The Base-sugar Conformation of Certain Derivatives of Adenosine

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Base-sugar conformations of a range of adenosine derivatives have been confirmed by n.m.r. and c.d. measurements. The implications of the conformations for certain chemical properties, such as the formation of 5',8-cyclo-derivatives, are discussed.

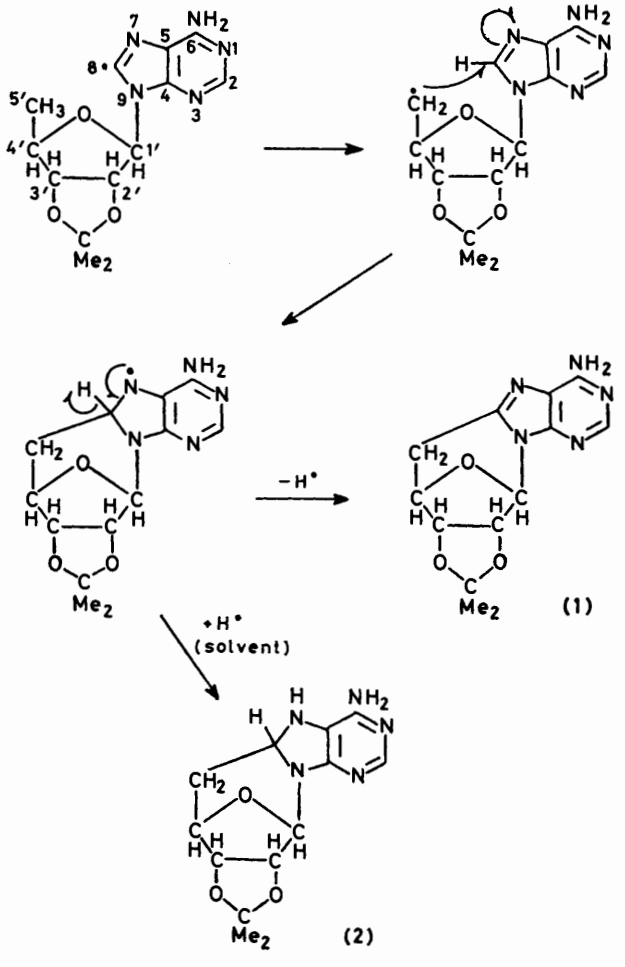
In a previous paper,[1] we have shown that the methyl group of 5'-deoxy-2'-*O*,3'-*O*-isopropylideneadenosine can be functionalised when the neighbouring C-8 position on the adenine ring is converted into a radical, *e.g.* by irradiation of the 8-phenylthio-derivative. Under these conditions cyclisation was spontaneous and the product (1) was isolated in high yield. The mechanism shown in the Scheme based on radical intermediates, is envisaged for the reaction, although we have found no evidence for a cyclised deoxydihydroadenosine (2), as observed in a similar reaction by a French group.[2] Somewhat lower yields were obtained when 8-bromo-5'-deoxy-2'-*O*,3'-*O*-isopropylideneadenosine was irradiated with tri-n-propylsilane in the presence of t-butyl peroxide as a radical initiator.[3]

Cyclisation of 2'-*O*,3'-*O*-isopropylidene-8-phenylthioadenosine by u.v. irradiation has been described by Matsuda *et al.*[4] when both (*R*)- and (*S*)-forms of the product, 2'-*O*,3'-*O*-isopropylidene-5',8-cycloadenosine [3(a) and 3(b), respectively], were obtained, together with up to 40% of 2'-*O*,3'-*O*-isopropylideneadenosine formed by hydrogen abstraction from the solvent. However, even after optimising the reaction conditions, the combined yield of both diastereoisomers of the cyclised product was only 30%, in contrast to the 5'-deoxy-series where reaction under similar conditions [1] gave almost quantitative conversion into the cyclised product (1). We have repeated Matsuda's experiments and have obtained comparable results, *viz.* *ca.* 20% of the (*S*)-5',8-cycloadenosine, *ca.* 10% of the (*R*)-isomer, 30% of the 2'-*O*,3'-*O*-isopropylideneadenosine, and *ca.* 2% of an unidentified fluorescent compound (possibly a dimer).

When the alternative method of cyclisation was applied to 8-bromo-2'-*O*,3'-*O*-isopropylideneadenosine, *i.e.* u.v. irradiation with tri-n-propylsilane in the presence of t-butyl peroxide, the (*S*)- and the (*R*)-isomers were obtained in yields of *ca.* 8 and 4%, respectively, together with 2'-*O*,3'-*O*-isopropylideneadenosine (*ca.* 10%). The similarity of the product ratios from these experiments suggested that all the cyclisations proceeded by the same fundamental mechanism, *viz.* the generation of a radical at C-8.

However, the striking difference in the yields of 5',8-cyclised products in the adenosine and 5'-deoxyadenosine series suggested that there may be conformational differences which depend on the presence or absence of the 5'-hydroxy-group.

The determination of the conformation of adenosines and other nucleosides has been the subject of many investigations in which three main techniques have been employed: *X*-ray crystallography (*e.g.* refs. 5 and 6),

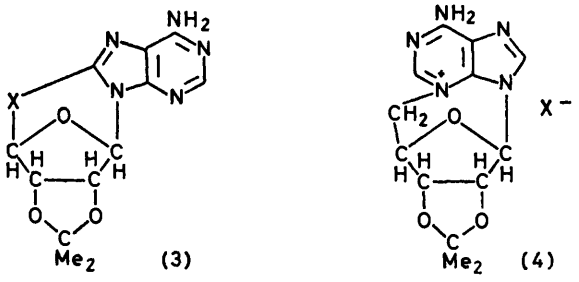


Scheme

and n.m.r. (*e.g.* refs. 7—9), and c.d. (*e.g.* refs. 10—13) spectroscopy. In addition, the base-sugar conformation of 5',3- and 5',8-cycloadenosine derivatives [compounds (4) and (1)] is fixed as *syn*- and *anti*-, respectively, and these compounds can be used as standards.

From the above accumulated physical evidence it is evident that, whereas adenosine itself exists in solution

predominantly in the *anti*-form [*cf.* compounds (1) and (3)], 8-bromoadenosine and its 2′-*O*,3′-*O*-isopropylidene derivative (5; R^1 = Br, R^2 = OH) exist predominantly in the *syn*-form. However, in the solid state two crystalline forms of the isopropylidene derivative (5; R^1 = Br, R^2 = OH) are known, which have been shown by *X*-ray crystallography [5] to differ in the base-sugar conformation. That obtained by slow crystallisation was shown to be the *syn*-isomer (Figure 1).

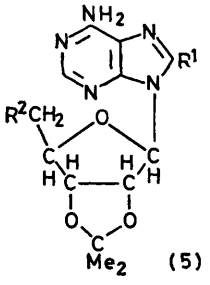


(3) (4)

a; X = HO, C, H (*R*-)

b; X = H, C, HO (*S*-)

Although it is tempting to ascribe the *syn*-conformation of 8-bromoadenosine to the presence of the bulky 8-substituent this cannot be the sole cause because of the difference, in both physical and chemical properties,



(5)

between 8-bromoadenosines and the corresponding 8-bromo-5′-deoxyadenosines, *e.g.* the ease of 5′,8-cyclonucleoside formation referred to above. Furthermore, the large difference (>50 °C) in m.p. between 8-bromoadenosine and 8-bromo-5′-deoxyadenosine suggested that internal hydrogen bonding, *e.g.* between N-3 and 5′-OH, might be playing a major role in the properties of the former compound.[14] The i.r. spectrum ($CDCl_3$) of the bromo-derivative (5; R^1 = Br, R^2 = OH) showed a sharp signal at 3 405 cm^{-1} (*ca.* 3 kJ mol^{-1}) associated with the (5′-OH)–(N-3)hydrogen bond.

