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SYNTHESIS OF CARBON-BRIDGED 8,5′-CYCLOPURINE NUCLEOSIDES: NUCLEOSIDES AND NUCLEOTIDES—XXIV[1]

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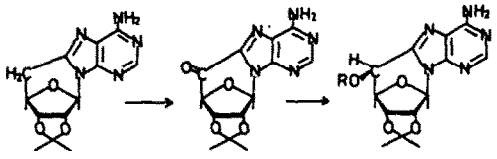
Abstract—Treatment of 2′,3′-O-isopropylidene-5′-deoxy-8,5′-cycloadenosine with selenium oxide afforded the 5′-oxo-compound. Reduction of the product with sodium borohydride proceeded stereoselectively to give the 8,5′(*S*)-cycloadenosine. The 5′-*R*-isomer was obtained by the inversion of the 5′-OH group of the *S*-epimer via the mesyloxy derivative. Hydrolytic deamination of 8,5′-cycloadenosines gave the inosine counterparts. Photo-irradiation of 2′,3′-O-isopropylidene-5′-deoxy-5′-phenylthio-N²-benzoylguanosine afforded the 8,5′-cyclo-5′-deoxyguanosine, which was also converted to the 5′-oxo-derivative. Reduction of the product also afforded to give the 8,5′-(*S*)-cycloguanosine. The CD spectra of these cyclonucleosides reflect the chiralities at the 5′-position.

In our recent studies on the synthesis of cyclopurine nucleosides we have observed a facile photo-cyclization of a 5′-deoxy-5′-phenylthioadenosine to a 8,5′-cyclo-5′-deoxyadenosine.[2] Furthermore, a 8-phenylthio derivative of adenosine was found to undergo cyclization to give 8,5′(*S* and *R*)-cycloadenosines by photo-irradiation.[3] In the latter case, the non-stereoselective cyclization proceeded and the yields were rather unsatisfactory for the purpose of a large scale preparation. The present paper describes another versatile route for the synthesis of 8,5′-cycloadenosines as well as the inosine and guanosine derivatives. A preliminary account of this work has appeared.[4]

It has been reported that 6-methyluracil[5] and its nucleoside[6] were oxidized by selenium oxide to give the respective 6-formyl derivatives. In 2′,3′-O-isopropylidene-5′-deoxy-8,5′-cycloadenosine[2] (1), the 5′-methylene bound to the 8-position of the adenine ring should have a similar reactivity to selenium oxide oxidation to give the 5′-oxo-derivative, as was found to be the case.

Treatment of 1 with selenium oxide in refluxing pyridine for 5 hr afforded, in high yield, 2′,3′-O-isopropylidene-5′-oxo-8,5′-cycloadenosine (2). The structure of 2 was determined by UV, IR, NMR and mass spectral measurements. The strong fluorescent property of 2 is also characteristic. The formation of 2 was previously observed[7] by treatment of 2′,3′ - O - isopropylideneadenosine - 5′ - carboxylic acid with methyllithium in a yield of ~5%. The physical constants reported for 2, however, are rather different with those of the compound prepared by the present route. The UV spectra of 2 in a neutral solution exhibited two absorption maxima at 265 and 336 nm. In acidic medium the hypsochromic and hypochromic shifts of the longer wave-length maximum were observed with a pKa of 3.3, probably due to the protonation of the N^1 of 2. In an alkaline medium a complete loss of the absorption at the longer wave-length was observed. This phenomenon would be rationalized by assuming a hydration of the 5′-oxo group of 2. The high field shift of the 4′-proton of 2 in NMR measurement and a loss of fluorescence in an alkaline medium would be the additional evidence for the 5′-hydration. The pK for the hydration was calculated as 9.4. The compound 2 previously prepared[7] was reported to exhibit a same spectra in the neutral and alkaline media.

Treatment of 2 with sodium borohydride in methanol afforded 2′,3′ - O - isopropylidene - 8,5′(*S*) - cycloadenosine (3a) in high yield. The structure of 3a was confirmed by the direct comparison with the authentic specimen,[3] together with the identities of the 5′-O-acetate (3b). The survey of the mixture of the hydride treatment of 2 failed to detect any formation of the *R*-epimer (5a), which showed the reduction proceeded in a stereoselective manner. This result is also to be contrasted with that reported.[7]

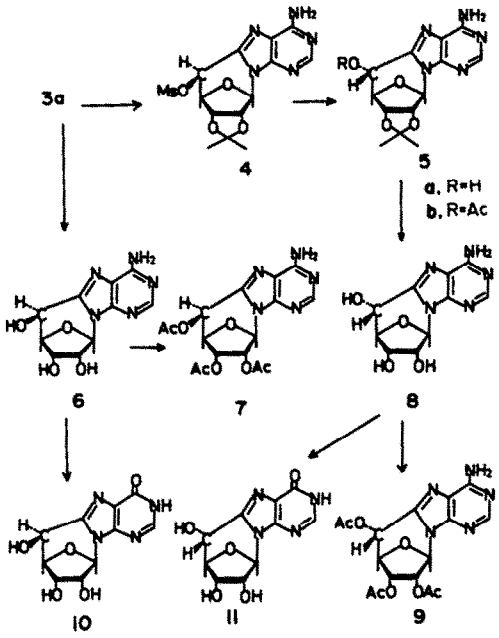


Scheme 1.

