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Preliminary communication

Enol acetates of nucleoside-5′-aldehydes: potential intermediates for substituent incorporation at C-4′

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Interest in the modification of nucleosides at C-4′ has been generated by the isolation and identification of the structure of nucleocidin[1,2] (**1**), which is thus far the only naturally occurring nucleoside having a substituent in place of the hydrogen atom on that carbon atom. During the past several years, some synthetic work in this area has appeared[3–7], including an excellent synthesis[7] of **1**. In the most direct sense, it seemed desirable that the operation of substituent incorporation at C-4′ should be so conducted that some kind of oxygen-containing group would be retained at C-5′. Thus far, approaches have utilized an *exo*-methylene group formed at the 4′,5′-terminus by an eliminative transformation; addition reactions are then needed in order to reintroduce groups at both C-4′ and C-5′, followed by appropriate steps to reinstitute an oxygen-containing group at C-5′. We decided that retention of an oxygen-containing group while still introducing 4′,5′-unsaturation would be possible simply by the use of a non-eliminative transformation; for example, by oxidation of suitably protected nucleosides to the 5′-aldehyde, followed by conversion into the enol acetate. Precedent for this type of reaction exists in the carbohydrate literature[8], and it seemed likely that nucleoside-5′-aldehydes would react similarly. We now report on our initial results in the preparation of nucleoside-4′,5′-enol acetates, and also give an example of substituent incorporation at C-4′ that utilizes an enol acetate.

Treatment of 2′,3′-*O*-cyclohexylideneuridine-5′-aldehyde[9]** (**2a**), obtained in 69% overall yield from uridine, with two equivalents of potassium carbonate in an excess of acetic anhydride for 0.75 h at 80° afforded the enol acetate **3a***** in 90% yield, together with traces of the N^3-acylated enol acetate (**3b**) and the 5′-diacetate (**2b**). Both proton and carbon-13 n.m.r. spectroscopy indicated the presence of only one isomer; p.m.r. datum****: δ 6.90 (s, 1, H-5′); c.m.r. data****: δ 115.1 (d, C-5′) and 144.8 (s, C-4′). The question of

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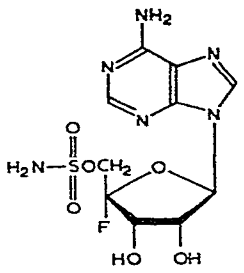
**Most, if not all, of the aldehydes reported herein exist as the monohydrates.

***Enol acetates that were major products for all reactions reported herein were fully characterized by spectral means, including high-resolution mass spectrometry on high-purity samples.

****All p.m.r. and c.m.r. data are for solutions in $CDCl_3$, with shifts downfield relative to tetramethylsilane, δ 0.00.



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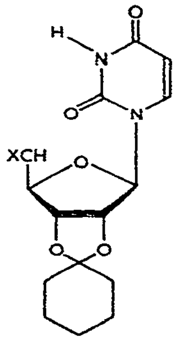
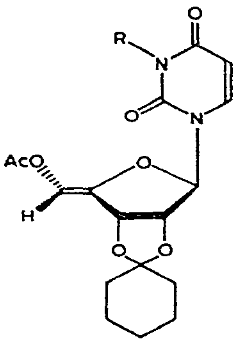


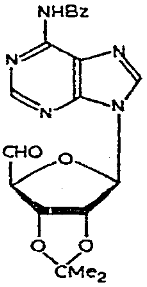
2a $X = O$
2b $X = (OAc)_2$



3a $R = H$
3b $R = Ac$

which isomer was formed was resolved by a nuclear Overhauser experiment; irradiation of H-3′ gave a 10% peak enhancement of H-5′ that corresponds[10] to an internuclear distance of ~290 pm, entirely consistent with a model of the *Z* isomer 3a. This result has precedent in recent work on carbohydrate enol acetates[8], wherein X-ray crystallography was used in one case to establish alkenic geometry.

The generality of the enol acetate reaction has been examined with several other nucleoside aldehydes. When subjected to conditions identical to those applied to 2, N^6-benzoyl-2′,3′-*O*-isopropylideneadenosine-5′-aldehyde[11] (4) gave an almost quantitative yield of the mono- and di-acylated enol acetates 5a and 5b. Each of these compounds was a single isomer; 5a, p.m.r. datum: δ 6.98 (s, 1, H-5′), and 5b, p.m.r. data: δ 2.57 (s, 3, $NHCOCH_3$) and 6.97 (s, 1, H-5′).