Another consequence of this intramolecular hydrogen bond in 8-bromoadenosine is to force the C-2′ ribose carbon out of the plane of the ring, thus causing the formation of a large dihedral angle between 1′-H and 2′-H which is reflected in the large n.m.r. coupling constant observed for these two hydrogen atoms.[7] A variable temperature n.m.r. study of the adenosine derivative (5; R^1 = Br, R^2 = OH) showed that the coupling interaction decreased with increasing temperature, but that the effect of the hydrogen bonding was evident even at

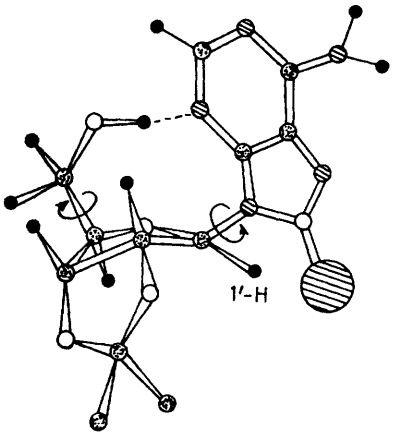


FIGURE 1 Schematic projection of *syn*-8-bromo-2′-*O*,3′-*O*-isopropylideneadenosine [5]

70 °C. The coupling constant for the equivalent interaction in the 5′-deoxy-analogue was small, suggesting a relatively planar 2′-*O*,3′-*O*-isopropylidene ribose configuration. Thus, it would appear that although 8-bromoadenosine exists predominantly in its *syn*-form, 8-bromo-5′-deoxyadenosine is not so restricted and does not exist exclusively as the *syn*-isomer. The *syn*-conformation of 8-bromo-2′-*O*,3′-*O*-isopropylideneadenosine (5; R^1 = Br, R^2 = OH) affects the course of its photolytic cyclisation, from which the (*S*)-5′,8-cycloadenosine enantiomer (3b) is the major product (see above). The van der Waals interaction between the 1′-H of the ribose grouping and the 8-bromo-substituent is such (Figure 1) that rotation about the (N-9)–(C-1′) bond is favoured in the direction in which this interaction is minimised. On incipient photolysis, the Br–C bond dissociation promotes the rotation which causes the C-5′-hydroxymethyl group to rotate in a sympathetic fashion because of its interaction through the hydrogen bond, during which time the bromine atom departs. If both the purine and the C-5′ hydroxymethyl groups rotate at the same rate, then the (*S*)-5′,8-cycloadenosine (3b) should be the major product, as is observed.

Furthermore, the fact that hydrogen abstraction from the solvent is more pronounced in the adenosine series during the cyclisations is a direct consequence of the inability of the compounds to rotate as quickly, because of internal hydrogen bonding, as their 5′-deoxyadenosine counterparts, *i.e.* the radical is exposed to the solvent for relatively long periods and therefore abstracts hydrogen. On the other hand, the 5′-deoxynucleoside can rotate freely about the (N-9)–(C-1′) bond and therefore abstracts preferentially, and intramolecularly, a hydrogen atom

from C-5′. Abstraction of hydrogen from the solvent is relatively less important in this series.

It seems, therefore, that the existence or otherwise of (N-3)–(5′-OH) hydrogen bonding is the most important effect governing the conformation of the adenosines and the course of their radical-induced 5′,8-cyclisation, and that this is more important than steric effects or electronic stabilisation of the intermediate 5′-radical. In order to test this theory we have examined the properties of 2′-*O*,3′-*O*-isopropylidene-5′-*O*-methyladenosine (5; R^1 = H, R^2 = OMe) which, lacking (N-3)–(5′-OH) hydrogen bonding, should resemble 5′-deoxy-2′-*O*,3-′*O*-isopropylideneadenosine in its behaviour rather than the corresponding adenosine, *i.e.* the generation of a C-8 radical should favour the formation of the 5′-*O*-methyl-5′,8-cycloadenosine at the expense of the solvent hydrogen abstraction product, 2′-*O*,3′-*O*-isopropylidene-5′-*O*-methyladenosine. This compound was obtained from the corresponding 5′-*O*-mesyl derivative by reaction with methanolic sodium methoxide, and was converted into its 8-bromo-derivative (5; R^1 = Br, R^2 = OMe) by direct bromination. In the n.m.r. spectrum of the 8-bromo-compound, the (1′-H)-(2′-H) coupling was 2 Hz which (see above) suggests that the ribose ring is not buckled, as there can be no hydrogen bonding between the base and the 5′-*O*-methyl group. For the cyclisation experiments the bromo-derivative (5; R^1 = Br, R^2 = OMe) was converted, with thiophenol in methanolic sodium methoxide, into the 8-phenylthio-derivative (5; R^1 = SPh, R^2 = OMe); this compound, like the parent bromo-compound, showed a coupling constant for (1′-H)–(2′-H) of only 2.5 Hz, thus suggesting a relatively planar ribose configuration. U.v. irradiation of the phenylthio-derivative (5; R^1 = SPh, R^2 = OMe) gave four products: the two major products were the (*R*)- and (*S*)-diastereoisomers of 2′-*O*,3′-*O*-isopropylidene-5′-*O*-methyl-5′,8-cycloadenosine [3; X = CH(OMe)] each in 35% yield (see Table). Some starting material

The product yields of 5′,8-cycloadenosines obtained by irradiation of various 5′-substituted 2′-*O*,3′-*O*-isopropylidene-8-phenylthioadenosines

Starting compound (5; R^1 = SPh)	Products (%)	
	5′,8-Cycloadenosine	8*H*-Adenosine
R^2 = H	90	5
R^2 = OH	30 [(*R*) : (*S*) 1 : 2]	40
R^2 = OMe	70 [(*R*) : (*S*) *ca.* 1 : 1]	5

(*ca.* 10%) was recovered, and 2′-*O*,3′-*O*-isopropylidene-5′-*O*-methyladenosine (5%), formed by hydrogen abstraction from the solvent, was isolated.

These results support the theory that (N-3)–(5′-OH) hydrogen bonding plays a major role in determining the conformation of 8-substituted adenosines, and thus their physical and chemical behaviour.

The study of the conformations of adenosines has been extended to a range of 8-substituted derivatives, *e.g.* compounds (5; R^1 = OH, OMe, SPh; R^2 = OH, OMe, Cl, H); their c.d. spectra are discussed below.

