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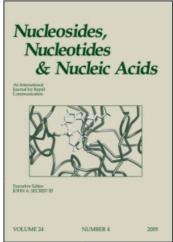
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8-Substituted Purine Ribosides: Synthesis and Biological Activity

Anita T. Shortnacy^a; John A. Montgomery^a; John A. Secriist III^a

^a Organic Chemistry Research Department, Southern Research Institute, Birmingham, AL

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8-SUBSTITUTED PURINE RIBOSIDES: SYNTHESIS AND BIOLOGICAL ACTIVITY

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 syntheses of a series of 8-substituted purine ribofuranosides are described. Reductive deamination of 8-bromoadenosine triacetate (1) provides the key intermediate (2) for subsequent displacement reactions. Four compounds show significant activity in two cell culture screens.

As a part of our program to design biologically active nucleosides with altered metabolism, we previously prepared 8-amino-6-fluoro- β -D-ribofuranosylpurine. This cytotoxic compound is a substrate for adenosine kinase and adenosine deaminase, and the monophosphate is a substrate for AMP-deaminase. The products formed by the action of the deaminases, 8-aminoinosine and 8-amino-IMP, are not significant contributors to the cytotoxicity of the compound. To reduce the loss of potency caused by the two deaminases, we prepared and tested a series of 8-substituted purine ribosides with hydrogen in the 6-position.

8-Bromoadenosine³ was acetylated⁴ and deaminated⁵ to give the crystalline intermediate 2 that was used in subsequent displacement reactions.^{6,7}

Treatment of 2 with NaOCH₃ in MeOH gave 4 in one step. Treatment of 2 with sodium in benzyl alcohol gave 8-benzyloxypurine riboside that was hydrogenated at atmospheric pressure to give 5. Reaction of 2 with NaSCH₃ in DMSO gave 8-methylthiopurine riboside triacetate. The protecting groups were removed with NaOH (3 eq.) in 1:1 MeCN:H₂O to give 6. Reaction of 2 with thiourea in EtOH followed by similar deprotection gave pure 8-thiopurine riboside (7). Treatment of 2 with dimethylamine in EtOH followed by deprotection gave 8. For compounds 4---8, the yield from 2 averaged 45%.

2 + NaOCH₃. MeOH

○ CH₃O Na
$$^{\oplus}$$
/H₂

NaSCH₃. DMSO/NaOH

NH₂C NaOH

(CH₃)₂NH/NH₃. EtOH

NaN₃. DMSO/NaOH

NaN₃. DMSO/NaOH

NaN₃. DMSO/H₂/NaOH

The most rapid displacement reaction in the series was observed when 2 was treated with NaN₃ in DMSO. The resulting triacetate was deprotected to give 9 in 35% yield. When 2 was treated with NaN₃, DMSO followed by hydrogenolysis and deprotection, a good yield of 10 was obtained.

Of the entire series, the 8-halo compounds were the most difficult to make. The 8-bromo (3) and 8-chloro (13) were prepared successfully, but all attempts to obtain the 8-fluoro so far have failed. In the case of the 8-bromo, conventional methods for deprotection of 2 resulted in bromine displacement or incomplete deacetylation. Treatment of 2 with pig liver esterase³ gave 3 in 39% yield. A variety of reaction conditions failed to produce the 8-chloro compound cleanly from the 8-bromo. Consequently, we elected to explore an alternate route. Compound 11 was prepared, and the TBDMS groups were replaced with acetyl groups using standard conditions. We were able to prepare 13 from 12 by a route identical to that used for 3.

Results from H.Ep.-2 and L1210 cell culture screens show some interesting structure-activity relationships. Compounds 4, 5, 7, and 8 show little or no cytotoxicity. But compounds 9, 10, 3, and 13 exhibit high cytotoxicities in both cell lines. We can presume that these four are substrates for adenosine kinase and are phosphorylated to the triphosphate level. We examined 10 for phosphorylation in L1210 cells and found conversion in large amount to a triphosphate.

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