THE SYNTHESIS OF A VARIETY OF AMINODEOXY-α-D-GLYCOPYRANOSIDES BY WAY OF A NOVEL REPLACEMENT REACTION

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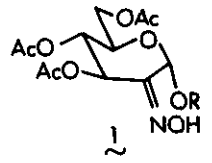
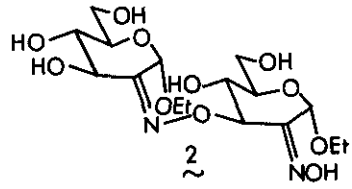
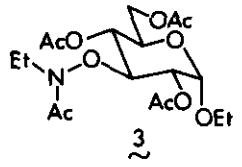
Abstract — Ethyl 3,4,6-tri-O-acetyl-2-deoxy-2-oximino-α-D-arabino-hexopyranoside was found to undergo replacement of the 3-acetoxy group when reacted with nucleophilic reagents such as sodium azide, potassium phthalimide, sodium borohydride and sodium thiophenoxide. The resulting products could be transformed, depending on the reaction sequence, to 3-deoxy,3,4-dideoxy, 3-amino-3-deoxy,2-amino-2,3-dideoxy, 2,3-diamino-2,3-dideoxy, or 2-amino-2,3,4-trideoxy derivatives of an ethyl α-D-glycopyranoside.

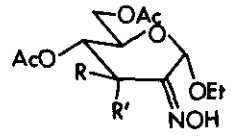
The first aminoglycoside-type antibiotics which were found to contain a 3-amino-3-deoxyaldose as a building unit were the kanamycins A, B and C reported in 1957 by Hamao Umezawa and his collaborators.[1] The structural unit proved to be the 3-amino-3-deoxy-α-D-glucopyranosyl group[2] and this group was found to be present in several other antibiotics.[3] It is therefore particularly gratifying to report a new approach to the synthesis of α-glycopyranosides of both this aminosugar and related structures to this commemorative issue.

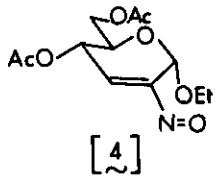
The reaction of the nitrosyl chloride adduct of acetylated glycals with an alcohol provides an effective way to establish an α-glycosidic linkage.[4] Thus, starting with 3,4,6-tri-O-acetyl-1,5-anhydro-D-arabino-hex-1-enitol (D-glucal triacetate), 3,4,6-tri-O-acetyl-2-deoxy-2-oximino-α-D-arabino-hexopyranosides (1) are obtained in good to excellent yield. In an attempt to de-O-acetylate 1 (R = ethyl) in aqueous methanol and using triethylamine as catalyst, it was discovered that the dimeric structure 2 was the major product (49% yield) of the reaction. The expected product (deacetylated 1) was formed in 30% yield and the remainder appeared to be mainly the trimeric structure of the type represented by 2. The structure of 2 [mp 146-150°, $[\alpha]_D$ + 138° (ethanol)] which could be anticipated by nmr and mass spectra was confirmed by deoximation with acetaldehyde in acid medium followed by borohydride reduction and acetylation to form a product characterized as compound 3











R' = H

5, R = B

7, R = N_3

9, R = NHAc (H = Ac)

13, R = Phthalimido

14, R = H

18, R = SC_6H_5

R = H

6, R' = B

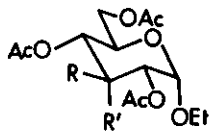
8, R' = N_3

10, R' = NHAc (H = Ac)

19, R' = SC_6H_5

(nmr) along with ethyl tetra-O-acetyl-α-D-glucopyranoside. It thus became apparent that the 3-acetoxy group of 1 is susceptible to elimination to form the nitroso-alkene reactive intermediate (4) which, subsequently, accepts a nucleophile (B) from the environment at the 3-position to produce 2-oximino-α-glycosides of types 5 and 6. We wish to communicate the results obtained using azide, phthalimide, thio-phenoxide and borohydride as nucleophilic reagents and some of the transformations of the products which were thus obtained.

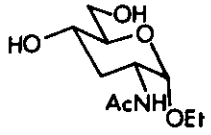
Formation of the nitrosoalkene (4) as the reactive intermediate proved rather sensitive to the experimental conditions used. Thus, treatment of 1 (R = ethyl or t-butyl) with sodium azide in ordinary commercial dimethylformamide (DMF) at either room temperature (30 h) or 65° (3 h) gave ethyl 4,6-di-O-acetyl-3-azido-2,3-dideoxy-2-oximino-α-D-arabino-hexopyranoside (7), mp 88-90°, $[\alpha]_D$ 55° ($CHCl_3$), and the ribo-epimer (8), mp 73-75°, $[\alpha]_D$ 123° ($CHCl_3$), in near equimolar amounts in 80% yield. However, when highly purified DMF was used, little reaction occurred after 12 h at 65°. On making the solution 1% in water, the reaction to yield 7 and 8 occurred at about the same rate as found to occur in the commercial DMF. Reaction was complete after 2 h at 65° in pure DMF when 18-Crown-6 [5] was present in the amount equivalent to the sodium azide (4 moles/mole of 1). It is apparent, therefore, that the role of the water is to assist in the separation of the sodium and azide ions and thereby assist both the elimination and the subsequent addition reactions. Treatment of either 7 or 8 with sodium azide in the wet DMF led to equilibration



11, R = NHAc, R' = H

12, R = H, R' = NHAc

15, R = R' = H (Ac = H)



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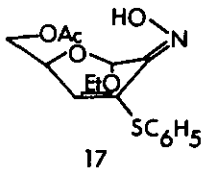

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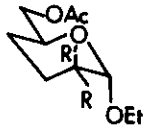

20, R = NHAc, R' = H

21, R = H, R' = NHAc

22, R = OAc, R' = H

of the two compounds.

