A synthesis of purine arabinosides

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ABSTRACT

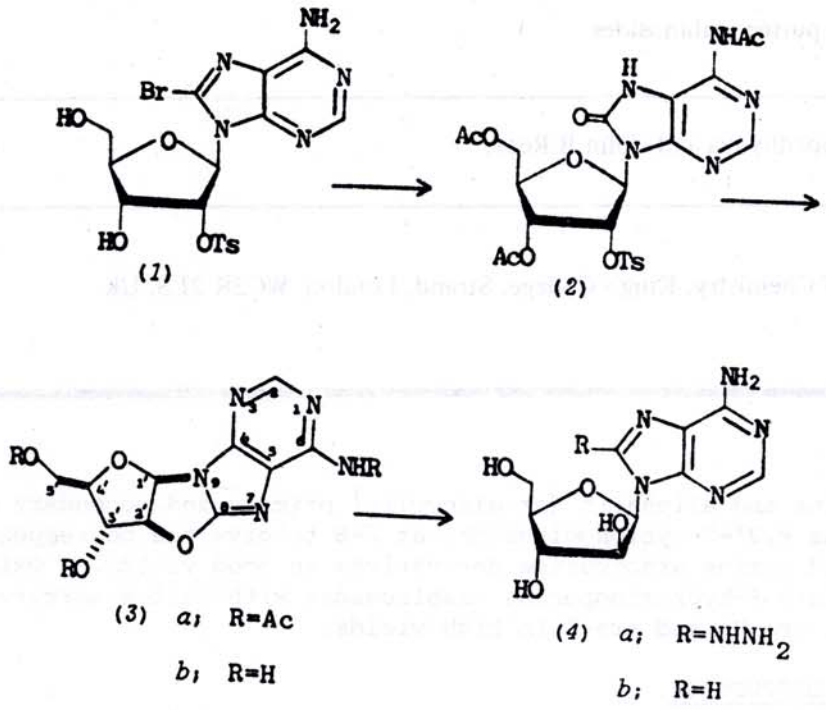
Hydrazine and aliphatic (or alicyclic) primary and secondary amines attack purine 8,2'-*O*-cyclonucleosides at *C*-8 to give the corresponding 8-substituted purine arabinoside derivatives in good yields. Oxidation of the appropriate 8-hydrazinopurine arabinosides with yellow mercury (II) oxide gives ara-A, ara-Hx and ara-G in high yields.

RESULTS AND DISCUSSION

9-β-D-Arabinofuranosyladenine (ara-A, *4b*) has been shown to have both anti-tumour[1] and anti-viral[2] activity. Several other purine arabinosides have also shown promise as anti-viral agents[3] but it is unlikely that a full evaluation of the biological activity of these compounds will be possible until they become more readily accessible. We now report a general synthesis of purine arabinosides in which the key step is the hydrazinolysis of the corresponding 8,2'-*O*-cyclonucleosides (*3b*, *5a* and *5b*).

The synthesis of ara-A (*4b*) by our procedure is indicated in Scheme 1. 8-Bromo-2'-*O*-tosyladenosine[4] (*1*) may readily be obtained[5] from adenosine in over 65% yield. Treatment of the latter compound (*1*) with sodium acetate in acetic acid-acetic anhydride gives[4] (*2*, 90%) which may conveniently be converted into (*3a*, 92%) by heating it with an excess of sodium acetate in dimethylformamide solution at 100°. When *3b*, which is obtained (55% overall yield, based on adenosine) by the action of methanolic ammonia on *3a*, is heated, under reflux, with an excess of hydrazine hydrate in ethanol solution for 16 hr, 8-hydrazino-ara-A (*4a*) is obtained[5] and may be isolated as a crystalline solid in over 85% yield. When *4a* is heated with an excess of yellow mercury(II) oxide in boiling aqueous ethanol, ara-A (*4b*) is obtained[5] as the sole product. The isolated yield of *4b* is over 93% (44% overall yield, based on adenosine). 8-Hydrazinoadenosine[6], which may be prepared from 8-bromoadenosine in 85% yield[7], may similarly be converted into adenosine in virtually quantitative yield[7]. It is interesting to note that Cech and

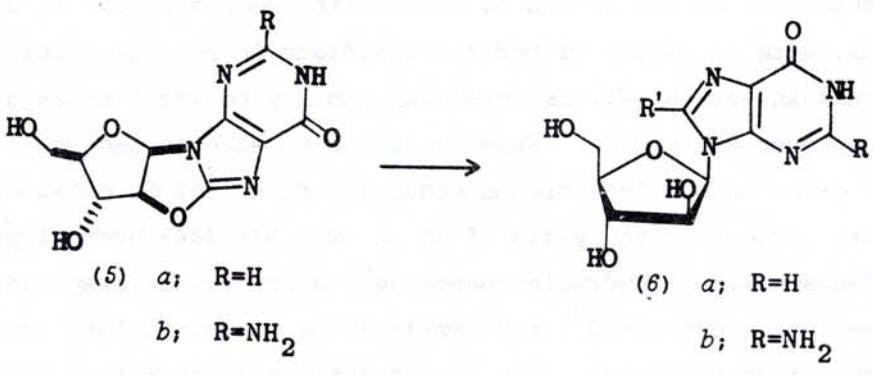
Scheme 1



Holý[8] have recently prepared 4-unsubstituted pyrimidine nucleosides by oxidation of the corresponding 4-hydrazino-derivatives with a variety of reagents.

