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A NEW APPROACH TO THE SYNTHESIS OF 2-AMINO-2-DEOXYGLYCOSIDES

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The recent publication by Serfontein, Jordaan and White (1) on the nitrosyl chloride addition products of glycals prompts us to report at this time the results of our own investigations along similar lines.

Addition of nitrosyl chloride to 3,4,6-tri-O-acetyl-D-glucal, in either methylene chloride or ether at -80°C, provided in near quantitative yields the compound (I) reported by Serfontein *et al* as 3,4,6-tri-O-acetyl-2-nitroso-2-deoxy-α-D-glucopyranosyl chloride. After three recrystallizations from ether, the compound melted at 129-130° to a blue-green liquid. The specific rotation was +149° (c,2.2 in chloroform). Under similar conditions, the corresponding derivatives (II and III) were prepared from tri-O-acetyl-D-galactal and di-O-acetyl-D-xylal, respectively. The physical constants for these compounds were m.p. 128-131° (blue-green melt), $[\alpha]_D^{23}$+128° (c,2.2 in chloroform) and m.p. 102-106° (blue-green melt), $[\alpha]_D^{23}$+164° (c,3.1 in chloroform), respectively. The proton magnetic resonance (NMR) spectra for the compounds showed the presence of

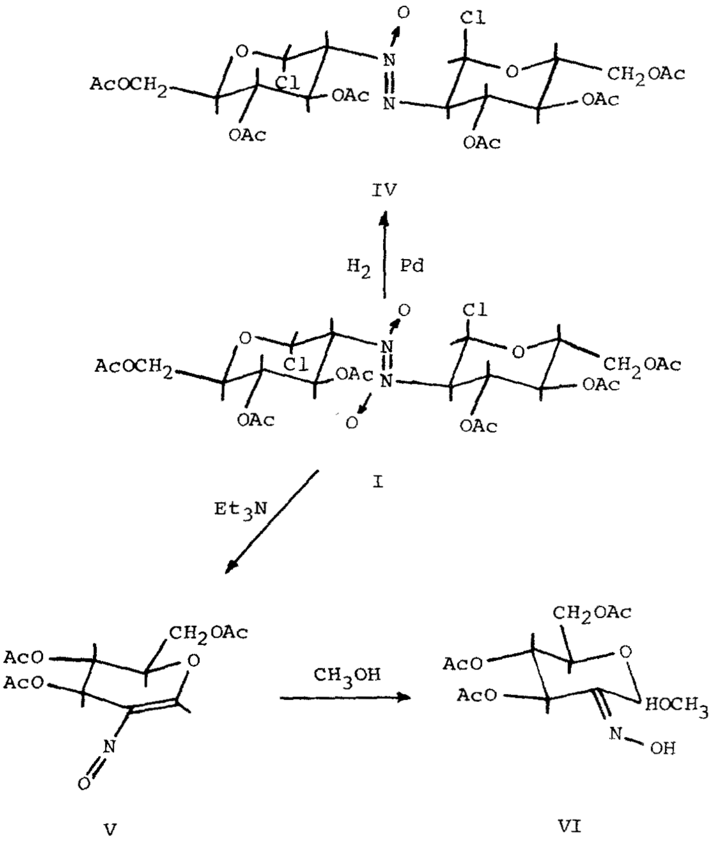
TABLE I

NMR Parameters for Dimeric Acetylated 2-Deoxy-2-nitrosoaldopyranosyl Chlorides

	Chemical Shifts, τ-Values			Spacings, c.p.s.		
	H_1	H_2	H_3	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$
α-D-*gluco* (I)	3.33	4.54	3.95	3.5	9.0	9.5
α-D-*galacto* (II)	3.31	4.47	4.08	3.7	11.1	3.6
α-D-*xylo* (III)	3.39	4.62	3.98	3.8	11.0	9.8

a proton at the 2-position and the spacings of the signals for the 1- and 2-protons required the compounds to possess the α-D-*gluco*, α-D-*galacto*, and α-D-*xylo* configurations (see Table I), in agreement with the *cis*-addition observed in the reactions of nitrosyl chloride with the acetates of D-glucal and D-arabinal (1). It should be noted, however, that the α-anomer has the more stable configuration for glycosyl halides and the β to α anomerization is often very facile for these compounds (2). However, since the adducts formed rapidly at -80° and, in the case of the addition to D-glucal triacetate using ether as solvent, the product crystallized directly and rapidly from the reaction mixture, it seems improbable that β to α anomerization occurred. Also, the anomerization seems unlikely in view of the relatively low reactivity of the chlorine in these glycosyl chlorides. Therefore, *cis*-addition by way of the four-centered polar transition state suggested by Meinwald (3) [rather than the radical mechanism suggested by Serfontein *et al* (1)], seems to be operating in these reactions. In this connection, it was observed that the product from the addition of nitrosyl chloride to norbornene, under the above reaction conditions, produced signals at 5.09τ and 5.62τ. Both of the signals appeared as quartets with spacings of 7.2 c.p.s. and about 2 c.p.s. The larger spacing must arise from coupling of the protons at the carbons bonded to the nitroso and chlorine groups and requires (4) these protons to be in cis-relationship as concluded by Meinwald (3). It should be noted, however, that the addition of chlorine in carbon tetrachloride to both D-glucal triacetate and D-galactal triacetate leads directly to the 1,2-cis-tri-O-acetyl-2-chloro-2-deoxy-α-D-glycopyranosyl chlorides (5) and, therefore, the cis-addition to acetylated glycals may be a special property of these acetylated cyclic vinyl ethers.

