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Synthesis of nucleoside analogues with a 1,5-anhydrohexitol moiety

A. Van Aerschot*, I. Verheggen and P. Herdewijn

Laboratory of Medicinal Chemistry (I.F.W.), Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium.

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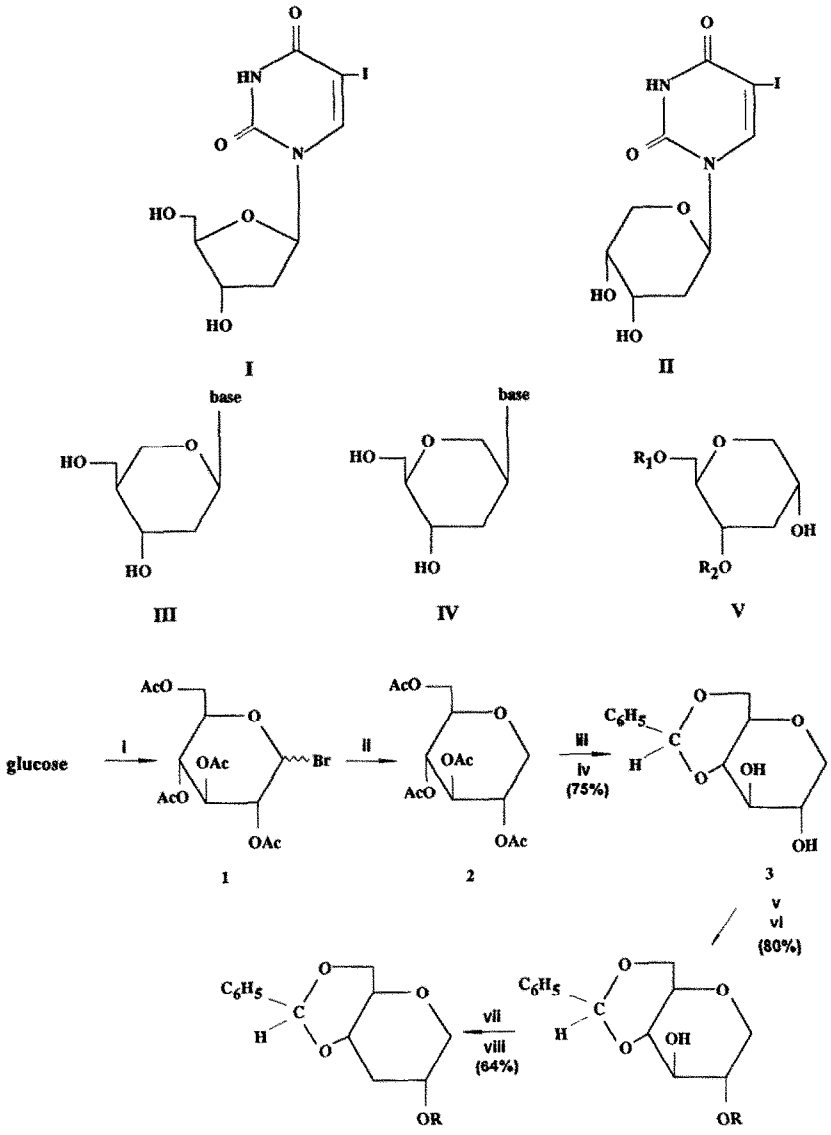
Abstract: *Glucose after conversion to a 3-deoxy-1,5-anhydro-D-glucitol moiety, was coupled at its 2-position to heterocyclic bases either by nucleophilic displacement or under Mitsunobu reaction conditions to afford new nucleoside analogues with a 1,5-anhydrohexitol moiety.*

Antiviral activity has been described for several classes of nucleoside analogues with modifications in their sugar part. Well known examples are acyclic nucleoside analogs (e.g. acyclovir), 2'-fluoro-2'-deoxyarabinofuranosylpyrimidine nucleosides (e.g. FMAU, FIAC), nucleosides with a four membered ring (e.g. oxetanocin), carbocyclic nucleosides (e.g. carbovir) and phosphonylated analogues of acyclic nucleosides [e.g. N^9-(phosphonylmethoxyethyl)adenine (PMEA)]. Nucleosides with a six-membered sugar moiety seldom have been found to possess antiviral activity.

