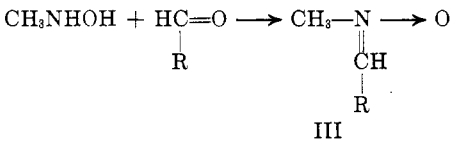
formation of a new C–N bond rather than the usual C–C bond.

The reductive amination of reducing sugars in the presence of amines,[7] ammonia,[8] and hydrazine[9] has been reported, as has the reduction of sugar oximes.[10] Since, in the preparation from which I was isolated,[4] a reduction was performed in which one would expect there to be small amounts of reducing sugar (D-xylose) and nitromethane as contaminants, a mixture of D-xylose and nitromethane was hydrogenated over platinum black in an aqueous acetic acid medium. The product of the hydrogenation was treated with nitrous acid and from that reaction I was isolated in high yield (70–80% based on D-xylose).

Similar yields of the corresponding products from D-ribose, D-lyxose, and D-arabinose were obtained using the same procedure.

Nitromethane does not appear to condense with reducing sugars under acidic conditions; therefore, the condensation probably involves a reduction product of nitromethane which is formed *in situ*. The final reduction product of nitromethane, methylamine, under the conditions used in the reduction does not give an appreciable yield of 1-deoxy-1-methylamino-D-xylitol (II). The yield of II after a greatly extended period of reduction was less than 20%. This finding is interpreted as indicating that a different condensation product is formed and reduced in the two cases.

The product of the second step in the reduction of nitromethane is probably methylhydroxylamine. Under acidic conditions the latter would condense with an aldehyde to form a nitrone (III) which on further reduction would form a methylamine derivative such as II.



III

In support of this hypothesis is the finding that, whereas a mixture of hydroxylamine and D-xylose is reduced to give a high yield of a basic nitrogenous derivative which can be deaminated with nitrous acid with the formation of 1,4-anhydro-D-xylitol, the substitution of ammonia for hydroxylamine gives essentially no condensation product.

The nitroso compounds derived from the pentoses are readily crystallizable, slightly yellow compounds. They consume 3 molar equiv. of periodate with the release of 2 molar equiv. of formic acid and 1 of formaldehyde. They give a typical Liebermann nitroso test. They have absorption maxima at 292 mμ and molar extinction coefficients of 27 ± 1. They can be reduced readily over platinum to the corresponding secondary amine.

Preliminary testing data from the Cancer Chemotherapy National Service Center indicates that the compounds described here are neither carcinostatic nor toxic.

(7) F. Kagen, M. A. Rebenstorf, and R. V. Heinzehman, *J. Am. Chem. Soc.*, **79**, 3541 (1957).

(8) F. W. Holly, E. W. Peel, R. Mozingo, and K. Folkers, *ibid.*, **72**, 5416 (1950).

(9) R. U. Lemieux, U. S. Patent 2,830,983 (1958); *Chem. Abstr.*, **52**, 14,668 (1958).

(10) L. Maquenne and E. Roux, *Compt. rend.*, **132**, 980 (1901).

Experimental[11]

1-Deoxy-1-(methylnitrosamino)-D-xylitol.[12]—To a solution of 10 g. (66 mmoles) of D-xylose and 10 ml. (185 mmoles) of nitromethane in 200 ml. of 25% aqueous acetic acid in a pressure bottle was added 1 g. of platinum oxide. The air in the system was displaced with hydrogen to a pressure of 30 lb.[13] and the bottle was shaken vigorously. The hydrogen uptake was complete in 24 hr. at which time 14.0 l. (0.60 mole) had been taken up. The catalyst was removed by filtration and washed with water. The combined filtrates were concentrated to dryness *in vacuo* at 60°. The residue was taken up in water and passed over a column containing 200 ml. of IR 120 (H^+). The column was washed until the eluate was neutral. Concentration of this acidic eluate gave 1.1 g. of a mixture of D-xylose and xylitol (determined by chromatography).

