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NUCLEIC ACID RELATED COMPOUNDS. 28. 2'-AMINO-araA [9-(2-AMINO-2-DEOXY-β-D-ARABINOFURANOSYL)ADENINE]. SYNTHESIS VIA NUCLEOSIDE-AZIRIDINE OR AZIDO INTERMEDIATES AND BIOLOGICAL EFFECTS.[1]

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Naturally occurring nucleosides, nucleoside antibiotics, and their analogues are compounds of increasing importance and interest as antitumor and antiviral agents.[3] In particular, araA (9-β-D-arabinofuranosyladenine, 1) exerts inhibitory activity against various tumor lines and against DNA viruses.[4] Clinical evaluation of 1 is in progress and appears promising in the treatment of certain herpes viral infections.[5] However, araA has extremely limited solubility in water and it also suffers rapid enzymatic deamination to 9-β-D-arabinofuranosylhypoxanthine which then undergoes enzymatic glycosyl cleavage to the natural metabolite, hypoxanthine.[6]

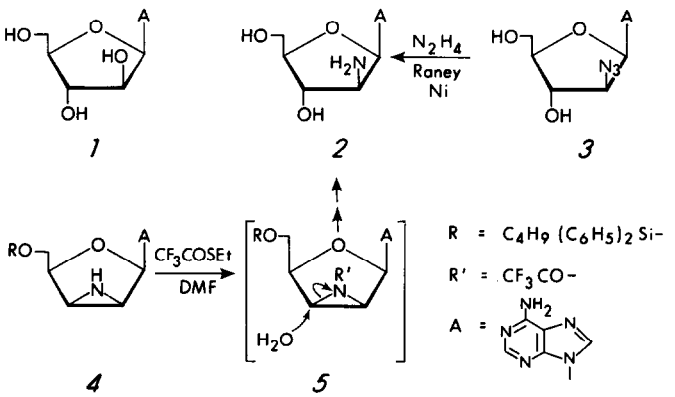
The 2'-amino-2'-deoxy ribo analogue of adenosine has been synthesized[7,8] and the corresponding guanosine 2'-amino analogue has been isolated as an antibiotic[9] and synthesized.[8] However, no examples of 2'-amino-2'-deoxy arabino analogues have been reported. We had hoped that substitution of the polar ionizable amine function for the hydroxyl group at C-2' of araA (1) would lead to a compound with enhanced aqueous solubility and altered deaminase-glycosyl cleavage substrate properties while retaining the inhibitory properties of the arabino nucleoside.

Developments in the modification of intact nucleosides and nucleoside antibiotics[10] have provided general access to the diastereomeric 2',3' aziridine-fused nucleoside systems.[11] We now report transformation of 9-(2,3-epimino-2,3-dideoxy-β-D-lyxofuranosyl)adenine[11] (4, R = H) to 2'-amino-araA (2). The epimino function of 4 is much more stable than the corresponding oxirane group and is not opened by direct treatment with several nucleophiles at 110°C. Activation by trifluoroacetylation of the imino nitrogen proved successful.

Treatment of the 5'-O-tert-butyldiphenylsilyl protected aziridine[11] (4, R = tert-Bu(Ph)$_2$Si) with excess ethylthio trifluoroacetate in warm DMF gave the desired ring-opened compound plus minor products. Deprotection using 4 N aqueous KOH containing ethanol gave the desired 9-(2-amino-2-deoxy-β-D-arabinofuranosyl)-adenine (2) in 49% yield after column chromatography on silica and diffusion

