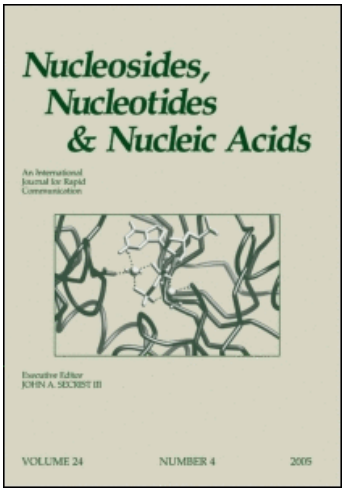

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Synthesis and Antiviral Evaluation of Adenosine-N¹-Oxide and 1-(Benzyloxy) Adenosines

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SYNTHESIS AND ANTIVIRAL EVALUATION OF ADENOSINE-N^1-OXIDE AND 1-(BENZYLOXY) ADENOSINES

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Summary: The antiviral activity of adenosine-N^1-oxide (1) and a variety of substituted 1-(benzyloxy) adenosines (2) has been re-investigated and significant *in vitro* activity *vs. Vaccinia virus* has been shown. *In vivo* activity in mice has also been demonstrated.

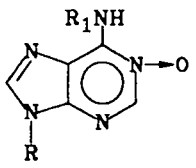
In connection with an antiviral synthesis project we have underway, it was decided to re-investigate compounds related to adenosine-N^1-oxide and its benzyloxy derivatives. The surprisingly good *in vitro* activity exhibited by the first few compounds, which had been prepared earlier in our laboratories,[1] encouraged us to pursue the preparation of additional N^1-oxides and a variety of substituted benzyloxyadenosines.

Adenosine-N^1-oxide and the related N^1-oxides (**1b-e**) were prepared in good yields by oxidation of the adenine-containing precursors with m-chloroperoxybenzoic acid using a modification of the procedures of Lewis and Townsend[2] and Robins and Uznanski.[3] In most cases the crude material obtained directly from the reaction was adequate for preparative purposes. The N^1-oxides were treated with the appropriate benzyl bromides in *N,N*-dimethyl acetamide to produce the 1-(benzyloxy) adenosine hydrobromides which were conveniently converted to the perchloric acid salts by treatment with a nearly saturated solution of NH_4ClO_4 in water.[4] A wide variety of substituted 1-benzyloxy (**2a-s**) derivatives has been made.

Biological Activity: Adenosine-N^1-oxide (**1a**) and 6-methylamino-9-β-D-ribofuranosyladenine-N^1-oxide (**1e**) were found to have high virus ratings (VR)[5] of 2.0 and 2.4 *vs. Vaccinia virus in vitro*. The 2'-deoxyadenosine-N^1-oxide (**1b**) was less active with a VR = 1.7. Many of the substituted 1-(benzyloxy) adenosines were found to have very high activity varying from VR = 2.0-3.3. Among the most active compounds were the three 1-(methylbenzyloxy) adenosines (**2a**), the two 1-(methoxybenzyloxy) adenosines (**2b**), the two 1-(difluorobenzyloxy) adenosines (**2e**) and the 1-(1-phenylethyloxy) adenosine (**2c**). All were far more active than Ara-A (VR = 1.0) which was used as the positive control.

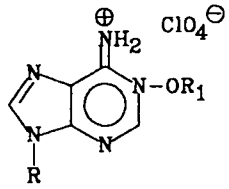
The 9-benzyl- and 9-methyladenine-N^1-oxides and their benzyloxy derivatives were all inactive.

In a *Vaccinia virus*-induced tailpox lesion model 1-(3-methylbenzyloxy) adenosine, perchloric acid salt (**2a**) has been shown to be equivalent to or slightly better than Ara-A *in vivo*. The



1

a) R = β-D-ribofuranosyl, R_1 = H
b) R = β-D-(2'-deoxy)ribofuranosyl, R_1 = H
c) R = benzyl, R_1 = H
d) R = methyl, R_1 = H
e) R = β-D-ribofuranosyl, R_1 = methyl



2

a) R = β-D-ribofuranosyl, R_1 = 2-, 3-, and 4-methylbenzyloxy[a]
b) R = β-D-ribofuranosyl, R_1 = 3- and 4-methoxybenzyloxy[b]
c) R = β-D-ribofuranosyl, R_1 = 1-phenylethyloxy
d) R = β-D-ribofuranosyl, R_1 = 2-, 3-, and 4-fluorobenzyloxy[a]
e) R = β-D-ribofuranosyl, R_1 = 2,4- and 3,4-difluorobenzyloxy[b]
f) R = β-D-ribofuranosyl, R_1 = 2-trifluoromethylbenzyloxy
g) R = β-D-ribofuranosyl, R_1 = 2,4- and 3,5-bis(trifluoro)benzyloxy[b]
h) R = β-D-ribofuranosyl, R_1 = 2- and 3-chlorobenzyloxy[b]
i) R = β-D-ribofuranosyl, R_1 = 2-, 3-, and 4-nitrobenzyloxy[a]
j) R = β-D-ribofuranosyl, R_1 = 2-, 3-, and 4-cyanobenzyloxy[a]
k) R = β-D-ribofuranosyl, R_1 = 2-methoxy-5-nitrobenzyloxy
l) R = β-D-ribofuranosyl, R_1 = 3-methoxy carbonylbenzyloxy
m) R = β-D-ribofuranosyl, R_1 = 2-phenylethyloxy
n) R = β-D-(2'-deoxy)ribofuranosyl, R_1 = 2-, 3-, and 4-methylbenzyloxy[a]
o) R = β-D-(2'-deoxy)ribofuranosyl, R_1 = 2-, 3-, and 4-fluorobenzyloxy[a]
p) R = benzyl, R_1 = 2-, 3-, and 4-methylbenzyloxy[a]
q) R = benzyl, R_1 = 2-, 3-, and 4-fluorobenzyloxy[a]
r) R = benzyl, R_1 = ethoxy
s) R = methyl, R_1 = 2- and 3-methylbenzyloxy[b]

[a]Three isomers.
[b]Two isomers.

adenosine-N^1-oxide (**1a**), while slightly less active than Ara-A, exhibits useful activity. The 1-(2-trifluoromethylbenzyloxy) (**2f**) and 1-(4-fluorobenzyloxy) (**2d**) derivatives were less active.

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