tion. One recrystallization from 250 ml. of 95% ethanol yielded 6.4 g. (80%) of tetrabenzoylsedoheptulosan of m.p. 165–166° and $[\alpha]^{20}D$ −188° in chloroform (*c* 0.88).

A similar experiment was made in which the 10% sulfuric acid solution of sedoheptulosan was heated on the steam-bath, reaching a constant rotation of $[\alpha]^{20}D$ −133° (calculated as sedoheptulosan) in 1.25 hours. A 75% yield of tetrabenzoylsedoheptulosan was then obtained by the procedure described above.

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[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, FEDERAL SECURITY AGENCY]

Proof of the Structure of Sedoheptulosan as 2,7-Anhydro-β-D-altroheptulopyranose[1]

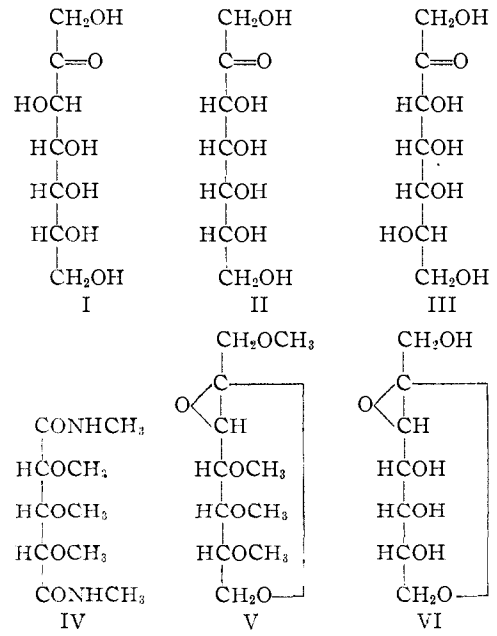
BY JAMES W. PRATT, NELSON K. RICHTMYER AND C. S. HUDSON

Oxidation of sedoheptulosan with periodate, hydrogenation of the resulting dialdehyde, and subsequent hydrolysis of the product yielded glycerol. Oxidation of tetramethylsedoheptulosan with nitric acid yielded as a final product the optically active N,N'-dimethyl-D-*arabo*-2,3,4-trimethoxyglutaramide and not the optically inactive *ribo* derivative reported by Hibbert and Anderson in 1930. These data permit sedoheptulosan to be formulated only with a normal pyranose ring and as either a 1,2- or a 2,7-anhydride. Four arguments have been advanced, all leading to the conclusion that sedoheptulosan is 2,7-anhydro-β-D-altroheptulopyranose.

In 1917 LaForge and Hudson[2] discovered in *Sedum spectabile* Bor. the ketoheptose that is now known as sedoheptulose. Its configuration as D-altroheptulose (I) was established in 1932 by Ettel,[3] and confirmed later by its degradation to D-altronic acid in this Laboratory.[4] Although the sugar itself has not yet been obtained in crystalline form, LaForge and Hudson described the transformation of sedoheptulose sirup in the presence of acids to the crystalline, non-reducing anhydride, sedoheptulosan, whose structure is the subject of this paper.

In 1930 Hibbert and Anderson[5] methylated sedoheptulosan with methyl iodide and silver oxide, oxidized the resulting crystalline tetramethylsedoheptulosan with nitric acid, and obtained a trimethoxyglutaric acid that was characterized by its methylamide melting at 145–146°. This methylamide was optically inactive, and, because at that time it was believed that sedoheptulose was either D-alloheptulose (II) or L-taloheptulose (III),[6] the new substance was presumed to be *ribo*-trimethoxyglutaric methylamide (IV).[7] Hibbert and Anderson then concluded that sedoheptulosan contained the usual 2,6-pyranose ring and a 2,7-anhydro ring, a decision that agreed with either formula II or III for sedoheptulose. The condensation of sedoheptulosan with an excess of trityl chloride to yield only a monotrityl derivative, indicating the presence of only one primary alcohol group, appeared to confirm their suggested structure.

However, when Ettel[3] advanced his conclusive proof that sedoheptulose is D-altroheptulose, and Levene and Compton[8] prepared from 2,3,4-trimethyl-D-ribose an authentic *ribo*-trimethoxyglutaric methylamide that agreed in its melting point and in its optical inactivity with the product described by Hibbert and Anderson,[5] the arguments for a 2,6:2,7-structure for sedoheptulosan were no longer tenable, and in 1938 one of us[9] drew the following conclusion: "Assuming the correctness of I for the configuration of sedoheptulose (from Ettel's work) and of the observation that tetramethylsedoheptulosan yields by oxidation *ribo*-trimethoxyglutaric acid (from the work of Hibbert and Anderson and of Levene and Compton) there



is only one stereostructure that can apply to tetramethylsedoheptulosan, namely, V, and there follows for sedoheptulosan necessarily the stereostructure VI." Hibbert and Anderson's observation regarding the monotrityl derivative applied equally well to formula VI for sedoheptulosan.

Because the combination of ethylene oxide and septanoid rings in formula VI was in such marked contrast to the 1,5- and 1,6-ring combination that

(1) A portion of this material has been taken from the thesis submitted by James W. Pratt to the Department of Chemistry of the Graduate School of Georgetown University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1951.

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

(3) V. Ettel, *Collection Czechoslov. Chem. Communs.*, **4**, 513 (1932).