In another series, a range of 8-substituted-5′-*O*-mesyl derivatives was synthesised, *e.g.* compounds (5; R^1 = H, OH, OMe, Br; R^2 = MsO). The presence of a good leaving group at C-5′ facilitated displacement by the N-3 lone pair to form the corresponding 3,5′-cycloadenosine salts. Among the factors which influenced the rate of cyclisation in this series was the conformation

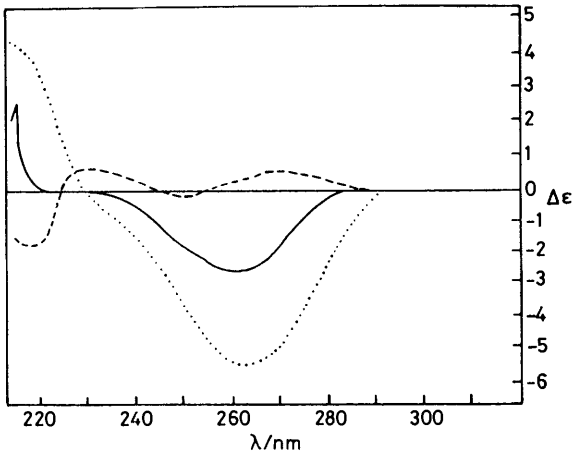


FIGURE 2 C.d. spectra of 2′-*O*,3′-*O*-isopropylidene-5′,8-cycloadenosine (1) (——), (5′*R*)-2′-*O*,3′-*O*-isopropylidene-5′-*O*-methyl-5′,8-cycloadenosine [3; X = (*R*)-CHOMe] (— — —), and (5′*S*)-2′-*O*,3′-*O*-isopropylidene-5′-*O*-methyl-5′,8-cycloadenosine [3; X = (*S*)-CHOMe] (· · · ·) in water. All are *anti*-conformers

of the adenosines, and the order of stability was found to be 8-Br < 8-OMe < 8-OH < 8-H, *i.e.* in qualitative agreement with the degree of *syn*-conformation, even after correction for electron density at N-3. Measurements of the c.d. spectra of the adenosine derivatives described here have been determined and conformations

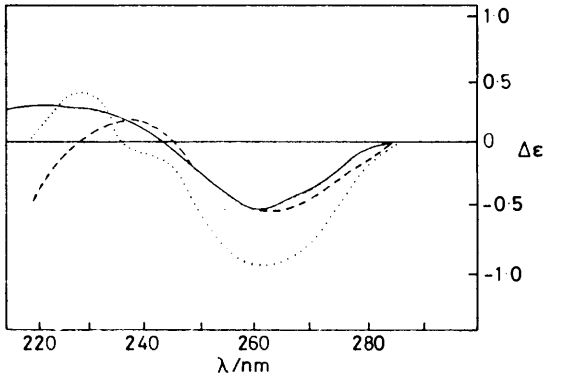


FIGURE 3 C.d. spectra of adenosine (· · · ·), 5′-chloro-5′-deoxyadenosine (— — —), and 5′-deoxy-2′-*O*,3′-*O*-isopropylideneadenosine (5; R^1 = R^2 = H) (——) in water

can be deduced within a series containing a common chromophore, although no overall generalisations can be made on the basis of c.d. spectra for compounds having markedly different structures. The 5′,8-cycloadenosines (3) can be taken as obvious examples of adenosines with an *anti*-configuration. However, substitution at the 5′-position, *e.g.* by methoxy as in compounds (3a)

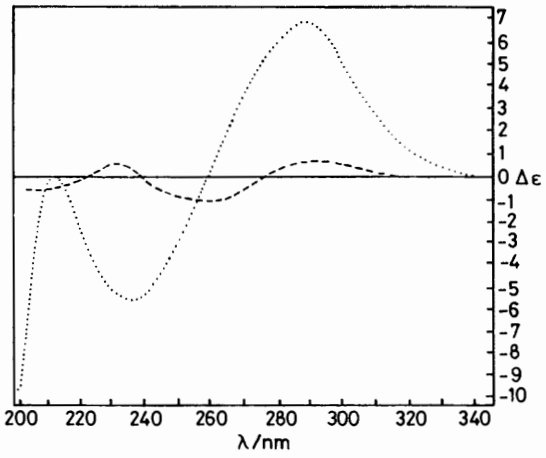


FIGURE 4 C.d. spectra of 8-bromo-2′-*O*,3′-*O*-isopropylidene-5′-*O*-mesyladenosine (5; R^1 = Br, R^2 = MsO) (– – – –) and the corresponding *syn*-3,5′-cycloadenosine (4) (· · · ·)

and (3b), has a profound effect on the spectrum (Figure 2) and structural deductions on the basis of line shapes have to be made with caution. Adenosine itself is known to possess the *anti*-configuration, and the c.d. spectra of some simple adenosines are given for comparison (Figure 3). Substitution of the non-hydrogen bonded 5′-hydroxy-group by chlorine or hydrogen has little effect on the spectrum.

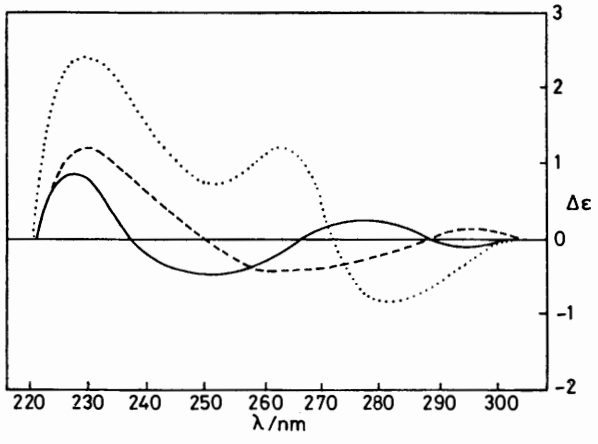


FIGURE 5 C.d. spectra of 8-bromo-2′-*O*,3′-*O*-isopropylideneadenosine (5; R^1 = Br, R^2 = OH) (· · · ·), 8-bromo-5′-deoxy-2′-*O*,3′-*O*-isopropylideneadenosine (5; R^1 = Br, R^2 = H) (– – – –), and 8-bromo-2′-*O*,3′-*O*-isopropylidene-5′-*O*-methyladenosine (5; R^1 = Br, R^2 = OMe) (——)

The 3,5′-cycloadenosine salts (4) obviously possess the *syn*-conformation, and the change in c.d. spectral shape between the parent 5′-*O*-mesyl derivatives and the corresponding 3,5′-cycloadenosine salts is very striking (Figure 4). The c.d. spectrum of 8-bromo-2′-*O*,3′-*O*-isopropylideneadenosine (5; R^1 = Br, R^2 = OH) is similar to that published [10] for 8-bromoadenosine, and in acetonitrile it showed only trivial changes in line shape over the temperature range −40 to + 60 °C. The c.d. spectrum of the deoxy-compound (5; R^1 = Br, R^2 = H) was weak in comparison and the line shape was markedly different (Figure 5); again, there was little change in the spectrum with increasing temperature. Furthermore, the spectrum of 8-bromo-2′-*O*,3′-*O*-isopropylidene-5′-*O*-methyladenosine (5; R^1 = Br, R^2 = OMe) resembled that of the 5′-deoxy-compound (5; R^1 = Br, R^2 = H) rather than the adenosine (5; R^1 = Br, R^2 = OH), indicating that the first two compounds, lacking the

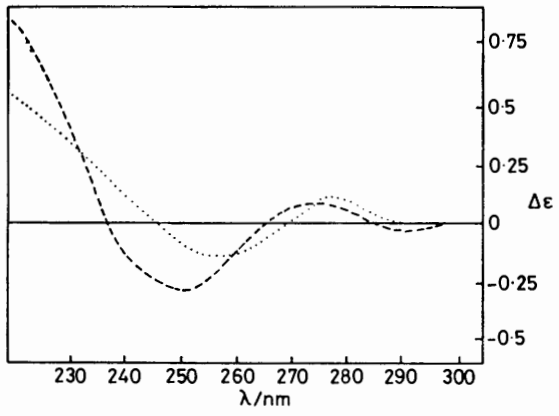


FIGURE 6 C.d. spectra of 8-methoxyadenosine (– – – –) and 5′-deoxy-2′-*O*,3′-*O*-isopropylidene-8-methoxyadenosine (5; R^1 = OMe, R^2 = H) (· · · ·)

(N-3)–(5-OH) hydrogen bond, do not exist entirely in the *syn*-conformation.

