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THE SYNTHESIS OF ALKYL-α-D-GLUCOPYRANOSAMINIDES FROM TRI-O-ACETYL-D-GLUCAL

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The presence of α-glucopyranosaminide residues in antibiotics such as streptomycin, paromomycin (1), trehalosamine (2) and in teichoic acids (3) has focused interest in improved methods for establishing the α-linkage between glucosamine and the hydroxyl group of the substance desired as aglycone. Of the various methods used, alcoholysis of the N-acetyl-glucosamine in the presence of acids proceeds in best yield (4). However, the method is inherently limited to alcohols used as solvent. For more complex alcohols, the syntheses based on Koenigs-Knorr type reactions have provided low yields of the α-D-glucopyranosaminyl derivatives of ribitol (3), glycerol (5), galactose (6) and deoxystreptamine (7). The purpose of this communication is to report recent results in our study of the preparation of glycosaminides by way of the nitrosyl chloride adducts of acetylated glycals (acetylated-1,2-dideoxyglyc-1-enepyranoses) (8,9). To date, our experience is limited to lower alcohols. Nevertheless, the success encountered shows considerable promise for general application of this new approach.

TABLE I

Physical Constants for Alkyl 3,4,6-Tri-O-acetyl-
2-oximino-α-D-arabino-hexopyranosides

Aglycon	m.p.	$[\alpha]_D^{25}$ (in chloroform)	N.M.R. Parameters Chemical Shifts τ-values H_1	H_3	H_4	Spacings c.p.s. $J_{3,4}$
Ethyl	147-149°	+72°	3.95	4.14	4.78	9.5
n-Propyl	73-75°	+74°	3.97	4.15	4.81	9.5
Isopropyl	85-87°	+79°	3.86	4.13	4.81	9.5

Reaction of equimolar amounts of the alcohol (ethanol, n-propanol and isopropanol) and 3,4,6-tri-O-acetyl-2-deoxy-2-nitroso-α-D-glucopyranosyl chloride (I) in refluxing dry methylene chloride for three hours gave quantitative yields of crude products which possessed n.m.r. spectra virtually identical to those of the pure products obtained by crystallization from dry isopropanol in yields better than 80%. The optical rotations and n.m.r. parameters reported in Table I require the compounds to be configurationally related. The assignments of the α-D-anomeric configuration is based on the formation of α-D-glucosides on catalytic reduction of the oximes to amines. The singlet and doublet characters of the signals for H_1 and H_3, respectively, together with the appearance of a signal at 0.28-0.75τ attributable to an oxime-hydroxyl group clearly indicated the oxime structure (Table I). The latter signal disappeared on exchange with deuterium oxide. The infrared absorption spectra were also in accord with this structure. The reaction of I with alcohols most likely proceeds by way of the tri-O-acetyl-2-nitroso-D-glucal (8,9).

The acetylated 2-oximinoglycosides (II) proved highly resistant to both chemical and catalytic reduction (9). However, the products obtained on deacetylation (III) were readily hydrogenated at 60 p.s.i. in N hydrochloric acid (equivalent amount) using 5% palladium-on-charcoal (60% of the weight of III) as catalyst. The product with the α-D-gluco configuration was formed in preference to the α-D-manno isomer in each case. The yield of isopropyl α-D-glucopyranosaminide hydrochloride, m.p. 209-211° (decomp.), $[\alpha]_D^{25}$ + 156° (c, 1 in water) was near quantitative as judged from the n.m.r. spectrum of the crude product. In the case of the ethyl and the n-propyl compounds the product with the α-D-gluco configuration again predominated. The N-acetyl derivatives of the ethyl and n-propyl α-D-glucopyranosaminides crystallized readily and possessed the expected melting points and rotations (10). The structures assigned are required by the n.m.r. spectra and hydrolysis in each case to D-glucosamine hydrochloride.

Reaction of I with a mole equivalent of pyridine in a misture of 1:1 tetrahydrofuran-benzene led to a rapid reaction with the precipitation of a crystalline N-(3,4,6-tri-O-acetyl-2-oximino-D-*arabino*-hexopyranosyl)-pyridinium chloride (IV), m.p. 82-84°, $[\alpha]_D^{23}$ + 54° (*c*, 0.5 in water). Compound IV was stable in methanol and therefore was not an intermediate in the following reactions. Reaction of I with molar equivalents of alcohols in the presence of two-molar equivalents of dry pyridine in tetrahydrofuran gave alkyl tri-O-acetyl-2-oximino-α-D-*arabino*-hexopyranosides identical to those mentioned above. Using tri-O-acetyl-2-deoxy-2-nitroso-α-D-galactopyranosyl chloride (8,9) instead of I, the methyl, *n*-propyl, and isopropyl tri-O-acetyl-2-oximino-D-*lyxo*-hexopyranosides were obtained. The rotations and n.m.r. spectra of these compounds inferred the α-D-*lyxo*-configuration. The syrupy product obtained in the reaction with methanol on deacetylation gave crystalline methyl-2-oximino-α-D-*lyxo*-hexopyranoside, m.p. 158-160° $[\alpha]_D^{23}$ + 118° (*c*, 0.8 in water).

The possibility for the application of these new methods for the synthesis of a number of natural products and their analogs is being investigated.

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