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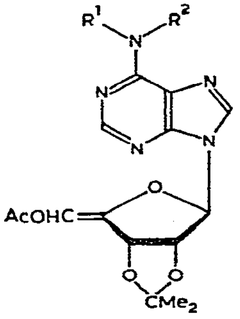
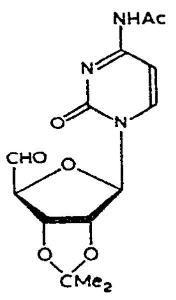


5a $R^1 = H, R^2 = Bz$
5b $R^1 = Ac, R^2 = Bz$

Similarly, N^4-acetyl-2′,3′-*O*-isopropylidenecytidine-5′-aldehyde (6) was converted into the enol acetate 7 (single isomer), obtained in 50% yield after purification; p.m.r. datum: δ 6.87 (s, 1, H-5′). (Preparation of 6 was accomplished from N^4-acetylcytidine[12] by protection with acetone in the presence of *p*-toluenesulfonic acid, oxidation of the acetal to the aldehyde with dicyclohexylcarbodiimide–dimethyl sulfoxide, isolation and



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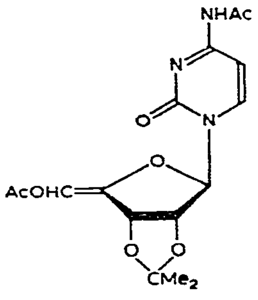

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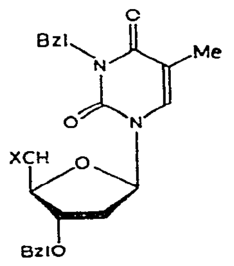
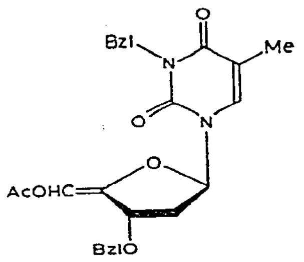
purification of the aldehyde as the imidazolidine derivative, and regeneration of the aldehyde hydrate under aqueous, acidic conditions.)

Two derivatives of thymidine have thus far been examined. N^3-Benzyl-3′-*O*-benzylthymidine was oxidized to the aldehyde **8a** as just described for **6**. Conversion of **8a** into a single isomer of the enol acetate **9** required 1.25 h at 80°. Purification of the product provided 45% of the pure enol acetate **9** and 11% of the 5′-diacetate **8b**; p.m.r. datum (**9**): δ 6.77 (s, 1, H-5′). When 3′-*O*-acetylthymidine-5′-aldehyde[13] (**10**) is subjected to the standard conditions, the enol acetate is apparently formed (t.l.c. and crude p.m.r. data), but it consistently suffers extensive decomposition during processing, perhaps due to the lability of the allylic acetate group.



8a X = O
8b X = (OAc)$_2$



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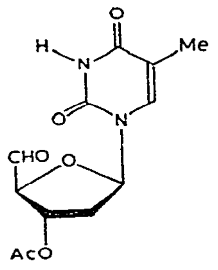

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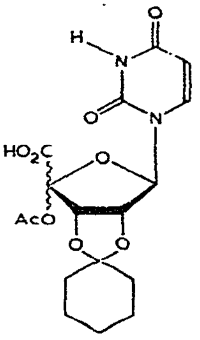
For an initial assessment of the reactivity of the double bond in these enol acetates, compound **3a** was treated with an excess of *m*-chloroperoxybenzoic acid in dichloromethane for 3 h at room temperature. The solid product, a single isomer, isolated in 71% yield by filtration and washing with ether, had structure **11**, with the configuration of C-4′ still in doubt. Support for this structure came from a variety of data, including those given by i.r., u.v., p.m.r. (two exchangeable protons downfield), and c.m.r. spectroscopy (acid carbonyl at δ 166.0). The reaction mechanism[14] apparently involves initial epoxidation followed by rearrangement to a pair of isomeric 5′-aldehydes, which are not stable to



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processing and isolation, but are detectable by thin-layer chromatography. One of these aldehydes, most probably that in the (less hindered) D-*ribo* configuration, is then oxidized to the carboxylic acid **11**.

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