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THE SYNTHESIS OF ANOMERIC 3-O-ACETYL-5-O-BENZOYL-2-AZIDO-2-DEOXY-D-ARABINOFURANOSYL CHLORIDES. VERSATILE SUGAR INTERMEDIATES FOR THE SYNTHESIS OF 2'-AZIDO-2'-DEOXY- AND 2'-AMINO-2'-DEOXY-β-D-ARABINOFURANOSYL NUCLEOSIDES.

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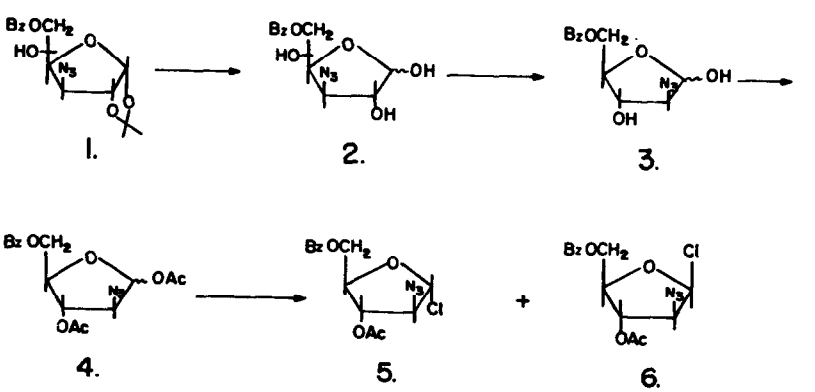
Considerable effort has been devoted over the years to the synthesis of amino nucleosides spurred on largely by the antibiotic properties exhibited by many of them.[1-4] However, the synthesis of 2'-amino-2'-deoxy nucleosides which have the amino group in the "up" (arabino) configuration has proved rather elusive.[5-8] Because of the potential of the β-D-arabinofuranosyl nucleosides to possess growth inhibitory properties,[9-12] a general synthesis of 2'-azido-2'-deoxy- and 2'-amino-2'-deoxy-β-D-arabinofuranosyl nucleosides was undertaken in this laboratory as part of our program of development of nucleosides of potential chemotherapeutical value.

The report that the azido group did not exert a neighboring group effect in the synthesis of 2-amino sugar oligosaccharides[13] suggested that a blocked 2-azido-2-deoxy-D-arabinofuranosyl 1-O-acetate or chloride would be suitable derivatives for the stereochemically controlled synthesis of the corresponding nucleosides. The reaction scheme first developed for preparing anomeric methyl-2-deoxy-4-thio-D-erythro-pentofuranosides[14] from 3-deoxy-hexofuranose was adapted to the synthesis of 2-azido-2-deoxy-D-arabinofuranose.



1. 2. 3. 4. 5. 6.

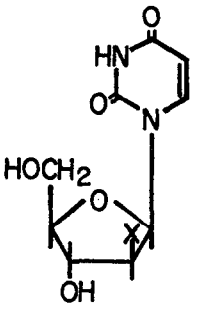
Benzoylation of 1,2-O-isopropylidene-3-azido-3-deoxy-α-D-glucofuranose[15] with 1.05 molar equivalent of benzoyl chloride gave a high yield (>90%) of 1,2-O-isopropylidene-6-O-benzoyl-3-azido-3-deoxy-α-D-glucofuranose (1). A sample of 1 was purified on silica gel ($CHCl_3$-ether; 3:1), NMR ($CDCl_3$, TMS internal standard) δ 7.36-8.18 (2m, 5, aromatic), 5.93 (d, 1, $J_{1,2}$ = 3.5 Hz, H-1), 4.67 (d, 1, $J_{1,2}$ = 3.5 Hz, H-2), 4.25 - 4.80 (m, 5, H-3,4,5,6), 1.50, 1.33 (2s, 6, $2CH_3$). Crude 1 which contained a small amount of 5,6-di-O-benzoate and a trace of 5-O-benzoate derivatives was hydrolyzed in dioxane-water (1:1) with Dowex 50 [H^+] ion exchange resin to give 6-O-benzoyl-3-azido-3-deoxy-D-glucofuranose (2). Compound 2 which gives a poorly resolved NMR spectrum was oxidized with sodium metaperiodate at 22-25° in water-dioxane containing $NaHCO_3$ overnight to give 5-O-benzoyl-2-azido-2-deoxy-D-arabinofuranose (3) which was purified by silica gel chromatography (CH_2Cl_2-ether; 3:1), NMR ($CDCl_3$-CD_3OD) δ 7.40 - 8.20 (2m, aromatic), 5.98(d, $J_{1,2}$ = 5 Hz) 5.89(s), anomeric protons.

Compound 3 was acetylated with pyridine-acetic anhydride to give an anomeric mixture (α:β ≃ 4:1, determined by NMR spectroscopy) of 1,3-di-O-acetyl-5-O-benzoyl-2-azido-2-deoxyarabinofuranose (4). For the α-anomer of 4 NMR ($CDCl_3$) δ 7.42 -8.36 (2m, 5 aromatic), 6.20 (s,1, H-1), 5.14 (dd, 1, $J_{2,3}$ = 1.5 Hz, $J_{3,4}$ = 2.0 Hz, H-3), 4.20 (d,1,$J_{2,3}$ = 1.5 Hz, H-2); for the β-anomer of 4 δ 7.42 - 8.36 (2m, 5, aromatic), 6.39 (d,1,$J_{1,2}$ = 4.5 Hz, H-1), 5.56 (dd,1,$J_{2,3}$ = 8.0 Hz, $J_{4,3}$ = 6.0 Hz, H-3), 4.09 (dd,1,$J_{1,2}$ = 4.5 Hz, $J_{2,3}$ = 8.0 Hz, H-2).