(4) N. K. Richtmyer, R. M. Hann and C. S. Hudson, THIS JOURNAL, **61**, 343 (1939).

(5) H. Hibbert and C. G. Anderson, *Can. J. Research*, **3**, 306 (1930).

(6) F. B. LaForge, *J. Biol. Chem.*, **42**, 367 (1920).

(7) The optically inactive *xylo*-trimethoxyglutaric methylamide melts at 167–168° [W. N. Haworth and D. I. Jones, *J. Chem. Soc.*, 2349 (1927)].

(8) P. A. Levene and J. Compton, *J. Biol. Chem.*, **116**, 184 (1936).

(9) C. S. Hudson, THIS JOURNAL, **60**, 1241 (1938).

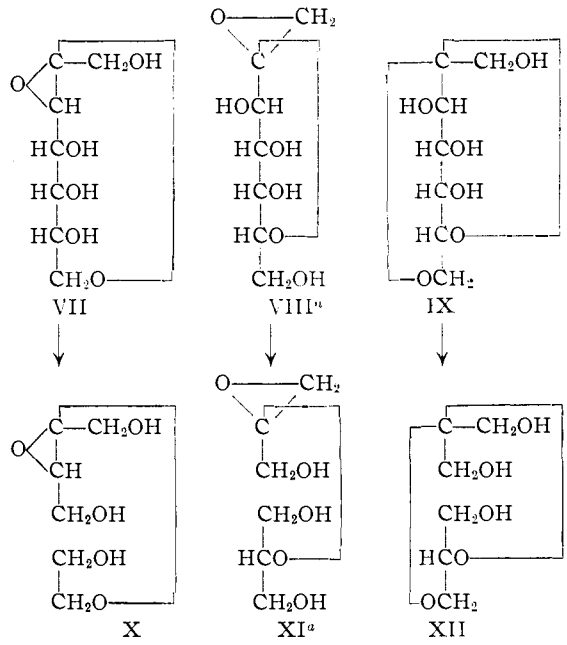
occurs in levoglucosan and many other aldosans, a confirmatory proof of structure for sedoheptulosan was sought in a study of its behavior toward periodate oxidation. In the preceding paper[10] it was reported that the reaction consumed two molecular equivalents of periodic acid and liberated one molecular equivalent of formic acid, but no formaldehyde; these data permit either a 2,3:2,7- or a 2,6:2,7-structure. The dialdehyde thus produced was oxidized further with hypobromite but the resulting dibasic acid appeared to be too stable to permit hydrolysis and subsequent identification of a cleavage product that would serve to distinguish between the two structures in the usual way.

In the present series of investigations we first verified the observation that the reaction of sedoheptulosan with periodate shows the presence of three contiguous secondary hydroxyl groups. This circumstance allows us to write three possible arrangements of two rings, namely, those shown in formulas VII, VIII and IX.[11] When the dialdehyde resulting from this oxidation was hydrogenated catalytically, as announced in our preliminary note,[12] the product could then be hydrolyzed with acid, and one of the cleavage products was isolated and identified as glycerol through its tri-(*p*-nitrobenzoate). We have since found that acetolysis of the reduced dialdehyde (X, XI, or XII) also resulted in cleavage of the molecule, and again one fragment, after deacetylation, was identified as glycerol through its reaction with tosyl chloride and pyridine for 14 days at room temperature. The product was the same crystalline dichlorotosyloxypropane that could be obtained by the tosylation of an authentic sample of glycerol under the same conditions.

From these experiments we must conclude that formula VII cannot apply to sedoheptulosan, for glycerol could have come only from structure XI or XII. However, this conclusion is at variance with that drawn previously by one of us[9] from Hibbert and Anderson's description of their methylation studies because a *ribo*-trimethoxyglutaric acid could not result from the oxidation of either methylated VIII or IX. We have, therefore, repeated Hibbert and Anderson's oxidation of tetramethylsedoheptulosan with nitric acid, esterified the resulting mixture of organic acids, and converted the fractionated esters to methylamides. From the ester fraction of highest methoxyl content we have obtained not *ribo*- but D-*arabo*-trimethoxyglutaric methylamide, and identified it through its melting point and rotation by direct comparison with an authentic sample. Again we must conclude that formula VII cannot apply to sedoheptulosan, and that the D-*arabo*-trimethoxyglutaric acid could have been obtained only from the tetramethyl derivative of VIII or IX.

How then can one explain the appearance of *ribo*-trimethoxyglutaric methylamide during Hibbert and Anderson's experiments? The most obvious answer would be to suggest that there are two sedoheptulosans, one with the formula VII and the other with formula VIII or IX. This possibility was quickly eliminated, for, through the courtesy of Professor Clifford B. Purves of McGill University, we were able to examine the remainder of the original sample of sedoheptulosan that LaForge had sent to Hibbert and Anderson for their experiments on its structure. After 21 years their sedoheptulosan sample was still the anhydrous modification (see Experimental section) melting at 152–155° and showing $[\alpha]^{20}D$ −145° in water (*c* 2), and a mixture of their sample with our starting material melted at 154–155°. Furthermore, the samples of tetramethylsedoheptulosan undoubtedly represented only one compound as shown by a comparison of the melting point (48–49°) and rotation ($[\alpha]^{20}D$ −137°) reported by Hibbert and Anderson with the melting points (52–53° and 52–55°) and rotations ($[\alpha]^{20}D$ −145° and −147°) reported in the preceding[10] and the present paper, respectively.