The preparation of the *R*-epimer (5a) was accomplished by the inversion of the 5′-OH group of 3a. The mesylation of 3a in pyridine afforded the 5′-O-mesylate (4). The retention of the configuration during the mesylation was confirmed by the NMR measurement. Treatment of 4 with sodium acetate in dimethylformamide at 80° gave a product in 40% yield, which was determined as 2′,3′ - O - isopropylidene - 8,5′(*R*) - cycloadenosine (5a). The 5′-O-acetate (5b) was not detected in the reaction. This epimerization was accomplished more readily by dissolving 4 in a buffered solution at pH 7.3. Desalting of the solution afforded 5a in 93% yield.

Fox *et al.* have reported[8] a base catalyzed equilibration of 5′ - O - acetyl(or mesyl) - 2′,3′ - O - isopropylidene - 6,5′ - (*S* or *R*) - cyclouridine to give the 5′(*S* and *R*)-epimeric mixture. The reaction was reported to involve the formation of a carbanion at the 5′-position as an intermediate. Similar treatment of 3b or 5b in pyridine, however, did not effect any epimerization, which suggests that the epimerization of 4 to 5a proceeded by the S_N2 mechanism.

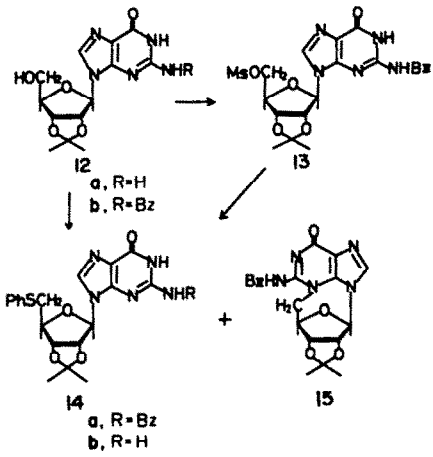
Deacetonation of 3a and 5a with 0.1N HCl afforded 8,5′(*S*)- and 8,5′(*R*)-cycloadenosines (6 and 8), respectively, as described already. Acetylation of 6 and 8 with acetic anhydride in pyridine to give the tri-O-acetate (7 and 9) also proceeded without epimerizations. Treatment of 6 and 8 with sodium nitrite in aqueous acetic acid



Scheme 2.

afforded the respective 8,5'(*S* and *R*)-cycloinosines (**10** and **11**) in high yields.

The synthesis of 8,5'-cycloguanosine was undertaken by a similar approach. Baker *et al.* reported[9] that the treatment of the 5'-O-tosylate of 2',3'-O-isopropylideneguanosine (**12a**) with sodium ethylsulfide gave the 5'-deoxy-5'-ethylthio derivative. Similar treatment of the mesylate of **12a** with sodium thiophenoxide by our hands, however, resulted in a formation of a N^3,5'-cycloguanosine. To preclude the undesirable cyclization the N^2-benzoyl derivative (**12b**) was utilized. Mesylation of **12b** in pyridine and subsequent treatment of **13** with sodium thiophenoxide in liquid ammonia afforded 2',3' - O - isopropylidene - 5' - deoxy - 5' - phenylthio - N^2 - benzoylguanosine (**14a**) in 57% yield, together with the N^3,5'-cyclonucleosides (**15**). Photo-irradiation of **14a** with trimethyl phosphite in acetonitrile, as adopted in the synthesis of **1**, afforded the expected 5' - deoxy - 2',3' - O - isopropylidene - 8,5' - cyclo - N^2 - benzoylguanosine (**16a**) in 47% yield. Oxidation of **16a** with selenium oxide in dioxane afforded the 5'-oxo derivative (**17a**). The structure of **17a** was confirmed on the basis of IR, NMR and mass spectra. Treatment of **17a** with sodium borohydride in methanol gave a product which was purified by a celite chromatography to afford 2',3' - O - isopropylidene - N^2 - benzoyl - 8,5'(*S*) - cycloguanosine (**18a**). The stereoselective reduction of the 5'-oxo derivative (**17a**) was also observed. Debenzoylation of **18a** with methanolic ammonia furnished 2',3' - O - isopropylidene - 8,5'(*S*) - cycloguanosine (**18b**) as a crystalline form.



Scheme 3.

Attempts to remove the isopropylidene group from **18b** resulted in a cleavage of the glycosylic linkage.

Treatment of **12a** with diphenyl disulfide and triphenylphosphine, the direct substitution method of the OH group to the alkylthio group devised by Nakagawa and Hata,[10] afforded the 5'-phenylsulfide (**14b**) in 61% yield. This was also photo-cyclized to give **16b** in high yield, which would provide an alternative method for the preparation of **18b**. A formation of the 5'-imino compound (**17b**) was observed in the treatment of **17a** with methanolic ammonia which was rapidly converted to the 5'-oxo derivative (**17c**) by treatment with water.

