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SYNTHESIS OF A BRANCHED CHAIN AMINOSUGAR NUCLEOSIDE[a]

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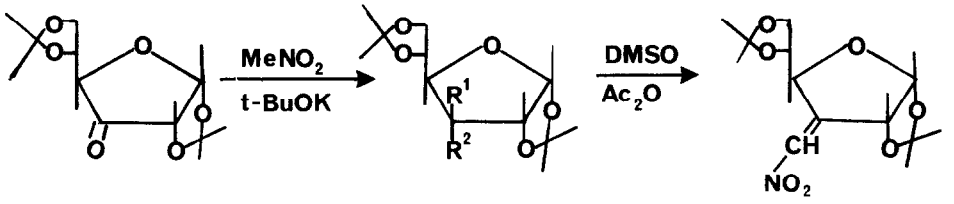
As part of a general program on the chemistry of nucleosides containing branched chain sugars,[1] we have developed a synthesis of such compounds containing nitromethyl and aminomethyl groups. Recent brief reports on the preparation of some related nitromethyl[2] and cyanomethyl[3] sugars have appeared but the corresponding nucleosides have not been described.

Condensation of 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose (I) with an excess of nitromethane and 0.1 molar equivalents of potassium t-butoxide in DMF at 20° gave crystalline IIa (mp 109-110°; $[\alpha]_D^{22}$ + 23.3°, c 1.1, $CHCl_3$)[b] in 85% yield. Treatment of IIa with dimethyl sulfoxide and acetic anhydride at 20° for 24 hours led to complete conversion to 3-dehydro-3-deoxy-1,2:5,6-di-O-isopropylidene-3-nitromethylene-α-D-ribo-hexofuranose (III, bp 140°/0.05mm; $[\alpha]_D^{22}$ + 173°, c 0.2, $CHCl_3$) with a preponderance of one geometrical isomer. Base catalysed hydration of III selectively gave the gluco epimer of IIa (IIb, mp 140-141°, $[\alpha]_D^{22}$ + 22.8°, c 1.10, $CHCl_3$). The configuration at C_3 of both IIa and IIb is consistent with the known steric control exerted by 1,2-O-isopropylidene functions[4] and is reflected in their ord spectra, IIa giving a negative Cotton effect and IIb an equal and opposite positive Cotton effect.[5] Condensation of I with nitromethane in the presence of excess butoxide led to a mixture of IIa and IIb presumably via dehydration of the initially formed IIa to III followed by readdition of water as above.

Reduction of III with sodium borohydride in ethanol was stereospecific and gave crystalline 3-deoxy-1,2:5,6-di-O-isopropylidene-3-nitromethyl-α-D-allofuranose (IV) in 88% yield (mp 82-83°; $[\alpha]_D^{22}$ + 88.1°, c 0.19, $CHCl_3$). The configuration of IV was confirmed by reduction with Raney nickel to the aminomethyl compound (acetate salt mp 119-

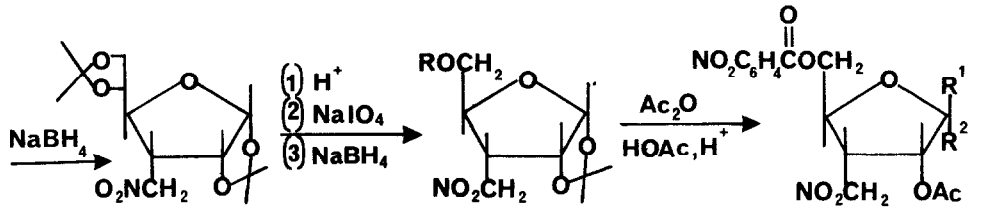
(a) Contribution No. 68 from the Institute of Molecular Biology.

(b) All compounds gave satisfactory elemental analyses and 100 MHz nmr spectra.



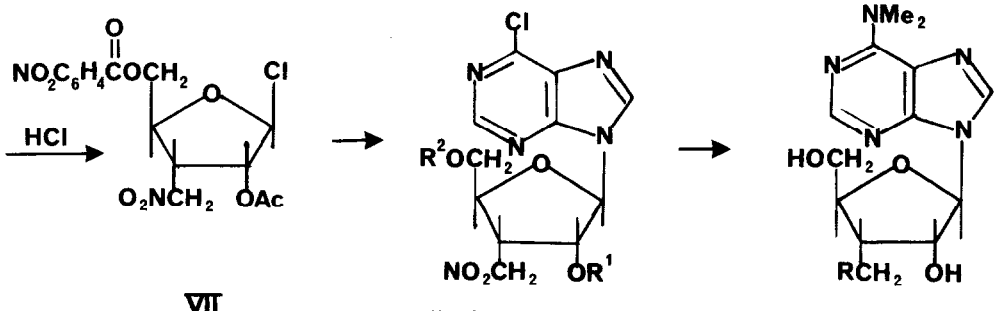
I II (a) $R^1=CH_2NO_2, R^2=OH$ III

(b) $R^1=OH, R^2=CH_2NO_2$



IV V (a) R=H VI (a) R^1 = OAc, R^2 = H

(b) R=pNO2benzoyl (b) R^2 = OAc, R^1 = H



VII VIII (a) R^1 = acetyl IX (a) R = NO_2

R^2 = p-NO_2benzoyl (b) R = NH_2

(b) $R^1 = R^2 = H$

121°; $[\alpha]_D^{22}$ + 50.5°, c 0.17, methanol), the nmr spectrum of which showed C_3H as a triplet ($J_{1,2} = J_{2,3} = 4$Hz) at 4.79 ppm consistent with an all cis arrangement of C_1H, C_2H and C_3H.

