[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

The Formation of 2,7-Anhydro-β-D-*manno*-heptulopyranose by the Action of Acid on D-*manno*-Heptulose and of Alkali on Phenyl α-D-*manno*-Heptulopyranoside; also 1,6-Anhydro-β-D-mannopyranose from D-Mannose in Acid Solution[1-3]

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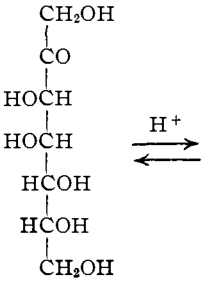
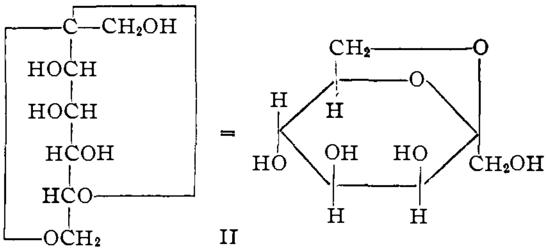
D-*manno*-Heptulose has been converted by hot dilute acid in about 8% yield to 2,7-anhydro-β-D-*manno*-heptulopyranose, whose structure has been established through periodate oxidation methods. D-Mannose has been transformed similarly in about 0.6% yield to 1,6-anhydro-β-D-mannopyranose. Acetylation of D-*manno*-heptulose with acetic anhydride and pyridine forms first the 1,3,4,5,7-pentaacetate (described earlier as the α-hexaacetate) and then, much more slowly, the true α-D-*manno*-heptulopyranose hexaacetate (melting point 86–89°, $[\alpha]^{20}D$ +41.5° in chloroform). Condensation of both the pentaacetate and the hexaacetate with phenol in the presence of *p*-toluenesulfonic acid as catalyst yielded phenyl α-D-*manno*-heptulopyranoside pentaacetate. Deacetylation, and subsequent degradation of the phenyl α-D-*manno*-heptulopyranoside with hot aqueous alkali gave about a 15% yield of the same 2,7-anhydro-β-D-*manno*-heptulopyranose that was formed by the action of acid on D-*manno*-heptulose.

The conversion of aldohexoses, aldoheptoses and heptuloses in dilute acid solution to equilibrium mixtures containing one or more monomeric, nonreducing anhydrides has been studied extensively in this Laboratory. In general, heptuloses are transformed to a significantly greater extent than are the corresponding aldoses, and production of the 2,7-anhydroheptulopyranoses has been reported to occur to the following extents: *altro*, 91; *ido*, 85; *gulo*, 80; *allo*, 50; *talo*, 32; *gluco*, 2.[4] In extending these studies to the *manno* configuration we now find that D-*manno*-heptulose (I) is converted by dilute acids to an equilibrium mixture from which we could isolate a crystalline anhydride melting at 159–160° and showing $[\alpha]^{20}D$ −80.4° in water. Its structure was proved by periodate oxidation methods to be 2,7-anhydro-β-D-*manno*-heptulopyranose (II). No trace of other anhydrides, such as the 2,7-anhydro-β-D-*altro*-heptulofuranose derived from sedoheptulose[2] or the dimolecular dianhydride derived from D-*gluco*-heptulose,[3] was found.



I



II

In the equilibrium mixture of sedoheptulose (= D-*altro*-heptulose) and sedoheptulosan, the amount of anhydride varies with the temperature,[2] being 91% at 20° and only 84.5% at 80°. With D-*manno*-heptulose the equilibrium is shifted in the opposite direction with a change in temperature so that at 40° there is only 3% anhydride while at 80° there is about 7% anhydride (Table I). According to the principle of LeChatelier and Braun these results might not be unexpected, because the effect of heat is to displace the equilibrium in the direction of the thermodynamically less-favored component.

TABLE I

THE EFFECT OF TEMPERATURE ON THE AMOUNTS OF D-*manno*-HEPTULOSE (I) AND ITS ANHYDRIDE ($II \cdot H_2O$) IN THE EQUILIBRIUM MIXTURE IN 0.2 *N* HYDROCHLORIC ACID

Time, hr.	Temp., °C.	$[\alpha]^{20}D$	% $II \cdot H_2O$[a]	% I[b]	Mole % DHEF[c]
119	40	+25.9°	2.8	94.9	..
237	40	+25.9	2.8	94.6	0.11
16	60	+23.5	5.2	93.0	.26
40	60	+23.6	5.1	93.3	..
3	80	+21.2	7.4	89.8	.55
5	80	+21.3	7.3	89.8	.88

[a] Calculated from the specific rotation on the assumption that the solution contained only D-*manno*-heptulose (I) and 2,7-anhydro-β-D-*manno*-heptulopyranose (II) as its monohydrate of $[\alpha]^{20}D$ −73.5°; total concentration, 0.1 molar. [b] Determined by a ferricyanide titration method. [c] Calculated from the ultraviolet spectra on the assumption that the molecular absorption coefficient of DHEF [= 5-(1,2-dihydroxyethyl)-2-furaldehyde] is about the same as that of HMF [= 5-(hydroxymethyl)-2-furaldehyde]. For further details of the methods, see reference 2.