Since there is no reason to believe that there are two sedoheptulosans, what was the source of Hibbert and Anderson's *ribo*-trimethoxyglutaric methylamide? Our experiments have proved that it could not have come from tetramethylsedoheptulosan. Yet the evidence that they had this methylamide in hand appears conclusive; it had not been known before and their record of its melting point, in addition to its analysis and lack of optical activity, was corroborated later by Levene and Compton,[8] who prepared it from authentic 2,3,4-trimethyl-D-ribose. It is difficult to answer this puzzling question. We can only hazard the surmise that Hibbert and Anderson obtained the *ribo* derivative as a result of their concurrent experiments on the epimerization of 2,3,4-trimethyl-L-arabonic acid rather than from tetramethylsedoheptulosan and became confused as to its origin.



[a] The β-modifications are depicted here, although α-modifications should be equally possible.

(10) W. T. Haskins, R. M. Hann and C. S. Hudson, THIS JOURNAL, 74, 2198 (1952).

(11) The representation of configuration at carbon 2 in these projection formulas supersedes that used in earlier formulas.

(12) J. W. Pratt, N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, 73, 1876 (1951).

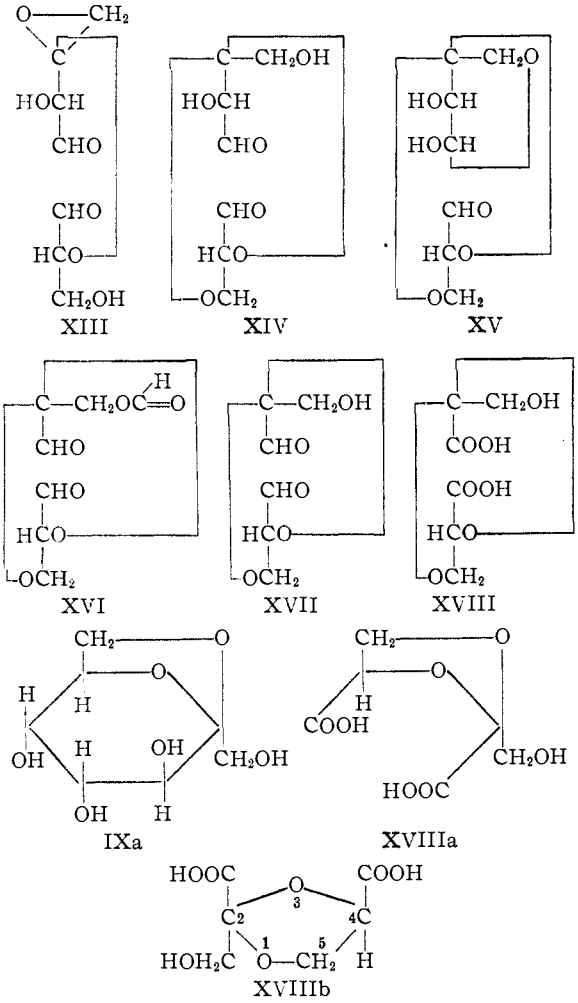
Still another argument against formula VII for sedoheptulosan that has developed during a study of L-guloheptulose and its anhydride will be presented in an accompanying contribution from this Laboratory.[13]

So far we have proved that sedoheptulosan cannot have the structure VII but must be represented by either VIII or IX. We shall now present the several separate pieces of evidence that led to the final selection of IX as the correct formula.

In the oxidation of sedoheptulosan with sodium metaperiodate the reaction occurred rapidly and the consumption of two moles of oxidant per mole of glycosan was complete within an hour. The optical activity, however, changed continuously over a period of about 12 days and the amount of liberated formic acid increased slowly from the initial values of 0.4 mole observed after 1 hour and 0.5 mole after 24 hours to a final constant value of 1.0 mole only after about 12 days. This behavior can be interpreted readily by applying the principles that were summarized by Hockett, Dienes and Ramsden[14] in their studies of lead tetraacetate oxidations; the extension of these principles to periodate oxidations seems to be justified. The principles may be restated as follows. (1) If two of three vicinal hydroxyl groups are themselves vicinal and *cis*, the structure is oxidized more rapidly than if all hydroxyl groups are vicinally *trans*. (2) An α-hydroxy aldehyde is attacked but the rate of oxidation is often low. (3) An α-hydroxy aldehyde will be oxidized relatively rapidly if another hydroxyl group in a position γ or δ to the carbonyl permits formation of a pseudoglycol structure by cyclic hemiacetalization.

In the light of these principles we see that both VIII and IX contain a pair of vicinal *cis* hydroxyl groups at C_4 and C_5 and we should expect the first stage of oxidation to be rapid, leading mainly to the α-hydroxy aldehydes XIII and XIV, respectively. Here the similarity ends, for XIII should be oxidized slowly with concomitant liberation of formic acid, whereas XIV can cyclize to form a furanose ring and the pseudoglycol XV should then be oxidized rapidly with the consumption of the second mole of oxidant. The resulting product XVI would then be an ester of formic acid[15] that might be expected to hydrolyze only slowly, with final production of the dialdehyde XVII. This interpretation fits the experimental observations so closely that formula IX rather than formula VIII must be selected for sedoheptulosan.