The CD spectra of the cyclonucleosides prepared in

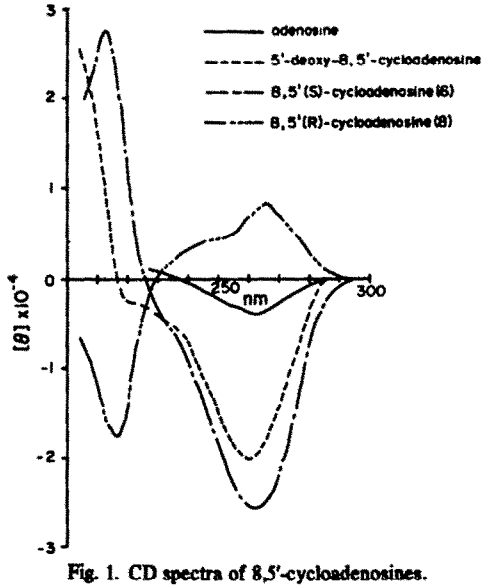
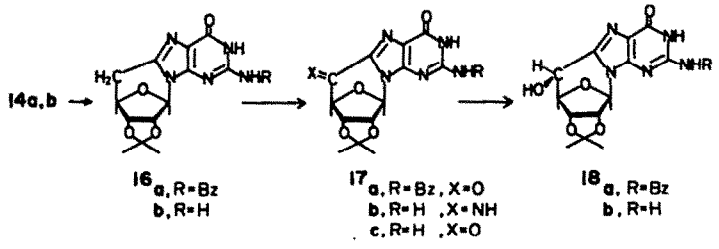


Fig. 1. CD spectra of 8,5'-cycloadenosines.



Scheme 4.

this study provide useful informations about the stereochemistry of the 5'-positions. As shown in Fig. 1, 5'-deoxy-8,5'-cycloadenosine showed an intense negative CD band around the main absorption maximum as compared with that of adenosine. Compound **6** showed a much stronger negative band whereas the band of the *R*-epimer (**8**) had a positive. It is apparent that the newly introduced chirality at the 5'-position of **6** and **8** would also contribute to the CD band at the same absorption region. Similar relation was observed in the CD spectra of 8,5'-cyclo-inosines and -guanosine. It can be stated that the 5'-*S*-chirality contributes to exhibit toward a negative ellipticity whereas the *R*-chirality affects as to compensate the negative Cotton effect of the "anti"-fixed adenosine.

Studies on the phosphorylation of the "anti"-fixed adenosines and inosines are in progress and their biological properties will be reported elsewhere.

EXPERIMENTAL

M.ps were determined with a Yanaco MP-3 m.p. apparatus and were uncorrected. UV spectra were recorded on a Shimazu UV-300 recording spectrophotometer. NMR spectra were taken with a Hitachi R-20B spectrometer and a JEOL JNM-FX 100FT NMR spectrometer, using TMS as an internal standard. Chemical shifts are recorded in parts per million (δ). Values for coupling constants (Hz) are first order. Mass spectra were measured with a Hitachi RMU-6E mass spectrometer. CD spectra were recorded on a JASCO J-40 automatic spectropolarimeter. The photoirradiations were performed with an apparatus of Eikosha PIL-60 60W low pressure Hg vapor lamp (quartz filter) in an argon atmosphere. Thin layer chromatography (TLC) was carried out with Merck TLC plates (silica gel $60F_{254}$, precoated). The fluorescence spectra were measured with a Hitachi MPF-2A fluorescence spectrophotometer.

2',3' - O - Isopropylidene - 5' - oxo - 8,5' - cycloadenosine (**2**). A soln of **1**[2] (4.0 g, 13.6 mmol) in anhyd pyridine (50 ml) was added selenium oxide (2.6 g, 23.4 mmol) and stirred under reflux for 5 hr. The progress of the reaction was checked by TLC ($CHCl_3$–EtOH, 10:1). The mixture was cooled to room temp., the ppt was removed by filtration, and washed with $CHCl_3$. The filtrate and washings were combined and evaporated to leave a yellow solid which was taken in $CHCl_3$ and applied to a silica gel chromatography (3.7 × 30 cm). The eluate with 8% EtOH in $CHCl_3$ gave 4.1 g (99%) of **2**. The product contains occasionally a trace amount of colloidal selenium oxide but is suitable for the next step. Analytical sample was obtained by a recrystallization from hot EtOH to give pure **2**, m.p. 279° (dec, the reported value, 232–234°[7]); UV $\lambda_{max}^{pH\ 1.35}$ 311 nm (ε, 1300), 261 nm (ε, 15,300); $\lambda_{max}^{pH\ 5.7}$ 336, 265 nm (ε, 3600 11,300); $\lambda_{max}^{pH\ 12.1}$ 266 nm (ε, 16,000); NMR (DMSO-d_6): 8.34 (s, 1, H-2), 8.03 (bs, 2, H_2N-6), 6.56 (s, 1, H-1'), 5.08 (d, 1, H-2' or 3'), 5.04 (s, 1, H-4'), 4.99 (d, 1, H-3' or 2'), 1.55 and 1.32 (s, 3+3, Me_2C); $J_{2',3'}$ = 7 Hz; (DMSO-d_6 + NaOD): 8.21 (s, 1, H-2), 6.20 (s, 1, H-1'), 5.14 (bs, 2, H-2',3'), 4.45 (s, 1, H-4'), 1.55 and 1.32 (s, 3+3, Me_2C); IR (Nujol, cm^{-1}): 1720 (C=O); *m/e* 303 (M^+); CD (H_2O): $(\theta)_{348}$ −10800, $(\theta)_{303}$ 0, $(\theta)_{286}$ +6400, $(\theta)_{267}$ 0, $(\theta)_{257}$ −3000, $(\theta)_{250}$ 0, $(\theta)_{235}$ +15,900; Fluorescence spectra (H_2O): λ_{max}^{ex} 360 nm, λ_{max}^{em} 470 nm; (pH 1.25): λ_{max}^{ex} 355 nm, λ_{max}^{em} 465 nm (1/1000, intensity). (Found: C, 51.36; H, 4.29: N, 22.81. Calc. for $C_{13}H_{13}N_5O_4$: C, 51.46; H, 4.33; N, 23.09%).