The acetylation of D-*manno*-heptulose by acetic anhydride and pyridine for 48 hours at 0° was reported by Montgomery and Hudson[5] to produce large prisms melting at 110° and showing $[\alpha]^{20}D$ +39.0° in chloroform. Carbon, hydrogen and acetyl analyses of their compound, as well as its

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(1) Presented in part before the Division of Carbohydrate Chemistry at the Atlantic City Meeting of the American Chemical Society, September 18, 1956.

(2) For the preceding paper on anhydro sugars, see N. K. Richtmyer and J. W. Pratt, THIS JOURNAL, **78**, 4717 (1956).

(3) For a recent paper on anhydro sugars that includes pertinent references to their preparation by both these methods, see L. C. Stewart, E. Zissis and N. K. Richtmyer, *Chem. Ber.*, **89**, 535 (1956).

(4) Although D-*altro*-heptulose appears to give the highest yield of anhydride yet reported, it should be noted that the 91% represents the amount as determined at the very favorable temperature of 20° whereas the values for the other sugars were obtained at 95–100°. It is expected that *ido*-heptulose and perhaps *gulo*-heptulose will generate more than 91% anhydride when they are allowed to stand in dilute acid solution at 20°.

(5) E. M. Montgomery and C. S. Hudson, THIS JOURNAL, **61**, 1654 (1939).

transformation to an "acetobromo" compound and subsequent reaction of the latter to form the methyl glycoside pentaacetate, led them to designate it the α-hexaacetate. We find, however, that their product was actually a pentaacetate: it showed clearly a hydroxyl band in its infrared spectrum and upon further reaction with acetic anhydride and pyridine it yielded the true α-D-*manno*-heptulopyranose hexaacetate as small prismatic needles melting at 86–89° and showing $[\alpha]^{20}D$ +41.5° in chloroform. Our further studies have shown that acetic anhydride and pyridine at 25° convert D-*manno*-heptulose rapidly to the pentaacetate stage (65% yield isolated after one hour), whereas complete acetylation is achieved only after about 5 days. Comparable results with D-*gluco*-heptulose had been reported earlier by Wolfrom and Thompson[6] and by Frush and Isbell.[7] The first-named pair of investigators found that their "acetobromo" compound, with silver carbonate and aqueous acetone, yielded α-D-*gluco*-heptulose pentaacetate, and they thus established that the free hydroxyl group was at C2 in the pentaacetate. We have found, similarly, that penta-*O*-acetyl-α-D-*manno*-heptulopyranosyl bromide[5] is converted by gentle hydrolysis to the pentaacetate, which must, therefore, also be designated the 1,3,4,5,7-pentaacetate.

Acetylated glycosyl bromides are usually prepared from the fully acetylated sugars. We have found, in agreement with the experiment described by Montgomery and Hudson,[5] that the α-D-*manno*-heptulopyranose pentaacetate, in which the hydroxyl group at C2 is unsubstituted, is converted, readily and in high yield, by hydrogen bromide in glacial acetic acid to penta-*O*-acetyl-α-D-*manno*-heptulopyranosyl bromide. Likewise, the reaction of Helferich and Schmitz-Hillebrecht[8] is usually carried out with the fully acetylated sugar. We have found that the condensation of α-D-*manno*-heptulopyranose 1,3,4,5,7-pentaacetate with phenol, in the presence of *p*-toluenesulfonic acid as catalyst, can be effected although the yield in our only experiment was not so good as when we used the hexaacetate later. The product of these reactions was phenyl α-D-*manno*-heptulopyranoside pentaacetate, melting at 103–104° and showing $[\alpha]^{20}D$ +35.9° in chloroform; upon catalytic deacetylation it yielded phenyl α-D-*manno*-heptulopyranoside, melting at 181–183° and showing $[\alpha]^{20}D$ +89.6° in water.