The column was then eluted at the rate of 5 ml. per minute[14] with 11.2% aqueous ammonia. The first 300 ml. of alkaline eluate was collected and concentrated *in vacuo* at 40° to give 8.6 g. of a slightly yellow sirup which was dissolved in 200 ml. of 25% aqueous acetic acid and 7 g. of sodium nitrite added. After 4 hr. the reaction was boiled to remove the excess nitrous acid, and then concentrated at 60° *in vacuo*. The residue was taken up in water, and after deionization with IR 120 (H^+) and IR 45 a pale yellow solution was obtained. Concentration *in vacuo* gave 8.0 g. of crystalline material which was taken up in hot isopropyl alcohol (50 ml). On cooling 7.4 g. of pale yellow crystals was obtained with m.p. 120–121°. A second crop of 0.8 g. was obtained from the mother liquors. Recrystallization from the same solvent gave 6.3 g. of material, m.p. 121–122°, $[\alpha]_D$ −16.5° (*c* 3, water), and mol. wt. 193 ± 2 (by osmometry).

Anal. Calcd. for $C_6H_{14}N_2O_5$ (194.2): C, 37.1; H, 7.28; N, 14.45. Found: C, 36.9; H, 7.39; N, 14.19.

Similar yields were obtained when D-xylose, D-arabinose, and D-ribose were used instead of D-xylose. The product from the D-ribose preparation was recrystallized from ethyl acetate containing a small proportion of methanol.

The derivatives had the properties shown in Table I.

TABLE I

1-Deoxy-1-(methylnitrosamino)-	M.p., °C.	$[\alpha]^{25}D$ (*c* 3, water)	Analysis, % C	H	N
D-ribitol	85–87	−17.2°	37.0	7.46	14.20
D-lyxitol	102–103	+ 3.7°	36.9	7.18	14.41
D-arabitol	142–144	+16.5°	37.1	7.19	14.63

(11) Melting points are corrected. Paper chromatograms (descending) were run on Whatman 31 with butanone–water (25:2 v./v.).

(12) The assumption is made that the configuration of the starting material is retained in the product.

(13) The reaction proceeds equally well at atmospheric pressure.

(14) The column must be eluted slowly to allow time for the heat of reaction of the ammonia with the resin to dissipate.

The Assignment of Configurations to Three Aminodeoxyheptulosans by Proton Magnetic Resonance

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In a recent communication,[1] the syntheses of three stereoisomeric 2,7-anhydro-4-nitro-4-deoxy-β-D-heptulopyranoses and of their reduction products, the corresponding amine hydrochlorides, was described. On the basis of experiences derived from analogous syntheses, it was assumed that the new compounds bear

(1) H. H. Baer, *J. Org. Chem.*, **28**, 1287 (1963).

their nitrogen functions in equatorial disposition. This would place the compounds into any three of the *allo*, *altro*, *gulo*, and *ido* series. Comparison of molecular rotation data lent support to that assumption and, in fact, made it possible to suggest tentatively the *gulo* configuration for one and the *altro* configuration for a second one of the stereoisomeric amino sugar derivatives. No such assignment was made for the third isomer.[1]

A study of the proton magnetic resonance (p.m.r.) spectra of the fully acetylated amino sugars has now served to confirm unequivocally the hitherto tentative *gulo* and *altro* configurations of the respective isomers, and to establish the *allo* configuration for the remaining isomer. The crystalline acetates prepared for the purpose of this investigation are 4-acetamido-4-deoxy-1,3,5-tri-*O*-acetyl-2,7-anhydro-β-D-alloheptulopyranose (I),[2a] 4-acetamido-4-deoxy-1,3,5-tri-*O*-acetyl-2,7-anhydro-β-D-guloheptulopyranose (II),[2b] and 4-acetamido-4-deoxy-1,3,5-tri-*O*-acetyl-2,7-anhydro-β-D-altroheptulopyranose (III).[2c]

It has been found by Lemieux, Kullnig, Bernstein, and Schneider[3] that in carbohydrates of pyranose structure axial acetoxy substituents resonate at lower field (τ-value) than equatorial substituents, and that the coupling constant between adjacent diaxial ring hydrogens is greater than that between axial–equatorial or equatorial–equatorial ring hydrogens. These findings have since been confirmed by many workers and have been used extensively to determine unknown configurations of carbohydrates. Of particular relevance to the present investigation was the study[4] of numerous 2,3,4-tri-*O*-acetyl- and 3-acetamido-3-deoxy-2,4-di-*O*-acetyl-1,6-anhydro-β-D-hexopyranoses. The fact that the precise stereochemistry of these hexosan derivatives could be determined by the p.m.r. method lent confidence to the deductions made herein on the closely related heptulosan system.