Starting from 109 g of 1,2-O-isopropylidene-3-azido-3-deoxy-α-D-glucofuranose, 86.4 g of 4 a (53.3% yield) was obtained. Compound 4 was converted to a mixture of 1-chloro derivatives 5 and 6 (5:6 ≃ 4:1) by treatment with $TiCl_4$ at 0-4° for 3 hr. Compounds 5 and 6 can be separated by silical gel chromatography (toluene-ethyl acetate, 8:1) . 5, NMR ($CDCl_3$), δ 7.32 - 8.20 (2m, 5H, aromatic), 6.13 (s,1,H-1), 5.10(d,1,J=4.5 Hz, H-3), 2.16 (s, 3H, Ac); 6 NMR ($CDCl_3$) δ 7.32 - 8.20 (2m, 5, aromatic), 6.25 (d,1,$J_{1,2}$ = 4.5 Hz, H-1), 5.65 (dd,1,$J_{2,3}$ = 8.5, $J_{3,4}$ = 6.0 Hz, H-3), 4.31 (dd,1,$J_{1,2}$ = 4.5 Hz, $J_{2,3}$ = 8.5 Hz, H-2), 2.13 (s, 3H, Ac).

Condensation of the anomeric mixture of 5-O-benzoyl-3-O-acetyl-2-azido-2-deoxy-D-arabinofuranosyl chlorides (5,6) with silylated uracil furnished a mixture of blocked α and β-anomers of 1-(2-azido-2-deoxy-D-arabinofuranosyluracil) in 11% and 35% yields, respectively. The anomers were separated by chromatography on silica gel ($CHCl_3$-ether, 2:1) and the protecting groups were removed by treatment with K_2CO_3 in methanol. The anomers were identified by NMR[16,17,18] and CD spectra. For the α-nucleoside H-1' appeared as a doublet ($J_{1',2'}$ = 7.0 Hz) at δ 6.15, whereas H-1' of the β-nucleoside also resonated as a doublet ($J_{1',2'}$ = 6.5 Hz) but a lower

field (δ 6.17). These anomeric assignments were supported by a positive Cotton effect for the β-anomer and a negative one for the α-anomer which is in agreement with the empirically determined rule.[19] α-Anomer UV (H_2O) λ_{max} 261 nm, NMR (DMSO-d_6) δ 7.51 (d,1,$J_{5,6}$=7.3 Hz, H-6), 6.15(d,1,$J_{1',2'}$=7 Hz, H-1'), 5.91(d,1,$J_{3',OH}$=5 Hz, 3'-OH), 5.65 (d,1,$J_{5,6}$=7.3 Hz, H-5), 4.94 (t,1,$J_{1',2'}$=7 Hz, H-2'), 4.76(t,1, $J_{5',OH}$=5.5 Hz, 5'-OH; β-anomer (7), UV (H_2O) λ_{max} 262 nm, NMR (DMSO-d_6) δ 7.87 (d,1,$J_{5,6}$= 8.3 Hz, H-6), 6.17 (d,1,$J_{1',2'}$= 6.5 Hz, H-1'), 6.01 (d,1,$J_{3',OH}$= 5.3 Hz, 3'-OH), 5.66 (d,1,$J_{5,6}$ = 8.3 Hz, H-5), 5.22(t,1,$J_{5',OH}$= 5 Hz, 5'-OH), 4.47(t,1,$J_{1',2'}$= $J_{2',3'}$ = 6.5 Hz, H-2'), 4.05(m,1,$J_{3',OH}$= 5.3, $J_{2',3'}$= 6.5, $J_{3',4'}$= 6.8 Hz, H-3'), ir 2120 cm^{-1} (N_3). Reduction of 7 furnished 1-(2-amino-2-deoxy-β-D-arabinofuranosyl)uracil (8).



7 x=N_3

8 x=NH_2

Compounds 1, 2, 3, 4 and 7 gave acceptable elemental analysis for carbon, hydrogen, and nitrogen. The chloro derivatives 5 and 6 were also used to synthesize 1-(2-azido-2-deoxy-β-D-arabinofuranosyl cytosine[20] and 1-(2-amino-2-deoxy-β-D-arabinofuranosyl cytosine[20], which showed significant antitumor activity *in vitro* and *in vivo*[21], and 2'-azido- and 2'-amino-β-D-arabinofuranosyl purine nucleosides.[22] While the 1-O-acetyl derivatives 4 can also be used for the synthesis of β-D-arabinofuranosyl nucleosides, the anomeric ratio depends strongly on the reaction conditions and the results of this work as well as the biological properties of these compounds will be reported later. At the time the synthesis of the 2'-azido- and 2'-amino-2'-deoxy-β-D-arabinofuranosyl nucleosides was completed, preparation of a sugar intermediate, methyl-2-azido-2-deoxy-β-D-arabinofuranoside, which can also lead to the synthesis of 2'-azido-2'-deoxyarabinofuranosyl nucleosides was reported.[23,24]

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