Oxidation of **1** with selenium oxide in refluxing dioxane for 3 days gave also **2** in 80% yield.

2',3' - O - Isopropylidene - 8,5'(S) - cycloadenosine (**3a**). A soln of **2** (2.0 g, 6.6 mmol) in MeOH (200 ml) was added 0.1M $NaBH_4$ in H_2O (50 ml, 5 mmol) and stirred for 30 min at room temp. The soln was neutralized with 1N HCl and evaporated to dryness. The residue was crystallized from hot H_2O to give **3a** (1.8 g, 89.6%), m.p. >300°. The product was identical with the authentic material.[3] The precise analyses of the NMR spectra of **3a** and **3b**[3] showed that the proton signal appearing at 5.00 (**3a**) or 5.08 (**3b**) was assigned for H-3'.

2',3' - O - Isopropylidene - 5' - O - mesyl - 8,5'(S) - cycloadenosine (**4**). A mixture of **3a** (100 mg, 0.33 mmol) and mesyl chloride (0.06 ml) in 5 ml of pyridine was stirred at room temp. overnight. Water was added to the mixture and, after 30 min, evaporated to leave a residue which was extracted with $CHCl_3$. The $CHCl_3$ soln was dried over Na_2SO_4, evaporated, and the residue was crystallized from EtOH–H_2O to give 124 mg (99%) of **4**, m.p. 186° (dec); NMR (DMSO-d_6): 8.27 (s, 1, H-2), 7.53 (bs, 2, H_2N-6), 6.39 (s, 1, H-1'), 6.29 (d, 1, H-5'), 5.10 (d, 1, H-4'), 5.02 (d, 1, H-3' or 2'), 4.81 (d, 1, H-2' or 3'), 3.61 (s, 3+3, Me_2C); $J_{2',3'}$ = 6 Hz, $J_{4',5'}$ = 6.5 Hz. (Found: C, 44.17; H, 4.45; N, 18.04; S, 8.00. Calc. for $C_{14}H_{17}N_5O_6S$: C, 43.84; H, 4.49; N, 18.27; S, 8.36%).

2',3'-O-Isopropylidene-8,5'(R)-cycloadenosine (**5a**). A soln of **4** (500 mg, 1.3 mmol) in 0.1M Tris-HCl buffer (pH 7.3, 70 ml) was heated at 97° for 9 hr. After cooling the soln was applied on a column of Amberlite XAD-4 (3.8 × 29 cm). The column was washed with H_2O and eluted with 70% EtOH to afford, after evaporation of the eluates, **5a**, crystallized from H_2O (371 mg, 93%), m.p. 291–292°. The product was identical with the authentic material.[3]

2',3',5' - Tri - O - acetyl - 8,5'(S) - cycloadenosine (**7**). A mixture of **6** (24 mg) and Ac_2O (0.2 ml) in pyridine (5 ml) was stirred for 20 hr at room temp. The mixture was concentrated and the residue was applied on a plate for preparative TLC (20 × 20 cm, 0.1 cm), and developed with $CHCl_3$–EtOH (10:1). The main band (triacetyl derivative) was collected and eluted with $CHCl_3$–EtOH (1:1), and the eluate was evaporated to leave a homogeneous powder (30 mg, 84.7%) of **7**. NMR (DMSO-d_6): 8.23 (s, 1, H-2), 7.45 (bs, 2, H_2N-6), 6.50 (s, 1, H-1'), 6.33 (d, 1, H-5'), 5.66 (d, 1, H-3' or 2'), 5.49 (d, 1, H-2' or 3'), 5.06 (d, 1, H-4'), 2.20, 2.17 and 2.08 (s, 3+3+3, Ac); $J_{2',3'}$ = 6 Hz, $J_{4',5'}$ = 6 Hz; *m/e* 391 (M^+).