The chemical shifts for the substituent resonances and where possible for the ring hydrogens of I, II, and III are shown in Table I. The ring-hydrogen resonances are shown in Fig. 1. Although the assignments of the H-3 and H-5 hydrogens are unequivocal in all cases, the remaining assignments are only tentative and are based on the band widths calculated from the splittings of the H-3 and H-5 multiplets. For all three compounds the resonance of highest field in the acetate region was assigned to the equatorial acetamido group.[5,6] One of the compounds (I) showed acetoxy resonances at τ 7.81, 7.84, and 7.91, which indicated that it had two axial and one equatorial acetoxy groups and hence that it had the D-*allo* configuration. Both the other compounds exhibited one axial and two equatorial acetoxy resonances so that they were evidently the D-*altro* and D-*gulo* isomers. A differentiation between the two had yet to be provided.

TABLE I

CHEMICAL SHIFTS[a] OF SOME HEPTULOSAN DERIVATIVES

Compound (configuration)	H-3	H-5	OAc-1	OAc-3	Ac-4	OAc-5	NH
I (D-*allo*)	4.77	5.13	7.91	7.84	8.02	7.81	4.38
II (D-*gulo*)	4.71	4.89	7.94	7.88	8.11	7.94	4.11
III (D-*altro*)	4.89	4.97	7.93	7.93	8.08	7.83	4.03
IV (D-*altro*)	4.71	4.71	8.03	7.92	7.96	7.83	

[a] In τ-values.

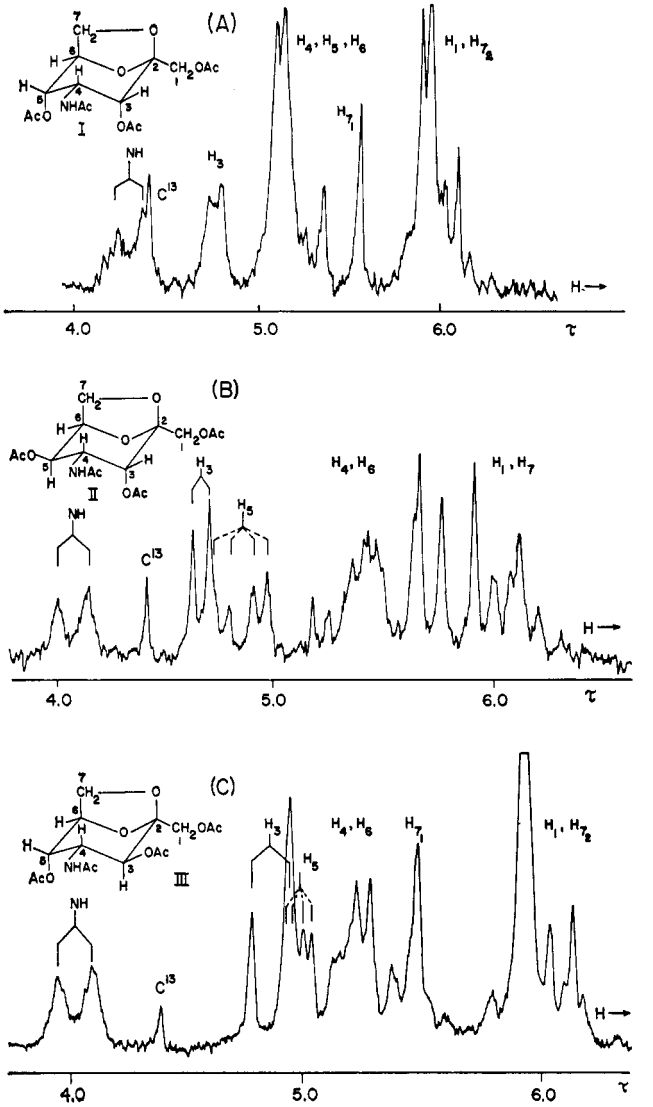

Fig. 1.—The ring hydrogen resonances of the tetraacetylaminodeoxyheptulosans I, II, and III. The peaks designated "C^{13}" arise from coupling of the solvent chloroform protons with the chloroform-C^{13} in natural abundance.

