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## Nucleosides, Nucleotides and Nucleic Acids

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### Synthesis and Antiviral Evaluation of Adenosine-N<sup>1</sup>-Oxide and 1-(Benzyloxy) Adenosines

Charles A. Krauth<sup>a</sup>; Anita T. Shortnacy<sup>a</sup>; John K. Montgomery<sup>a</sup>; John A. Secrist III<sup>a</sup>

<sup>a</sup> Organic Chemistry Research Department, Southern Research Institute, Birmingham, AL

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SYNTHESIS AND ANTIVIRAL EVALUATION OF ADENOSINE-  
N<sup>1</sup>-OXIDE AND 1-(BENZYLOXY) ADENOSINES

Charles A. Krauth, Anita T. Shortnacy, John A. Montgomery,  
and John A. Secrist III\*

Organic Chemistry Research Department, Southern Research Institute,  
P. O. Box 55305, Birmingham, AL 35255-5305

**Summary:** The antiviral activity of adenosine-N<sup>1</sup>-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.

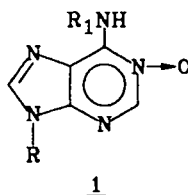
In connection with an antiviral synthesis project we have underway, it was decided to re-investigate compounds related to adenosine-N<sup>1</sup>-oxide and its benzyloxy derivatives. The surprisingly good *in vitro* activity exhibited by the first few compounds, which had been prepared earlier in our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

Adenosine-N<sup>1</sup>-oxide and the related N<sup>1</sup>-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<sup>2</sup> and Robins and Uznanski.<sup>3</sup> In most cases the crude material obtained directly from the reaction was adequate for preparative purposes. The N<sup>1</sup>-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<sub>4</sub>ClO<sub>4</sub> in water.<sup>4</sup> A wide variety of substituted 1-benzyloxy (2a-s) derivatives has been made.

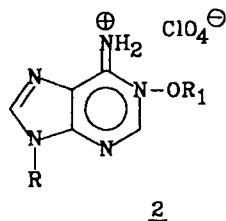
**Biological Activity:** Adenosine-N<sup>1</sup>-oxide (1a) and 6-methylamino-9-β-D-ribofuranosyladenine-N<sup>1</sup>-oxide (1e) were found to have high virus ratings (VR)<sup>5</sup> of 2.0 and 2.4 vs. *Vaccinia virus in vitro*. The 2'-deoxyadenosine-N<sup>1</sup>-oxide (1b) was less active with a 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-phenylethoxy) 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<sup>1</sup>-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



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



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

<sup>a</sup>Three isomers.

<sup>b</sup>Two isomers.

adenosine-N<sup>1</sup>-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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