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Interconversion of 8,2′-*O*-Cycloadenosine and 2′,3′-Anhydro-8-oxyadenosine

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Summary Treatment of 8,2′-*O*-cycloadenosine (**1a**) and its benzoylation product with alkali gives 2′,3′-anhydro-8-oxyadenosine (**2a**) and its 6-*N*-benzoyl derivative (**2b**), respectively; under mildly alkaline conditions (**2a**) is converted back into (**1a**).

IN an attempt to prepare 6-*N*-benzoyl-8,2′-*O*-cycloadenosine (**1b**), we allowed 8,2′-*O*-cycloadenosine[1] (**1a**) to react with an excess of benzoyl chloride in pyridine solution and then treated the products, in pyridine–ethanol solution, with aqueous sodium hydroxide. However, no (**1b**) was

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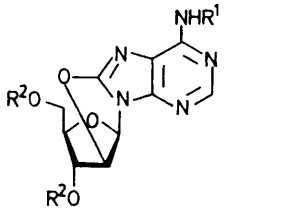
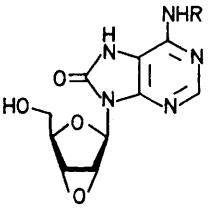
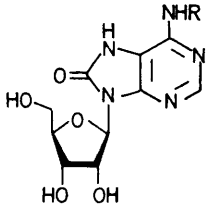
obtained. The only product detected was isolated as a colourless crystalline solid in 81% yield and characterized† as 6-*N*-benzoyl-2′,3′-anhydro-8-oxyadenosine (**2b**) on the basis of spectroscopic data. The u.v. absorption spectrum of the latter compound (**2b**) is closely similar to that of 6-*N*-benzoyl-8-oxyadenosine (**3b**) in both neutral and alkaline solutions. Furthermore the chemical shifts and the multiplicities of the resonance signals assignable to the sugar protons in the ^{1}H n.m.r. spectra of (**2b**) and 2′,3′-anhydroadenosine[2] (**4**) also correspond closely. However,



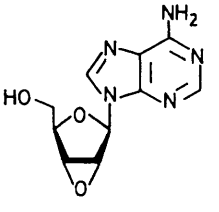
(1) a; $R^1 = R^2 = H$
b; R^1 = PhCO, R^2 = H
c; R^1 = H, R^2 =



(2) a; R = H
b; R = PhCO



(3) a; R = H
b; R = PhCO

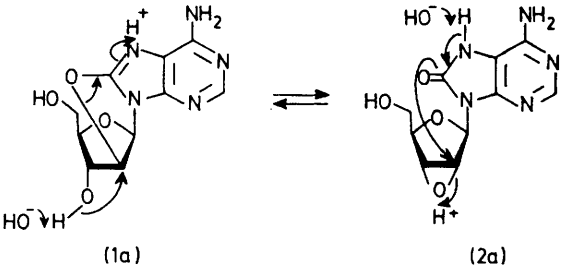


(4)

the most convincing evidence in support of this structural assignment comes from ^{13}C n.m.r. spectroscopic data.‡

When 8,2′-*O*-cycloadenosine[1] (**1a**) was treated with 1·25 mol. equiv. of M-sodium hydroxide in dimethyl sulphoxide–water (4:1 v/v) at room temperature for 12 min, 2′,3′-anhydro-8-oxyadenosine (**2a**) was obtained. The latter compound (**2a**) was isolated as a crystalline solid in 88% yield and characterized on the basis of spectroscopic data: its u.v. absorption spectrum was closely similar to that of 8-oxyadenosine (**3a**) and its ^{1}H n.m.r. spectrum corresponded in the appropriate region with that of 2′,3′-anhydroadenosine[2] (**4**). Again the most convincing evidence for this structural assignment was provided by ^{13}C n.m.r. spectroscopic data.‡

The conversion of (**1a**) into (**2a**) is reversible. Thus, when (**2a**) was treated with an excess of morpholine in dimethyl sulphoxide solution at 78 °C for 19 h, it was completely consumed and crystalline (**1a**) was isolated from the products in 61% yield. It therefore appears that (**1a**) and (**2a**) may be regarded (see Scheme) as tautomers (ring–ring rather than ring–chain) with (**1a**) predominating in mildly alkaline and (**2a**) in strongly alkaline media. This hypothesis is reasonable inasmuch as the pK_a of the 3′-hydroxy group of (**1a**) would be expected to be several units higher than that of 7,8-lactam system in (**2a**). Further experimental support for this hypothesis was obtained in the following way: solutions of (**1a**) and (**2a**) were kept at pH 11



