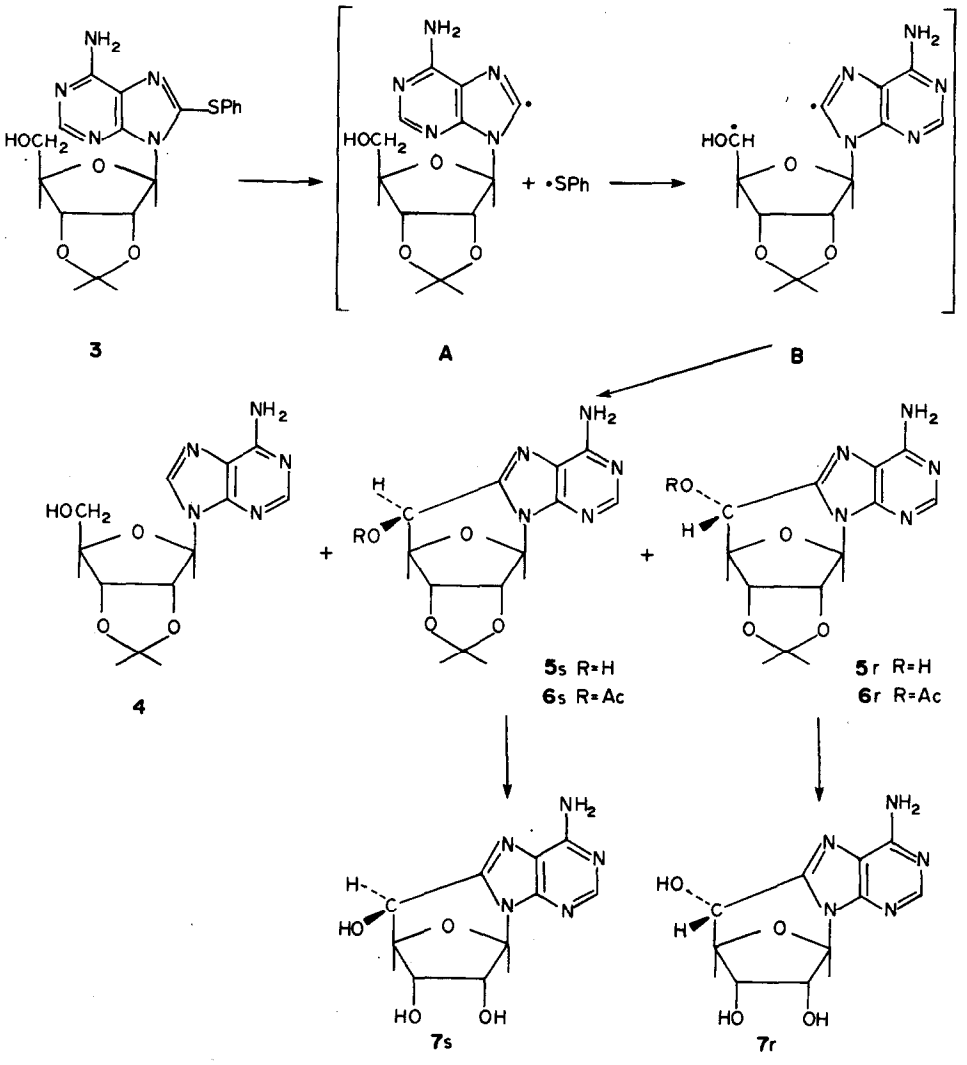
It has been reported that an alkyl group was directly introduced to the position 8 of adenine by photochemical or radiochemical processes. Adenosine undergoes photochemical hydroxyalkylation with alcohols to give the 8-substituted derivative.[7] Since adenosine itself contains a hydroxymethyl group at the 4'-position it is expected to furnish the desired cyclonucleoside through the intramolecular addition of the generated 4'-hydroxymethine radical with the position 8 on UV irradiation. No such cyclisation was however observed by the irradiation of adenosine or 2',3'-O-isopropylideneadenosine in the presence or absence of radical initiators. On the other hand we had experienced ready desulfurisation of 8-alkylthioguanosine by UV irradiation.[8] Furthermore we have found that the protection of the 2'- and 3'-OH groups by acetonation was essential in the cyclisation of 2 to the isopropylidene derivative of 1.[3a] These findings led us to investigate the photolysis of 2',3'-O-isopropylidene-8-phenylthioadenosine(3).