In a recent paper[3] we reported that the reaction of phenyl α-D-*gluco*-heptulopyranoside with hot aqueous potassium hydroxide produced at least a 34% yield of 2,7-anhydro-β-D-*gluco*-heptulopyranose. Phenyl α-D-*manno*-heptulopyranoside appears to be degraded similarly to the extent of about 15%, and 8.4% of crystalline 2,7-anhydro-β-D-*manno*-heptulopyranose was isolated from the reaction mixture. In both cases there was extensive destruction of the remainder of the material. Earlier studies had shown that phenyl β-D-glucopyranoside is converted practically quantitatively to 1,6-anhydro-β-D-glucopyranose, and the reaction mechanism has been established satisfactorily.[9] Phenyl heptulosides, however, have a CH_2OH group attached to the glycosidic carbon atom (C2), and this situation tends to complicate the picture. Thus, we have suggested two possible, simple mechanisms for the degradation of phenyl α-D-*gluco*-heptulopyranoside to the anhydro sugar,[3] postulating inversion of configuration at the glycosidic carbon atom at each step. With phenyl α-D-*manno*-heptulopyranoside also, we may write similar one- and three-step reaction mechanisms. The first, delineated in the simplest manner, represents the reaction as involving elimination of the elements of phenol between C2 and C7, with inversion of configuraton at C2 (III → II). The alternate mechanism involves elimination of the elements of phenol between C2 and C3 and the formation of the 2,3-epoxide IV; this may be followed by rearrangement (reversible) to the 1,2-epoxide V, and a final rearrangement to the anhydro sugar II, which is stable to hot alkali. Other pathways may lead through the epoxide IV or through the isomeric 1,2-epoxide VI to free D-*manno*-heptulose (I), which is not stable to alkali and forms tarry decomposition products.

We hope that additional experiments now in progress on appropriately substituted heptuloses will contribute further to the study of these reaction mechanisms.

As a result of our earlier studies on the transformation of reducing sugars to monomeric, non-reducing anhydrides in dilute acid solution, we should expect that D-mannose, like D-*manno*-heptulose, would form an anhydride but to a smaller extent. This prediction was verified, even though it was necessary to heat 144 g. of D-mannose at about 83° in 0.2 *N* sulfuric acid in order to obtain, finally, 0.87 g. of crystalline 1,6-anhydro-2,3-*O*-isopropylidene-β-D-mannopyranose[10] for identification purposes. Although this amount represents only a 0.5% yield actually isolated, rotational data at several stages indicated that possibly as much as 0.7% of the D-mannose was transformed to its known anhydride under those conditions.

Experimental

2,7-Anhydro-β-D-*manno*-heptulopyranose (II) from D-*manno*-Heptulose (I).—After a preliminary experiment had led to the isolation of a crystalline anhydride, 100 g. of D-*manno*-heptulose in 800 ml. of 0.5 *N* sulfuric acid was boiled under a reflux condenser until the rotation had dropped from $[\alpha]^{20}D$ +29.2° to +18.5° (approximately constant) at the end of 3 hours. The solution was neutralized cautiously with aqueous barium hydroxide, filtered through carbon, and concentrated *in vacuo* to a sirup from which 60 g. of D-*manno*-heptulose was recovered by crystallization from ethanol. The remaining sugar was removed by heating its aqueous solution with excess barium hydroxide, neutralizing with sulfuric acid, filtering through carbon, and deionizing with Amberlite IR-120 and Duolite A-4 ion-exchange resins. The solution, upon concentration to a small volume, was levorotatory; it was concentrated further to a sirup that was crystallized from ethanol to yield a total of 3.3 g. of the anhydride. The 2,7-anhydro-β-D-*manno*-heptulopyranose separated as clusters of prisms from aqueous ethanol,

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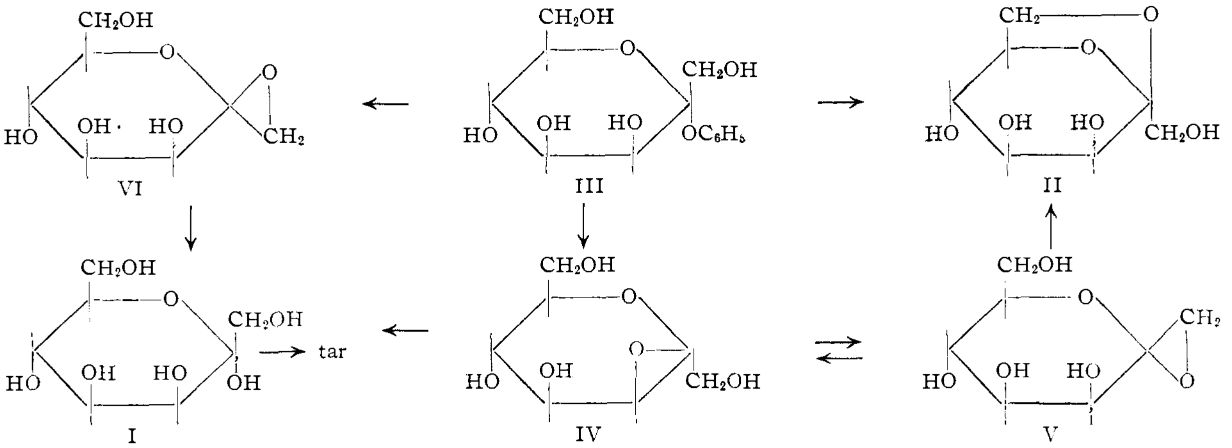
[6] M. L. Wolfrom and A. Thompson, THIS JOURNAL, **56**, 1804 (1934).