A situation similar to that observed with the 8-bromo-compounds exists in the 8-phenylthio-series, *i.e.* 2′-*O*,3′-*O*-isopropylidene-8-phenylthioadenosine (5; R^1 = SPh, R^2 = OH) exists in the *syn*-conformation, but the corresponding 5′-*O*-methyl ether, lacking the (N-3)–(5′-OH) hydrogen bond, possesses a less rigid conformation.

The c.d. spectra of the 8-substituted-2′-*O*,3′-*O*-isopropylideneadenosines (5; R^1 = OMe, R^2 = H, OH) and (5; R^1 = OH, R^2 = OH, Cl) were similar (Figures 6 and 7) and all differed from the c.d. spectrum of 8-bromo-2′-*O*,3′-*O*-isopropylideneadenosine (Figure 5). The c.d. and n.m.r. spectra of these compounds suggest that (N-3)–(5′-OH) hydrogen bonding does not occur to any sig-

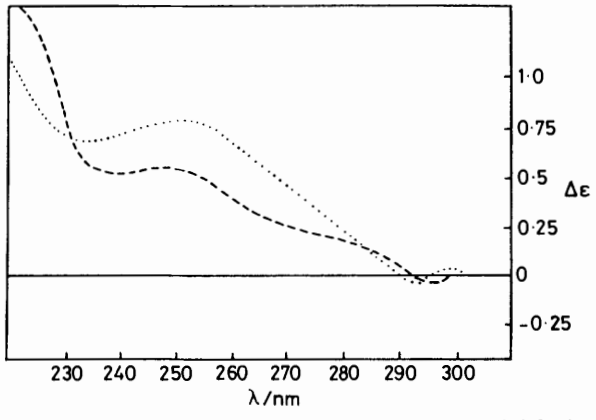


FIGURE 7 C.d. spectra of 5′-chloro-8-hydroxy-2′-*O*,3′-*O*-isopropylideneadenosine (5; R^1 = OH, R^2 = Cl) (– – – –), and 8-hydroxy-2′-*O*,3′-*O*-isopropylideneadenosine (5; R^1 = R^2 = OH) (· · · ·)

nificant extent when the 8-substituent is hydroxy or methoxy. In the 8-hydroxy- and 8-methoxy-compounds (5; R^1 = OH, OMe) there appears to be relatively free rotation about the (N-9)–(C-1′) bond and no particular conformation is favoured.

EXPERIMENTAL

Spectra were measured on the instruments detailed in a previous paper.[1] C.d. spectra were recorded using a JASCO J4OCS spectrometer. The spectra were repeated for each sample, at a slow scan speed, and the mean of the two curves calculated. All the samples were prepared so that the optical density at $\lambda_{max.}$ was between 0.7 and 1.4 absorbance units. Variable temperature c.d. experiments were conducted on the same machine using an internal thermocouple to monitor the sample temperature. All mass spectra showed fragmentation patterns corresponding to the postulated structures.

2′-O,3′-O-*Isopropylidene*-5′-O-p-*tosyladenosine* (5; R^1 = H, R^2 = TsO).—This compound was prepared following Todd, Clark, and Zussman,[15] δ[$(CD_3)SO$] 8.3 (1 H, s, 8-H), 8.03 (1 H, s, 2-H), 7.4 and 6.9 (4 H, m, AB,B′A′ type *p*-substituted benzene coupling), 7.15 (2 H, br s, NH_2), 6.05 (1 H, d, *J* 2 Hz, 1′-H), 5.10 (1 H, m, 2′-H), 4.75 (1 H, m, 3′-H), 4.1 (3 H, m, 4′-H and 5′-H_2), 2.2 (3 H, s, Me of tosyl), and 1.35 and 1.15 (3 H, s, acetonide).

2′-O,3′-O-*Isopropylidene*-5′-O-*mesyladenosine* (5; R^1 = H, R^2 = MsO).—2′-*O*,3′-*O*-Isopropylideneadenosine (1.2 g, 3.9 mmol) was dissolved in dry pyridine (15 ml). The solution was cooled to 0 °C and methanesulphonyl chloride (0.55 g, 4.8 mmol) was added dropwise with stirring during 5 min. After 90 min at 10 °C the excess of the sulphonyl chloride was hydrolysed with ice–water (5 ml) and the solution neutralised with 2M-aqueous potassium hydroxide. The solvents were removed under reduced pressure and the residue partitioned between chloroform (80 ml) and water (20 ml). The organic layer was separated, washed, and evaporated to yield 1.4 g (90%) of the 5′-*O*-mesyl compound, R_F 0.4 (on silica plates in $CHCl_3$–EtOH 10 : 1) (Found: M^+, 385. $C_{14}H_{19}N_5O_6S$ requires *M*, 385); $\lambda_{max.}$ (H_2O, pH 7) 259 nm (ε 16 000), changing to 280 nm on heating to 60 °C for 4 h; δ($CDCl_3$ with D_2O) 8.05 (1 H, s, 2-H), 7.64 (1 H, s, 8-H), 5.90 (1 H, d, *J* 2 Hz, 1′-H), 5.30 (1 H, dd, *J* 6 and 2 Hz, 2′-H), 4.95 (1 H, m, 3′-H), 4.31 (3 H, m, 4′-H and 5′-H_2), 2.80 (3 H, s, MsO), and 1.53 and 1.31 (3 H, s, acetonide).