2',3',5' - Tri - O - acetyl - 8,5'(R) - cycloadenosine (**9**). Compound **8** (52 mg) was acetylated as described above and **9** was obtained as a homogenous powder (73 mg, 95%); NMR (DMSO-d_6): 8.24 (s, 1, H-2), 7.49 (bs, 2, H_2N-6), 6.53 (s, 1, H-1'), 6.18 (bs, 1, H-5'), 5.57 (d, 1, H-2' or 3'), 5.37 (d, 1, H-3' or 2'), 5.00 (bs, 1, H-4'), 2.16, 2.12 and 2.11 (s, 3+3+3, Ac); $J_{2',3'}$ = 6 Hz, $J_{4',5'}$ = 1 Hz; *m/e* 391 (M^+).

Treatment of **3b** *and* **5b** *with pyridine.* (a) A soln of **3b** (25 mg) in pyridine (3 ml) was stirred under reflux for 22 hr. The soln was concentrated to dryness and the residue was crystallized from EtOH–H_2O to give 22 mg. This product was identical with the starting material.[3] (b) A soln of **5b** (72 mg) in pyridine was treated as described above and the recovered material (62 mg, from EtOH–H_2O) was identical with the starting material.

8,5'(S)-Cycloinosine (**10**). A soln of **6** (30 mg) in 90% AcOH was added 100 mg of $NaNO_2$ and stirred for 24 hr at room temp. After further addition of 100 mg $NaNO_2$ and stirring for 3 days, the mixture was concentrated and the residue was crystallized from hot H_2O to afford 22.5 mg (74.7%) of **10**; m.p. 300°; UV $\lambda_{max}^{0.5N\ HCl}$ 254 nm (ε, 13,200), $\lambda_{max}^{H_2O}$ 253 nm (ε, 14,100), $\lambda_{max}^{0.5N\ NaOH}$ 260 nm (ε, 14,500); NMR (DMSO-d_6 + D_2O, 100 FT): 8.03 (s, 1, H-2), 5.98 (s, 1, H-1'), 5.01 (d, 1, H-5'), 4.48 (bs, 2, H-3', 4'), 4.01 (d, 1, H-2'); $J_{2',3'}$ = 6.1 Hz, $J_{4',5'}$ = 5.8 Hz; CD (H_2O) $(\theta)_{254}$ −24,200, $(\theta)_{219}$ 0, $(\theta)_{205}$ −9000. (Found: C, 45.01; H, 3.75; N, 21.08. Calc. for $C_{10}H_{10}N_4O_5$: C, 45.11; H, 3.79; N, 21.05%).

8,5'(R)-Cycloinosine (**11**). The deamination of **8** (23 mg) by the procedure described above afforded **11** (16 mg, 69.4%) from H_2O; m.p. >300°; UV $\lambda_{max}^{0.5N\ HCl}$ 254 nm (ε, 13,400), $\lambda_{max}^{H_2O}$ 253.5 nm (ε, 14,200), $\lambda_{max}^{0.5N\ NaOH}$ 259 nm (ε, 14,800); NMR (DMSO-d_6 + D_2O, 100 FT): 8.05 (s, 1, H-2), 6.01 (s, 1, H-1'), 4.60 (d, 1, H-5'), 4.41 (bs, 1, H-4'), 4.05 (d, 1, H-3'), 3.92 (d, 1, H-2'); $J_{2',3'}$ = 5.9 Hz, $J_{4',5'}$ = 1.2 Hz; CD (H_2O): $(\theta)_{254}$ +4900, $(\theta)_{240}$ +3700, $(\theta)_{217.5}$ 0, $(\theta)_{204}$ −19,500. (Found: C, 44.88; H, 3.83; N, 20.84. Calc. for $C_{10}H_{10}N_4O_5$: C, 45.11; H, 3.79; N, 21.05%).

2',3'-O-Isopropylideneguanosine (**12a**). Guanosine (10 g, 35 mmol) was suspended in 1000 ml acetone and stirred under ice-cooling. To this suspension was added 8 ml 70% $HClO_4$ during 5 min and the stirring was continued for 1 hr at room temp. The soln was neutralized with conc. NH_4OH and was evaporated to leave a residue which was crystallized from hot

H_2O to give 8.6 g (75.4%) of **12a**, m.p. 300° (dec, ref. 11 299°, dec).

2',3' - O - Isopropylidene - N^2 - benzoylguanosine (**12b**). Compound **12a** (6.0 g, 18.5 mmol) was suspended in 160 ml anhyd pyridine to which was added benzoyl chloride (5.5 ml, 47 mmol) dropwise in a period of 30 min on an ice-cooled bath. The stirring was continued for 30 min at room temp., then for 2 hr at 65°. The mixture was concentrated to one third of its volume and poured into ice-water with vigorous stirring. The ppt was collected by filtration to give 9.57 g of the 5'-O,N^2-dibenzoate; UV λ_{max}^{EtOH} 295, 260, and 234 nm; *m/e* 531 (M^+). A soln of the dibenzoate (5.31 g, 10 mmol) in 150 ml of abs MeOH and 2N NaOMe (7 ml) was stirred for 45 min at room temp. The soln was neutralized with Dowex 50 × 8 (H^+ form) and the resin was removed by filtration. The filtrate was concentrated to leave crystals of **12b** (3.16 g, 74%); m.p. 153–155°; UV λ_{max}^{EtOH} 294, 260 and 240 nm; NMR (DMSO-d_6): 8.27 (s, 1, H-8), 8.05 and 7.65 (m, 5, phenyl), 6.12 (d, 1, H-1'), 5.31 (dd, 1, H-2'), 5.07 (dd, 1, H-3'), 4.16 (m, 1, H-4'), 3.55 (m, 2, H-5'), 1.52 and 1.35 (s, 3 + 3, Me_2C); $J_{1',2'}$ = 1.5 Hz, $J_{2',3'}$ = 6 Hz, $J_{3',4'}$ = 3 Hz; *m/e* 427 (M^+). (Found: C, 56.12; H, 5.04; N, 16.64. Calc. for $C_{20}H_{21}N_5O_6$: C, 56.20; H, 4.95; N, 16.39%).