[7] H. L. Frush and H. S. Isbell, *J. Research Natl. Bur. Standards*, **34**, 111 (1945).

[8] B. Helferich and E. Schmitz-Hillebrecht, *Ber.*, **66**, 378 (1933).

[9] See, for example, C. E. Ballou, *Advances in Carbohydrate Chem.*, **9**, 59 (1954).

[10] A. E. Knauf, R. M. Hann and C. S. Hudson, THIS JOURNAL, **63**, 1447 (1941).



VI III II I IV V

and after several recrystallizations melted at 159–160° and showed $[\alpha]^{20}_{\rm D}$ −80.4° in water (*c* 2.0).

Anal. Calcd. for $C_7H_{12}O_6$: C, 43.75; H, 6.30. Found: C, 43.54; H, 6.38.

After the experiments at 40, 60 and 80°, summarized in Table I, had been completed, a final run was made in which 21.02 g. of D-*manno*-heptulose in 1 liter of 0.2 *N* sulfuric acid was heated for 3 hours at 90°. The rotation $[\alpha]^{20}_{\rm D}$ +19.6° indicated the formation of 9.0% of 2,7-anhydro-β-D-*manno*-heptulopyranose, while an estimation of reducing sugar by the ferricyanide method indicated that 87.6% of the D-*manno*-heptulose remained. From an ultraviolet absorption spectrum of the very slightly colored solution we could estimate the presence of about 1.6 mole % of DHEF. The mixture was heated with excess barium hydroxide for 20 hours on the steam-bath, neutralized with carbon dioxide until the solution was no longer alkaline to phenolphthalein, filtered, deionized, and concentrated *in vacuo* to a small volume. At that point, the rotation of the solution corresponded to 1.73 g. (9.0%) of 1,6-anhydro-β-D-*manno* - heptulopyranose; crystallization from ethanol yielded 1.54 g. (8.0%) of material that upon recrystallization gave 1.38 g. (7.2%) of pure anhydride melting at 159–160°. The mother liquor from the 1.54 g., when examined by paper chromatography, showed only the anhydride and a trace of heptulose, with no evidence either of a furanose anhydride such as was obtained from D-*altro*-heptulose[2] or of a dimolecular dianhydride such as was obtained from D-*gluco*-heptulose.[3]

Oxidation of 2,7-Anhydro-β-D-*manno*-heptulopyranose (II) with Periodate.—The oxidation of 0.3865 g. of the anhydride with a 20% excess of sodium metaperiodate appeared to be complete within 1 hour at 20° as indicated by the constant rotation $[\alpha]^{20}_{\rm D}$ −17.3° (calculated as the expected dialdehyde). This value is comparable to the average −17.2° found for the four other anhydroheptuloses of this stucture reported previously.[3] Titration of small samples at the end of 24 hours showed the consumption of 2.10 molar equivalents of oxidant and the liberation of 0.98 molar equivalent of formic acid. No formaldehyde could be detected. The remaining 90% of the solution was neutralized with barium hydroxide and enough additional barium ions were added as barium chloride to precipitate the iodate and periodate ions present. The solution (*p*H *ca.* 6.6) was concentrated *in vacuo* to dryness, and the dialdehyde extracted with 40 ml. of warm methanol. To the filtered solution was added 0.8 g. of 2,5-dichlorophenylhydrazine, and the mixture concentrated and heated on the steam-bath for 1 hour. Because inorganic material crystallized during this process, and especially when pentane was added to the methanol solution, it was necessary to concentrate finally on the steam-bath to a sirup and then extract the sirup with ether. Upon the addition of pentane to the clear ether solution, the product crystallized readily; wt. 0.6 g., m.p. 154–156°. After two recrystallizations, the m.p. was 157–158° and showed no depression when the material was mixed with an equal amount of 4-D-*glycero*-2-hydroxymethyl-1,3-dioxolane-2,4-*cis*-dicarboxaldehyde bis-2,5-dichlorophenylhydrazone derived in similar fashion from sedoheptulosan.[3] The rotation, $[\alpha]^{20}_{\rm D}$ +40.0° in chloroform (*c* 0.5), was in good agreement with the value +40.6° reported previously.