As noted previously,[12] the failure of tetratosylsedoheptulosan to react at 100° with sodium iodide[10] is in accord with formula IX for sedoheptulosan. Even though it must contain a primary tosyloxy group, tetratosylsedoheptulosan behaves like the 1-tosylketose derivatives that have been reported elsewhere.[16] On the other hand, a normal replacement by an iodine atom of the primary tosyloxy group at C_7 would be expected if sedoheptulosan had the formula VIII.



A third cogent reason for preferring formula IX to VIII comes from the knowledge that sedoheptulosan is quite resistant to the action of hot aqueous alkali. A compound of the type VIII contains an ethylene oxide ring which would normally be expected to open under the influence of alkali. Substances of the type IX, however, differing from it only in having an H atom in place of the CH_2OH group, are well known for their stability to alkali; in fact, 1,6-anhydro-β-D-mannopyranose, 1,6-anhydro-β-D-glucopyranose (= levoglucosan), and similar anhydrides may be prepared in nearly quantitative yields by the alkaline degradation of their respective phenyl glycosides.[17]

Still another reason in favor of IX is derived from the observation of Haskins, Hann and Hudson[10] that the dibasic acid obtained by the oxidation of sedoheptulosan with periodate followed by hypobromite is resistant to acid hydrolysis just as Jack-

(13) L. C. Stewart, N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **74**, 2206 (1952).

(14) R. C. Hockett, M. T. Dienes and H. E. Ramsden, *ibid.*, **65**, 1474 (1943).

(15) In a recent discussion of our proposed mechanism, Dr. R. C. Hockett, of the Sugar Research Foundation, Inc., New York, informed us that in a somewhat analogous oxidation he had successfully isolated such an intermediate formic acid ester; his results will be published later.

(16) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **120**, 607 (1937); T. S. Gardner and J. Lee, *J. Org. Chem.*, **12**, 733 (1947); see also H. Müller and T. Reichstein, *Helv. Chim. Acta*, **21**, 263 (1938); and W. T. J. Morgan and T. Reichstein, *ibid.*, **21**, 1023 (1938).

(17) E. M. Montgomery, N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **64**, 1483 (1942); **65**, 1848 (1943); *J. Org. Chem.*, **10**, 194 (1945).

son and Hudson[18] found to be true for their dibasic acid produced from levoglucosan. Formula VIII for sedoheptulosan would yield as a final oxidation product a substance with a glycosidic linkage at the original C_2; formula IX, on the other hand, would lead to a dibasic acid XVIII whose structure would be strictly analogous to that already proved for the product from levoglucosan. The dibasic acid from sedoheptulosan is indeed sufficiently stable to permit formation from it of a dibenzimidazole under the drastic conditions recommended by Moore and Link.[19] Incidentally, this dibenzimidazole furnishes an excellent reference compound that has already proved useful in elucidating the structure of some other heptulosans to be described in subsequent papers from this Laboratory.

We have thus established that sedoheptulosan is to be represented as IX by the Fischer projection formula, or as IXa by the Haworth projection formula. The dibasic acid can then be written as XVIII or XVIIIa. According to the nomenclature elaborated by Jackson and Hudson,[18,20] compound XVIII would be named D′-hydroxymethyl-L′-oxy-D-methylenediglycolic acid and XVII would be the corresponding diglycolic aldehyde. However, for indexing purposes and for showing the spatial arrangements of the several functional groups it now seems desirable to write and name such substances as derivatives of 1,3-dioxolane. The dibasic acid XVIII is thus written as XVIIIb. The carbon atom in position 4 of the dioxolane ring has the same configuration that it had as C_6 in the original sedoheptulose, and XVIIIb is named accordingly as 4-D-*glycero*-2-hydroxymethyl-1,3-dioxolane-2,4-*cis*-dicarboxylic acid; XVII then becomes 4-D-*glycero*-2-hydroxymethyl-2,4-*cis*-diformyl-1,3-dioxolane; and the reduced dialdehyde XII becomes 4-D-*glycero*-2,2,4-tri-(hydroxymethyl)-1,3-dioxolane.

Experimental

Sedoheptulosan (IX) and Sedoheptulosan Hydrate.—About 5 kg. of fresh leaves and stalks of *Sedum spectabile* was forced through a food grinder, the product mixed with an equal volume of water, and the liquid separated with a small press. The press cake was disintegrated, covered with water, and allowed to stand overnight, then pressed again and the extracts combined. The solution was heated with activated carbon, filtered, and concentrated *in vacuo* to a thin sirup that was poured into 2 liters of warm 95% ethanol. The granular precipitate was removed by filtration, the ethanol distilled *in vacuo*, and the residue diluted to 1 liter with water. Fifteen milliliters of concentrated sulfuric acid was added and the mixture heated for 5 hours on the steam-bath to transform the sedoheptulose to its equilibrium mixture containing 80% of its anhydride. The solution was cooled, neutralized with solid barium carbonate, filtered, deionized by passage through a suitable pair of ion-exchange resins such as Amberlite IR-120 and Duolite A-4, and concentrated *in vacuo* to a thick sirup. Solution of the sirup in hot methanol, followed by cooling and inoculation with a seed crystal, produced sedoheptulosan in a yield of about 0.75% in good agreement with that expected on the basis of an estimated 1% of sedoheptulose in the fresh *Sedum* plant. Additional sedoheptulosan can be obtained by concentrating the mother liquor, and especially by combining several mother liquors and treating them with acid to convert the remaining sedoheptulose to its equilibrium mixture with the anhydride. The product, purified by recrystallization from methanol, consisted of large, clear, chunky prisms of m.p. 155–156° and $[\alpha]^{20}D$ −146° in water (*c* 2).