It was possible to distinguish between the isomers II and III by a study of the ring-hydrogen resonances. For reasons pointed out previously[1] it was assumed at this stage that the acetamido substituent at C-4 was oriented equatorially in these compounds. Consequently, H-4 was to be regarded as axial. Direct proof of the correctness of this assumption came from the observation of large couplings (*ca.* 10 c.p.s.) both in II and in III. These indicated the presence of neighboring, diaxial hydrogens, a condition requiring H-4 to be axial. With an axial H-4, then, the isomer bearing an axial

(2) Prepared from the aminodeoxyheptulosan hydrochlorides referred to in ref. 1 as (a) compound IVa, $[\alpha]_D$ −55°; (b) compound IVb, $[\alpha]_D$ +39°; and (c) compound IVc, $[\alpha]_D$ −126°.

(3) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

(4) L. D. Hall and L. Hough, *Proc. Chem. Soc.*, **382** (1962); a detailed account of this work is in preparation (L. D. Hall, L. Hough, and K. A. McLaughlan).

(5) A. C. Richardson and K. A. McLaughlan, *J. Chem. Soc.*, 2499 (1962).

(6) F. A. L. Anet, R. A. B. Bannard, and L. D. Hall, *Can. J. Chem.* **41**, 2331 (1963).

acetoxy at C-3 (*i.e.*, the *gulo* isomer II) should show a small splitting (*ca.* 2 c.p.s.) for the H-3 doublet, whereas the isomer having an equatorial C-3 acetoxy substituent (*i.e.*, the *altro* isomer III) should show H-3 as a doublet with a large splitting (*ca.* 10 c.p.s.). Additional proof of these assignments should follow from the measurements of the splittings of the H-5 resonance if these could be observed. It was indeed fortunate that the downfield shift of H-3 and H-5, caused by the adjacent acetoxy substituents, was sufficient for both these hydrogens to be resolved, and hence for II and III to be distinguished. One isomer exhibited a doublet, which could only be H-3, at τ 4.71 (splitting, 4.6 c.p.s.) and three lines of a partially concealed quartet, which must be H-5, at τ 4.89 (splittings, 3.5 and 10.4 c.p.s.); clearly, this must be the *gulo* isomer II. The remaining isomer showed the H-3 doublet at τ 4.89 (splitting, 9.9 c.p.s.) and a partially concealed quartet for H-5 at τ 4.97 (splittings, 2.1 and 4.4 c.p.s.), all of which is consistent with the *altro* configuration (III).

Although the ring hydrogens of the *allo* isomer I were not well resolved, they were consistent with the assigned configuration. H-3 occurred as a poorly resolved doublet at τ 4.77 (splitting, *ca.* 4 c.p.s.), and while H-5 overlapped with the resonances of two other hydrogens the total band width was insufficient to accommodate an axial–axial coupling of *ca.* 10 c.p.s.

Also included in Table I are the acetoxy resonances of fully acetylated 2,7-anhydro-β-D-altroheptulopyranose (sedoheptulosan, IV), although this product could not be obtained in crystalline condition. However, the resonances were as expected, showing one axial and three equatorial substituents.

Experimental

The 60-Mc./sec. p.m.r. spectra were measured in a Varian V-4302B spectrometer for chloroform solutions. A Varian V-3521 integrator was used for base line stabilization. Calibration was by the usual side-band technique with tetramethylsilane as internal reference. The chemical shifts and multiplet splittings in Table I are averaged values from at least three spectra.