The change in ring size going from a furanose to a pyranose structure gives a profound alteration of the spatial orientation of the substituents. Therefore it is not unpredictable that pyranose nucleosides having a 2,4-dideoxy-ß-D-*erythro*-hexopyranosyl[1], a 3,4-dideoxy-ß-D-*erythro*-hexopyranosyl[2] or a 2,3-dideoxy-ß-D-*erythro*-hexopyranosyl[3-5] sugar moiety do not show antiviral activity. The discovery of biologically active pyranose nucleosides through molecular design is also hampered by the fact that the carbohydrate part of furanose nucleosides is conformationally flexible and therefore not very useful as a model for drug design.

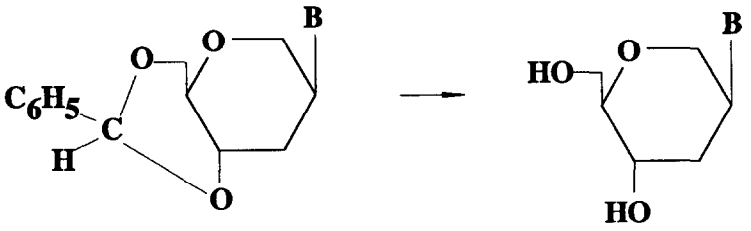
However, by superimposing the crystal structures of 5-iodo-2'-deoxyuridine (I) and 1-(2-deoxy-ß-D-ribopyranosyl)-5-iodouracil (II)[7] one can easily see that substituting the 4-hydroxyl of II with a hydroxymethyl in the R position (*cis* with the base moiety), could give compounds with a structure closely related to I. We therefore were encouraged to synthesize the new nucleoside analogue series of formula III and IV. Here we present a preliminary report on the synthesis of the pyranose-like nucleoside analogues IV.

The target compounds would be obtained in a straightforward manner, synthesizing first the 1,5-anhydrohexitol moiety with a (R)-hydroxyl substituent at the 2-position (V). Following activation, nucleophilic displacement with a purine or pyrimidine base would afford the desired nucleoside analogues.



Scheme I

i : $(CH_3CO)_2O$, CH_3COOH , HBr ; ii : Bu_3SnH , Et_2O ; iii : $NaOCH_3$, CH_3OH ; iv : C_6H_5CHO , $ZnCl_2$;
v : Bu_2SnO , C_6H_6 , 16 h , 80°C ; vi : $C_4H_8O_2$, $CH_3C_6H_4SO_2Cl$ or $CH_3C_6H_4COCl$, 6 h , 50°C ;
vii : CH_2Cl_2 , DMAP , $CSCl_2$, 1 h , 25°C ; then 2,4 - $Cl_2C_6H_3OH$, 2 h , 25°C ; viii : $CH_3C_6H_5$, Bu_3SnH , 80°C , 16 h .



9, 11, 14, 16, 18 **10, 12, 13, 15, 17, 19**

9, 10	**B : adenin - 9 - yl**	**14, 15**	**B : 5 - iodouracil - 1 - yl**
11, 12	**B : 2 - amino - 6 - chloropurine**	**16, 17**	**B : thymin - 1 - yl**
13	**B : guanin - 9 - yl**	**18, 19**	**B : cytosin - 1 - yl**

The 1,5-anhydro-4,6-*O*-benzylidene-3-deoxy-glucitol ring was synthesized according to scheme I. Glucose was converted to tetra-*O*-acetyl-glucopyranosyl bromide (1)[8] which was reduced to 2[9] with tri-n-butyltinhydride. The acetyl groups were removed with sodium ethoxide, followed by protection of the 4,6-position with a benzylidene moiety[10] affording 3. Although reaction of 3 with p-toluenesulphonyl chloride in pyridine afforded a mixture, selective reaction of the hydroxyl at position 2 was feasible following activation with dibutyltin oxide. Position 2 either was selectively protected as an ester (e.g. R = $CH_3C_6H_4CO$, 5) or was functionalized with a leaving group moiety (e.g. R = $CH_3C_6H_4SO_2$, 4)[11]. The hydroxyl group at position 3 was removed through introduction of a 2,4-dichlorophenoxythiocarbonyl[1] moiety followed by Barton deoxygenation[12], affording respectively 6 and 7.

