

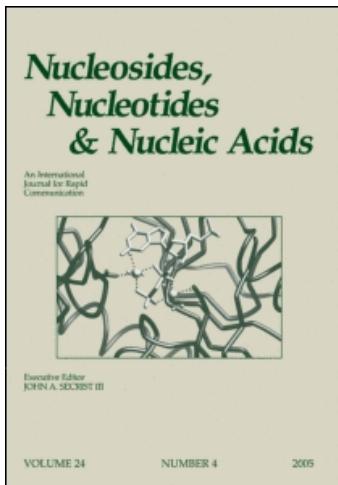
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## Nucleosides, Nucleotides and Nucleic Acids

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### The Synthesis of Bicyclic N<sup>4</sup>-Amino-2'-deoxycytidine Derivatives

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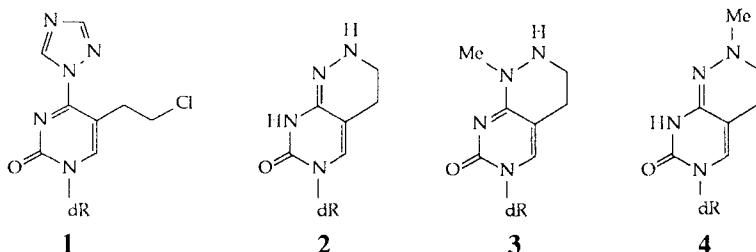
THE SYNTHESIS OF BICYCLIC N<sup>4</sup>-AMINO-2'-DEOXYCYTIDINE DERIVATIVES.

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**ABSTRACT.** A number of bicyclic N<sup>4</sup>-amino-2'-deoxycytidine derivatives have been prepared. Their ambivalent hydrogen bonding potential makes them of interest for mutagenesis studies, and for incorporation into oligonucleotides for probes and primers.

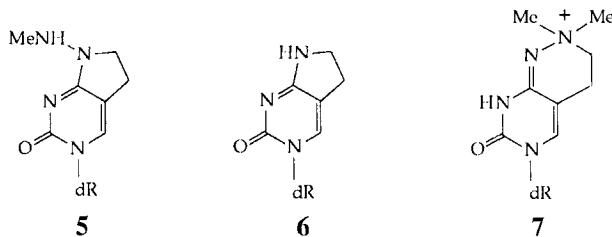
As part of our work to develop bases capable of ambivalent hydrogen bonding, we have previously developed two bicyclic N<sup>4</sup>-oxy-2'-deoxycytidine derivatives<sup>1,2</sup>. One of these<sup>1</sup> has found use as a degenerate pyrimidine base for probes and primers, though it has been shown to behave more like thymine<sup>3</sup>. These compounds are also of interest for mutagenesis studies due to their ambivalent hydrogen bonding potential. In an attempt to prepare pyrimidine nucleosides which have tautomeric constants closer to unity we have turned our attention to N<sup>4</sup>-amino-2'-deoxycytidine derivatives<sup>4</sup>.



dR = 3,5-di-O-acetyl-2-deoxyribofuranosyl.

Treatment of the triazolo derivative<sup>1</sup> **1** with anhydrous hydrazine led to an immediate reaction to give the expected product **2**. This compound, however, was found to be unstable, and therefore unsuitable for incorporation into oligomers, presumably undergoing oxidative cleavage of the newly formed ring. It was therefore decided to prepare a derivative of **2** with alkyl protection, such as **4**, in the hope that this might stabilise the product towards oxidation. Treatment of **1** with 1-methylhydrazine, however, led to **3**, the structure for which was confirmed by NOE measurements.

It has been shown<sup>5</sup> that the methylamino group of methylhydrazine is the more nucleophilic, and so the formation of **3** is to be expected. However, the bicyclic product **3** is a fixed tautomer, and so it was decided to prepare a protected methylhydrazine in order to prepare **4**. Thus treatment of the triazolo derivative **1** with N<sup>1</sup>-benzyloxycarbonyl protected methylhydrazine<sup>6</sup> led in a slower reaction to displacement of the triazolo group by the amino group as expected. When the benzyloxycarbonyl group was removed (Pd/C, H<sub>2</sub>) the product obtained was not the expected bicyclic product **4**, but a 5-membered analogue **5**. This product must arise by displacement of the halogen by the N<sup>4</sup>-amino nitrogen, and not the terminal one. The structure of **5** was confirmed from its nmr spectrum which showed the N-methyl group as a doublet ( $\delta$  2.67 ppm,  $J$ =5.5 Hz), which became a singlet after a D<sub>2</sub>O wash.



The reduction was also carried out under acidic conditions (HOAc or 0.1M HCl), conditions that we hoped would not lead to ring closure after removal of the protecting group, and that the cyclisation might then be controlled to give the desired product. But it was found that cyclisation had occurred, and that the exocyclic amino group had additionally been reductively cleaved to give **6**. However, treatment of the triazolo derivative **1** with ammonia in dioxan did not give the product **6** but the un-cyclised 5-(2-chloroethyl)-2'-deoxycytidine. This is somewhat surprising in view of the fact that cyclisation did occur during the reduction to give the 5-membered analogue **5**.

In an attempt to further clarify this unexpected ring closure we carried out the displacement of the triazole using N,N-dimethylhydrazine. We expected to synthesise from this route the dimethylamino analogue of **5**. This reaction, however, gave rise to two new products; the minor product was shown to be the product arising from displacement of the triazole by the hydrazine. The second, major product was a charged product which proved difficult to purify but for which we have assigned the structure **7**.

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