2',3' - O - Isopropylidene - 5' - deoxy - 5' - phenylthio - N^2 - benzoylguanosine (**14a**). Mesyl chloride (1.15 ml, 14.9 mmol) was added dropwise to the ice-cold soln of **12b** (4.27 g, 10 mmol) in pyridine (50 ml) under stirring. After 5 hr, water was added to the mixture and the solvents were evaporated to leave a residue. This was taken in EtOAc and H_2O and the organic layer was dried over Na_2SO_4, and evaporated to give **13**. Compound **13** was added to a soln previously mixed Na (310 mg, 13.5 mmol) and thiophenol (2 ml, 19.4 mmol) in liquid ammonia (80 ml) and kept overnight in a flask stoppered with NaOH tube. The residue was partitioned with EtOAc and H_2O and the organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was dissolved in $CHCl_3$ and applied to a column of silica gel (3.7 × 25 cm). After elution of thiophenol with $CHCl_3$, **14a** was eluted with 2% EtOH in $CHCl_3$ to give, after evaporation and crystallization from EtOH–diisopropyl ether, 2.98 g (57.3%); m.p. 114–116°; NMR ($CDCl_3$): 10.49 (bs, 1, N^1-H), 7.84 (s, 1, H-8), 7.7–7.1 (m, 10, phenyl), 5.97 (d, 1, H-1'), 5.39 (dd, 1, H-2'), 5.06 (dd, 1, H-3'), 4.43 (dt, 1, H-4'), 3.24 (bd, 2, H-5'), 1.58 and 1.38 (s, 3 + 3, Me_2C); $J_{1',2'}$ = 1.5 Hz, $J_{2',3'}$ = 6 Hz, $J_{3',4'}$ = 3 Hz, $J_{4',5'}$ = 7.5 Hz; *m/e* 519 (M^+). (Found: C, 59.87; H, 4.96; N, 13.48; S, 6.15. Calc. for $C_{26}H_{25}N_5O_5S$: C, 60.09; H, 4.86; N, 13.48; S, 6.16%).

2',3' - O - Isopropylidene - N^3,5' - cyclo - N^2 - benzoylguanosine (**15**). The eluates of the above column with 8% EtOH in $CHCl_3$ gave **15** by evaporation of the solvent and crystallization from EtOH in a yield of 436 mg (11%), m.p. 282–284°; UV λ_{max}^{EtOH} 308, 251 nm; NMR (DMSO-d_6): 13.59 (bs, 1, HN-2), 8.08 (s, 1, H-8), 8.25 and 7.5 (m, 5, phenyl), 6.52 (s, 1, H-1'), 5.71 (dd, 1, H-5'b), 5.00 (bs, 1, H-4'), 4.96 (d, 1, H-2'), 4.53 (d, 1, H-3'), 3.88 (dd, 1, H-5'a), 1.49 and 1.27 (s, 3 + 3, Me_2C); $J_{4',5'a}$ = 1.5 Hz, $J_{4',5'b}$ = 1.5 Hz, $J_{5'a,5'b}$ = 15 Hz, $J_{2',3'}$ = 5.5 Hz; *m/e* 409 (M^+). (Found: C, 58.86; H, 4.68; N, 17.13. Calc. for $C_{20}H_{19}N_5O_5$: C, 58.68; H, 4.64; N, 17.11%).

2',3' - O - Isopropylidene - 5' - deoxy - 5' - phenylthioguanosine (**14b**). A mixture of **12a** (3.23 g, 10 mmol), diphenyl disulfide (6.5 g, 29.8 mmol), and tri-n-butylphosphine (7.5 ml, 30 mmol) in 50 ml of dimethylformamide was stirred at room temp. overnight. The soln was concentrated and the residual syrup was added into 200 ml of EtOH with vigorous stirring. The ppts were collected and washed with ether to give 2.55 g (61.4%) of **14b**. An analytical sample was obtained by crystallization from EtOH–H_2O; m.p. 290–292°; NMR (DMSO-d_6): 10.77 (bs, 1, H-N^1), 8.91 (s, 1, H-8), 7.45–7.1 (m, 5, phenyl), 6.57 (bs, 2, H_2N-2), 6.01 (d, 1, H-1'), 5.37 (dd, 1, H-2'), 5.12 (dd, 1, H-3'), 4.15 (dt, 1, H-4'), 3.26 (bd, 2, H-5'), 1.47 and 1.32 (s, 3 + 3, Me_2C); $J_{1',2'}$ = 1.5 Hz, $J_{2',3'}$ = 6 Hz, $J_{3',4'}$ = 3 Hz, $J_{4',5'}$ = 7.5 Hz; *m/e* 415 (M^+). (Found: C, 54.86; H, 5.09; N, 16.60; S, 7.58. Calc. for $C_{19}H_{21}N_5O_4S$: C, 54.91; H, 5.11; N, 16.86; S, 7.71%).

