The Cyclization of 8-Carboxamido-2′-*O*-tosyladenosine. A New Preparation of 9-β-D-Arabinofuranosyladenine (ara-A)

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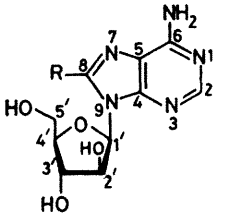
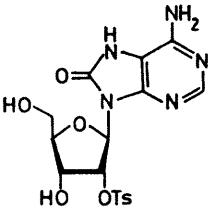
Summary In alkaline solution, 8-carboxamido-2′-*O*-tosyladenosine (**4e**; $R^2 = R^3 = H$), which may be prepared from adenosine in 7 steps, readily cyclizes to give (**5**); in neutral or weakly basic solution, it undergoes virtually quantitative conversion into ara-A (**1a**).

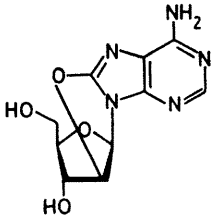
As 9-β-D-arabinofuranosyladenine (ara-A, **1a**) is an antiviral[1] and anti-tumour[2] agent of potentially great importance in chemotherapy, much effort has recently been put into the development of methods for its synthesis[3–6] and for the synthesis of related purine arabinosides.[7]



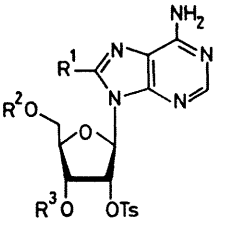
(1) a, R = H



(2)



(3)



(4)

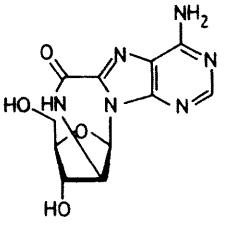
a, R^1 = Br
b, R^1 = 4-MeC_6H_4S
c, R^1 = Ts
d, R^1 = NC
e, R^1 = H_2NCO

Perhaps the most obvious approach to the synthesis of ara-A (**1a**) is to convert adenosine into a suitably reactive 2′-derivative and then to treat it with an oxygen nucleophile (*e.g.* acetate ion). Although ribonucleosides may readily be converted[8] into their 2′-*O*-tosyl derivatives in good yields, the latter are apparently not suitable substrates for external nucleophiles. The most successful conversions of adenosine into ara-A (**1a**) so far reported have depended on inverting C-2′ with an internal nucleophile †. Thus 8-oxo-2′-*O*-tosyladenosine (**2**) may readily be converted[9] into 8,2′-*O*-cycloadenosine (**3**) which, in turn, reacts with hydrogen sulphide[3] in pyridine or with hydrazine[6] in ethanol to give 8-mercapto-ara-A (**1**, R = SH, with the thiolactam tautomeric form presumably predominating) or 8-hydrazino-ara-A (**1**, R = $NHNH_2$). Each of the latter compounds[3,6] may be converted into ara-A (**1a**) itself in high yield.

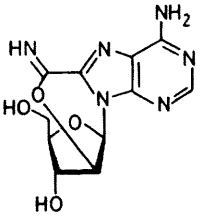
If inversion at C-2′ is to be effected by intramolecular nucleophilic attack, it is clearly desirable that the nucleophilic group (at C-8) should be easy to introduce into the adenosine molecule and easy to remove at the end of the synthesis. We now report that the 8-carboxamido group meets the first and especially the second of these criteria satisfactorily.

