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Preliminary communication

Synthesis of 8-β-D-arabinofuranosyladenine*

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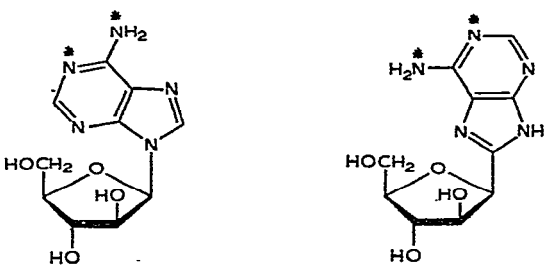
We are involved in a program aimed at the synthesis of the *C*-analogs of *N*-nucleoside antibiotics for biological evaluation, and have recently described the synthesis of cordycepin-C [8-(3-deoxy-β-D-*erythro*-pentofuranosyl)adenine[1,2]] and of various 8-(hydroxyalkyl)adenines[3]. In the present article, we report the synthesis of a *C*-analog of 9-β-D-arabinofuranosyladenine (1, Ara-A), namely, 8-β-D-arabinofuranosyladenine (8-Ara-A, 2);

Ara-A (1) is a broad-spectrum antibiotic active against such DNA viruses as herpes simplex[4–7], but not against RNA viruses[4]. It also shows some activity against plasmodia, probably because of the ability of the parasite to phosphorylate Ara-A, rendering it a competitive inhibitor[8] of ATP.

The rationale for the synthesis of the analog 8-Ara-A (2), arises from the fact that the chirality of an 8-substituted adenine nucleoside allows the active sites (position of hydrogen bonds) to occupy the same position in space as those of the corresponding, naturally occurring, 9-substituted nucleoside, suggesting that the 8-substituted nucleosides could be incorporated in nucleic acid macromolecules or attached to enzyme systems in the same way as their 9-substituted-purine nucleoside counterparts[1,2].



1 2

Fig. 1. *Nitrogen atoms involved in hydrogen bonding in adenine nucleosides.

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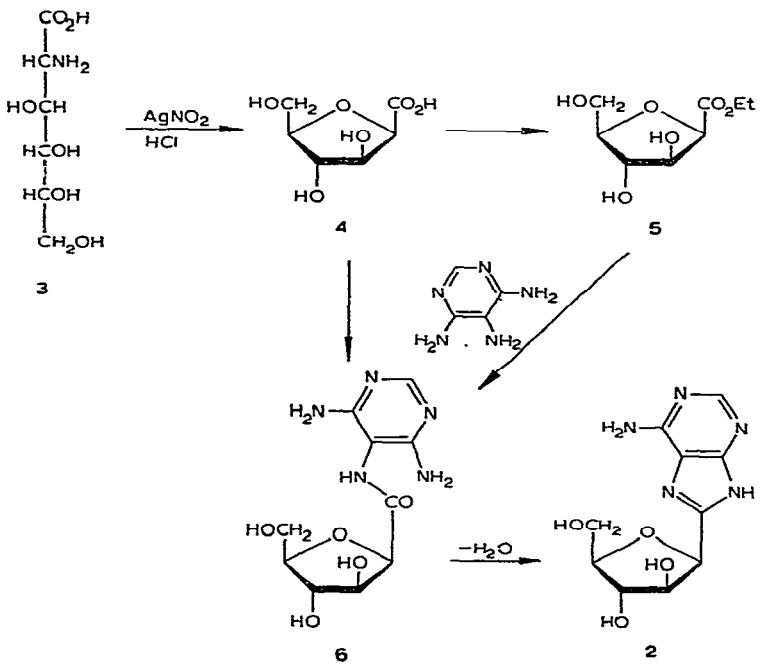
Our approach to the synthesis of 8-Ara-A was the same as in our previous investigations[1—3] and in the Bobek and Farkaš synthesis[9] of 8-β-D-ribofuranosyladenine, namely, by reaction of the appropriate 2,5-anhydroaldonic acid (4) with 4,5,6-triaminopyrimidine to give an amide (6) which, on pyrolysis, cyclized to give the desired nucleoside (7).

The acid needed, 2,5-anhydro-D-gluconic acid (4), was synthesized by a method developed by Hardegger *et al.*[10], who used nitrous acid produced from silver nitrite and hydrochloric acid to deaminate and cyclize 2-amino-2-deoxy-D-gluconic acid and 3. The 2,5-anhydro-D-gluconic acid produced was a syrup contaminated with unchanged 2-amino-2-deoxy-D-gluconic acid (t.l.c.), and this crude material was not suitable for amide formation, as it yielded a large proportion of black byproducts. Purification of acid 4 was achieved by passing its solution through a column of Dowex 1 X-8 (OAc^-) anion-exchange resin and washing with 6% acetic acid to remove the weaker amino acid (3); elution with 7% formic acid then afforded 4 (pure by t.l.c.).



Refluxing of an equimolar mixture of acid 4 and 4,5,6-triaminopyrimidine in M hydrochloric acid for 2 h afforded 4,6-diamino-5-(2,5-anhydro-D-gluconoyl)amino-pyrimidine (6); this amide was separated by adsorption on a column of Dowex 50W X-8 (H^+) cation-exchange resin and, after washing with water, eluting with 2M ammonia.

After purification, acid 4 yielded a crystalline ethyl ester (5) which, likewise, could be used for the preparation of amide 6.

Cyclization of amide 6 was achieved by heating for 1 h at 200°; the resulting melt

was extracted with water in a Soxhlet apparatus, and concentration of the extract gave the desired 8-β-D-arabinofuranosyladenine (2) in crystalline form, m.p. 303°. This *C*-nucleoside analog gave correct elemental analyses, and its i. r. and mass spectra were compatible with the structure assigned.

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