Sedoheptulosan thus obtained was considered to be stable in the air until in May, 1948, a sample that had been prepared earlier by another worker in this Laboratory was found to be a chalky white powder with m.p. 100–140°. A freshly crystallized sample of sedoheptulosan was then exposed to the air, and in the course of 6 weeks the crystals gradually lost their transparency, became white, and gained 8.7% in weight (calcd. for 1 H_2O: 9.4%). A portion of the same material, powdered, reached a constant weight in air in about 1 week, and analysis showed it to have the composition of a sedoheptulosan monohydrate; its $[\alpha]^{20}D$ value of −134° in water (*c* 2) corresponded to $[\alpha]^{20}D$ −146° when calculated as the anhydrous substance.

Anal. Calcd. for $C_7H_{12}O_6 \cdot H_2O$: C, 40.00; H, 6.71; H_2O, 8.57. Found: C, 40.18; H, 6.92; H_2O (at 57° in high vacuum), 8.44.

In January, 1949, some sedoheptulose sirups were treated with sulfuric acid as described above and the neutralized and deionized solutions concentrated *in vacuo*. During the distillation of the second portion of these, crystals appeared in the aqueous solution before the sirupy sedoheptulosan stage was reached, and sedoheptulosan hydrate was thus obtained directly in crystalline form for the first time. When the hydrate crystallizes in this manner it is well to add methanol and recover the product by filtration. To obtain the anhydrous modification from the hydrate, the latter is recrystallized from about 15 parts of methanol; the anhydrous sedoheptulosan, if filtered rapidly and placed in a desiccator, may be kept in that form practically unchanged for years. Recrystallization of either form from about 7 parts of 90% ethanol yields clear, columnar prisms of sedoheptulosan hydrate, which is now the stable form in this Laboratory.[21] The hydrate melts at 101–102° after preliminary sintering at 91°, and shows $[\alpha]^{20}D$ −134° in water (*c* 2).

Anal. Calcd. for $C_7H_{12}O_6 \cdot H_2O$: H_2O, 8.57. Found (at 57° in vacuum): H_2O, 8.45. Calcd. for $C_7H_{12}O_6$: C, 43.75; H, 6.30. Found (on dried sample): C, 43.83; H, 6.47.

The X-ray powder diffractions of sedoheptulosan and its hydrate have been obtained recently by Wolfrom, Berkebile and Thompson, and will be reported in another place.[22]

Sedoheptulosan appears to be completely stable toward alkali. A 10-g. sample of the hydrate in 250 ml. of *N* sodium hydroxide was heated in a silver flask on the steam-bath for 45 hours. At the end of that time the solution was colorless, its rotation was identical with that of the original solution, and, after deionization and concentration, crystalline sedoheptulosan was recovered in nearly quantitative yield.

Oxidation of Sedoheptulosan with Sodium Metaperiodate.—A solution of 0.3157 g. of sedoheptulosan in 25 ml. of water was cooled in an ice-bath and 10 ml. of an approximately 0.5 *M* solution of sodium metaperiodate was added. The solution was kept in the ice-bath for 10 minutes after mixing, then allowed to warm slowly to room temperature. The volume was adjusted exactly to 50 ml. by the addition of water, the optical activity of the solution was noted, and an aliquot was titrated for oxidant consumed and acid produced. The first titration, 52 minutes after addition of the oxidant, showed 1.98 moles of oxidant consumed per mole of glycosan, and this value did not change throughout the course of the experiment, a total of 17 days. However, only 0.4 mole of acid per mole of glycosan was liberated in the first hour; this value increased to 0.5 mole in 24 hours, and reached a constant value of 1.01 moles of acid per mole of sedoheptulosan in about 12 days. During this time the observed rotation changed from an initial $\alpha^{20}D$ −0.17° to a final $\alpha^{20}D$ −0.25° in a 4-dm. tube. Repetition of the oxidation using 6.30 g. of sedoheptulosan in a total volume of 250 ml. of solution gave $[\alpha]^{20}D$ −16.9° as the specific rotation calculated for the expected dialdehyde (XVII).

4-D-*glycero*-2-Hydroxymethyl-1,3-dioxolane-2,4-*cis*-dicarboxylic Acid (XVIII) and Its Calcium Salt.—The solution of

(18) E. L. Jackson and C. S. Hudson, THIS JOURNAL, **62**, 958 (1940).

(19) S. Moore and K. P. Link, *J. Biol. Chem.*, **133**, 293 (1940).

(20) E. L. Jackson and C. S. Hudson, THIS JOURNAL, **59**, 994 (1937).

(21) A preliminary announcement of the appearance of sedoheptulosan hydrate was made in the paper by L. C. Stewart, N. K. Richtmyer and C. S. Hudson, *ibid.*, **71**, 3532 (1949).