2',3'-O-Isopropylidene-8-bromoadenosine[9] was treated with sodium thiophenoxide in methanol to give 3. Compound 3 and trimethyl phosphite were irradiated with 400W high pressure Hg lamp with a pyrex filter for 3.25 hr in acetonitrile. A survey of the mixture with tlc showed that the reaction proceeded almost completely to leave three products (Rf 0.28, 0.17 and 0.09) and the starting material (Rf 0.59) was found to be negligible. The main product having the highest Rf value was identified as 2',3'-O-isopropylideneadenosine(4) by the comparison of its Rf value, UV, mass and NMR spectra with the authentic material. The products having Rf 0.17 (13%, 5*S*) and 0.09(8%, 5*R*) had UV absorption maximum at 264 and 266 nm, respectively. The mass spectra of both compounds showed a molecular ion peak at *m/e* 305 with high intensities. The NMR spectra of 5(*S* and *R*) showed singlets for anomeric protons and absence for the C–8 protons which are good indications of the cyclonucleoside structures involving C–5' and C–8 in 5. Since the signals of the sugar protons other than at the C–1' were overlapped, the determination of the absolute configurations of 5*S* and 5*R* at the C–5' was impossible. Acetylation of 5*S* and 5*R* gave the respective 5'-O-acetates(6*S* and 6*R*). The NMR signal of H–5' in 6*S* appeared as a doublet at 6.4 ppm ($J_{4',5'} = 6.5$ Hz) coupled with H–4' at 4.96 ppm. The signals of H–5' and H–4' of 6*R*, on the other hand, appeared as the signlets at 5.92



1 2

Scheme 1.



Scheme 2.

and 4.84 ppm, respectively. Since the H–4′ of both **6***S* and **6***R* did not couple with H–3′, the sugar puckerings in these cyclonucleosides must be of 1′-0-exo type[3a].

Inspection of the molecular models of **6***S* and **6***R* revealed that the large coupling constant between H–5′ and H–4′ of **6***S* can be rationalized by assuming the *S* configuration at the C–5′ where the dihedral angle of $H_{5'}$–$C_{5'}$–$C_{4'}$–$H_{4'}$ is ~30°. The $J_{4',5'}$ value for the *R* epimer (**6***R*) should be zero since the dihedral angle in that case is ~90°. Fox *et al.* have recently reported [3e] the absolute configuration of 6,5′(*R* and *S*)-cyclouridines by the similar bases. Although Harper and Hampton reported[3b] a synthesis of a mixture of **5***R* and **5***S* by the reduction of 5′-oxo-8,5′-cycloadenosine derivative the separation and characterization of the epimers were not accomplished.

Treatment of **5**(*S* and *R*) with 0.1N HCl at 90° for 1 hr afforded 8,5′(*S*)- and 8,5′(*R*)-cycloadenosine (**7***S* and **7***R*), respectively, in high yields.

Some experiments directed to the improvements in the yields of **5** were carried out and results were summarized in Table 1. Replacement of the solvent by acetone or methanol on the photocyclisation reduced the yield of **5** with the increased formation of **4**. Addition of t-butyl hydroperoxide, di-t-butyl peroxide, or dicumyl peroxide as the radical initiator with the omission of trimethyl phosphite resulted in a small increase of the yields of **5**. The formation of **5** under irradiation without the peroxide or the phosphite in acetonitrile was detected but the yield was the lowest.