Treatment of 7 (1 mmol) in 6 mL of 0.2 N hydrochloric acid with acetaldehyde (3 mmol) for 3.5 h at room temperature, then cooling to 0° and adding, in portions, 5 mmol of sodium borohydride[6] provided on work-up a substance which was hydrogenated in methanol in the presence of palladium on charcoal. Acetylation of the product led to the isolation of 3-acetamido-2,4,6-tri-O-acetyl-3-deoxy-α-D-glucopyranoside (11), mp 132-134°, $[\alpha]_D$ +94° ($CHCl_3$), in 63% yield. The similar treatment of 8 provided the allo compound 12, mp 120-121°, $[\alpha]_D$ + 85° ($CHCl_3$), in 61% yield.

The azido groups of the oximes (7 and 8) could be preferentially hydrogenated in the presence of the palladium catalyst. Acetylation of the products provided compounds 9 [mp 185°, $[\alpha]_D$ + 90° ($CHCl_3$)] and 10 [mp 139-140°, $[\alpha]_D$ + 76° ($CHCl_3$)]. It is expected that borane reduction of either the oximes 7 and 8 or the oximes 9 and 10 would produce 2,3-diamino-2,3-dideoxy glycosides but this matter has not yet been examined.

It was anticipated that reaction of 1 (R = ethyl) with potassium phthalimide would lead to the exclusive formation of the equatorially-oriented substituent, i.e. the arabino isomer (13). This was indeed the case but the yield was only 35% [mp 157-158°, $[\alpha]_D$ 171° ($CHCl_3$)]. However, the reaction was not studied except in a very preliminary manner. The dimer 2 was an important by-product (20% yield).

When 1 (R = ethyl) was treated with sodium borohydride in DMF at room temperature, ethyl 4,6-di-O-acetyl-2,3-dideoxy-2-oximino-α-D-erythro-hexopyranoside

(14) was obtained in 70% yield as a 1:2 mixture of the Z and E isomers. The product was deoximated and the resulting uloside was reduced with sodium borohydride to produce, after deacetylation, ethyl 3-deoxy-α-D-ribo-hexopyranoside (15), mp 92-93°, $[\alpha]_D$ 145° (CH_3OH), in 85% yield. Reduction of 14 with borane[7] and N-acetylation of the product afforded ethyl 2-acetamido-2,3-dideoxy-α-D-ribo-hexapyranoside (16), mp 186-188°, $[\alpha]_D$ 140° (CH_3OH), in 80% yield.

When sodium thiophenoxide in DMF was used as the nucleophilic reagent, reaction of 1 (R = ethyl) was complete in 1.5 h at 70°. The unsaturated oxime (17) was the main product (38%, oil). The expected products 18 [mp 80-84°, $[\alpha]_D$ 64° ($CHCl_3$)] and 19 [mp 96-97°, $[\alpha]_D$ 164° ($CHCl_3$)] were isolated in 27 and 6% yields, respectively. Reductive desulfurization of 18 using Raney nickel and in the presence of hydrazine in methanol led to a product which was acetylated. Chromatography led to the isolation of ethyl 2-acetamido-6-O-acetyl-2,3,4-trideoxy-α-D-erythro-hexopyranoside (20) [mp 58-61°, $[\alpha]_D$ 112° ($CHCl_3$)] in 77% yield. The threo-isomer (21) was obtained as an oil in 15% yield. It thus became apparent that H-3 of 18 is sufficiently acidic to render facile the elimination of the 4-acetoxy group to form the unsaturated oxime 17. Indeed, 20 and 21 were also the products of the reductive desulfurization of 17 *in the presence of hydrazine.*

Deoximation of 18 and borohydride reduction of the product, as outlined above for the preparation of 11, gave a product which was subjected to a reductive desulfurization in the presence of hydrazine. The material was acetylated and separated into 3 fractions by chromatography. The major fraction, isolated as an oil, appeared (^{1}Hmr) definitely to be ethyl 2,6-di-O-acetyl-3,4-dideoxy-α-D-erythro-hexopyranoside (22).

The composition of the above-described compounds were all, within experimental error, in agreement with the structures proposed. Also, the ^{1}H- and ^{13}Cmr spectra were in accord with expectation. The specific rotations were measured at room temperature.

In view of the above-described observations, it is apparent that the replacement of the 3-acetoxy group of an acetylated 2-deoxy-2-oximino-α-D-glycopyranoside followed by appropriate transformation of the product can lead to a wide range of *structures of interest to the field* of aminoglycoside-type antibiotics.[3] As was mentioned above, the 3-amino-3-deoxy-α-D-glucopyranosyl group is of widespread occurrence. Antibiotics such as kasugamycin, sisomycin, tobramycin and lividomycin contain a 2-amino-2,3-dideoxy-α-glycopyranosyl group.[3] A 2,3-diamino-2,3-dideoxy-

α-glycopyranosyl group occurs in the antibiotic seldomycin factor 5.[8] A 2-amino-2,3,4-trideoxy-α-glycopyranosyl group is present in the gentamicin C antibiotics.[3] In principle, the above-described reaction pathways allow the synthesis of each of these kinds of glycosyl units. However, it must be expected that elimination of the aglycon competes with elimination of the 3-acetoxy group and may become the dominant route of reaction in the case of complex, electronegative aglycons. Nevertheless, the transformations reported herein definitely establish facile synthetic routes to a wide variety of important deoxyaminosugars.

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