(22) M. L. Wolfrom, J. M. Berkebile and A. Thompson, *ibid.*, **74**, 2197 (1952).

dialdehyde (XVII) obtained above from 6.30 g. of sedoheptulosan was oxidized further with hypobromite and the dibasic acid isolated as the calcium salt as described in the preceding paper.[10] After one recrystallization from aqueous ethanol it showed $[\alpha]^{20}D$ +41.8°in water (*c* 1), as compared with the previously reported value of +43.5° (*c* 0.88).

Anal. Calcd. for $C_6H_6O_7Ca \cdot 3H_2O$: C, 25.35; H, 4.26; Ca, 14.10. Found (air-dried material): C, 25.65; H, 4.45; Ca, 14.16.

4-D-*glycero*-2-Hydroxymethyl-2,4-*cis*-di-(2-benzimidazolyl)-1,3-dioxolane.—Following the method of Moore and Link,[19] 2 g. of the hydrated calcium salt of XVIII was placed in a large test-tube with 1.7 g. of *o*-phenylenediamine, 2.5 ml. of concentrated hydrochloric acid, 4 ml. of water and 0.5 ml. of 95% ethanol. The mixture was heated in an oil-bath at 135 ± 5° for 3 hours, then diluted with 10 ml. of water, heated with a small amount of activated carbon, and filtered. The solution was made strongly alkaline with concentrated aqueous ammonia, whereupon a sirupy mass was deposited and soon became crystalline. Upon recrystallization from 95% ethanol there was obtained 0.75 g. (31%) of nearly colorless, rectangular platelets. The air-dried material appeared to be a monohydrate, for it lost 5.9% of its weight (calcd. 5.1%) when heated for 4 hours at 100° and 0.1 mm. The anhydrous product thus obtained melted at about 137° to a stiff sirup that showed a characteristic complete liquefaction at about 160°. The anhydrous benzimidazole showed the rotation $[\alpha]^{20}D$ −12.9 ± 1.5° in *N* hydrochloric acid (*c* 1.6).

Anal. Calcd. for $C_{18}H_{16}N_4O_3$: C, 64.27; H, 4.80; N, 16.66. Found (anhydrous crystals): C, 64.32; H, 4.92; N, 16.75.

4-D-*glycero*-2,2,4-Tri-(hydroxymethyl)-1,3-dioxolane (XII).[23]—Fifty grams of sedoheptulosan was oxidized to the dialdehyde XVII with an excess of paraperiodic acid. The solution was made barely alkaline to phenolphthalein with barium hydroxide, filtered to remove the precipitated barium iodate and periodate, balanced with sulfuric acid, concentrated to 1 liter under diminished pressure, then diluted with ethanol to remove any remaining salts, and again concentrated. The resulting sirup was dissolved in 600 ml. of 50% aqueous ethanol and shaken at 100° for 8 hours with 10 g. of Raney nickel catalyst under hydrogen at 3000 p.s.i. (about 200 atmospheres). The solution was filtered, deionized by passage through Amberlite IR-120 and Duolite A-4 ion-exchange resins, and concentrated *in vacuo* to a thick sirup that did not crystallize.

Hydrolysis of 4-D-*glycero*-2,2,4-Tri-(hydroxymethyl)-1,3-dioxolane.[23]—A 21.3-g. portion of the sirupy dioxolane derivative XII in 200 ml. of 5 *N* hydrochloric acid was heated under a reflux condenser for 2 hours. The rotation observed in a 4-dm. tube changed from an initial $\alpha^{20}D$ −1.58° to a final value of 0°. During the heating the solution became dark brown, gave off a strong odor of burnt sugar, and amorphous material collected on its surface; these phenomena were presumably due to the action of the concentrated acid on the liberated dihydroxyacetone. The solution was decolorized, filtered, deionized, and concentrated *in vacuo* to a clear, pale yellow, viscous liquid weighing 11 g. A small amount of this liquid, heated with dry potassium bisulfate, produced strongly lachrymatory fumes that in water solution gave a positive test for acrolein with acidified hydrogen peroxide and phloroglucinol.[24] One gram of the viscous liquid in dry pyridine was allowed to react with *p*-nitrobenzoyl chloride, yielding 1.9 g. (30%, based on the sirupy dioxolane XII) of once-recrystallized ester of m.p. 193–195°. This melting point was not depressed when the compound was mixed with authentic glycerol tri-(*p*-nitrobenzoate).

Acetolysis of 4-D-*glycero*-2,2,4-Tri-(hydroxymethyl)-1,3-dioxolane.—A 4.6-g. portion of the sirupy dioxolane derivative XII was dried by repeatedly heating it with benzene and then evaporating the solution on the steam-bath in a current of dry air. The resulting sirup was mixed with 20 ml. of acetic anhydride, cooled in an ice-bath, and 5 ml. of concentrated sulfuric acid added to it dropwise with constant stirring. The solution rapidly turned dark brown. Within 2 hours the observed rotation had changed from $\alpha^{20}D$ −0.20° (calculated) to +0.23°, but no further observations could be made because of the deep coloration of the solution. The mixture was kept for 18 hours in the refrigerator, then poured on cracked ice; the odor of sulfur dioxide was pronounced. The acetylated products were isolated with chloroform in the usual manner, and the sirupy material then deacetylated catalytically in methanol by the addition of sodium methoxide to the chilled solution. The deacetylated material was deionized, concentrated *in vacuo*, and dried by repeated solution in benzene and evaporation on the steam-bath in a current of dry air. Tosylation of the dry sirup in pyridine with excess *p*-toluenesulfonyl chloride for 12 days at 20° did not yield the expected crystalline tritosylglycerol; the resulting sirup, therefore, was dissolved in benzene–hexane (2:1), chromatographed on a column of activated alumina, and eluted fractionally with the same mixture of solvents. Three of the first fractions crystallized readily, yielding 0.8 g. of material that separated from 95% ethanol as large, colorless prisms melting at 65–67° and showing no observable rotation in chloroform.