From these observations it can be assumed that the phenylthio group in **3** is photoactivated initially to yield a radical intermediate (**A**) and penylthiyl radical. The intermediate **A** is then converted to the next biradical intermediate(**B**) by the action of phenylthiyl radical or a radical initiator added. Intramolecular binding of the biradical in **B** affords **5***S* and **5***R*. The uptake of hydrogen(s) in **A** or **B** would form **4**. The relatively low yields of the desired cycloadenosine might be attributed to the fact that the generated radical **A** from **3** posseses the syn conformation, which must rotate to take the anti position so as to link with the 5′-hydroxymethine radical within the life time of **A**. The *S*:*R* ratio of the products(**5**) may be determined by the ratio of the prochiral hydrogens to be abstracted from the 5′-position of **A**.

Studies on the interations of these nucleosides and their phosphates with enzymes utilizing adenosine, AMP

Table 1. Product distributions of the photo-irradiation of 3 under various conditions

Solvent	Additive	Time(hr)[a]	Yield(%)[b] 4	5S	5R
CH_3CN	$(CH_3O)_3P$	3.25	41.8	13.0	8.1
$(CH_3)_2CO$	"	6.5	53.1	9.6	———
CH_3OH	"	3	63.5	4.2	6.6
CH_3CN	BHP[c]	4	6.2	19.1	10.1
"	DBP[d]	4.5	36.0	13.4	7.4
"	DCP[e]	3	20.5	20.2	13.1
"	———	3[f]	23.0	5.0	3.0

a) No starting materials detected under their irradiation time. b) Given by the isolated yield. c) t-Butyl hydroperoxide d) Di-t-butyl peroxide e) Dicumyl peroxide f) The recovery of 3 was 45%.

and ATP are currently undertaken and will be reported elsewhere.

EXPERIMENTAL

M.ps. were determined with a Yanaco MP-3 m.p. apparatus and were uncorrected. UV spectra were recorded with a Shimazu UV-300 recording spectrophotometer. NMR spectra were taken with a Hitachi H-60 spectrometer using TMS as an internal standard. Mass spectra were measured with a Hitachi RMU-6E mass spectrometer. TLC was carried out with Merck TLC plate (silica gel 60 F_{254}, precoated) and preparative tlc was carried out with plates coated with silica gel (Merck 60 F_{254}, 20×20 cm, 0.1 cm). The photo-irradiation was performed with an apparatus of Riko UVL-400 400 W high pressure Hg vapor lamp (pyrex filter) in an argon atmosphere.

2',3' - O - Isopropylidene - 8 - phenylthioadenosine(3). 2',3' - O - Isopropylidene-8-bromoadenosine(4.37 g) was dissolved in 115 ml abs MeOH followed by the addition of 2.5 ml thiophenol and 8.5 ml 2N-NaOMe in MeOH. The mixture was warmed at 60°, then kept at room temp. overnight. The soln was neutralized with NHCl, concentrated to dryness, and the residual oil was diluted with $CHCl_3$ and applied to a column of silica gel (3.5×21 cm). After the elution of thiophenol with $CHCl_3$ 3 was eluted with 1% EtOH–$CHCl_3$. The combined eluates were evaporated and the residue was crystallized from H_2O–EtOH to yield 3.99 g (85.3%), m.p. 141–143°; UV $\lambda_{max}^{H_2O}$ 282 nm; NMR ($CDCl_3$) δ 8.23 (s, 1, H–2), 7.46 (m, 7, phenyl and 6–NH_2), 6.29 (d, 1, H–1', $J_{1',2'}$ = 3 Hz), 5.61 (dd, 1, H–2', $J_{2',3'}$ = 6 Hz), 5.09 (dd, 1, H–3', $J_{3',4'}$ = 3 Hz), 4.29 (m, 1, H–4'), 3.64 (bd, 2, H–5', $J_{4',5'}$ = 5 Hz), 1.51 and 1.32 (s, 3+3, Me_2C). (Found: C, 55.06; H, 5.11; N, 16.68; S, 7.48. Calc. for $C_{19}H_{21}N_5O_4S$: C, 54.94; H, 5.06; N, 16.78; S, 7.71%).