2′-O,3′-O-*Isopropylidene*-5′-O-*methyladenosine* (5; R^1 = H, R^2 = OMe).—To a solution of 2′-*O*,3′-*O*-isopropylidene-5′-*O*-mesyladenosine (800 mg, 2.1 mmol) in methanol (15 ml) was added a small piece of sodium (200 mg, 8.7 mmol) and the mixture was heated to 60 °C for 2 h and then cooled to room temperature overnight. The solution was treated with ice–water (5 ml) and was neutralised with 2M-hydrochloric acid. The methanol was removed under reduced pressure, the aqueous residue extracted with chloroform (3 × 15 ml), and the organic layer reduced in volume to 5 ml and applied to two silica plates (each 1 m × 20 cm × 1.2 mm) and eluted ($CHCl_3$–EtOH 10 : 1). The least polar band (R_F 0.48) was removed and worked up to yield 300 mg (50%) of 2′-*O*,3′-*O*-isopropylidene-5′-*O*-methyladenosine as white crystals together with starting material (20%) and the 3,5′-cycloadenosine salt (20%), m.p. 137—139 °C (from EtOH–H_2O 1 : 1) (Found: M^+, 321. $C_{14}H_{19}N_5O_4$ requires *M*, 321); $\lambda_{max.}$ (H_2O, pH 7) 259 nm (ε 15 800); δ($CDCl_3$ with D_2O) 8.15 (1 H, s, 2-H), 7.81 (1 H, s, 8-H), 6.03 (1 H, d, *J* 2.5 Hz, 1′-H), 5.18 (1 H, dd, *J* 6 and 2.5 Hz, 2′-H), 4.85 (1 H, dd, *J* 2.5 and 6 Hz, 3′-H), 4.35 (1 H, m, 4′-H), 3.48 (2 H, d, *J* 4 Hz, 5′-H_2), 3.23 (3 H, s, OMe), and 1.59 and 1.36 (3 H, s, acetonide).

5′-*Chloro*-5′-*deoxyadenosine*.—This compound was prepared following Kikugawa and Ichino[16] (see also Gani *et al.*[17]); the product had m.p. 190 °C (H_2O) (lit.,[16] 190 °C) (Found: C, 40.8; H, 4.75; Cl, 12.25; N, 23.7. Calc. for $C_{10}H_{12}ClN_5O_3$: C, 40.8; H, 4.45; Cl, 12.05; N, 23.75%); δ[$(CD_3)_2SO$] 8.33 (1 H, s, 8-H), 8.18 (1 H, s, 2-H), 7.26 (2 H, br s, NH_2), 5.97 (1 H, d, *J* 7 Hz, 1′-H), 4.87 (1 H, m, 2′-H), 4.23 (1 H, m, 3′-H), 4.11 (1 H, m, 4′-H), and 3.92 (2 H, d, *J* 3 Hz, 5′-H_2); δ (^{13}C) [$(CD_3)_2SO$] 155.95 (C-6), 152.73 (C-2), 149.33 (C-4), 139.80 (C-8), 119.06 (C-5), 87.66 (C-1′), 83.55 (C-4′), 72.94 (C-2′), 71.21 (C-3′), and 44.81 (C-5′).

A sample prepared by dilute acid hydrolysis of the 2′-*O*,3′-*O*-isopropylidene derivative [1] was identical with the above product.

8-*Bromoadenosine*.—This compound was prepared following Ikehara and Kaneko.[18] The product had m.p. 205 °C (decomp.) [lit.,[18] >200 °C (decomp.)] (Found: C, 35.1; H, 4.0; N, 20.2. Calc. for $C_{16}H_{12}BrN_5O_4$: C, 34.7; H, 3.5; N, 20.2%); $\lambda_{max.}$ (H_2O at pH 7) 265 nm; δ[$(CD_3)_2SO$] 7.98 (1 H, s, 2-H), 7.41 (2 H, br ds, NH_2), 5.72 (1 H, d, *J* 7 Hz, 1′-H), 5.05 (1 H, m, 2′-H), 4.09 (1 H, m, 3′-H), 3.82 (1 H, m, 4′-H), and 3.51 (2 H, m, 5′-H_2).

The corresponding 2′-*O*,3′-*O*-isopropylidene derivative was prepared (70%) according to Ikehara, Tada, and Kaneko[19] and had m.p. 221—222 °C (decomp.) (lit.,[17] 221—222 °C) (Found: C, 40.1; H, 4.5; N, 17.9. Calc. for $C_{13}H_{16}BrN_5O_4$: C. 40.4; H, 4.2; N, 18.1%); $\lambda_{max.}$ (H_2O at pH 7) 264 nm (ε 17 500); δ($CDCl_3$) 7.97 (1 H, s, 2-H), 5.87 (1 H, d, *J* 5 Hz, 1′-H), 5.75 (2 H, br s, NH_2), 5.13 (1 H, dd, *J* 5 and 6 Hz, 2′-H), 4.91 (1 H, dd, *J* 6 and 5 Hz, 3′-H), 4.32 (1 H, m, 4′-H), 3.75 (2 H, m, 5′-H_2), and 1.57 and 1.30 (3 H, s, acetonide); δ[$(CD_3)_2SO$] 8.00 (1 H, s, 2-H), 7.37 (2 H, br s, NH_2), 5.93 (1 H, d, *J* 3 Hz, 1′-H), 5.63 (1 H, dd, *J* 6 and 3 Hz, 2′-H), 5.02 (1 H, dd, *J* 3 and 6 Hz, 3′-H), 4.21 (1 H, m, 4′-H), 3.55 (2 H, d, *J* 6 Hz, 5′-H_2), and 1.69 and 1.48 (3 H, s, acetonide).

8-*Bromo*-2′-O,3′-O-*isopropylidene*-5′-O-*mesyladenosine* (5; R^1 = Br, R^2 = MsO).—8-Bromo-2′-*O*,3′-*O*-isopropylideneadenosine was treated with methanesulphonyl chloride as described above to yield the mesyl ester (90%) as an amorphous solid [Found: M^+, 465, 463. $C_{14}H_{18}BrN_5O_6S$ requires *M*, 465, 463 (Br isotopes)]; $\lambda_{max.}$ (H_2O, pH 7) 266 nm (ε 17 500), changing to 297 nm (ε 12 500) after heating at 60 °C for 90 min; δ($CDCl_3$) 8.05 (1 H, s, 2-H), 6.05 (1 H, d, *J* 2 Hz, 1′-H), 5.52 (1 H, dd, *J* 6 and 2 Hz, 2′-H), 5.10 (1 H, dd, *J* 3 and 6 Hz, 3′-H), 4.35 (3 H, m, 4′-H and 5′-H_2), 2.84 (3 H, s, MsO), and 1.57 and 1.36 (3 H, s, acetonide).

8-*Bromo*-2′-O,3′-O-*isopropylidene*-5′-O-*methyladenosine* (5; R^1 = Br, R^2 = OMe).—2′-*O*,3′-*O*-Isopropylidene-5′-*O*-methyladenosine (as above; 180 mg) was stirred in a solution of methanol (3 ml), water (25 ml), and acetic acid (1 ml), containing sodium acetate (2 g), and saturated bromine water was added dropwise until the colour just persisted. The solution was kept overnight and then treated with sodium metabisulphite until the bromine colour was just discharged. The solution was extracted with chloroform (2 × 25 ml) and the solvent evaporated under reduced pressure to yield 155 mg (70%) of 8-bromo-2′-*O*,3′-*O*-isopropylidene-5′-*O*-methyladenosine as an off-white solid, m.p. 154 °C (decomp.) [Found: M^+, 401, 399. $C_{14}H_{18}BrN_5O_4$ requires *M*, 401, 399 (Br isotopes)]; $\lambda_{max.}$ (H_2O, pH 7) 264 nm (ε 17 500); δ($CDCl_3$) 7.91 (1 H, s, 2-H), 5.96 (1 H, d,

J 2 Hz, 1′-H), 5.46 (1 H, dd, *J* 6 and 2 Hz, 2′-H), 4.93 (1 H, dd, *J* 4 and 6 Hz, 3′-H), 4.16 (1 H, m, 4′-H), 3.47 (2 H, s, *J* 6 Hz, 5′-H_2), 3.20 (3 H, s, OMe), and 1.60 and 1.39 (3 H, s, acetonide).