Nucleophilic displacement of the tosylate in 6 with adenine/NaH worked well affording 9 in 56% yield[13]. Deprotection with acetic acid gave the 2'-deoxyadenosine analogue 10[14]. Displacement reactions with other bases were rather low yielding, affording many degradation products. 2-Amino-6-chloropurine reacted with 6 in DMF in the presence of potassium carbonate (1.5 eq) and 18-crown-6 (0.5 eq) to afford 11 in 19% yield . Deprotection with 80% acetic acid (giving 12) followed by enzymatic hydrolysis of the 6-chlorine with adenosine deaminase[15,16] afforded the 2'-deoxyguanosine analogue 13.

Reaction of the sodium salt of 5-iodouracil (2 eq)[17] and 18-crown-6 (0.4 eq) with 6 afforded 42% of 14 which was deprotected to 15 with 80% acetic acid. Reaction of 6 with thymine or cytosine, however, gave only traces of the desired coupling product. Moreover, reaction with cytosine afforded mainly an O^2-coupled product. We therefore introduced these base moieties starting from the alcohol 8, obtained

from 7, making use of Mitsunobu reaction conditions[18]. As recently described[19] these reactions conditions can be used for introduction of nucleic bases on an unactivated carbon. Although side products were detected by TLC, no product with retention of configuration was isolated and reactions therefore are believed to run essentially with inversion of configuration.

Indeed, 17 was prepared in 50% yield[20] from 8 making use of 2 eq of N^3-benzoylthymine[21] and 2.5 eq of both triphenylphosphine and diethylazodicaboxylate (DEAD) followed by deprotection of N^3-benzoylated 16. Likewise N^4-benzoylcytosine[22] (2 eq) was reacted with 8 in the presence of Ph_3P (2.5 eq) and DEAD (2.5 eq) in anhydrous dioxane to afford 37% of N^4-benzoylated 18, which upon deprotection afforded 19 in 29% yield from 8[23].

Except for the thymidine analogue, all derivatives display biological activity, exemplified by compound 15, which inhibited the proliferation of herpes simplex virus type I and herpes simplex virus type II for 50% at 0.07μg/mL while being virtually non toxic to the human embryonic skin-muscle cells[24].

Acknowledgements

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References and notes

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11. 1,5-Anhydro-4,6-O-benzylidine-2-O-*p*-toluenesulphonyl-D-glucitol: (4). 400MHz ^1H NMR (DMSO-d_6) 2.42 (s, 3H, CH_3), 3.35-3.42 (m, 2H, H-4, H-5), 3.49 (t, J=11Hz, 1H, H-1α), 3.61 (m, 1H, H-6), 3.67 (m, 1H, H-3), 3.87 (dd, J=5.5Hz and 11Hz, 1H, H-1ß), 4.14-4.25 (m, 2H, H-2, H-

6'), 5.05 (s, 1H, PhCH), 5.12 (d, J=5.5Hz, 1H, OH), 7.35-7.50 (m, 7H, aromatic H), 7.85 (m, 2H, aromatic H) ppm.

