Anhydridization of Carbohydrate C-Nitroheptitols[1]

JOHN C. SOWDEN,[2] CAROLINE H. BOWERS, AND KENNETH O. LLOYD

Department of Chemistry, Washington University, St. Louis, Missouri

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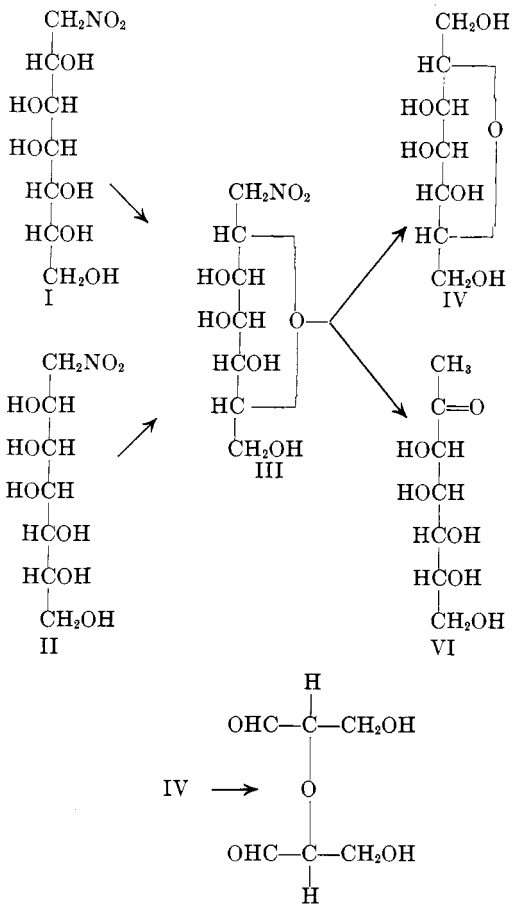
Heating aqueous solutions of 1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol or 1-deoxy-1-nitro-D-*glycero*-D-*talo*-heptitol results in the formation of 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol (III). The structure of III was established by periodate oxidation studies and conversion, by reduction to the amine followed by treatment with nitrous acid, to 2,6-anhydro-D-*glycero*-D-*galacto*-heptitol. The nitrosation reaction also gave 1-deoxy-D-*manno*-heptulose. Periodate oxidation of III gives a method for the determination of the structure of any 2,6-anhydro-1-deoxy-1-nitroheptitol. The method was applied to 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol obtained by the anhydridization of 1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol or 1-deoxy-1-nitro-D-*glycero*-L-*gluco*-heptitol.

The anhydridization of 1-deoxy-1-nitrohexitols has been studied by Sowden and Oftedahl.[3] They showed that epimeric pairs of nitrohexitols give the same 2,6-anhydro-1-deoxy-1-nitrohexitol and postulated a common intermediate, probably a nitroolefin, to account for this.

We have now extended the scope of the anhydridization reaction to include the 1-deoxy-1-nitroheptitols. Studies on the anhydridization of 1-deoxy-1-nitro-D-*glycero*-L-*manno*-hepitol recently have been reported by Hough and Shute.[4] They have shown that a 2,6-anhydro compound again is formed as the main product and have proven the configuration of the compound by application of Hudsons' isorotation rules. We have studied the anhydridization of the four 1-deoxy-1-nitroheptitols obtained by the application of the nitromethane synthesis[5] to D-mannose and D-galactose. The structure of the products was determined by periodate cleavage and, in one case, by deamination of the corresponding amine.

Following the procedure of Sowden and Oftedahl,[3] 1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol (I) and 1-deoxy-1-nitro-D-*glycero*-D-*talo*-heptitol (II), prepared from D-*mannose*, were refluxed in aqueous solution for 48 hr. In each case 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol (III) was obtained as the main product. A minor product of each reaction was D-mannose. It was identified by chromatography and the preparation of D-mannose phenylhydrazone from the anhydridization reaction of I. The formation of aldose is not unexpected and is explained by re-equilibration of the nitroalditol with nitromethane and aldose.[3]

The ring structure of the 2,6-anhydro product was proven by the observation that it rapidly consumed two moles of periodate with the concomitant formation of one mole of formic acid. The configuration of III was established by periodate oxidation studies on the 2,6-anhydroheptitol obtained from III by a procedure used by Sowden and Oftedahl to prove the configurations of the anhydronitrohexitols. Reduction of the 2,6-anhydronitroheptitol (III) to the amine (not isolated) and nitrosation of the latter gave a 2,6-anhydroheptitol which had to be either 2,6-anhydro-D-*glycero*-D-*galacto*-heptitol (IV) or 2,6-anhydro-D-*glycero*-D-*talo*-heptitol



(V). Another crystalline product, which will be discussed later, also was isolated from this reaction.