8-*Methoxyadenosine*.—This compound was prepared by a modification of the method of Holmes and Robins.[20] The product (70%) had m.p. 204 °C (decomp.) [lit.,[20] 206—208 °C (decomp.)], $\lambda_{max.}$ (H_2O at pH 7) 260 nm; $\lambda_{max.}$ (pH 1) 261 nm; δ[$(CD_3)_2SO$] 8.00 (1 H, s, 2-H), 6.91 (2 H, s, NH_2), 5.71 (1 H, d, *J* 7 Hz, 1′-H), 5.2 (3 H, br s, 2′-, 3′-, and 5′-OH), 4.85 (1 H, t, *J* 7 Hz, 2′-H), 4.1 (3 H, s, OMe), 4.1 (1 H, m, 3′-H), 3.9 (1 H, m, 4′-H), and 3.55 (2 H, m, 5′-H_2).

The corresponding 2′-*O*,3′-*O*-isopropylidene derivative (5; R^1 = OMe, R^2 = OH) was obtained from 8-bromo-2′-*O*,-3′-*O*-isopropylideneadenosine (as above; 3.9 mmol; 1.5 g), which was dissolved in dry methanol (70 ml) and sodium (0.6 g, 26 mmol) added. The solution was sealed in a dry pre-heated (50 °C) bomb and the bomb heated to 95 °C for 1 h. It was allowed to cool, the contents tipped into water (15 ml) and the solution neutralised with 5M-hydrochloric acid. The solvent was removed under reduced pressure and the resulting aqueous phase extracted with chloroform (4 × 50 ml), back-washing with water (2 × 10 ml). The organic phase was dried ($MgSO_4$) and evaporated to yield 0.84 g (65%) of a pale-yellow solid (Found: M^+, 337. Calc. for $C_{14}H_{19}N_5O_5$: M^+, 337); $\lambda_{max.}$ (H_2O, pH 7) 259 nm; δ($CDCl_3$–D_2O 5 : 1),[8] 7.96 (1 H, s, 2-H), 5.85 (1 H, d, *J* 4 Hz, 1′-H), 5.19 (1 H, dd, *J* 5 and 4 Hz, 2′-H), 4.99 (1 H, dd, *J* 1 and 5 Hz, 3′-H), 4.40 (1 H, m, 4′-H), 4.08 (3 H, s, OMe), 3.78 (2 H, s, 5′-H_2), and 1.67 and 1.44 (3 H, s, acetonide).

The 5′-*O*-mesyl derivative (5; R^1 = OMe, R^2 = MsO) was obtained as a white amorphous solid (Found: M^+, 415. $C_{15}H_{21}N_5O_7S$ requires *M*, 415); $\lambda_{max.}$ (H_2O at pH 7) 259 nm (ε 15 800), which changed to 282 nm after 2 h at 60 °C; δ($CDCl_3$–D_2O) 7.95 (1 H, s, 2-H), 5.95 (1 H, d, *J* 2 Hz, 1′-H), 5.35 (1 H, dd, *J* 7 and 2 Hz, 2′-H), 5.02 (1 H, m, 3′-H), 4.15 (3 H, m, 4′-H and 5′-H_2), 4.02 (3 H, s, OMe), 2.85 (3 H, s, MsO), and 1.53 and 1.32 (3 H, s, acetonide).

5′-*Deoxy*-2′-O,3′-O-*isopropylidene*-8-*methoxy*-5′-*phenylthioadenosine* (5; R^1 = OMe, R^2 = SPh).—The foregoing mesyl derivative (450 mg) was dissolved in tetrahydrofuran (THF) (40 ml; dried over Na) and a solution of sodium (50 mg) and thiophenol (1 g) in methanol (5 ml) was added. The solution was warmed to 55 °C for 6 h and then cooled. Water (50 ml) was added dropwise during 2 min with rapid stirring followed by 2N-hydrochloric acid until neutral. The THF was removed under reduced pressure and the residual aqueous phase extracted with chloroform (3 × 40 ml). The solvent was removed from the chloroform extract leaving a brown oil which was dissolved in more chloroform (8 ml) and applied to two silica plates (1 m × 20 cm × 1.2 mm), using chloroform–ethanol (10 : 1) for elution. Two major bands were observed and these were removed separately from the chromatogram. The less polar band (R_F 0.68) gave 5′-*deoxy*-2′-O,3′-O-*isopropylidene*-8-*methoxy*-5′-*phenylthioadenosine* as a colourless amorphous solid (210 mg, 35%) (Found: M^+, 429. $C_{20}H_{23}N_5O_4S$ requires *M*, 429); $\lambda_{max.}$ (H_2O at pH 7) 288 nm; δ($CDCl_3$–D_2O) 7.89 (1 H, s, 2-H), 7.00 (5 H, m, SPh), 5.86 (1 H, d, *J* 2 Hz, 1′-H), 5.42 (1 H, dd, *J* 6 and 2 Hz, 2′-H), 4.94 (1 H, dd, *J* 3 and 6 Hz, 3′-H), 4.11 (1 H, td, *J* 7 and 3 Hz, 4′-H), 3.99 (3 H, s, OMe), 3.07 (2 H, d, *J* 7 Hz, 5′-H_2), and 1.50 and 1.32 (3 H, s, acetonide).

The more polar band (R_F 0.38) yielded 2′-*O*,3′-*O*-isopropylidene-5′-*O*,8-cyclo[illegible] (5; [illegible]) as colourless needles (235 mg, 55%), m.p. 231—233 °C (lit.,[21] 222—224 °C) (Found: M^+, 305. $C_{13}H_{15}N_5O_4$ requires *M*, 305); $\lambda_{max.}$ (H_2O at pH 7) 259 nm; δ[$CDCl_3$–$(CH_3)_2SO$, 1 : 1] 7.88 (1 H, s, 2-H), 6.47 (2 H, br s, NH_2), 5.99 (1 H, s, 1′-H), 4.95 (1 H, d, *J* 6 Hz, 2′-H), 4.63 (1 H, d, *J* 6 Hz, 3′-H), 4.5—3.1 (3 H, m, 4′-H and 5′-H_2), and 1.49 and 1.31 (3 H, s, acetonide).