Anal. Calcd. for $C_{10}H_{12}Cl_2O_3S$: C, 42.41; H, 4.27; Cl, 25.04; S, 11.32. Found: C, 42.59; H, 4.36; Cl, 25.23; S, 11.15.

The compound just described has the composition of a **dichlorotosyloxypropane**, and was presumably formed by the action of pyridine hydrochloride on the tritosylglycerol that was first formed.[25] Confirmatory evidence of such a reaction was secured by permitting a mixture of 3.7 g. of glycerol, 22.3 g. of *p*-toluenesulfonyl chloride, and 100 ml. of pyridine to stand at 20° for 14 days. It was noted that pyridine hydrochloride crystallized during the first 3 hours and then completely redissolved within the succeeding 3 days. The reaction mixture was decomposed with ice, and 1.3 g. (11%) of once-recrystallized material was obtained as described above. The product melted at 65–67°, a value not depressed when the sample was mixed with the compound of identical melting point obtained from the sedoheptulosan experiments above.

Oxidation of Tetramethylsedoheptulosan with Nitric Acid.—Twenty-eight grams of tetramethylsedoheptulosan (m.p. 52–55°, $[\alpha]^{20}D$ −147° in water), prepared conveniently by the methylation of sedoheptulosan with methyl sulfate and sodium hydroxide according to the general method of West and Holden,[26] was dissolved in 300 ml. of nitric acid (d. 1.42) and the temperature raised gradually to 90° in the course of 5 hours. The flask was heated for an additional 9 hours on the steam-bath. The evolution of nitric fumes became appreciably less after heating 10 hours, but did not cease altogether even during the later heating. The solution was diluted with an equal volume of water and the mixture was subjected to distillation under diminished pressure, additional water being added from time to time, until practically all the nitric acid had been removed. To the sirup was then added absolute ethanol, the mixture was concentrated, and the process was repeated several times to complete the removal of moisture. Finally the sirup was dissolved in absolute ethanol containing 1% hydrogen chloride and the mixed acids esterified by refluxing 9 hours. The ethanol solution was cooled, freed from hydrogen chloride with silver carbonate, filtered, and concentrated *in vacuo*. The resulting sirup was extracted with ether and filtered to remove any remaining salts, and the extract was concentrated *in vacuo* to a yellowish, rather mobile liquid weighing 15 g. The liquid was dissolved in a mixture of benzene and hexane (3:1) and the solvents distilled under diminished pressure to remove the ethanol. The residual sirup was redissolved in benzene–hexane (3:1) and chromatographed on a column of activated alumina. The first large fraction, which was eluted by running additional amounts of the benzene–hexane mixture through the column, consisted of 2.5 g. of a clear, pale yellow, mobile liquid containing 53.0% alkoxyl, reported as methoxyl. The theory for a diethyl trimethoxyglutarate is 55.8% alkoxyl, calculated as methoxyl. Subsequent benzene–hexane eluates yielded progressively more viscous sirups containing diminishing amounts of alkoxyl.

(23) These are the experimental details relating to our earlier note, ref. 12.

(24) E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," Order I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 45.

(25) Tosylation accompanied by chlorination has been reported also by K. Hess and H. Stenzel [*Ber.*, **68**, 981 (1935)]; they showed that chlorination could be effected on the primarily formed tosyl groups by pyridine hydrochloride. Our experiments support their observations.

(26) E. S. West and R. F. Holden, THIS JOURNAL, **56**, 930 (1934).

For conversion to methylamides the 2.5 g. of the first fraction described above was dissolved in 25 ml. of methanol, and the solution chilled in an ice-bath, saturated with dry methylamine, and allowed to warm slowly to room temperature (25–35°). After 60 hours the solvent was removed under diminished pressure, leaving a semi-solid mass from which could be obtained 1.6 g. of crystalline material. Attempts to purify this product showed several types of crystals and accordingly resort was had to flowing chromatography on a column of activated alumina. The dried material was dissolved in dioxane, poured on the column, and followed with benzene as the initial eluent. In this way two fractions were obtained weighing 0.44 and 0.68 g., respectively. Subsequent elutions with benzene and ether yielded negligible amounts of material and final elution with ethyl acetate brought the total recovery to 1.41 g. The 0.68-g. fraction was dissolved in 20 parts of methanol and diluted with an equal volume of ether. Overnight in the refrigerator the solution deposited 30 mg. of crystalline material that, without further purification, melted at 205–206° and showed $[\alpha]^{20}D$ −11.2 ± 2° in methanol (*c* 0.5). From these data and its analysis it would appear to be a slightly impure sample of N,N′-dimethyl-*meso*-2,3-dimethoxysuccinamide.[27]

Anal. Calcd. for $C_8H_{16}N_2O_4$: C, 47.04; H, 7.90; N, 13.72; CH_3O, 30.39. Found: C, 47.17; H, 7.65; N, 13.61; CH_3O, 30.45.