Periodate oxidation of the 2,6-anhydroheptitol gave an optically inactive dialdehyde. Of the two possible structures only IV will give a *meso* dialdehyde on oxidation. The dialdehyde from V is the same as the dialdehyde obtained by the periodate oxidation of 2,5-anhydro-D-mannitol and is known to have a $[\alpha]_D$ of $+33.5°$.[6] This positive value shows that the optically inactive solution formed by the oxidation of IV is not due to racemization of the product. Hence this reaction sequence unequivocally establishes the configuration about C-2 and shows that III is 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol.

Once the structure of this anhydro compound is known a simple method is available for the proof of the configuration about C-2 of any 2,6-anhydro-1-deoxy-1-nitro-D-heptitol. Periodate cleavage of III will result in a nitrodialdehyde which will have the structure VII.

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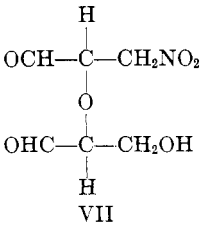
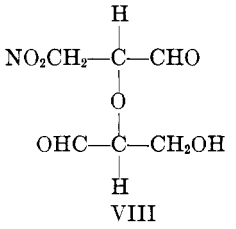


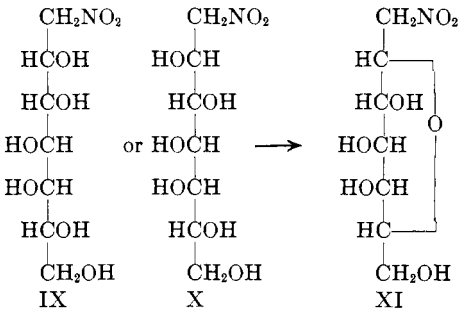
VII



VIII

The observed specific rotation of the dialdehyde formed from III (but not isolated) was $-17°$. After anhydridization of a nitro-D-heptitol only VII or VIII can be formed by periodate oxidation. Thus if the resulting dialdehyde has a rotation of $-17°$ then the configuration about C-2 is the same as in 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol. If it is not $-17°$ then the opposite configuration is indicated. The same argument can be applied to the nitro-L-heptitols except that the rotation will be $+17°$ in one case and in the other case will be opposite in sign to the rotation of VIII but, more importantly, it will not be $+17°$. Thus, knowing the structure of the original nitroheptitol the configuration of the 2,6-anhydro compound resulting from its anhydridization can be determined by a simple periodate cleavage.

The method was demonstrated by its application to the determination of the structure of the product obtained by the anhydridization of the two nitroheptitols formed by the condensation of nitromethane with D-galactose. Both 1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol (IX) and 1-deoxy-1-nitro-D-*glycero*-L-*gluco*-heptitol (X) gave the same 2,6-anhydronitroheptitol as the main product.



IX X XI

The ring size was demonstrated by periodate oxidation. The dialdehyde formed by periodate cleavage had a specific rotation of $-17.5°$. This demonstrates that the anhydro compound has the same configuration about C-2 as III and is, therefore, 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol (XI). Chromatography indicated that, in addition to XI, three minor products are formed during the anhydridization reaction. One of these has the same R_f as galactose and the other two are probably other anhydro products.[4] Apparently the products formed are in equilibrium with each other. This was demonstrated by refluxing an aqueous solution of XI for 20 hr. Chromatography of the reaction mixture showed four products. The chromatograms were identical with those of the anhydridzation reaction mixtures of 1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol (IX). The existence of this equilibrium means that the anhydro ring is labile.

It is interesting to note that the major product formed by the anhydridization of each pair of isomers is the one having the chair conformation with the smaller number of nonbonded interactions. Thus, 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol can assume a chair configuration with only one bulky group (hydroxyl) in an axial position whereas the epimeric D-*glycero*-D-*talo* isomer has at least two bulky axial groups in the chair conformation. Similarly, 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol which can exist in a chair configuration with only one hydroxyl group axial is formed in great excess over the D-*glycero*-L-*gluco* product. The formation of the same product from both isomers supports the theory, postulated by Sowden and Oftedahl, of a common intermediate in the anhydridization reaction.