Treatment of IV with 0.1% hydrochloric acid in aqueous methanol selectively removed the 5,6-acetonide giving 79% of 3-deoxy-1,2-O-isopropylidene-3-nitromethyl-α-D-allofuranose with mp 57-58.5°; $[\alpha]_D^{22}$ + 106.5° (c 0.23, methanol); nmr ($CDCl_3$) 5.83 ppm (d,1,$J_{1,2}$ = 4Hz,C_1H). Oxidation of the diol with sodium periodate in aqueous methanol followed by reduction of the resulting aldehyde with sodium borohydride gave crystalline 3-deoxy-1,2-O-isopropylidene-3-nitromethyl-α-D-ribofuranose (Va) with mp 67-69°; $[\alpha]_D^{22}$ + 87.7° (c 0.16, $CHCl_3$) in 84% yield. The latter was converted into its 5-O-p-nitrobenzoyl derivative (Vb, 81%), with mp 80-82°; $[\alpha]_D^{22}$ + 56.7° (c 0.15, $CHCl_3$) and then treated with acetic anhydride-acetic acid (1:1) containing 2% concentrated sulfuric acid giving 73% of crystalline 1,2-di-O-acetyl-3-deoxy-5-O-p-nitrobenzoyl-3-nitromethyl-β-D-ribofuranose (VIa), with mp 128-129°; $[\alpha]_D^{22}$ + 2.7° (c 0.27, $CHCl_3$); nmr ($CDCl_3$) 6.17 ppm (s,1,C_1H), and 12% of the α-epimer (VIb) as a syrup; $[\alpha]_D^{22}$ + 37.4° (c 0.34, $CHCl_3$); nmr ($CDCl_3$) 6.45 ppm (d,1,$J_{1,2}$ = 4Hz,C_1H) which were separated by chromatography on silicic acid. Reaction of VIa with ether saturated with hydrogen chloride at 0° for three days gave 78% of 2-O-acetyl-3-deoxy-5-O-p-nitrobenzoyl-3-nitromethyl-β-D-ribofuranosyl chloride (VII) with mp 100-101°; $[\alpha]_D^{22}$ - 13.5° (c 0.1, methylene chloride); nmr ($CDCl_3$) 6.09 ppm (s,1,C_1H).

Condensation of VII with the chloromercuri salt of 6-chloropurine in toluene under reflux for 2 hours gave 33% of 6-chloro-9(2-O-acetyl-3-deoxy-5-O-p-nitrobenzoyl-3-nitromethyl-β-D-ribofuranosyl)-purine (VIIIa) as a homogeneous foam isolated by preparative thin layer chromatography; nmr ($CDCl_3$) 6.04 ppm (d,1,$J_{1',2'}$ = 1.5 Hz,$C_{1'}H$). More conveniently, VIIIa could be prepared in 41% yield by fusion of VIa with 6-chloropurine at 160° for 30 minutes under vacuum without addition of any acid. Treatment of VIIIa with concentrated ammonium hydroxide at 20° for

2 hours cleaved both ester groups giving 61% of the 6-chloropurine nucleoside (VIIIb) with mp 165-167° (d); λ_{max}^{MeOH} 265mμ (ε9,200); $[\alpha]_D^{22}$ - 23.3° (c 0.14, dimethylformamide); ord (MeOH) negative Cotton effect; nmr (d_6DMSO) 6.17 ppm (d,1, $J_{1',2'}$=1.5Hz,C_1,H). With aqueous dimethylamine at 20° for one hour, however, VIIIa gave 59% of crystalline 6-dimethylamino-9-(3-deoxy-3-nitromethyl-β-D-ribofuranosyl)-purine (IXa) with mp 230-231°; λ_{max}^{MeOH} 275mμ (ε16,500), 213mμ (ε15,400): $[\alpha]_D^{22}$ - 56° (c 0.1 DMF); nmr (d_6DMSO) 6.03 ppm (d,1,$J_{1',2'}$=2.5Hz,C_1,H). Hydrogenation of IXa in aqueous methanol containing acetic acid and using a palladium on carbon catalyst gave a 72% yield of 6-dimethylamino-9-(3-aminomethyl-3-deoxy-β-D-ribofuranosyl)-purine (IXb) with mp 204-205°; $\lambda_{max}^{H_2O}$ 275mμ (ε16,300), 213mμ (ε14,400); $[\alpha]_D^{22}$-52.5° (c 0.12, DMF); nmr (d_6DMSO) 5.97 ppm (d,1,$J_{1',2'}$=2Hz,C_1,H).

The relationship between IXb and the aminonucleoside of puromycin is obvious and we will shortly describe both the aminoacylation of the branched chain nucleoside and the preparation of base analogs of IX.

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