α-D-*manno*-Heptulopyranose 1,3,4,5,7-Pentaacetate and α-D-*manno*-Heptulopyranose Hexaacetate from the Acetylation of D-*manno*-Heptulose in Pyridine at 5°.—A suspension of 120 g. of D-*manno*-heptulose (powdered to pass through an 80-mesh sieve) in 600 ml. of dry pyridine was cooled in ice-water and to it was added 600 ml. of acetic anhydride. The mixture was shaken overnight at 5° and the resulting solution kept an additional 4 days at that temperature. The reaction mixture was then poured into 4 liters of cracked ice and water and left overnight in the refrigerator. The acetylated material was divided between the aqueous pyridine solution and the precipitated gum. The latter was dissolved in chloroform and the chloroform solution washed with ice-cold, dilute sulfuric acid and then with water, dried over sodium sulfate, filtered through a small amount of carbon, and concentrated *in vacuo* to a thin sirup. This was diluted with pentane and inoculated with seed crystals of "D-mannoheptulose α-hexaacetate" remaining from the earlier researches of Montgomery and Hudson.[5] The crystals grew slowly at room temperature into large prisms and after repeated additions of pentane during the next two weeks there was obtained 52.3 g. of product originally designated as the hexaacetate but now identified as α-D-*manno*-heptulopyranose 1,3,4,5,7-pentaacetate. After recrystallization from ether–pentane the pentaacetate melted at 105–106° and showed $[\alpha]^{20}_{\rm D}$ +39.4° in chloroform (*c* 2). Montgomery and Hudson[5] reported m.p. 110° and $[\alpha]^{20}_{\rm D}$ +39.0° in chloroform (*c* 2) for their "hexaacetate"; their original sample, now about 20 years old, melted at 99–103° and in admixture with our pentaacetate melted at 100–105°. After one recrystallization from ether, their sample melted at 104–106° with no depression of melting point when mixed with our pentaacetate. The infrared spectrum of their original sample in chloroform solution was practically identical with that of our pentaacetate, with both showing clearly a hydroxyl band at 3570 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{24}O_{12}$: C, 48.57; H, 5.75; CH_3CO, 51.2. Found: C, 48.61, 48.49; H, 6.11, 5.93; CH_3CO, 52.6.

The chloroform–pentane mother liquor from the 52.3 g. of pentaacetate was concentrated to a sirup that was covered with about a liter of water and left at room temperature for two weeks with occasional stirring. At that time, small prismatic needles had begun to appear in the sirup and upon refrigeration for a week the sirup crystallized completely. The product was filtered, washed with water, and dried in the air; wt. 61.3 g. After recrystallization from 90 ml. of warm ethanol by the cautious addition of 90 ml. of water, the new, authentic α-D-*manno*-heptulopyranose hexaacetate melted at 85–88°, a value that was raised to 86–89° by additional recrystallizations in the same manner. The hexaacetate showed $[\alpha]^{20}_{\rm D}$ +41.5° in chloroform (*c* 1). Its ultraviolet absorption spectrum showed no absorption in the region of 280 mμ, indicating no ketone group and thus verifying the cyclic structure of the hexaacetate.

Anal. Calcd. for $C_{19}H_{26}O_{13}$: C, 49.35; H, 5.67; CH_3CO, 55.9. Found: C, 49.17; H, 5.51; CH_3CO, 56.1.

The original aqueous pyridine solution was extracted with chloroform, and the extract washed, dried and concentrated in the usual manner. Dilution of the residual thin sirup with pentane afforded 62 g. of the pentaacetate. The mother liquor was concentrated to a sirup; extraction of this sirup by stirring with several liter portions of water removed the more soluble pentaacetate, which could then be extracted with chloroform. In this fashion an additional 9.3 g. of pentaacetate was isolated. The remaining, less soluble sirup yielded an additional 10.5 g. of hexaacetate. In summary, acetylation of 120 g. of D-*manno*-heptulose as described above furnished 123.6 g. (51.5%) of the 1,3,4,5,7-pentaacetate and 71.8 g. (27.2%) of the new hexaacetate.

Conversion of α-D-*manno*-Heptulopyranose 1,3,4,5,7-Pentaacetate to α-D-*manno*-Heptulopyranose Hexaacetate.—A solution of 5.4 g. of the pentaacetate in 25 ml. of pyridine and 25 ml. of acetic anhydride showed an initial rotation of $[\alpha]^{20}\mathrm{D}$ +7°; after 5 days at 20° the rotation had become constant at $[\alpha]^{20}\mathrm{D}$ +35°, calculated as the hexaacetate. The dark-colored solution was poured into ice-water and the mixture left in the refrigerator overnight. The crystalline hexaacetate was filtered, washed with cold water, and dried in the air. It weighed 4.7 g. (79%) and after recrystallization from aqueous ethanol melted at 85–88°.

Preparation of α-D-*manno*-Heptulopyranose Hexaacetate and of α-D-*manno*-Heptulopyranose 1,3,4,5,7-Pentaacetate at 20–25°.—When 21 g. of D-*manno*-heptulose was dissolved in 250 ml. of pyridine and 100 ml. of acetic anhydride added, the observed rotation at 20° in a 1-dm. tube dropped rapidly from +2.84 to +0.59° within an hour and then began to rise, with values of +1.97, +2.56, +2.98, +3.25 and +3.98° being observed at the end of 1, 2, 3, 4 and 7 days, respectively. The dark-colored reaction mixture was poured onto cracked ice and left at 5° overnight to crystallize. The resulting hexaacetate was filtered, washed with water, and dried; it weighed 21.2 g.; and an additional 17.4 g. was isolated by extraction of the aqueous pyridine solution with chloroform in the usual manner, giving a total yield of 38.6 g. (83.6%).