8-*Methoxy*- *and* 8-*Hydroxy*-5′-*chloro*-5′-*deoxy*-2′-O,3′-O-*isopropylideneadenosines* (5; R^1 = OMe, R^2 = Cl) *and* (5; R^1 = OH, R^2 = Cl).—2′-*O*,3′-*O*-isopropylidene-8-methoxyadenosine (as above; 800 mg, 2.4 mmol) was stirred in dry pyridine at 0 °C and thionyl chloride (1.5 ml, 12.5 mmol) added. The reaction mixture was warmed to 60 °C for 30 min and then cooled for 5 min. Water (5 ml) was added with cooling and the solution immediately neutralised with 5M-potassium hydroxide. The solvent was removed under reduced pressure and the brown residue dissolved in chloroform (100 ml) and washed with water (3 × 5 ml). The chloroform extract was dried ($MgSO_4$) and evaporated leaving a brown oily residue which was dissolved in chloroform (2 ml) and applied to four (20 × 20 cm × 1.2 mm) silica plates. After elution ($CHCl_3$–MeOH, 8 : 1), the two strong bands, with R_F 0.6 (A) and R_F 0.82 (B), were removed from the glass plates and suspended in chloroform–ethanol (3 : 1). The silica was removed, washed with chloroform and the filtrate evaporated to yield a pale yellow solid (A), 5′-*chloro*-5′-*deoxy*-8-*hydroxy*-2′-O,3′-O-*isopropylideneadenosine* (5; R^1 = OH, R^2 = Cl) (120 mg, 20%), *m/z* 306 (M^+ − Cl); $\lambda_{max.}$ (H_2O–MeOH, 10 : 1, pH 7) 268 nm; $\nu_{max.}$ 1 700 cm^{-1} (lactam carbonyl); δ($CDCl_3$–D_2O, 4 : 1) 7.93 (1 H, s, 2-H), 5.93 (1 H, d, *J* 2 Hz, 1′-H), 5.41 (1 H, dd, *J* 2 and 6 Hz, 2′-H), 4.99 (1 H, dd, *J* 3.5 Hz, 3′-H), 4.25 (1 H, td, *J* 7 Hz, 4′-H), 3.57 (2 H, dd, *J* 4 and 7 Hz, 5′-H_2), and 1.56 and 1.37 (3 H, s, acetonide).

Extraction of band B gave a white amorphous solid (150 mg, 20%) identified as 5′-*chloro*-5′-*deoxy*-2′-O,3′-O-*isopropylidene*-8-*methoxyadenosine* (5; R^1 = OMe, R^2 = Cl) (Found: M^+, 355. $C_{14}H_{18}ClN_5O_4$ requires *M*, 355); $\lambda_{max.}$ (H_2O–MeOH, 10 : 1) 259 nm (ε 16 000); δ($CDCl_3$–D_2O 4 : 1), 8.00 (1 H, s, 2-H), 5.95 (1 H, d, *J* 2 Hz, 1′-H), 5.43 (1 H, dd, *J* 6 Hz, 2′-H), 5.05 (1 H, dd, $J_{3',4'-H}$ 3 Hz), 4.29 (1 H, td, *J* 7 Hz, 4′-H), 4.09 (3 H, s, OMe), 3.54 (2 H, dd, *J* 4.5 Hz, 5′-H_2), and 1.60 and 1.41 (3 H, s, acetonide).

8-*Hydroxy*-2′-O,3′-O-*isopropylideneadenosine* (5; R^1 = R^2 = OH).—8-Bromo-2′-*O*,3′-*O*-isopropylideneadenosine (as above; 1 g, 2.6 mmol) was dissolved in dry methanol (30 ml) and sodium (0.2 g, 8.7 mmol) was added. The yellow solution was transferred to a pre-warmed bomb at 60 °C just before dissolution of the sodium was complete. The bomb was sealed and heated to 105 °C for 3 h, then allowed to cool slowly. The methanolic solution was treated with 1M-acetic acid until it reached pH 6 and the solvent was removed under reduced pressure. The residue was dissolved in chloroform (80 ml) and washed with saturated sodium hydrogen carbonate (5 ml) and then water (10 ml). The solution was evaporated to 5 ml and applied to six (20 × 20 cm × 1.2 mm) silica gel plates (using $CHCl_3$–MeOH, 10 : 1, for development). The least polar band (R_F 0.7) was removed from the plates to give 2′-*O*,3′-*O*-isopropylidene-8-methoxyadenosine (210 mg, 24%). The most polar band (R_F 0.45) was removed from the plates and suspended in chloroform–methanol (3 : 1). Separation of the silica followed by evaporation of the solvent gave 8-*hydroxy*-2′-O,3′-O-*isopropylideneadenosine* [22] (5; R^1 = R^2 = OH) (280 mg, 40%) as a pale yellow solid m.p. 150 °C (decomp.) (Found: M^+, 323. Calc. for $C_{13}H_{17}N_5O_5$: *M*, 323); $\lambda_{max.}$

(H_2O, pH 7) 269, 255sh nm; δ($CDCl_3$–D_2O) 8.00 (1 H, s, 2-H), 6.05 (1 H, d, *J* 5 Hz, 1'-H), 5.34 (1 H, dd, *J* 6 and 5 Hz, 2'-H), 4.95 (1 H, dd, *J* 2.5 and 6 Hz, 3'-H), 4.36 (1 H, m, 4'-H), 3.83 (2 H, m, 5'-H_2), and 1.53 and 1.32 (3 H, s, acetonide).

The corresponding 5'-O-*mesyl derivative* was obtained as a white amorphous solid (Found: M^+, 306. $C_{14}H_{19}N_5O_7S$ – CH_3SO_3 requires *M*, 306); $\lambda_{max.}$ 268 nm (ε 16 000), changing to 294 nm after 2 h at 60 °C; δ($CDCl_3$–D_2O) 7.91 (1 H, s, 2-H), 5.99 (1 H, d, *J* 1.5 Hz, 1'-H), 5.35 (1 H, dd, *J* 6 and 1.5 Hz, 2'-H), 4.92 (1 H, dd, *J* 2 and 6 Hz, 3'-H), 4.30 (3 H, m, 4'-H and 5'-H_2), 2.89 (3 H, s, MsO), and 1.52 and 1.33 (3 H, s, acetonide).

2'-O,3'-O-*Isopropylidene*-5'-O-*methyl*-8-*phenylthioadenosine* (5; R^1 = SPh, R^2 = OMe).—8-Bromo-2'-*O*,3'-*O*-isopropylidene 5'-*O*-methyladenosine (120 mg, 0.3 mmol) was dissolved in dry methanol (10 ml) and a solution of 2M-sodium methoxide (in MeOH, 1.5 ml) and then thiophenol (100 mg, 0.91 mmol) was added. The solution was warmed to 45 °C for 4 h after which t.l.c. revealed two major bands, R_F 0.58 and 0.42 (starting material, R_F 0.51). The reaction mixture was poured into ice–water (20 ml), neutralised, and the methanol removed under reduced pressure. The aqueous residue was extracted with chloroform (3 × 25 ml), the solvent reduced in volume to 5 ml and the residue applied to a silica t.l.c. plate (1 m × 20 cm × 1.2 mm) using chloroform–ethanol as eluant. The bands with R_F 0.58 and 0.42 were removed and the less polar band (R_F 0.58) yielded 2'-O,3'-O-*isopropylidene*-5'-O-*methyl*-8-*phenylthioadenosine* (5; R^1 = SPh, R^2 = OMe) (75 mg, 60%) as a fawn coloured amorphous solid (Found: M^+, 429. $C_{20}H_{23}N_5O_4S$ requires *M*, 429); $\lambda_{max.}$ (H_2O at pH 7) 282 nm (ε 17 200); δ($CDCl_3$–D_2O) 8.03 (1 H, s, 2-H), 7.15 (5 H, m, SPh), 6.16 (1 H, d, *J* 2.5 Hz, 1'-H), 5.49 (1 H, dd, *J* 6 and 2.5 Hz, 2'-H), 4.94 (1 H, dd, *J* 3.5 and 6 Hz, 3'-H), 4.20 (1 H, m, 4'-H), 3.45 (2 H, d, *J* 6 Hz, 5'-H_2), 3.20 (3 H, s, OMe), and 1.53 and 1.32 (3 H, s, acetonide).