crystallization[12] (95% EtOH, diffusion of Et_2O). This product had mp 227-231°C (dec.); $[\alpha]_D^{24}$ -3.9° (c 0.5, H_2O pH 6.0); uv (H_2O pH 6.0) max 259.5 nm (ε 14,900) min 227 nm (ε 2630), (0.1 N HCl) max 262 nm (ε 14,600) min 227 nm (ε 1960), (0.1 N NaOH) max 260.5 nm (ε 15,600) min 228 nm (ε 3430); ^{1}H NMR (Me_2SO-d_6, Me_4Si internal) δ 1.50 (br s, 2, 2'-NH_2), 3.48 (m, $J_{2',3'}$ = 7 Hz, 1, H-2'), 3.55-3.86 (m, 3, H-4',5',5"), 4.02 (m, 1, H-3'), 4.7-5.5 (br, 1, 5'-OH), 5.37 (d, $J_{3'\text{-OH-}3}$ ~ 4.5 Hz, 3'-OH), 6.18 (d, $J_{1',2'}$ = 6.5 Hz, 1, H-1'), 7.16 (s, 2, 6-NH_2), 8.10 & 8.26 (s & s, 1 & 1, H-2 & H-8); MS (E.I.) m/e 267.1201 (calcd. for M + 1: 267.1206, 1.6% rel. to m/e 164, B + 30, 100%); MS (C.I., NH_3) m/e 267 (M + 1, 58% rel. to m/e 136, B + 2, 100%). Anal. ($C_{10}H_{14}N_6O_3$) C, H, N.

A small quantity of the diastereomeric 9-(3-amino-3-deoxy-β-D-xylofuranosyl)adenine[13] arising from attack of water at C-2' was observed in the filtrate along with 2. No trace of the xylo isomer was detected in the crystalline 2'-amino-araA (2) by NMR or tlc. Thus, opening of the presumed N-trifluoroacetylaziridine intermediate (5) by water occurs predominantly at C-3' in analogy with nucleophilic openings of the corresponding lyxo epoxide intermediate.[14]



An alternative route to 2 involved hydrogenolysis of 9-(2-azido-2-deoxy-β-D-arabinofuranosyl)adenine[14] (3), the very minor (~1%) product of treatment of 2',3'-anhydroadenosine with azide. Compound 3 had mp 198-200°C; uv (MeOH) max 259 nm (ε 15,100) min 227 nm (ε 2700); ^{1}H NMR δ 6.40 (d, $J_{1',2'}$ = 6.3 Hz, 1, H-1'); MS (E.I.) m/e 292.1027 (calcd. for M^+ 292.1032, 1% rel. to m/e 136, B + 2H, 100%). Anal. ($C_{10}H_{11}N_8O_3$) C, H, N. The product of hydrogenolysis of 3 crystallized in 65% yield with mp 224-228°C (dec.) and had identical tlc and spectroscopic properties with 2 obtained from opening of the aziridine intermediate (5).

As hoped, 2'-amino-araA is dramatically more soluble in water (>34 mg/ml) than araA (~0.5 mg/ml).[15] The relative initial velocities of enzymatic deamination of 2'-amino-araA and some known substrates[4b,16] are given in Table I. All substrate concentrations (530 μM) were well above reported K_M values.[4b] It is

apparent that the amino sugar analogues would have considerably longer lifetimes in biological systems with significant levels of adenosine deaminase. These expectations appear to be borne out in preliminary cell culture data.[17] Upon 48 hr exposure of a cultured murine leukemia cell line (L1210/C2), 2'-amino-araA produced ~20% of the growth inhibitory activity of araA. This activity was approximately doubled in the presence of the potent adenosine deaminase inhibitor 2'-deoxycoformycin.[17] In contrast, the growth inhibitory effect of araA at low concentrations is enhanced approximately ten-fold by 2'-deoxycoformycin.[18] Of considerable interest is the observation that 2'-amino-araA exhibited an approximately equal inhibitory effect on a derived araA resistant line as on the parent cell line.[17] Therefore, an apparent absence of cross-resistance to 2'-amino-araA exists.

TABLE I[a]

Compound	Rel. V_I
Adenosine	100
2'-Deoxyadenosine	120
araA (1)	26
2'-Amino-araA (2)	11
3'-Amino-xyloA	15

[a] Relative initial velocities of substrates of adenosine aminohydrolase (E.C. 3.5.4.4; Sigma Chemical Co. Type II) determined spectrophotometrically[16] at 265 nm.

This first reported synthesis of 2'-amino-araA (2) demonstrates the potential of epimino nucleosides[11] for the preparation of stereoisomeric amino sugar nucleosides.[19] Syntheses and biological response properties of novel mono, di, and tri-amino sugar derivatives will be reported from these laboratories.

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