8,2'-*O*-Cycloinosine[9] (*5a*) may be isolated in 84% yield[10] from the products of the reaction between 8,2'-*O*-cycloadenosine[4,5] (*3b*) and sodium nitrite in acetic acid at 20°; when *5a* is heated, under reflux, with an excess of neat hydrazine hydrate (Scheme 2) for 4 min, 8-hydrazino-ara-Hx (*6a*; R' = $NHNH_2$) is obtained[10] in nearly quantitative yield. Oxidation of the latter compound with yellow mercury(II) oxide gives ara-Hx[11] (*6a*; R' = H) which may be isolated[10] as a crystalline solid in 77% overall yield, based on *5a*. Similarly, when 8,2'-*O*-cycloguanosine[4] (*5b*), which may be prepared from

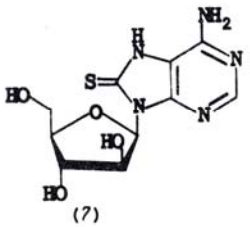
Scheme 2



8-bromoguanosine in 67% overall yield[10], is heated, under reflux, with a large excess of hydrazine hydrate for 25 min, 8-hydrazino-ara-G (*6b*; R' = $NHNH_2$) is obtained[10] (Scheme 2) in 88% isolated yield. Oxidation of the latter compound under the above conditions gives ara-G[12] (*6b*; R' = H) in 92% yield.

We previously reported[5] that 8,2'-*O*-cycloadenosine (*3b*) reacts with aliphatic and alicyclic primary and secondary amines to give the corresponding 8-amino-ara-A derivatives (*4*; R = R^1NH or R^1R^2N) in good yields. This observation has since been confirmed by Kaneko *et al.*[13] 8,2'-*O*-Cycloinosine (*5a*) and 8,2'-*O*-cycloguanosine (*5b*) undergo aminolysis in the same way to give[10] good yields of the corresponding 8-amino-ara-Hx and 8-amino-ara-G derivatives (respectively, *6a* and *6b*; R' = R^1NH or R^1R^2N). Thus, when *5a* is heated, under reflux, with neat n-butylamine, benzylamine and pyrrolidine, *6a* (R' = NHC_4H_9, $NHCH_2Ph$ and $N(CH_2)_4$) are obtained[10] in isolated yields of 68, 78 and 77%, respectively; *5b* may similarly be converted[10] into *6b* (R' = $NHCH_2Ph$ and $N(CH_2)_4$) in isolated yields of 76 and 67%, respectively. It is encouraging to note that *4* (R = $NH(CH_2)_3CH_3$), *6a* (R' = $NHCH_2Ph$) and *6b* (R' = $NHCH_2Ph$) show considerable activity against Le Page Gardner $6C_3HED$ lymphosarcoma in mice.

Apart from hydrazine and other amino compounds, the only really effective reagent which has been reported to attack 8,2'-*O*-cyclonucleosides at *C*-8 to give the corresponding 8-substituted arabinosides is hydrogen sulphide. Thus Ikehara and Ogiso[14] obtained *7*, an alternative precursor of ara-A, in good yield by heating 8,2'-*O*-cycloadenosine (*3b*), with hydrogen sulphide in pyridine solution at 100° for 14 hr in a sealed tube. However, the same workers[14] obtained *8* and no 8-ethylmercapto-ara-A (*4*; R = SEt) by heating 8,2'-*O*-cycloadenosine (*3b*) with sodium thioethoxide in dimethylformamide solution. A third mode of nucleophilic attack on 8,2'-*O*-cycloadenosine (*3b*) is exhibited in its reaction with hydroxide ion. The latter attacks neither at *O*-2' nor at *C*-8 but removes a proton from the 3'-hydroxy group. Rearrangement then occurs[15] to give 2',3'-anhydro-8-oxyadenosine (*9*) in high yield. Finally, it



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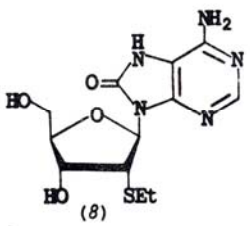

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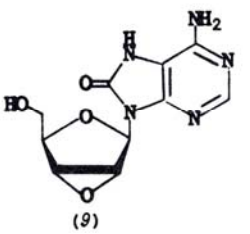

(9)

is noteworthy that the isomerization of *3b* to *9* may be reversed under mildly basic conditions[15].

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