The more polar band was separated similarly and yielded 2'-O,3'-O-*isopropylidene*-5'-O-*methyl*-8-*methoxyadenosine* (5; R^1 = R^2 = OMe) (20 mg, 20%) as a white amorphous solid (Found: M^+, 351. $C_{15}H_{21}N_5O_5$ requires *M*, 351); $\lambda_{max.}$ (H_2O at pH 7) 255 nm (ε 15 200); δ($CDCl_3$–D_2O) 7.98 (1 H, s, 2-H), 5.95 (1 H, d, *J* 2.5 Hz, 1'-H), 5.41 (1 H, dd, *J* 6 and 2.5 Hz, 2'-H), 4.90 (1 H, dd, *J* 3.5 and 6 Hz, 3'-H), 4.15 (1 H, m, 4'-H), 4.02 (3 H, s, 8-OMe), 3.45 (2 H, d, *J* 6 Hz, 5'-H), 3.22 (3 H, s, 5'-OMe), and 1.55 and 1.35 (3 H, s, acetonide).

5'-*Deoxy*-2'-O,3'-O-*isopropylidene*-5',8-*cycloadenosine* (3; X = CH_2).—(a) 2'-*O*,3'-*O*-Isopropylidene-8-phenylthioadenosine (5; R^1 = SPh, R^2 = OH) (100 mg, 0.24 mmol) was dissolved in acetonitrile (80 ml) and t-butyl hydroperoxide (4 ml) was added. The solution was purged with argon for several min and then exposed to an 800 W u.v. reactor (200—300 nm) for 20 h at 35 °C.[1] T.l.c. [$CHCl_3$–MeOH, 5 : 1) then showed four bands: R_F 0.58 (fluorescent *ca.* 2%), R_F 0.43 (*ca.* 30), R_F 0.35 (*ca.* 25), and R_F 0.28 (*ca.* 10). The solution was evaporated and the residue dissolved in chloroform (2 ml) and applied to four (20 × 20 cm × 1.2 mm) silica plates using chloroform–methanol (5 : 1) as eluant. The bands were removed, and each was suspended in chloroform–ethanol (3 : 1) followed by removal of the silica gel, and the solvent evaporated. The band with R_F 0.43 gave 2'-*O*,3'-*O*-isopropylideneadenosine (25 mg, 30%) (formed by hydrogen abstraction from the solvent) (Found: M^+, 307. Calc. for $C_{13}H_{17}N_5O_4$: *M*, 307); $\lambda_{max.}$ (H_2O at pH 7) 261 nm.

The band at R_F 0.35 ($CHCl_3$–MeOH 7 : 1) yielded a colourless product (18 mg, 25%) identified as (*S*)-2'-*O*,3'-*O*-isopropylidene-5',8-cycloadenosine (3b) (Found: M^+, 305. Calc. for $C_{13}H_{15}N_5O_4$: *M*, 305); $\lambda_{max.}$ (H_2O at pH 7) 265 nm; δ($CDCl_3$–CD_3OD 1 : 1) 7.93 (1 H, s, 2-H), 6.04 (1 H, s, 1'-H), 5.05 (1 H, d, *J* 6 Hz, 2'-H), 4.95 (1 H, d, *J* 6 Hz, 4'-H), 4.51 (2 H, m, 3'- and 5'-H), and 1.46 and 1.24 (3 H, s, acetonide).

The band at R_F 0.28 ($CHCl_3$–MeOH 7 : 1) yielded a colourless product (10 mg, 15%) identified as (*R*)-2'-*O*,3'-*O*-isopropylidene-5',8-cycloadenosine (3a) (Found: M^+, 305); $\lambda_{max.}$ (H_2O at pH 7) 264 nm; δ($CDCl_3$–CD_3OD 1 : 1) 7.91 (1 H, s, 2-H), 6.10 (1 H, br s, 1'-H), 5.1—4.5 (4 H, m, 2'-, 3'-, 4'- and 5'-H), and 1.49 and 1.27 (3 H, s, acetonide).

(b) The same three compounds were also formed (yields 8, 7 and 2%, respectively) when 8-bromo-2'-O,3'-*O*-isopropylideneadenosine (300 mg, 0.8 mmol) was irradiated under identical conditions in the presence of di-t-butyl peroxide (2.5 ml) and tri-n-propylsilane (3 ml). The products were characterised by R_F mobility and u.v., n.m.r., and mass spectroscopy.

2'-O,3'-O-*Isopropylidene*-5'-O-*methyl*-5',8-*cycloadenosines* (3; X = CHOMe).—2'-*O*,3'-*O*-Isopropylidene-5'-*O*-methyl-8-phenylthioadenosine (60 mg, 140 mmol) was dissolved in acetonitrile (20 ml) and t-butyl hydroperoxide (500 mg of a 70% solution in water, 3.9 mmol) was added. The solution was purged with argon for 5 min and was irradiated for 8 h, after which examination by t.l.c. showed that two major products had been formed and only a trace of starting material remained. The acetonitrile was removed under reduced pressure and the residual oil was dissolved in chloroform (5 ml) and applied to three silica plates (20 × 20 cm × 1.2 mm) using chloroform–ethanol (10 : 1) as eluant. The individual bands were separated and the products isolated: (i) R_F 0.32 (least polar band) yielded (*S*)-2'-*O*,3'-*O*-isopropylidene-5'-*O*-methyl-5',8-cycloadenosine (15 mg, 35%) as white crystals, m.p. 210 °C (decomp.) (Found: M^+, 319. $C_{14}H_{17}N_5O_4$ requires *M*, 319); $\lambda_{max.}$ 263 nm (ε 17 500); δ($CDCl_3$–D_2O) 8.35 (1 H, s, 2-H), 6.28 (1 H, s, 1'-H), 5.09 (1 H, d, *J* 6 Hz, 5'-H), 4.84 (1 H, d, *J* 6 Hz, 4'-H), 3.8 (3 H, s, 5'-OMe), and 1.55 and 1.28 (3 H, s, acetonide).

(ii) R_F 0.22 (most polar band) yielded (*R*)-2'-*O*,3'-*O*-isopropylidene-5'-*O*-methyl-5',8-cycloadenosine as colourless crystals (15 mg, 35%), m.p. 223 °C (decomp.) (Found: M^+, 319. $C_{14}H_{17}N_5O_4$ requires *M*, 319); $\lambda_{max.}$ 262 nm (ε 17 500); δ($CDCl_3$–D_2O) 8.33 (1 H, s, 2-H), 6.37 (1 H, s, 1'-H), 4.89 (1 H, s, 5'-H), 4.58 (1 H, d, *J* 4 Hz, 2'-H), 4.32 (1 H, s, 4'-H), 3.80 (1 H, d, *J* 4 Hz, 3'-H), 3.62 (3 H, s, 5'-OMe), and 1.56 and 1.28 (3 H, s, acetonide).

A trace (1 mg, 2—3%) of another product was detected which was probably formed by hydrogen abstraction from the solvent.

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