The side product formed during the nitrosation of the amine from III was isolated as a white crystalline solid. Analysis of the compound indicated a molecular formula of $C_7H_{14}O_6$. It was identified as 1-deoxy-D-*manno*-heptulose (VI). The compound reduces Fehling's reagent very readily and forms a crystalline osazone also. A positive iodoform test confirmed the presence of a CH_3–CO group. The possibility of a 2-deoxy sugar was eliminated because the compound gave only a pale green color in the Dische deoxy sugar test.[7] 2-Deoxy-D-*erythro*-pentose gave a purple color and fructose a pale green color. The compound gave a positive Seliwanoff ketose test.[8] The identity of VI was confirmed by reduction with sodium borohydride to crysta line 1-deoxy-D-*glycero*-D-*galacto*-heptitol. This heptitol has been synthesized by the reductive desulfurization of D-*glycero*-D-*galacto*-heptose diethyl mercaptal.[9] A second product of the borohydride reduction could not be crystallized and was probably the other isomer, 1-deoxy-D-*glycero*-D-*talo*-heptitol. The formation of VI during the deamination reaction resembles the nitrosation of 1-aminoglycerol to give acetol[10] and the formation of deoxyinoses by nitrosation of inosamines.[11] The mechanism is probably similar to the one proposed by Foster[12] for the deamination of 1,2-amino alcohols, although in our case the anhydro ring must open either before or during the migration of the hydrogen atom from C-2.

Only one other 1-deoxyketose is reported in the literature. Wolfrom, *et al.*,[13] synthesized 1-deoxy-D-*arabino*-hexulose tetraacetate by condensing diazomethane with aldehydo-D-arabinose tetraacetate. On the other hand a simple method is available for the preparation of 1-deoxy-2-keto sugars in the addition of nitroethane to aldose sugars.[5]

Experimental

All melting points are uncorrected. Paper chromatography was carried out on Whatman No. 1 paper with the upper phase of 1-butanol–ethanol–water (4:1:5 v/v).[14] Compounds were detected with periodate–benzidine spray.[15]

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2,6-Anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol (III).—A solution of 50 g. of 1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol (I)[16] in 500 ml. of water was refluxed for 48 hr. Chromatography of the reaction mixture showed the presence of III (R_f 0.38) and mannose (R_f 0.20). The solution was evaporated to about 60 ml. and cooled. Filtration gave 18.9 g. (41%) of III, m.p. 146–152°. Several recrystallizations from 95% 1-butanol yielded 12.9 g. (27%) of pure product, m.p. 151–152° and $[\alpha]^{25}D$ −26.1° (*c* 2.5, water). From the combined mother liquors another 9.6 g. of III, m.p. 151–152°, was isolated to give a total yield of 49%.

Anal. Calcd. for $C_7H_{13}O_7N$: C, 37.65; H, 5.87; N, 6.28. Found: C, 37.79; H, 5.91; N, 6.28.

From 0.50 g. of sirupy mother liquors a crystalline phenylhydrazone was prepared,[17] m.p. 187.5° dec. The decomposition point of D-mannose phenylhydrazone is 186–187°.[18]

When 1-deoxy-1-nitro-D-*glycero*-D-*talo*-heptitol[16] was heated in water as before, the major product (42%) was again 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol, m.p. 151–152° and $[\alpha]^{25}D$ −26.1° (*c* 3.2, water).

Oxidation of 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol in aqueous solution with sodium periodate[19] showed the consumption of two molecular equivalents of oxidant after 4 hr. with the production of one molecular equivalent of formic acid and no formaldehyde. At this stage the specific rotation based on the dialdehyde was −17° (*c* 2.0). After 26 hr. the values were unchanged.

2,6-Anhydro-D-*glycero*-D-*galacto*-heptitol (IV).—A solution of 5.0 g. of 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol in 110 ml. of water was treated with 200 mg. of Adams' platinum catalyst and 3 ml. of glacial acetic acid. The mixture was reduced with hydrogen at 1 atm. for 3.5 hr. The catalyst then was removed by filtration and 5.0 ml. of glacial acetic acid was added to the filtrate. The solution was stirred and 4.63 g. of sodium nitrite was added. After 20 hr. the solution was deionized over Dowex 50(H^+) and Amberlite XE-168(OH^-) and concentrated to a sirup. The sirup was taken up in ethanol, decolorized with charcoal, and the solution evaporated to a small volume. The crystals obtained were filtered to yield 2.5 g (58%) of crude 2,6-anhydro-D-*glycero*-D-*galacto*-heptitol, m.p. 138–140°. Recrystallization from ethanol gave 0.86 g. of pure hygroscopic material, m.p. 142–144° and $[\alpha]^{25}D$ −33.6° (*c* 1.5, water).

Anal. Calcd. for $C_7H_{14}O_6$: C, 43.29; H, 7.28. Found: C, 43.33; H, 7.28.