The mother liquor from the succinamide derivative was evaporated to dryness, the residue dissolved in 3 parts of hot ethyl acetate, and the product allowed to crystallize slowly. This procedure yielded 150 mg. of clear, colorless, prismatic needles melting at 145–164°. This material was sublimed *in vacuo:* a small amount of substance, which was not investigated further, sublimed at 50–80° (bath) and 0.7 mm. while the major portion sublimed at 150–160° (bath) and 0.4 mm. Eighty milligrams of the latter portion, of m.p. 151–167°, was recrystallized from 1.6 ml. of hot ethyl acetate, yielding 40 mg. of feathery needles of m.p. 165–170° and $[\alpha]^{20}D$ −70.1 ± 0.8° in methanol (*c* 1.2). The product was identified as N,N′-dimethyl-D-*arabo*-2,3,4-trimethoxyglutaramide through its analysis and by direct comparison, including a mixed melting point, with an authentic sample prepared as described below.

Anal. Calcd. for $C_{10}H_{20}N_2O_5$: C, 48.37; H, 8.12; N, 11.29; CH_3O, 37.50. Found: C, 48.58; H, 7.98; N, 11.47; CH_3O, 37.29.

Preparation of N,N′-Dimethyl-D-*arabo*-trimethoxyglutaramide from D-Arabinose.—After completing the isolation of the methylamide from sedoheptulosan as described above, we synthesized it in the following manner. **Methyl β-D-arabinopyranoside** was first prepared by a modified procedure that gave excellent yields with a minimum of effort. A suspension of 200 g. of D-arabinose in 900 ml. of methanol and 40 ml. of concentrated aqueous hydrochloric acid was boiled under a reflux condenser for 1 hour. The clear solution was inoculated as it cooled slowly to room temperature and then left in the refrigerator overnight. The filtered product weighed 46.2 g. The mother liquor was boiled in an open flask for 1 hour at such a rate that its volume was reduced to about 650 ml. Overnight the seeded and chilled solution deposited an additional 46.0 g., while a second and a third concentration to 450 ml., then to 225 ml., yielded 29.2 and 26.3 g., respectively, for a total of 147.7 g. of nearly pure methyl β-D-arabinopyranoside. By further concentration to 115 ml. and subsequent dilution of the mother liquor with an equal volume of ether two additional crops of crystals were obtained. These were purified by one recrystallization from 10 parts of methanol to raise the total yield to 175 g. (81%).

Methylation of 13.5 g. of methyl β-D-arabinopyranoside by the procedure of West and Holden,[26] followed by crystallization of the sirupy product from 10 ml. of ether and 90 ml. of pentane in a bath of Dry Ice and acetone, and filtration at −5°, yielded 11 g. of methyl trimethyl-β-D-arabinopyranoside. Its low melting point (not determined) and its rotation $[\alpha]^{20}D$ −248° in water (*c* 1) clearly identified it as the enantiomorph of the methyl trimethyl-β-L-arabinopyranoside of m.p. 44–46° and $[\alpha]^{20}D$ +250° in water (*c* 1) described by Hirst and Robertson.[28] The D form was first prepared by McOwan[29] who reported m.p. 43–45° and $[\alpha]^{16}D$ −217° in methanol.

Oxidation of 10.7 g. of the methyl trimethyl-β-D-arabinopyranoside in 110 ml. of nitric acid (d. 1.42) was accomplished by heating the mixture at 40–50° for 45 minutes, then at 60° for 1 hour, at 70° for 1 hour, and finally at 95° for 2 hours. The evolution of nitric fumes became vigorous when the temperature first reached 40° and then diminished gradually and became almost negligible after heating for about 2 hours. The product was converted to the methylamide in the usual manner. The crude crystalline product weighed 7.6 g. It was recrystallized twice from ethyl acetate and dried at 100° *in vacuo*. The N,N′-dimethyl-D-*arabo*-trimethoxyglutaramide thus obtained melted at 171–174°, resolidified on cooling, and melted again at the same temperature when reheated. Its rotation in water (*c* 1.3) was $[\alpha]^{20}D$ −60.0° and in methanol (*c* 1.2) −66.2°. The m.p. and rotation in water are in good agreement with the m.p. 172° and $[\alpha]^{20}D$ −60.0 to −61.0° in water reported by Lake and Peat[30] for the same compound obtained from tetramethyl-D-altropyranose and are comparable to the m.p. 172° and $[\alpha]^{18}D$ +59.9° in water (*c* 1) recorded by Haworth and Jones[7] for the enantiomorphous L-*arabo* derivative.

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(27) W. N. Haworth and D. I. Jones [*J. Chem. Soc.*, 2349 (1927)] reported the optically inactive *meso* compound to melt at 210°, and the D-compound to melt at 205° and show $[\alpha]^{17}D$ −132° in water (*c* 1.6).

(28) E. L. Hirst and G. J. Robertson, *ibid.*, **127**, 358 (1925); T. Purdie and R. E. Rose [*ibid.*, **89**, 1204 (1906)] had earlier reported m.p. 43–45°, $[\alpha]^{20}D$ +251° in water (*c* 10), and +223° in methanol (*c* 12).

(29) G. McOwan, *ibid.*, 1747 (1926).

(30) W. H. G. Lake and S. Peat, *ibid.*, 1417 (1938).