When the acetylation of D-*manno*-heptulose was interrupted near the point of minimum rotation, good yields of the 1,3,4,5,7-pentaacetate could be obtained. Preliminary experiments on 5-g. batches were run for 30, 45, 60, 75 and 90 minutes, and when these were poured onto cracked ice and left at 5° overnight, the portions of crystalline pentaacetate weighed 4.3, 5.3, 7.0, 6.6 and 5.5 g., respectively. The product thus obtained was a fairly unstable, pyridine-solvated form melting at 73–75°; it could be converted to the solvent-free modification by heating overnight at 55°, by longer standing at room temperature in the air or in an evacuated desiccator over concentrated sulfuric acid, or by recrystallization. In a final experiment, 10 g. of D-*manno*-heptulose was dissolved in 130 ml. of warm pyridine, the solution was cooled and to it was added 50 ml. of acetic anhydride. The reaction generated a small amount of heat. The solution was kept at 25° for 1 hour, poured into 500 ml. of ice-water, and the mixture allowed to stand for several hours at room temperature. Upon extracting with chloroform and washing the solution with cold acid in the usual manner, the resulting sirup weighed 18.7 g. Crystallization from ether–pentane afforded a total of 13.1 g. (65.5%) of D-*manno*-heptulose 1,3,4,5,7-pentaacetate

Penta-*O*-acetyl-α-D-*manno*-heptulopyranosyl Bromide from α-D-*manno*-Heptulopyranose 1,3,4,5,7-Pentaacetate.—Five grams of the pentaacetate was dissolved in 25 ml. of glacial acetic acid saturated with hydrogen bromide at 0°, the mixture left at room temperature for 2 hours, diluted with 60 ml. of chloroform, poured into ice-water, and the product isolated in the usual manner. The resulting sirup crystallized readily from ether, depositing 5.2 g. (90%) of prisms melting at 84–90°. After recrystallization from ether–pentane the bromide melted at 87–92° and showed $[\alpha]^{20}\mathrm{D}$ +106° in chloroform (*c* 1), in good agreement with the values 92 and +104.0°, respectively, reported by Montgomery and Hudson.[6] In an unsuccessful attempt to condense 2.3 g. of the penta-*O*-acetyl-α-D-*manno*-heptulopyranosyl bromide with *p*-toluenethiol, 0.6 g. (30%) of D-*manno*-heptulopyranose 1,3,4,5,7-pentaacetate was recovered; it was undoubtedly formed as a result of hydrolysis of a portion of the bromide by the sodium salt of the thiol.

Phenyl α-D-*manno*-Heptulopyranoside Pentaacetate.—A fused mixture of 30 g. of α-D-*manno*-heptulopyranose hexaacetate, 27 g. of phenol and 1.5 g. of *p*-toluenesulfonic acid monohydrate was heated for 1 hour at 65–75° and 15 mm. pressure. The dark reaction mixture was dissolved in 450 ml. of chloroform and the solution washed twice with equal volumes of 3% aqueous sodium hydroxide and then with water, dried over sodium sulfate, filtered through decolorizing carbon, and concentrated to a thick sirup. Seed crystals were obtained by rubbing a small amount of the sirup with water and then allowing it to dry to a powdery residue. The remainder of the sirup was dissolved in warm ethanol and the solution cooled, seeded and diluted slowly with water. There was thus obtained 22.7 g. (70.5%) of shiny plates. After recrystallization in the same manner the phenyl α-D-*manno*-heptulopyranoside pentaacetate melted at 103–104° and showed $[\alpha]^{20}\mathrm{D}$ +35.9° in chloroform (*c* 1); these values were unchanged by further recrystallizations. The same product was obtained when α-D-*manno*-heptulopyranose pentaacetate was used instead of the hexaacetate, but the yield was smaller.

Anal. Calcd. for $C_{23}H_{28}O_{12}$: C, 55.64; H, 5.69; CH_3CO, 43.4. Found: C, 55.83; H, 5.75; CH_3CO, 43.1.

Phenyl α-D-*manno*-Heptulopyranoside (III).—The catalytic deacetylation of 20.0 g. of phenyl α-D-*manno*-heptulopyranoside pentaacetate with sodium methoxide in methanol furnished 10.0 g. (87%) of the free glycoside. It separated as flat prisms from 3 parts of absolute ethanol and after two recrystallizations it melted at 181–183° and showed $[\alpha]^{20}\mathrm{D}$ +89.6° in water (*c* 0.6).

Anal. Calcd. for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.63; H, 6.09.