2',3' - O - Isopropylidene - 5' - deoxy - 8,5' - cyclo - N^2 - benzoylguanosine (**16a**). Compound **14a** (300 mg, 0.58 mmol) and trimethyl phosphite (1 ml) were dissolved in 300 ml of acetonitrile and argon gas was bubbled through the soln for 30 min. The soln was irradiated for 90 min under argon atmosphere. The soln was concentrated and the residue was crystallized from hot MeOH to give 112 mg (47.4%) of **16a**, m.p. 253° (dec); UV λ_{max}^{EtOH} 304, 264 and 239 nm; NMR (DMSO-d_6): 7.95 and 7.55 (m, 5, phenyl), 6.13 (s, 1, H-1'), 4.80 (bs, 3, H-2',3',4'), 3.36 (dd, 1, H-5'b), 2.90 (d, 1, H-5'a), 1.46 and 1.28 (s, 3 + 3, Me_2C); $J_{4',5'b}$ = 6 Hz, $J_{5'a,5'b}$ = 18Hz; *m/e* 409 (M^+). (Found: C, 57.64; H, 4.89; N, 16.66. Calc. for $C_{20}H_{19}N_5O_5.0.5H_2O$: C, 57.41; H, 4.83; N, 16.75%).

2',3' - O - Isopropylidene - 5' - deoxy - 8,5' - cycloguanosine (**16b**). A soln of **16a** (108 mg) in ethanolic ammonia (60 ml) was kept at 65° for 18 hr in a steel tube. The soln was concentrated to leave a solid which was crystallized from hot EtOH to give 78 mg (99%) of **16b**, m.p. >300°; UV $\lambda_{max}^{0.5N\ HCl}$ 255 nm (ε, 13,900), 280 nm (sh, ε, 9200); $\lambda_{max}^{H_2O}$ 253 nm (ε, 14,950), 272 nm (sh, ε, 10,400); $\lambda_{max}^{0.5N\ NaOH}$ 270 nm (ε, 12,800), 260 nm (sh, ε, 12,300); NMR (DMSO-d_6–$CDCl_3$): 10.61 (bs, 1, H-N^1), 6.46 (bs, 2, H_2N), 5.87 (s, 1, H-1'), 4.78 (d, 1, H-2' or 3'), 4.72 (dd, 1, H-4'), 4.60 (d, 1, H-3' or 2'), 3.27 (dd, 1, H-5'b), 2.83 (dd, 1, H-5'a), 1.44 and 1.25 (s, 3 + 3, Me_2C); $J_{2',3'}$ = 6 Hz, $J_{4',5'a}$ = 1 Hz, $J_{4',5'b}$ = 6 Hz, $J_{5'a,5'b}$ = 17 Hz; *m/e* 305 (M^+); CD (H_2O): $(\theta)_{252}$ −5500, $(\theta)_{223}$ 0. (Found: C, 51.14; H, 4.93; N, 23.03. Calc. for $C_{13}H_{15}N_5O_4$: C, 51.12; H, 4.96; N, 22.94%).

Irradiation of **14b** (300 mg) carried out in EtOH (10 ml) and acetonitrile (300 ml) with trimethyl phosphite (2.5 ml) for 2 hr afforded 198 mg (89%) of **16b**.

2',3' - O - Isopropylidene - 5' - oxo - 8,5' - cyclo - N^2 - benzoylguanosine (**17a**). A mixture of **16a** (242 mg, 0.58 mmol) and selenium oxide (500 mg, 8.2 mmol) in 80 ml of anhydrous dioxane was stirred for 20 hr under refluxing. The mixture was evaporated to dryness and the residue was taken in a small volume of dimethylformamide. The soln was applied to a column of silica gel (3.3 × 8 cm) and eluted with 3% EtOH in $CHCl_3$. The eluate was concentrated to leave a pink colored solid which was crystallized from EtOH to give 168 mg (65.8%) of **17a**, m.p. >300°, NMR (DMSO-d_6): 12.52 and 12.26 (bs, 1 + 1, H-N^1 and H-N^2), 8.02 and 7.62 (m, 5, phenyl), 6.38 (s, 1, H-1'), 5.06 (bs, 2, H-2' and 3'), 5.02 (s, 1, H-4'), 1.48 and 1.30 (s, 3 + 3, Me_2C); *m/e* 423 (M^+); IR (Nujol): 1735 cm^{-1} (C=O). (Found: C, 54.77; H, 4.44; N, 15.70. Calc. for $C_{20}H_{17}N_5O_5.H_2O$: C, 54.40; H, 4.35; N, 15.87%).