2,6-Anhydro-D-*glycero*-D-*galacto*-heptitol consumed 2 moles of periodate in 3 hr. and gave an optically inactive solution. After 10 hr. the values were unchanged.

1-Deoxy-D-*manno*-heptulose (VI).—Five grams of 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol was reduced and the amine treated with nitrous acid as was described. 2,6-Anhydro-D-*glycero*-D-*galacto*-heptitol (IV) was removed from the reaction mixture by crystallization. Chromatography of the mother liquors showed the presence of IV (R_f 0.23) and 1-deoxy-D-*manno*-heptulose (R_f 0.30). The sirupy mixture (3.5 g.) was separated by chromatography on a cellulose column[20] by elution with 90% 1-butanol. Fractions containing only 1-deoxy-D-*manno*-heptulose were combined and evaporated to yield 0.76 g. (17.3%) of sirup. The sirup was dissolved in hot ethanol, and petroleum ether (b.p. 63–69°) was added to turbidity. Cooling and filtration gave 0.32 g. (8%) of VI, m.p. 87–89°. Recrystallization from ethanol–petroleum ether yielded a product having m.p. 90–91° and $[\alpha]^{25}D$ +24.2° (*c* 3.4, water, 30 min., constant over 8 hr.).

Anal. Calcd. for $C_7H_{14}O_6$: C, 43.29; H, 7.27. Found; C, 42.70; H, 7.43.

An iodoform test[21] on the compound was positive. Alkaline sodium hypoiodite solution converted the compound to iodoform, m.p. 120°.

An osazone was prepared in the usual manner.[22] From 0.47 g. of compound 0.26 g. of crystalline product was obtained, m.p. 135–137° dec. The material was difficult to recrystallize but several recrystallizations from ethanol–water raised the melting point to 176–178° dec.

Reduction of 1-Deoxy-D-*manno*-heptulose.—A solution of 0.5 g. of sodium borohydride in 20 ml. of water was added dropwise at room temperature to a stirred solution of 1.1 g. of 1-deoxy-D-*manno*-heptulose in 25 ml. of water. After 3.25 hr. processing the reaction mixture in usual manner yielded 0.30 g. (27%) of crystalline 1-deoxy-D-*glycero*-D-*manno*-heptitol, m.p. 173–175°. Recrystallization from methanol gave 0.12 g. of pure material, m.p. 181–182° and $[\alpha]^{25}D$ +1.14° (*c* 2.6, water).

Anal. Calcd. for $C_7H_{16}O_6$: C, 42.84; H, 8.09. Found: C, 43.0; H, 8.19.

Zissis, *et al.*,[9] report m.p. 181–182° and $[\alpha]^{25}D$ +1.1° in water for 1-deoxy-D-*glycero*-D-*manno*-heptitol.

Evaporation of the mother liquors gave a sirupy residue (0.48 g.), which failed to crystallize.

2,6-Anhydro-1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol (XI).—A solution of 13.1 g. of 1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol[23] in 131 ml. of water was refluxed for 48 hr. Chromatography of the reaction mixture showed the presence of XI (R_f 0.36), a reducing compound, presumably galactose (R_f 0.12), and two minor unidentified products (R_f 0.45 and R_f 0.55). Evaporation to dryness and crystallization of the residue from 90% ethanol gave 7.36 g. (62%) of XI. Recrystallization from the same solvent yielded 6.45 g. (55%) of pure product, m.p. 199.5–200.5° and $[\alpha]^{25}D$ +36.0° (*c* 2.9, water).

Anal. Calcd. for $C_7H_{13}O_7N$: C, 37.65; H, 5.87; N, 6.28. Found: C, 37.56; H, 5.55; N, 6.24.

When 1-deoxy-1-nitro-D-*glycero*-L-*gluco*-heptitol[23] was heated in aqueous solution as before, the main product was again 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol (65%), m.p. 199.5–200.5° and $[\alpha]^{25}D$ +36.0° (*c* 2.9, water)

2,6-Anhydro-1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol consumed 2 moles of periodate in 2 hr. with the production of 2 moles of formic acid and no formaldehyde. The values were unchanged after 24 hr. and at this time the specific optical rotation (based on dialdehyde) was −17.6° (*c* 2.1).

Equilibration of 2,6-Anhydro-1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol (XI) in Hot Aqueous Solution.—A solution of 0.57 g. of XI in 5.7 ml. of water was refluxed for 20 hr. Chromatographic examination of the solution showed four components, R_f values: 0.14, 0.36, 0.45, and 0.55. The chromatograms were identical with those taken during the formation of XI as described previously.

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