2,7-Anhydro-β-D-*manno*-heptulopyranose (II) from Phenyl α-D-*manno*-Heptulopyranoside (III).—A solution of 9.9 g. of the phenyl glycoside in 250 ml. of *N* aqueous potassium hydroxide was boiled under a reflux condenser until the rotation became constant, after 3.5 hours, at $[\alpha]^{20}\mathrm{D}$ −12° calculated as anhydroheptulose. On the assumption that the only optically active material present was the anhydro-*manno*-heptulose of $[\alpha]^{20}\mathrm{D}$ −80.4°, the value $[\alpha]^{20}\mathrm{D}$ −12° would correspond to a 15% yield. The dark-brown reaction mixture was made slightly acid with sulfuric acid to facilitate its decolorization with activated carbon; after that step the solution was neutralized to phenolphthalein with potassium hydroxide and concentrated *in vacuo*. The dry residue was extracted thrice by boiling with 100-ml. portions of absolute ethanol. The combined extracts were concentrated and an aqueous solution of the residual material was deionized by passage through Amberlite IR-120 and Duolite A-4 ion-exchange resins. The solution was concentrated *in vacuo* to a sirup whose solution in absolute ethanol deposited a total of 0.56 g. (8.4%) of chunky prisms. After one recrystallization from absolute ethanol the product melted at 156–159°, showed $[\alpha]^{20}\mathrm{D}$ −77.9° in water, and suffered no depression of melting point when mixed with an equal amount of 2,7-anhydro-β-D-*manno*-heptulopyranose prepared by the action of acid on the sugar as described earlier in this paper.

2,7-Anhydro-β-D-*manno*-heptulopyranose Tetrabenzoate.—Benzoylation of 0.5 g. of the anhydride II in the usual manner yielded a sirup. This was dissolved in warm ethanol and left at 5° overnight. The gum that deposited was dissolved in chloroform and the solution clouded with pentane and left at −5° for several days. The thick prisms that separated were filtered and washed with pentane; wt. 1.0 g. The product appeared to melt at 38–39° to a viscous sirup, and the same melting point was observed after recrystallization from chloroform–pentane. However, attempts to obtain an analytical sample by drying in the air at 20–25° resulted in liquefaction and either chloroform or pentane of crystallization was suspected. The product showed no tendency to crystallize from ethanol. For analysis and rotation the sample was heated to constant weight at 77° in a high vacuum; $[\alpha]^{20}\mathrm{D}$ −67° in chloroform (*c* 1.5).

Anal. Calcd. for $C_{35}H_{28}O_{10}$: C, 69.07; H, 4.64. Found: C, 68.94; H, 4.64.

2,7-Anhydro-β-D-*manno*-heptulopyranose Tetratosylate.—A mixture of 0.5 g. of the anhydride II and 4 g. of *p*-toluenesulfonyl chloride in 8 ml. of pyridine was kept at room temperature for 3 days and then poured onto cracked ice. A quantitative yield of the crystalline tosylate resulted. The product was recrystallized from 50 parts of absolute ethanol; it separated as fine needles that weighed 2.1 g. and melted at 145–147°. Recrystallization from chloroform–pentane then produced needles that melted at 85–100°, even after being dried at 60° overnight, and the product may have been solvated. A final recrystallization from ethanol gave the original, higher-melting form with m.p. 145–147° and $[\alpha]^{20}_{D}$ +29.4° in chloroform (*c* 1.2).

Anal. Calcd. for $C_{35}H_{36}O_{14}S_4$: C, 51.97; H, 4.49; S, 15.85. Found: C, 52.24; H, 4.55; S, 15.65.

2,7-Anhydro-3,4-*O*-isopropylidene-β-D-*manno*-heptulopyranose.—A mixture of 1.0 g. of the anhydride II, 10 g. of anhydrous copper sulfate and 100 ml. of acetone was stirred mechanically for 48 hours, filtered and the solution concentrated to a sirup (1.26 g.) that crystallized spontaneously. From acetone–pentane there was obtained 0.85 g. of the *O*-isopropylidene derivative; it separated as clusters of acicular prisms and, after three recrystallizations, melted at 106–107° and showed $[\alpha]^{20}_{D}$ −21.8° in water (*c* 2). Assignment of the *O*-isopropylidene group to the 3,4-positions is by analogy with 1,6-anhydro-β-D-mannopyranose and similar compounds.

Anal. Calcd. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.95. Found: C, 51.70, 51.91; H, 6.91, 6.95.