2',3' - O - Isopropylidene - 8,5'(S) - cyclo - N^2 - benzoylguanosine (**18a**). Compound **17a** (275 mg, 0.65 mmol) was dissolved in 200 ml of MeOH and $NaBH_4$ (50 mg, 1.3 mmol) was added, and stirred for 1 hr at room temp. The soln was neutralized with 1N HCl and passed through a celite column. Evaporation of the eluates afforded a crystalline **18a** (230 mg, 83%), m.p. 258–261° (dec); *m/e* 425 (M^+).

2',3' - O - Isopropylidene - 8,5'(S) - cycloguanosine (**18b**). A soln of **18a** (160 mg) in methanolic ammonia (20 ml) was kept at 50° for 24 hr in a steel tube. The soln was evaporated and the residue was crystallized from hot H_2O to give 111 mg (91.8%) of **18b**, m.p. >300°; UV $\lambda_{max}^{0.5N\ HCl}$ 257.5 nm (ε, 13,400), 276 nm (pl, ε, 9000); $\lambda_{max}^{H_2O}$ 257 nm (ε, 15,800), 270 nm (sh, ε, 12,100); $\lambda_{max}^{0.5N\ NaOH}$ 261 nm (sh, ε, 12,600), 271 nm (ε, 13,400); NMR (DMSO-d_6 + D_2O): 6.86 (s, 1, H-1'), 5.19 (d, 1, H-3'), 4.98 (d, 1, H-5'), 4.58 (d, 2, H-2' and 4'), 1.44 and 1.26 (s, 3 + 3, Me_2C); $J_{2',3'}$ = 6.1 Hz, $J_{4',5'}$ = 6.1 Hz; *m/e* 321 (M^+); CD (H_2O): $(\theta)_{260}$ −8100, $(\theta)_{238}$ 0; $(\theta)_{212}$ +23,000. (Found: C, 48.33; H, 4.62; N, 21.88 Calc. for $C_{13}H_{15}N_5O_5$: C, 48.59; H, 4.71; N, 21.81%).

2',3' - O - Isopropylidene - 5' - imino - 8,5' - cycloguanosine (**17b**). A suspension of **17a** (98 mg) in 15 ml of methanolic ammonia was kept at 50° for 12 hr in a steel tube. The ppts in the mixture were collected to yield 61.3 mg (86.7%) of crystalline **17b**, m.p. >300°; *m/e* 318 (M^+); IR (Nujol) 1710, 1635, 1600 cm^{-1}. (Found: C, 48.96; H, 4.39; N, 25.96. Calc. for $C_{13}H_{14}N_6O_4$: C, 49.04; H, 4.44; N, 26.40%). The sample was contaminated with a small amount of **17c**.

2',3' - O - Isopropylidene - 5' - oxo - 8,5' - cycloguanosine (**17c**). A suspension of **17b** (30 mg) in H_2O (150 ml) was heated at 90° for 3 hr and the solvent was concentrated. The separated crystals were collected to afford 23.5 mg (73.9%) of **17c**, m.p. >300°; UV $\lambda_{max}^{0.5N\ HCl}$ 335 nm (ε, 8800), min 303 nm (ε, 2470), 271 *nm* (*sh*, ε, 7000), max 250 nm (ε, 9560), min 232 mn (ε, 7940); $\lambda_{max}^{H_2O}$ 356 nm (ε, 11,600), min 297 nm (ε, 1420), 260 nm (sh, ε, 8160), max 247 nm (ε, 9580), min 234 nm (ε, 9240), max 225 nm (ε, 9390), min 218 nm (ε, 9240); $\lambda_{max}^{0.5N\ NaOH}$ 271.5 nm (ε, 12,470), 260 (sh, ε, 7940), min

250 nm (ϵ, 4670); Fluorescence spectra: λ^{ex}_{max} in H_2O 275 nm, λ^{em}_{max} 455 nm; λ^{ex}_{max} in 0.1N HCl 375 nm, λ^{em}_{max} 455 nm (intensity, *ca.* 1/2 of the neutral); NMR (DMSO-d_6): 11.00 (bs, 1, H-N^1), 6.95 (bs, 2, H_2N^2), 6.19 (s, 1, H-1'), 4.98 (d, 1, H-2' or 3'), 4.87 (d, 1, H-3' or 2'), 4.86 (s, 1, H-4'), 1.46 and 1.28 (s, 3+3, Me_2C); $J_{2',3'} = 5.6$ Hz; *m/e* 319 (M^+); IR (Nujol): 1730, 1695, 1635, 1596 cm^{-1}; CD (H_2O): $(\theta)_{368}$ −15,500, $(\theta)_{338}$ 0, $(\theta)_{321}$ +5900, $(\theta)_{281}$ 0, $(\theta)_{273}$ −3500, $(\theta)_{262}$ 0, $(\theta)_{243}$ +17,200, $(\theta)_{211}$ 0, $(\theta)_{202}$ −12,400. (Found; C, 46.23; H, 4.45; N, 20.00. Calc. for $C_{13}H_{13}N_5O_5.H_2O$: C, 46.25; H, 4.49; N, 20.75%).

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