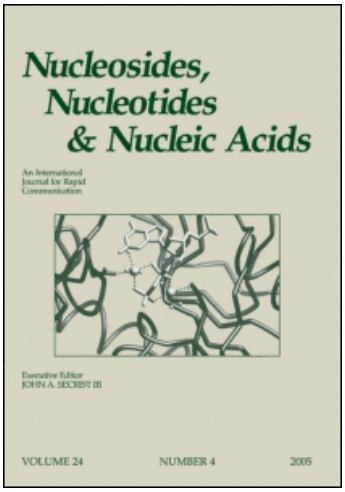

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SYNTHESIS AND EVALUATION OF 2',3'-DIDEOXY-9-DEAZAADENOSINE AND SOME RELATED DERIVATIVES

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Abstract In this paper we report the synthesis of 2',3'-dideoxy-9-deazaadenosine (**2**) and the corresponding 2',3'-unsaturated- and 3'-deoxy- analogs, **6** and **8**. These C-nucleosides are very stable towards acid and thus overcome one of the main drawbacks of 2',3'-dideoxy- *purine*-nucleosides, such as the antiviral agent 2',3'-dideoxyadenosine (ddA). However, evaluation of these compounds and some related 2'-deoxy derivatives (**10-14**) in the antiviral assay for the human immunodeficiency virus has revealed no significant activity.

2',3'-Dideoxyadenosine (ddA) is a potent inhibitor of the cytopathic effect of human immunodeficiency virus (HIV)[1] and is currently undergoing clinical development as an agent for the treatment of AIDS. This compound, however, is extremely unstable towards acid, with a $t_{1/2}$ of only 35 sec at pH 1.0 at 37°C.[2] Thus this presents a potential problem with the oral use of this drug candidate. In addition, formation of the cleavage product, adenine, and its metabolites such as 8-hydroxy- and 2,8-dihydroxy-adenines would add complicating toxicity. This problem, associated with acid instability, is not unique for ddA, but is common for 2',3'-dideoxy-purine-nucleosides. With this in mind, we felt it desirable to design a new acid-stable "*purine*" dideoxynucleoside analog.

9-Deazaadenosine (**1**), a C-nucleoside analog of adenosine, has been reported to be a potent cytotoxic agent with ED_{50} as low as 10^{-8} M in several human solid tumor cell lines.[3] It is resistant to adenosine deaminase and due to the stable sugar-base linkage, it is acid stable and resistant to purine nucleoside phosphorylase.[4] For this reason, 2',3'-dideoxy-9-deazaadenosine (**2**) is envisaged to be a close analog of ddA which has the desired stability. Herein, we report the synthesis and anti-HIV evaluation of this compound and some related derivatives.

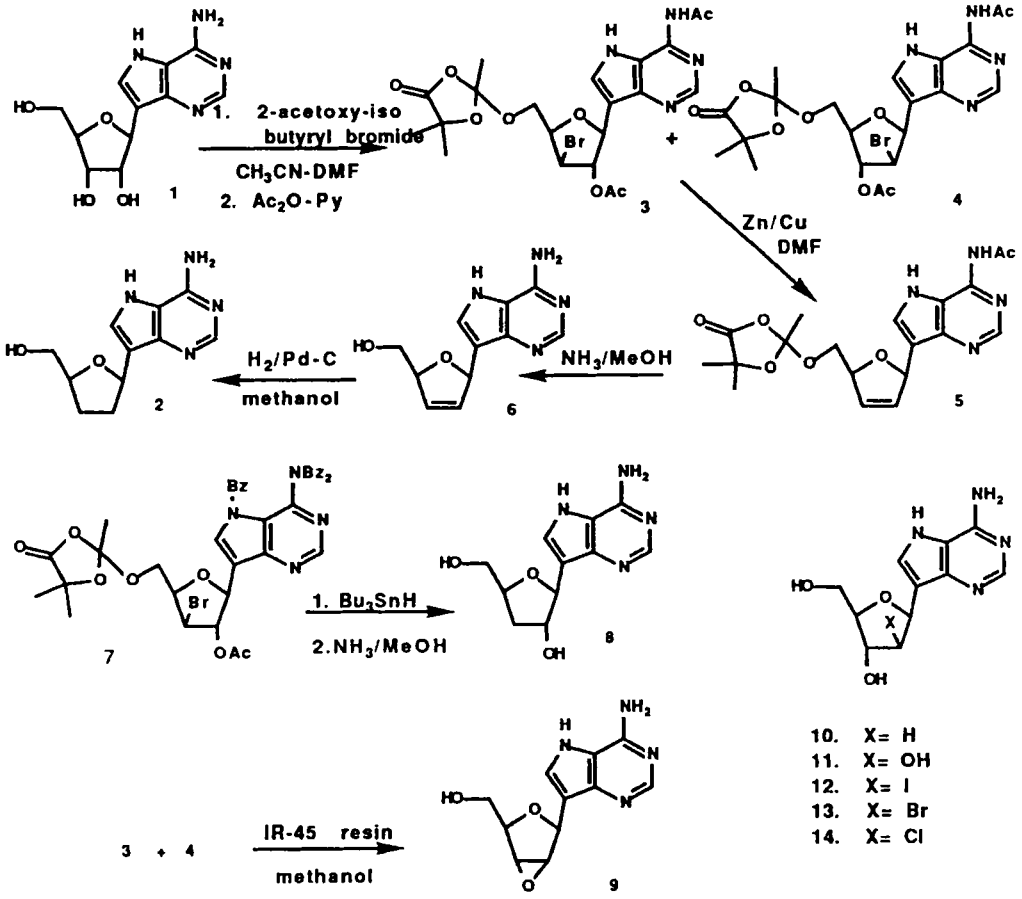
The starting material, 9-deazaadensoine,**1**,was synthesized by the previously published method.[5] Reaction of **1** with 2-acetoxy-isobutyryl bromide according to the procedure developed by Moffatt et.al.,[6] followed by acetylation, afforded the bromoacetates, **3** and **4**. This mixture on stirring with zinc-copper couple in DMF gave the 2',3'-unsaturated C-nucleoside,**5**. Treatment with methanolic ammonia followed by catalytic hydrogenation then afforded the desired product **2**.

The 3'-deoxy derivative, **8**, was prepared from **7** via a tributyltin hydride dehalogenation, followed by base hydrolysis. The starting material was separated from its 2',3'-regioisomer by column chromatography. Without separation, the mixture of **3** and **4** on stirring with IR-45 (OH^-) resin formed the *ribo*-epoxide **9**.

Syntheses of the compounds **10-14** have been reported earlier.[7]

Stabilities of ddA, compounds **2** and **6** were compared at pH 3.0 (phosphate buffer) at room temperature. Aliquots were removed at timed intervals and injected directly on a Hamilton PRP-1 column (25 cm x 4.6 mm) using a Waters Wisp Automatic Injecter. Elution was with 15% acetonitrile in water at 1.0 ml/min and monitored by UV using a Hewlett-Packard 1040A HPLC Detection System. Under these conditions, the $t_{1/2}$ of ddA was 3 hours, whereas for **2** and **6**, it was >7 days in both cases.

The anti-viral activity was measured by the ability of the test compound to protect ATH-8 cells from the cytopathic effect of the HIV-1 virus according to the previously published method.[8] Cytotoxicity was determined in the same assay by measuring the effect of compound on the control cells which were not exposed to the virus. None of the compounds reported in this paper showed significant selective anti-HIV activity.



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