Reaction of 8,2′-*O*-Cycloadenosine with Hydrazine and Amines. Convenient Preparations of 9-β-D-Arabinofuranosyladenine and its Derivatives

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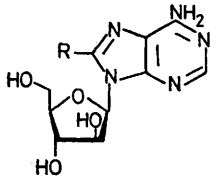
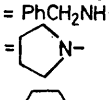
Summary Reaction between 8,2′-*O*-cycloadenosine (**2**) and hydrazine gives a high yield of (**1b**) which on oxidation with yellow mercuric oxide is converted into ara-A (**1a**) in quantitative yield; reaction between (**2**) and the appropriate amines gives the 8-amino-ara-A derivatives (**1c**—**g**) in good to high yields.

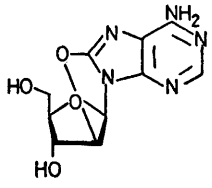
THE potentially great importance of 9-β-D-arabinofuranosyladenine (ara-A, **1a**) as an anti-viral drug[1] has stimulated a search for convenient methods for its synthesis. Following the first report[2] of its preparation by a rather lengthy procedure, syntheses of ara-A (**1a**) from a protected arabinose derivative[3] and from arabinose itself[4] have been described. However, now that 8,2′-*O*-cycloadenosine[5] (**2**) is obtainable in relatively large quantities from the readily accessible 2′-*O*-tosyl-8-bromoadenosine† (**3**), we thought that it was important to investigate the utility of (**2**) as a synthetic precursor for ara-A (**1a**) and its derivatives.

Ikehara and his co-workers have reported[5] that (**2**) reacts with H_2S–pyridine in a steel tube at 100 °C to give 8-mercapto-ara-A which may be converted[4-6] into ara-A itself in good yield. However, a less volatile sulphur nucleophile which attacks (**2**) selectively at its 8-position has not yet been found.[5,7] We demonstrated earlier[8] that

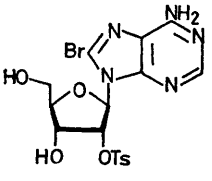


(1)

a; R = H
b; R = H_2NNH–
c; R = MeNH–
d; R = $Me[CH_2]_3NH$–
e; R = $PhCH_2NH$–
f; R = 
g; R = 
h; R = N_3



(2)



(3)

† 8,2′-*O*-Cycloadenosine may be prepared from 21 g of adenosine in 8—10 g batches (38—47% overall yield). Bromination of adenosine gives 8-bromoadenosine (M. Ikehara and M. Kaneko, *Tetrahedron*, 1970, **26**, 4251) in 75—80% yield. The latter compound may be converted *via* its 2′,3′-*O*-(dibutylstannylene)-derivative (D. Wagner, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.*) 1974, **39**, 24) into (**3**) in 85% yield. We have modified the published procedure (M. Ikehara and T. Maruyama, *Tetrahedron*, 1975, **31**, 1369) for the conversion of (**3**) into (**2**) by effecting the final deacetylation and cyclization reactions with Et_3N–EtOH (60 h, reflux, instead of with NH_3–MeOH in a sealed tube at 60 °C.

hydroxide ion is an unsuitable nucleophile for this purpose in that it reacts with (**2**) to give 2′,3′-anhydro-8-oxyadenosine. However, we now report that when 8,2′-*O*-cycloadenosine (**2**) is heated, under reflux, with a 6-fold excess of hydrazine in ethanol solution for 16 h, crystalline 8-hydrazino-ara-A‡ (**1b**) may be isolated from the products in 85% yield. When the latter compound (**1b**) is heated, under reflux, with an excess of yellow mercuric oxide in ethanol–water (2 : 1 v/v) for 40 min, ara-A (**1a**) is obtained quantitatively and may be isolated from the products as a crystalline compound in 93·5% yield. Alternatively, (**1b**) may be converted into ara-A (**1a**) in high yield by stirring it with sodium methoxide in ethanol solution in an open vessel for 1 h at room temperature. We are not aware that hydrazine has been used previously to effect such a transformation (*i.e.* RX → RH) in nucleoside or indeed in any other area of heterocyclic chemistry.

As it seemed likely that derivatives of ara-A might also prove to be biologically active, we have investigated the reaction between 8,2′-*O*-cycloadenosine (**2**) and other amino-compounds. Treatment of (**2**) with 33% methylamine in ethanol solution at 20 °C for 52 h gives 8-methylamino-ara-A (**1c**) as a crystalline compound in 89% isolated yield. When (**2**) is heated, under reflux, with neat n-butylamine (18 h) and neat benzylamine (25 min), the corresponding 8-alkylamino-ara-A derivatives [(**1d**) and (**1e**)] may be isolated as crystalline compounds in 82 and 73% yields, respectively. Similarly, when (**2**) is heated, under reflux, for 19 h with neat pyrrolidine and neat piperidine, (**1f**) and (**1g**) may be isolated as crystalline compounds in 74 and 63% yields, respectively. All of these ara-A derivatives are being screened for anti-viral and anti-tumour activities.

Other reactions of 8-hydrazino-ara-A (**1b**) have also been examined. Thus when (**1b**), which gives high yields of crystalline hydrazone and 3,5-dimethylpyrazole derivatives on treatment, respectively, with acetone and pentane-2,4-dione, is treated with an excess of pentyl nitrite in dilute hydrochloric acid at 20 °C, 8-azido-ara-A (**1h**) is obtained in high yield. Hydrogenolysis of (**1h**) in the presence of 10% Pd–C gives a high yield of 8-amino-ara-A[9] (**1**; R = NH_2).§ When (**1h**) is treated with NaOMe–MeOH at 20 °C, it is rapidly converted into 8,2′-*O*-cycloadenosine (**2**).

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‡ Satisfactory microanalytical and spectroscopic (^1H and ^{13}C n.m.r., u.v., and mass) data have been obtained for all new compounds described.

§ Ikehara and Ogiso have reported (ref. 5) that (**2**) reacts with NH_3–pyridine at 130 °C to give (**1**; R = NH_2) in *ca.* 34% isolated yield. In contrast to its reactivity towards 33% $MeNH_2$–EtOH, (**2**) remains completely unchanged when it is stirred with aqueous NH_3 (*d* 0·88) or with NH_3–MeOH (half-saturated at 0 °C) for several days at 20 °C.

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