The colorless needles of the nitrosyl chloride adducts give only faintly-blue colored solutions when dissolved in solvents like benzene, chloroform, ethanol or acetic acid, even at high concentrations. The intensity of the solutions increased only slightly on warming. However, a freshly prepared solution of I in methylene chloride possesses a deep blue color with maximum absorption at 662 mμ. It is therefore apparent that I is obtained as a colorless dimer and that the point of equilibrium in solution strongly favors the dimeric state. This contention was confirmed by osmometric molecular weight determinations. The expected molecular weights for the D-glucal and D-galactal derivatives as dimers are 675.5. The values found were 600 and 674, respectively. Also, catalytic hydrogenations of I in methanol using 5% palladium on charcoal led to a rapid uptake of one mole of hydrogen per mole of I (as a dimer) to yield (60%) the azoxy compound (IV), m.p. 201-202° (with



decomposition to a brown melt), $[\alpha]_D^{23}$+204° (c,1.8 in chloroform), calculated molecular weight, 658, found 654. The NMR spectrum of IV showed two signals for anomeric protons at 3.43τ and 3.47τ in the form of doublets each with a spacing of 3.5 c.p.s.

Our interest in these investigations was to develop new approaches to the preparation of glycosides of 2-amino-2-deoxy-sugars in order to attempt the synthesis of glycosides related to a number of aminosugar - containing antibiotics. The 2-deoxy-2-nitrosoglycosyl chlorides proved unpromising as reagents for this purpose. However, it was observed that treatment of the acetylated 2-deoxy-2-nitrosoglycosyl chlorides with triethylamine in benzene at 0° led to the rapid development of a deep blue coloration with the quantitative precipitation of triethylamine hydrochloride. The blue coloration disappeared almost instantaneously on the addition of water, acetic acid, alcohols, mercaptans, primary amines, and secondary amines. Starting from I, the addition of methanol to the product of dehydrochlorination, followed by evaporation, led to the isolation of a colorless sirup which was deacetylated in aqueous methanol using triethylamine. The solution was passed through a column of Amberlite IR-120, decolorized with charcoal and evaporated to a solid which was crystallized from n-butanol-ether. The compound decomposed above 160°, $[\alpha]_D^{23}$ +60° (c,2 in water). The NMR spectrum showed a singlet of intensity one at 4.13τ and an O-methyl signal at 6.5τ. The singlet must arise from the anomeric hydrogen and the lack of coupling together with the strongly positive ferric chloride test for oxime given by the compound indicated the oxime structure (VI) for this substance.

It was therefore apparent that acetylated 2-deoxy-2-nitrosoglucosyl chloride (I) is highly susceptible to the dehydrochlorination to produce 2-nitroso-D-glucal triacetate (V) and that V readily adds alcohols to form 2-oximinoglycosides (VI). Since reagents such as V would be of great synthetic utility for the preparation of 2-amino-2-deoxyglycosides, their preparation and reactions are under study.

Compound VI was also obtained by treating I in methanol with a molar equivalent of sodium methoxide. When I was dissolved in acetic anhydride and 1.25 mole of triethylamine added, triethylamine hydrochloride was precipitated. The product was a colorless amorphous solid which appeared virtually pure on paper chromatograms (6) and gave a NMR spectrum in excellent agreement with that expected for penta-O-acetyl-2-oximino-D-glucopyranose. The singlet for the 1-hydrogen was at 3.37τ and H_3 produced a doublet, J = 7.5 c.p.s., at 3.84τ. The signal for H_4 was a triplet at 4.45τ. In addition to absorption at 1750 $cm.^{-1}$ characteristic for C-acetoxy carbonyl, the infrared spectrum showed absorption at 1785 $cm.^{-1}$ for the N-acetoxy carbonyl and a weak C = N absorption at 1650 $cm.^{-1}$ (7). The substance was deacetylated in aqueous methanol using triethylamine and the product was hydrogenated in dilute hydrochloric acid with 5% palladium on charcoal at 50 p.s.i. Evaporation and trituration of the residue with ethanol gave a semicrystalline product which on paper chromatography using ethyl acetate-pyridine-water (8:2:1) showed ninhydrin positive spots with R_f values and colors identical to those obtained with D-glucosamine and D-mannosamine. The mannosamine appeared to be the main product.

The nitrosyl chloride-D-xylal diacetate addition compound (III) was highly labile as compared to I and II and, in efforts to bring about purification by recrystallization from methylene chloride-hexane, was converted in low yield to a colorless, chlorine-free, crystalline product (VII), m.p. 128-129°, $[\alpha]_D^{23}$ -319° (c.2.1 in chloroform). The NMR spectrum had a singlet of intensity one at 1.56τ, signals for H_3, H_4 and the two H_5's at 4.02, 4.88, 5.43 and 5.91τ, respectively, and signals for two acetoxy groups. The position of the low-field singlet for the anomeric proton together with infrared absorption at 1643 $cm.^{-1}$ suggest a 2-nitroso-D-xylal diacetate structure for this compound. However, the colorless compound had the approximate molecular weight for the monomeric state and the elemental composition was in much better agreement for a 2-nitro-D-xylal diacetate structure. Anal. Calcd. for $C_9H_{11}NO_7$: C, 44.08; H, 4.52; N, 5.71%. Found: C, 44.19; H, 4.54; N, 5.69%. Furthermore, the compound showed strong absorption at 1509 $cm.^{-1}$, an absorption in the region characteristic for α, β-unsaturated nitro groups (8). Thus, it is apparent that the nitroso group was oxidized either by atmospheric oxygen or through disproportionation. The compound VII was also obtained on reacting D-xylal diacetate with dinitrogen tetroxide at -80°. The NMR spectra of the sirupy products obtained on treating the triacetates of D-glucal and D-galactal with dinitrogen tetroxide were very similar to the spectrum for VII, except, of course, for the signals of the protons at the 5- and 6-positions.

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