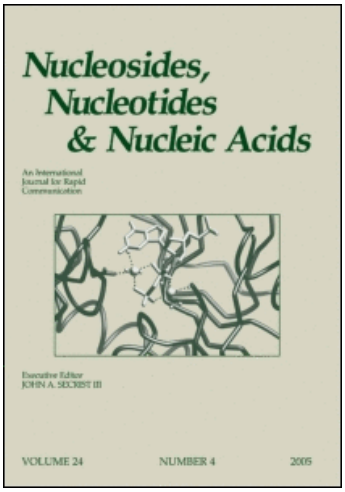

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Novel Analogues of the Nucleoside Antibiotics Coroyepin

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NOVEL ANALOGUES OF THE NUCLEOSIDE ANTIBIOTIC, CORDYCEPIN

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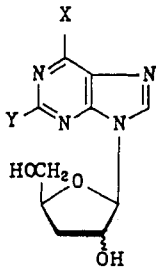
Abstract. The syntheses of novel compounds of the cordycepin family including stereochemically modified analogues are described. Hypoxanthine counterparts of these compounds have also been obtained.

The nucleoside antibiotic, cordycepin (3'-deoxyadenosine), was originally isolated from Cordyceps militaris and Aspergillus nidulans.[1] Cordycepin is known to have antiviral activity against a number of RNA viruses.[2] The biochemical basis for this mechanism of action is thought to be a result of the inhibition of the viral RNA polymerase activity by cordycepin 5'-triphosphate. Analogues of cordycepin would therefore be of potential antiviral interest. However, very few examples of compounds related to this nucleoside antibiotic have been described. This paper reports on the synthesis of some novel compounds of the cordycepin family. Synthesis of analogues of the hypoxanthine counterpart of cordycepin as well as stereochemically modified analogues have also been investigated. The target compounds can be illustrated by the general structure 1 where X



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may be NH_2 or OH and Y represents a variety of functional groups such as -I, -OH, -CN, -CHO, $-CONH_2$, $-CH=CH_2$, $-C\equiv CH$, and others.

The strategy for the syntheses involved starting with readily available natural guanosine, tailoring it to an appropriate precursor, sequentially modifying the carbohydrate and base moieties, and finally elaborating the immediate product. A key intermediate for the cordycepin analogues in this sequence of reactions was protected 2-iodo-3'-deoxyadenosine, synthesized from 2-amino-6-chloropurine nucleoside in five steps involving the following reactions and positions: bis-silylation (2',5'), deoxygenation (3'), iodination (2), and nucleophilic displacement with ammonia (6). Introduction of specific functionality at the 2-position and their elaboration were carried out by metal mediated functionalizations, photochemical reactions, and ozonolysis.[3,4] Hypoxanthine nucleoside counterparts were synthesized by related methodologies. Cordycepin analogues where the stereochemistry is inverted (i.e. β) at the 2'-position have also been investigated. Confirmation of structures of intermediate regioisomers and stereoisomers and products were made using high-field ^1H and ^{13}C NMR data including COSY NMR data.

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