1,6-Anhydro-β-D-mannopyranose from D-Mannose in Acid Solution and Isolation as Its 2,3-*O*-Isopropylidene Derivative.—Preliminary experiments showed that D-mannose suffered only negligible loss of rotatory power when a 0.1 *M* solution in 0.2 *N* hydrochloric acid was heated at 40° and at 60°. When a 0.2 *M* solution in 0.2 *N* hydrochloric acid was equilibrated overnight at 20° it showed $[\alpha]^{20}_{D}$ +13.99°; after the solution had been heated at 80° for 3 and 6 hours, the rotations were +13.82 and +13.70°, respectively. For the attempted isolation of the expected very small amount of anhydride, three portions of D-mannose, totaling 144.13 g. and made to 4 liters at 20° in volumetric flasks with 0.2 *N* sulfuric acid, were allowed to stand overnight at that temperature. The rotations were $[\alpha]^{20}_{D}$ +13.98, +13.96 and +14.06°. The first liter portion was heated 24 hours at about 70° and then showed $[\alpha]^{20}_{D}$ +13.38°. The second liter portion was heated 32 hours at about 83° and then showed $[\alpha]^{20}_{D}$ +13.24°. The third, 2-liter portion was heated 24 hours at about 83° and then showed $[\alpha]^{20}_{D}$ +13.17°. These final values correspond to the presence of 0.5, 0.6 and 0.7%, respectively, of 1,6-anhydro-β-D-mannopyranose, calculated on the assumption that the solutions contained only D-mannose and its known anhydride. Reducing sugar determinations by the ferricyanide method indicated a small loss but the values were not considered reliable because the apparent change was less than the limit of accuracy of the method. Ultraviolet absorption data showed that less than 0.2% of 5-(hydroxymethyl)-2-furaldehyde was generated by heating D-mannose under these conditions.

The unchanged D-mannose in the 4 liters of solution was sacrificed by heating with excess barium hydroxide, and then neutralizing, filtering, deionizing and concentrating in the usual manner. The sirupy residue had a levorotation corresponding to 0.62 g. of the expected anhydride, but it weighed 9 g. and still contained material that reduced Fehling solution. Accordingly, it was treated again with barium hydroxide and the new sirup weighed 3.1 g. and had a levorotation corresponding to 0.91 g. (0.70%) of the expected anhydride. When an attempt to isolate 1,6-anhydro-β-D-mannopyranose by direct crystallization was unsuccessful, the sirup was extracted with 300 ml. of acetone at room temperature and the extract shaken with 10 g. of anhydrous copper sulfate for 42 hours. The filtered and concentrated solution crystallized readily. The product, isolated in two batches with the aid of 2-propanol and 1-butanol, weighed 0.87 g. (0.54%) and after one recrystallization from 1-butanol was identified as 1,6-anhydro-2,3-*O*-isopropylidene-β-D-mannopyranose[10] by melting point and mixed melting point of 160–161° and specific rotation $[\alpha]^{20}_{D}$ −57.5° in water (*c* 1.8). Knauf, Hann and Hudson[10] reported m.p. 161–162° and $[\alpha]^{20}_{D}$ −58.8° in water (*c* 2.08).

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[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

Crystalline 3-Deoxy-α-D-*ribo*-hexose. Preparation and Properties of 1,6-Anhydro-3-deoxy-β-D-*arabino*-hexopyranose, 1,6-Anhydro-3-deoxy-β-D-*ribo*-hexopyranose and Related Compounds[1,2]

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3-Deoxy-D-*arabino*-hexose and 3-deoxy-D-*ribo*-hexose have been shown to form their 1,6-anhydrides in aqueous acid to the extent of 29 and 10%, respectively. The 1,6-anhydrides were characterized as their di-*O*-acetyl derivatives. 3-Deoxy-α-D-*ribo*-hexopyranose and the phenyl 3-deoxy-α- and β-D-*ribo*-hexopyranosides have been obtained crystalline.

When LaForge and Hudson[3] established that hot aqueous acid acts on sedoheptulose (= D-*altro*-heptulose) to form a non-reducing anhydride, they were led to assume that this sugar is unique in this respect since their observation had no precedent, and, of course, many sugars had previously been subjected to such conditions on many occasions. An extension of this idea to include all sugars possessing the *altro* configuration was strongly suggested by the fact that D-altrose exhibits the same property.[4] Subsequently, the results of a number of investigations in this Laboratory have shown that although the amount of anhydride at equilibrium varies from more than 90% to less than 1%, the reaction is quite general among the aldohexoses, aldoheptoses and heptuloses.

Reeves[5] has sought to explain the ease of formation of the altrose[4] and idose[6] anhydrides in dilute aqueous acid in terms of the ring conformation of the parent aldohexose. His suggestion that the conformation of the β-D-pyranose ring exerts a con-

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[1] Presented in part before the Division of Carbohydrate Chemistry at the Atlantic City Meeting of the American Chemical Society, September 18, 1956.

[2] For the preceding paper on anhydro sugars see E. Zissis, L. C. Stewart and N. K. Richtmyer, THIS JOURNAL, **79**, 2593 (1957).

[3] F. B. LaForge and C. S. Hudson, *J. Biol. Chem.*, **30**, 61 (1917).

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[5] (a) R. E. Reeves, *ibid.*, **72**, 1499 (1950); (b) *Advances in Carbohydrate Chem.*, **6**, 107 (1951).

[6] E. Sorkin and T. Reichstein, *Helv. Chim. Acta*, **28**, 1 (1945).