When 8-bromo-2′-*O*-tosyladenosine (**4a**, R^2 = R^3 = H), which was prepared[6,9] in two steps from adenosine in 77% overall yield, was allowed to react with *p*-thiocresol (1·5 mol equiv.) and triethylamine (2·0 mol equiv.) in methanol (6 h, reflux), 8-(*p*-tolylmercapto)-2′-*O*-tosyladenosine (**4b**, R^2 = R^3 = H), m.p. 213 °C, was obtained in 92% yield ‡. Acetylation of the latter compound gave its 3′,5′-diacetate (**4b**, R^2 = R^3 = Ac) (m.p. 91·5 °C, 92% yield) which, on oxidation with potassium permanganate (1·5 mol equiv.) in acetic acid–water (7:3 v/v) (*ca.* 3·5 h, 15—20 °C), gave the corresponding 8-sulphone (**4c**, R^2 = R^3 = Ac), m.p. 107 °C, in 88% yield. Treatment of the sulphone with sodium cyanide (3·0 mol equiv.) in anhydrous dimethylformamide (3·5 h, room temperature) gave[10] a mixture of the 3′,5′-di-*O*-acetyl-(*ca.* 3 parts) and 5′-*O*-acetyl-(1 part) derivatives of 8-cyano-2′-*O*-tosyladenosine (**4d**, R^2 = R^3 = Ac, and R^2 = Ac R^3 = H, respectively) in *ca.* 84% combined yields. Neither of the latter compounds was obtained crystalline but their structures were based on their method of preparation and on i.r. and n.m.r. spectroscopic data. Finally, when the nitrile mixture (**4d**, R^2 = R^3 = Ac and R^2 = Ac, R^3 = H) was treated with an excess (*ca.* 4 mol equiv.) of 0·27 M-aqueous sodium hydroxide[10] (1 h, room temperature), the desired 8-carboxamido-2′-*O*-tosyladenosine (**4e**, R^2 = R^3 = H) was obtained as virtually the sole nucleoside product and was isolated as a crystalline compound, m.p. 175—176 °C, in *ca.* 70% yield.

When 8-carboxamido-2′-*O*-tosyladenosine (**4e**, R^2 = R^3 = H) was heated with $N^1N^1N^3N^3$-tetramethylguanidine (5·0 mol equiv.) in dioxan–water (1·1 v/v) (16 h, reflux) (**5**) was obtained as the sole nucleoside product and was isolated as a high melting (>260 °C) crystalline solid in over 90% yield. The latter cyclonucleoside (**5**) was identified on the basis of microanalytical and spectroscopic data.



(5)



(6)

In contrast to its behaviour in alkaline solution, when 8-carboxamido-2′-*O*-tosyladenosine (**4c**, R^2 = R^3 = H) was heated in pyridine–water (9:1 v/v) solution (12 h, reflux), ara-A (**1a**) was obtained as the sole nucleoside product and

† Recently, R. Ranganathan and D. Larwood (*Tetrahedron Lett.*, 1978, 4341) have reported the preparation of a 2′-*O*-acetyl-ara-A derivative by treating the corresponding 2′-*O*-trifluoromethanesulphonyladenosine derivative with acetate ion. However, the procedure described was not particularly convenient inasmuch as the preparation of the trifluoromethanesulphonyl derivative involved three steps starting with 2′-*O*-tosyladenosine.

‡ Satisfactory microanalytical and spectroscopic data were obtained for all new crystalline compounds described.

was isolated as a crystalline solid in 94% yield. Thus, while the carboxamido group (or presumably its conjugate base) acts as a nitrogen nucleophile at high pH, it acts as an oxygen nucleophile in neutral and weakly basic media. It was not possible to detect the putative initial cyclization product (**6**), 8-carboxamido-ara-A (**1**; R = $CONH_2$) or any other intermediate in the conversion of (**4e**; $R^2 = R^3 = H$) into (**1a**) by t.l.c. Presumably (**6**) or its conjugate acid undergoes further hydrolysis *via* the corresponding lactone to give ara-A-8-carboxylate (**1**; R = CO_2^-) which would be expected[10] to undergo decarboxylation readily to give ara-A (**1a**) itself.

We believe that the present investigation has led to the most convenient practical procedure§ yet described for the conversion of adenosine into ara-A (**1a**); we further believe that it should be possible to extend it and thereby provide a general method for the conversion of purine 9-β-ribofuranosides into the corresponding arabinosides.

We thank the Cancer Research Campaign for generous financial support.

(*Received*, 21*st August* 1980; *Com.* 918.)

§ In a preparative-scale experiment, ara-A (**1a**) was obtained in *ca.* 80% yield directly from the nitrile mixture (**4d**; $R^2 = R^3 = Ac$ and $R^2 = Ac$, $R^3 = H$). The latter mixture was treated first with 0·27 M sodium hydroxide (*ca.* 4 mol. equiv.) in dioxan–water (4:7 v/v) at room temperature for 2·5 h. After the products [containing (**4e**; $R^2 = R^3 = H$)] had been neutralized (to pH *ca.* 7·5) with acetic acid, the resulting solution was heated (16 h; reflux). The overall yield of isolated ara-A (**1a**) was *ca.* 67% for the two steps based on crystalline 8-sulphone (**4c**; $R^2 = R^3 = Ac$) as the starting material and nearly 39% for the seven steps based on adenosine as the starting material.

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