Photoirradiation of 3 *and isolation of* 4, 5*S and* 5*R*. Compounds 3 (350 mg) and t-butyl hydroperoxide (2ml) in 350 ml acetonitrile were irradiated for 4 hr. The soln was concentrated and the residue was applied on 5 plates for preparative tlc. These were developed with $CHCl_3$–EtOH (10:1) for several times until a satisfactory separation was accomplished. Main bands were collected and eluted with $CHCl_3$–EtOH (1:1), and the soln was evaporated to leave the following products.

2',3'-O-Isopropylideneadenosine (4). Compound 4 was obtained from the band of the highest *Rf* value in a yield of 6.2% (16.1 mg), m.p. 215–217° (lit.[10] 217.5–218°). The UV, NMR and mass spectra of the product were identical with those of the authentic material.

2',3' - O - Isopropylidene - 8,5'(S) - cycloadenosine(5S). The compound collected from the second band was crystallized from EtOH–H_2O to give 5*S* (49 mg, 19.1%), m.p. >300°; UV $\lambda_{max}^{H_2O}$ 264 nm; NMR (DMSO-d_6) δ 8.07 (s, 1, H–2), 7.14 (bs, 2, 6–NH_2), 6.40 (m, 1, 5'–OH), 6.10 (s, 1, H–1'), 5.00 (m, 2, H–2', 4'), 4.55 (m, 2, H–3', 5'), 1.41 and 1.22 (s, 3+3, Me_2C); *m/e* 305 (M^+). (Found: C, 51.08; H, 4.95; N, 22.74. Calc. for $C_{13}H_{15}N_5O_4$: C, 51.15; H, 4.92; N, 22.95%).

2',3' - O - Isopropylidene - 8,5'(R) - cycloadenosine(5R). The compound collected from the third band was crystallized from H_2O to give 5*R* (25.9 mg, 10.1%), m.p. 291–292° (*dec.*); *UV* $\lambda_{max}^{H_2O}$ 266 nm; NMR (DMSO-d_6) δ 8.22 (s, 1, H–2), 7.32 (bs, 2, 6–NH_2), 6.28 (bs, 1, 5'–OH), 4.5–5.0 (m, H–2', 3', 4', 5'), 1.46 and 1.24 (s, 3+3, Me_2C); *m/e* 305 (M^+). (Found: C, 51.05; H, 4.88; N, 22.75. Calc. for $C_{13}H_{15}N_5O_4$: C, 51.15; H, 4.92; N, 22.95%). The results of the photo-irradiations under various conditions were summarized in Table 1.

2',3' - O - Isopropylidene - 5' - O - acetyl - 8,5'(S) - cycloadenosine (6S). To the soln of 67.7 mg of 5*S* in 5 ml pyridine was added 1 ml Ac_2O and stirred for 1 hr at room temp. After evaporation of the solvent the residue was dissolved in $CHCl_3$ and charged on a plate of silica gel and developed with $CHCl_3$–EtOH (10:1). The main band was collected, eluted with $CHCl_3$–EtOH (1:1), and evaporated to leave 6*S* (70 mg, 86%): m.p. 132–133° (from EtOH–H_2O); UV $\lambda_{max}^{H_2O}$ 266 nm (ϵ, 15100); NMR ($CDCl_3$) δ 8.36 (s, 1, H–2), 6.65 (bs, 2, 6–NH_2), 6.40 (d, 1, H–5', $J_{4',5'}$ = 6.5 Hz), 6.39 (s, 1, H–1'), 5.08 (d, 1, H–3' or H–2', $J_{2',3'}$ = 6 Hz), 4.96 (d, 1, H–4'), 4.72 (d, 1, H–2' or H–3'), 2.18 (s, 3, Ac), 1.56 and 1.32 (s, 3+3, Me_2C); *m/e* 347 (M^+). (Found: C, 49.26; H, 5.26; N, 18.95. Calc. for $C_{15}H_{17}N_5O_5.H_2O$: C, 49.28; H, 5.25; N, 19.17%).

