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Synthesis of 4'-*aza* analogues of 2',3'-dideoxythymidine by 1,3-Dipolar Cycloadditions of Nitrones to 1-*N*-vinyl-thymine

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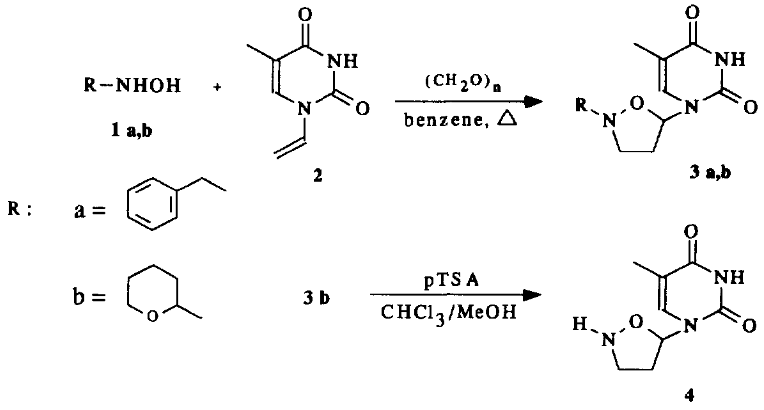
Abstract: The title compounds have been obtained by 1,3-dipolar cycloadditions of methylene nitrones, prepared *in situ* from suitably protected hydroxylamines, to 1-*N*-vinyl-thymine. The 4'-*aza*-2',3'-dideoxyerythrofuranoside (4), an analogue of 2',3'-dideoxythymidine, might exhibit antiviral activity.

Nucleoside analogues are versatile drugs active against HIV-1, HBV and HSV-1 infections, and are also effective in the treatment of some tumoral forms.[1] They can be directly used[2] or can be incorporated into *antisense* oligonucleotide strands.[3,4]



Scheme

The screening[5] of the biological activity of a number of nucleosides derivatives has shown that modifications at the 2' and 3' positions of the ribose ring do not change extensively the molecular recognition properties of the drugs.

The 2',3'-dideoxyribofuranosyl derivatives of adenine and thymine are effective in AIDS therapy, even though the lability of the glycosidic bond and their toxicity represent the major drawbacks in clinical applications. Azathymidine, a pyrrolidinyl nucleoside, has been recently incorporated into *antisense* oligonucleotides.[4] Isoxazolidine **4** (scheme), a 1,3-dipolar cycloaddition product easily achievable from 1-*N*-vinyl-thymine,[6] can be considered as the 4'-*aza*-2',3'-dideoxy-erythrofuranosyl derivative of thymine, thus an analogue of 2',3'-dideoxythymidine. The structural feature of the molecule ensures that (i) the replacement of the 4' chiral carbon with the achiral nitrogen gives more conformational degrees of freedom to the molecule, (ii) a nucleophilic site is still available in the modified carbohydrate moiety which might undergo phosphorylation and (iii) the basicity of the hydroxylamino nitrogen atom should confer enhanced stability to the glycosidic linkage in acid media. The methylene nitrone, produced *in situ* from benzylhydroxylamine (**1a**) and paraformaldehyde, afforded 63% isolated yield of **3a**,[7] after 10 hours refluxing in dry benzene with **2**[6] in the presence of traces of 4-*tert*-butylcatechol and 4 Å molecular sieves. In similar conditions 5-hydroxypentanal oxime, in equilibrium[8] with the cyclic hydroxylamine **1b**, and **2** gave 58% isolated yield[9] of **3b**, after 72 hours treatment at 85 °C in benzene, in a screw capped vial. ^{1}H NMR showed overlapping resonances for the expected pair of diastereoisomers, which were clearly distinguishable from the peaks due to the thymine 6-H proton.[9] Even the diastereoisomeric mixture of **3b**, gave nearly overlapping, but distinct, spots on tlc plates their separation was not attempted since both *re* and *si* faces of the vinyl moiety were equal accessible to the nitrone thus affording pairs of enantiomers for each diastereoisomers, regardless the *exo* (or *endo*) orientation of dipole and dipolarophile substituents in the transition state. No traces of base induced modification by $(CH_2O)_n$ were observed, as experienced when 9-*N*-vinyl-adenine was used as a dipolarophile.[10]

The usefulness of the method is related to the regioselectivity of the cycloaddition processes which was expected [11] on the ground of both the structure and electronic properties of the electron-rich mono-substituted vinyl moiety of **2**. The synthesis of **3a** has permitted the evaluation of the reactivity of the thymine derivative towards the potential hydroxymethylation[12] of the nucleobase in the adopted experimental conditions. The cycloadduct thus obtained after debenzylation and ring-opening by 10% Pd/C catalytic hydrogenation afforded an open chain derivative of thymine which can be used for further derivatizations. **3b** was designed in order to have an acid labile protecting group on the nuclear nitrogen which could be removed in mild acid media. When **3b** was treated with p-toluensulfonic acid in chloroform/methanol (70:30, v/v), for 1 hour at room temperature, 81% isolated yield of the target dideoxythymidine analogue **4** was obtained as a colourless solid[13] with good solubility properties in water.

The easiness of the removal of the tetrahydropyranyl group suggests that at low pH the modified nucleotide should be protonated on the glycone moiety, thus enhancing the stability of the glycosyl bond. It is expected also that the lack of a chiral carbon at the position 4' of the nucleus should affect at lesser extent the molecular recognition properties of both enantiomers.

The availability of vinylnucleobases[6] allows the extension of the cycloaddition approach to other modified nucleosides. The designing of appropriate dipoles is now under investigation aiming at introducing at the 4' and 3' position of the isoxazolidine nucleus functional groups suitable for the incorporation of these species into oligonucleotide strands.

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7. m.p. 153-155°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{TMS}:1.68 (s, 3H, CH_3), 2.32 (m, 1H, 2'-H), 2.77 (m, 2H, 3'H+2'-H), 3.45 (m, 1H, 3'H), 3.90 (d, 1H, *CH*$_2$Ph), 4.09 (d, 1H, *CH*$_2$Ph), 6.09 (dd, 1H, 1'-H), 7.32(m, 5H, Ar-H), 7.50 (s, 1H, 6-H), 11.27 (s_{broad}, 1H, 3-NH); FABMS [(glycerol, 8KeV, Xe), *m/z* (%)]: (+) *288* [100, (M+H$^+$)], *162* (45), *136* (16), *127* (27); (-) *286* [21 (M-H)$^-$], *153* (47), *151* (28), *125* (100).
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9. Diasteromeric mixture. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{TMS}: 7.57 [s, 1H, 6-$H_{\alpha(\beta)}$], 7.61 [s, 1H, 6-$H_{\beta(\alpha)}$]; FABMS [(m-nitrobenzyl alcohol, 8KeV, Xe), *m/z* (%)]: *282* [16 (M+H)$^+$], *165* (27), *85* (100).

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13. m.p. 178-180°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{TMS}: 1.81 (s, 3H, CH_3), 2.23 (m, 1H, 2'-H), 2.53 (m, 1H, 2'-H), 3.00-3.16 (m, 1H, 3'-H), 3.22-3.44 (m, 1H, 3'-H), 6.06 (dd, 1H, 1'-H), 7.01 (m, 1H, 4'-NH), 7.54 (s, 1H, 6-H), 11.36 (s_{broad}, 1H, 3-NH); FABMS [(glycerol, 8KeV,Xe), *m/z* (%)]: *198* [67 $(M+H)^+$], *127* (100).

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