(1a) (2a)

SCHEME

(sodium phosphate buffer), pH 12 (NaOH–KCl buffer), and pH 13 (NaOH–KCl buffer) at room temperature and the changes in their u.v. absorption spectra with time were monitored. In the pH 11 buffer solution, (**1a**) was stable for 24 h while (**2a**) was completely converted into (**1a**) within 48 h; in the pH 12 buffer solution, both substrates (**1a** and **2a**) were converted into virtually the same equilibrium mixture containing *ca.* 75% of (**1a**) within 48 h; in the pH 13 buffer solution, (**1a**) was completely converted into (**2a**) within 24 h while (**2a**) showed no tendency to be transformed into (**1a**). Some decomposition, as evidenced by a decrease in u.v. absorption, occurred at pH 13. 3′,5′-Di-*O*-methoxytetrahydropyranyl-8,2′-*O*-cycloadenosine (**1c**) was completely unchanged after it had been kept in 0·83M-sodium hydroxide in dioxan–water (2:1 v/v) solution at room temperature for 24 h.

We are unaware of any previous reports in the literature relating to an equilibrium between a cyclonucleoside and a ribonucleoside 2′,3′-epoxide. However, it has been suggested[3] that 2′,3′-anhydrouridine is an intermediate in the reaction between 2,2′-*O*-cyclouridine and ethyl mercaptide ion. It is further interesting to note that Ikehara and Ogiso have reported[4] that when 8,2′-*O*-cycloadenosine (**1a**)

† Satisfactory microanalytical data were obtained for all new compounds described.

‡ ^{13}C n.m.r. spectra were measured at 22·628MHz in $(D_3C)_2SO$ solution with Me_4Si as internal standard. The chemical shifts (p.p.m., downfield from Me_4Si) of C-1′, C-2′, C-3′, C-4′, and C-5′ resonance signals, respectively, for the following compounds are given in parentheses: 2′,3′-anhydroadenosine (**4**; 81·9, 58·6, 57·7, 81·0, and 60·8), adenosine (88·2, 73·7, 70·9, 86·1, and 61·9), 6-*N*-benzoyl-2′,3′-anhydro-8-oxyadenosine (**2b**; 80·9, 59·1, 57·4, 80·1, and 60·5), 6-*N*-benzoyl-8-oxyadenosine (**3b**; 85·7, 70·6, 69·9, 85·2, and 62·1), 2′,3′-anhydro-8-oxyadenosine (**2a**; 80·6, 59·1, 57·5, 80·1, and 60·5), 8-oxyadenosine (**3a**; 85·3, 70·8, 70·1, 85·2, and 62·2) and 8,2′-*O*-cycloadenosine (**1a**; 88·3, 98·5, 74·2, 84·9, and 60·5). It is possible that the C-1′, C-4′ and the C-2′, C-3′ assignments should be interchanged for all the compounds except adenosine (L. F. Johnson and W. C. Jankowski, 'Carbon-13 NMR Spectra,' Wiley, New York, 1972, p. 375) and 8,2′-*O*-cycloadenosine (**1a**). It is clear that the C-2′ and C-3′ resonance signals for the 2′,3′-anhydronucleosides (**4**), (**2b**), and (**2a**) are both between 11 and 15 p.p.m. upfield from the C-2′ and C-3′ signals in the corresponding ribonucleosides. The aglycone ^{13}C n.m.r. resonance signals for the following pairs of compounds correspond closely: (**4**) and adenosine, (**2b**) and (**3b**), (**2a**) and (**3a**). It should finally be noted that C-2′ of 8,2′-*O*-cycloadenosine (**1a**) resonates considerably downfield from C-2′ of adenosine and 8-oxyadenosine (**3a**).

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is heated in 0·01 M-aqueous sodium hydroxide solution at 60 °C for 3 h, it is converted into 8,5′-anhydro-9-β-D-arabinofuranosyladenine and that this transformation is reversible. Although, in the light of our results, it is surprising that the latter compound was obtained, it is clear from reported[4] spectroscopic data that 2′,3′-anhydro-8-oxyadenosine (**2a**) was not the product isolated.

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