Acetylation of Aminodeoxyheptulosans.—Aminodeoxyheptulosan (about 100 mg.) in pyridine (2 ml.) was treated with acetic anhydride (2 ml.) at room temperature for 2 days. Excess anhydride was destroyed by the addition of methanol and the solution was evaporated *in vacuo*. The sirupy residue was taken up in 15 ml. of chloroform which was then extracted once with 6 ml. of *N* sulphuric acid and twice with 6 ml. of a saturated sodium hydrogen carbonate solution. After drying over anhydrous sodium sulfate and evaporation of the chloroform solution, the crystalline acetylated aminodeoxyheptulosan was obtained from, and recrystallized with, chloroform–ether. The three isomers were obtained in yields of 50–65% and had the following properties: **4-acetamido-4-deoxy-1,3,5-tri-*O*-acetyl-2,7-anhydro-β-D-alloheptulopyranose** (I, from compound IVa[1]), oblong flat platelets, m.p. 213–214° dec., $[\alpha]^{22}D$ −60.9° (*c* 1, chloroform); **4-acetamido-4-deoxy-1,3,5-tri-*O*-acetyl-2,7-anhydro-β-D-guloheptulopyranose** (II, from compound IVb[1]), thin prisms, m.p. 128–129°, $[\alpha]^{22}D$ +43.7° (*c* 1, chloroform); **4-acetamido-4-deoxy-1,3,5-tri-*O*-acetyl-2,7-anhydro-β-D-altroheptulopyranose** (III, from compound IVc[1]), fine needles, m.p. 189–190°, $[\alpha]^{22}D$ −145.5° (*c* 1, chloroform).

Anal. Calcd. for $C_{15}H_{21}NO_9$ (359.3): C, 50.13; H, 5.89. Found for I: C, 50.07; H, 5.72. Found for II: C, 49.74; H, 5.78. Found for III: C, 50.36; H, 5.56.

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2-Deoxy Sugars. VI. Concurrent One-Step Formation of Both Anomeric Monodigitoxosides of Digitoxigenin[1]

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This paper deals with the direct coupling of digitoxose (2,6-dideoxy-β-D-*ribo*-hexose, I) with digitoxigenin [3β,14β-dihydroxy-5β-card-20(22)-enolide, II] to give not only the α-monodigitoxoside (III) but the β-anomeric form (IV) as well. The β-, or "natural," anomer was obtained originally by a controlled, partial hydrolysis of digitoxin,[3] but when we attempted to synthesize the material by coupling 2,6-dideoxy-3,4-di-*O*-*p*-nitrobenzoyl-β-D-*ribo*-hexosyl chloride with digitoxigenin (II), we obtained the alternate anomeric form (III) instead (see Scheme I).[4]

The presently described reaction was carried out by treating a solution of digitoxigenin (II) and an excess of digitoxose (I) in pure dioxane with a small quantity of hydrogen chloride–dichloromethane solution. After neutralizing the acid, the reaction products were dissolved in aqueous methanol and were extracted with chloroform to remove all extraneous carbohydrate materials. Thin-layer chromatograms disclosed two major spots corresponding chromatographically to the α- and β-monodigitoxosides III and IV, respectively.

The extracted material was resolved by first chromatographing on formamide–cellulose powder[5] which brought about an incomplete separation of II, III, and IV. The fractions containing the latter were recombined and were chromatographed on silicic acid giving a complete separation, from which the monosides III and IV were obtained in a combined yield of 10% based on the genin II.

The formation of an α-glycoside (III) is of interest and may be accounted for satisfactorily in terms of the "anomeric" effect (structure A)[6] which allows for an attraction between the axially oriented α-glycosidic oxygen atom and C-5 which carries a partial positive charge. Such an attraction would overcome, at least in part, the conformational instability imposed by the erected oxygen atom. In the case of pyranosides which are not deoxygenated at C-6, the added electron-

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(2) (a) To whom all enquiries concerning this paper should be addressed; (b) U. S. Public Health Service Predoctoral Fellow; (c) visiting scientist, Georgetown, University, 1961–1963.

(3) F. Kaiser, E. Haack, and H. Spingler, *Ann. Chem.*, **603**, 75 (1957).

(4) (a) W. W. Zorbach and T. A. Payne, *J. Am. Chem. Soc.*, **81**, 1519 (1959); (b) **82**, 4079 (1960).

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(6) R. U. Lemieux and P. Chu, Abstracts, 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April, 1958, p. 31N. The suggestion that the formation of α-cardenolides is due most likely to this effect was communicated privately by Professor Lemieux to whom the authors are most grateful.