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13. Typical procedure for the nucleophilic displacement reaction:
1,5-Anhydro-4,6-O-benzylidene-2-(adenin-9-yl)-2,3-dideoxy-D-arabinohexitol (9)
A mixture of 1.35 g (10 mmol) of adenine, 400 mg of sodium hydride (60% dispersion, 10 mmol) and 529 mg (2 mmol) of 18-crown-6 in 60 mL of dry DMF was stirred at 80°C for 1 h. After adding a solution of 1.95 g (5 mmol) of 6 in 30 mL anhydrous DMF, stirring was continued for 16 h at 100°C. The reaction mixture was cooled and evaporated. The residue was dissolved in ethyl acetate (100 mL) and the organic phase was washed with saturated $NaHCO_3$ solution (50 mL) and H_2O (2x25mL), dried and evaporated. The solid residue was purified by column chromatography (CH_2Cl_2-MeOH, 97:3) affording 989 mg (2.8 mmol, 56% yield) of 9. An amount of 190 mg (0.49 mmol, 9%) of the unreacted tosylate 6 was recovered.
14. 1,5-Anhydro-2-(adenin-9-yl) 2,3-dideoxy-D-arabinohexitol (10)
mp : 237-239°C (MeOH-Et_2O); UV (MeOH) : δ_{max} 261 nm (1 = 13500); CIMS (NH_3) m/z : 266 (MH^+), 136 (BH_2^+); ^1H NMR (DMSO-d_6) δ 1.89 (ddd, ^2J = 13 Hz, $^3J_{3',4'}$ = 11 Hz, $^3J_{3',2'}$ = 4 Hz, 1H, H-3'ax), 2.29 (dm, ^2J = 13.5 Hz, 1H, H-3'eq), 3.20 (m, $^3J_{4',5'}$ = 9 Hz, 1H, H-5'), 3.52 (m, $=^3J_{4',5'}$ = 9 Hz; 1H, H-4'), 3.59 (m, 1H, H-6'), 3.70 (ddd, ^2J = 12 Hz, $^3J_{OH}$ = 5 Hz, $^3J_{5'6'}$ = 2.5 Hz, 1H, H-6"), 3.87 (dd, ^2J = 12.5 Hz, ^3J = 2 Hz, 1H, H-1'ax), 4.21 (dt, ^2J = 12.5 Hz, ^3J = 2.5 Hz, ^4J = 1.5 Hz, 1H, H-1'eq), 4.67 (t, ^3J = 5.5 Hz, 1H, 6'-OH), 4.78 (m, $^3J_{2'3'ax}$ = 4Hz, 1H, H-2'), 4.92 (d, ^3J = 5 Hz, 1H, 4'-OH), 7.25 (s, 2H, NH_2), 8.15 (s, 1H), 8.30 (s, 1H) (H-2, H-8) ppm; ^{13}C NMR (DMSO-d_6) 36.03 (C-3'), 50.18 (C-2'), 60.59 (C-6'), 60.85 (C-4'), 68.11 (C-1'), 83.11 (C-5'), 118.40 (C-5), 139.70 (C-8), 149.47 (C-4), 152.49 (C-2), 156.11 (C-6) ppm.
Anal. ($C_{11}H_{15}N_5O_3$ x 0.35 Et_2O) C, H, N.
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20. Typical procedure for introduction of nucleic bases under Mitsunobu reaction conditions :
1,5-Anhydro-2,3-dideoxy-2-(thymin-1-yl)-D-*arabino*hexitol (17)
A suspension of 2.40 g (10.46 mmol) of N^3-benzoylthymine[21], 1.23 g (5.23 mmol) of the alcohol 8 and 3.43 g (13.08 mmol) of triphenylphosphine in 100 mL of anhydrous dioxane was treated with 2.06 mL (13.08 mmol) of diethylazodicarboxylate (DEAD) in 15 mL anhydrous THF. The solution was stirred overnight at room temperature after which the volatiles were removed *in vacuo*. The residue was taken up in 100 mL of methanol saturated with ammonia. Evaporation and coevaporation with toluene left an oil which was purified on silica gel (CH_2Cl_2 - MeOH, 98:2). This yielded 3.5 g of crude 16 which also contained hydrazine dicarboxylate. The crude 16 was taken up in 50 mL 80% acetic acid and heated at 80°C for 5 h. After evaporation and coevaporation with toluene, the residue was dissolved in water and purified on silica gel (CH_2Cl_2 - MeOH, 93:7). Crystallization from MeOH - Et_2O afforded 671 mg of 17 as white crystals (2.62

mmol, 50% overall yield).
mp 169-171°C; UV (MeOH) ε_{max} 272 nm (ε = 9500); CIMS (iC_4H_{10}) m/e : 257 (MH^+); ^{13}C NMR (DMSO-d_6) 12.3 (CH_3), 35.2 (C-3'), 50.1 (C-2'), 60.3, 60.8 (C-4', C-6'), 66.9 (C-1'), 82.4 (C-5'), 108.3 (C-5), 138.9 (C-6), 150.9 (C-2), 163.8 (C-4)ppm; Anal. ($C_{11}H_{16}N_2O_5$ x O.5 H_2O) C, H, N.

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