2',3' - O - Isopropylidene - 5' - O - acetyl - 8,5'(R) - cycloadenosine (6R). Compound 5*R* (30 mg) was treated with Ac_2O as described above and 6*R* was obtained from EtOH–H_2O (30 mg, 88%, m.p. 239–240°); UV $\lambda_{max}^{H_2O}$ 268 nm (ϵ, 14700); NMR ($CDCl_3$): δ 8.33 (s, 1, H–2), 6.40 (s, 1, H–1'), 6.25 (bs, 2, 6–NH_2), 5.92 (s, 1, H–5'), 4.84 (s, 1, H–4'), 4.76 (d, 1, H–3' or H–2', $J_{2',3'}$ = 6 Hz), 4.57 (d, 1, H–2' or H–3'), 2.15 (s, 3, Ac), 1.54 and 1.32 (s, 3+3, Me_2C); *m/e* 347 (M^+). (Found: C, 51.01; H, 4.93; N, 19.91. Calc. for $C_{15}H_{17}N_5O_5$. 1/3 H_2O: C, 50.97; H, 5.05: N. 19.82%).

8,5'(S)-Cycloadenosine (7S). Compound 5*S* (150 mg) was dissolved in 20 ml of 0.1 N HCl and heated at 85–90° for 1 hr. After neutralization by addition of 2N NH_4OH the soln was concentrated to dryness, the residue crystallized from hot H_2O to leave 7*S* (107 mg, 81.7%), m.p. >300°; UV $\lambda_{max}^{H_2O}$ 265 nm (ϵ, 16200), $\lambda_{max}^{0.5NHCl}$ 262 nm (ϵ, 16400), $\lambda_{max}^{0.5NNaOH}$ 267 nm (ϵ, 16500); NMR (DMSO-d_6-D_2O, measured on a Jeol JNM-FX 100 FTR NMR spectrometer): δ 8.11 (s, 1, H–2), 5.99 (s, 1, H–1'), 5.05 (d, 1, H–5', $J_{4',5'}$ = 5.9 Hz), 4.49 (d, H–4'), 4.47 (d, 1, H–2', $J_{2',3'}$ = 6.3 Hz), 3.97 (d, 1, H–3'); *m/e* 265 (M^+). (Found: C, 45.35; H, 4.18; N, 26.62. Calc. for $C_{10}H_{11}N_5O_4$: C, 45.28; H, 4.15; N, 26.42%).

8,5'(R)-Cycloadenosine (7R). Compound 5*R* (65 mg) was deacetonated in a same manner as described above and 7*R* (56 mg, 97%) was obtained from hot H_2O, m; 266° (dec.); UV $\lambda_{max}^{H_2O}$ 266 nm (ϵ, 15700), $\lambda_{max}^{0.5NHCl}$ 262 nm (ϵ, 16500), $\lambda_{max}^{0.5NNaOH}$ 267 nm (ϵ, 16500); NMR (DMSO-D_6-D_2O, measured at 100 MHz): δ 8.13 (s, 1, H–2), 6.03 (s, 1, H–1'), 4.63 (s, 1, H–5'), 4.42 (s, 1, H–4'), 4.02 (d, 1, H–2', $J_{2',3'}$ = 5.6 Hz), 3.94 (d, 1, H–3'); *m/e* 265 (M^+). (Found: C, 45.15; H, 4.38; N, 26.68. Calc. for $C_{10}H_{11}N_5O_4$: C, 45.28; H, 4.15; N, 26.42%).

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