

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

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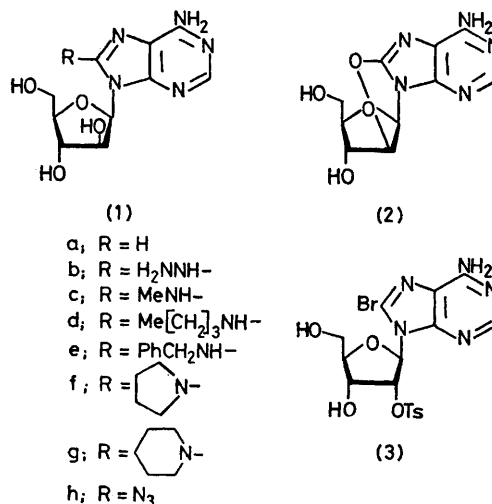
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Summary Reaction between 8,2'-O-cycloadenosine (**2**) and hydrazine gives a high yield of (**1b**) which on oxidation with yellow mercuric oxide is converted into ara-A (**1a**) in quantitative yield; reaction between (**2**) and the appropriate amines 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 drug¹ has stimulated a search for convenient methods for its synthesis. Following the first report² of its preparation by a rather lengthy procedure, syntheses of ara-A (**1a**) from a protected arabinose derivative³ and from arabinose itself⁴ have been described. However, now that 8,2'-O-cycloadenosine⁵ (**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 reported⁵ that (**2**) reacts with H₂S-pyridine in a steel tube at 100 °C to give 8-mercapto-ara-A which may be converted⁴⁻⁶ 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 earlier⁸ that



† 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 Et₃N-EtOH (60 h, reflux, instead of with NH₃-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 $\ddagger$ (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 $\rightarrow$ 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-A⁹ (1; R = NH₂).§ When (1h) is treated with NaOMe-MeOH at 20 °C, it is rapidly converted into 8,2'-*O*-cycloadenosine (2).

We thank the Cancer Research Campaign for generous financial support.

(Received, 1st April 1977; Com. 310.)

$\ddagger$ Satisfactory microanalytical and spectroscopic (¹H and ¹³C 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 NH₃-pyridine at 130 °C to give (1; R = NH₂) in *ca.* 34% isolated yield. In contrast to its reactivity towards 33% MeNH₂-EtOH, (2) remains completely unchanged when it is stirred with aqueous NH₃ (*d* 0.88) or with NH₃-MeOH (half-saturated at 0 °C) for several days at 20 °C.

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