column. Elution of this zone with acetone and separation of the pale yellow acetate by evaporation of the solvent, resulted in a sirup which still failed to crystallize.

An amount of 10 g. of the above crude sirup, dissolved in 150 ml. of glacial acetic acid containing 0.01 g. of cupric acetate, was heated at reflux for 20 min. One hundred ml. of solvent was removed under reduced pressure and the residual solution was treated with decolorizing charcoal. This solution of crude *keto*-D-altroheptulose hexaacetate was diluted to 750 ml. with *N* HCl and refluxed for 3 hr. After treatment with decolorizing charcoal the solvent was removed under reduced pressure and the resultant sirup was dissolved in 50 ml. of 80% ethanol. The large crystals of sedoheptulosan monohydrate[4,11] that formed on slow evaporation of the solution at room temperature were recrystallized from hot 80% ethanol; yield 2.0 g., m.p. 100–102° with sintering at 90–92° unchanged on admixture with an authentic specimen[12] of like melting point behavior. X-Ray powder diffraction data (identical with those of an authentic specimen): 7.83[13]–4,[14] 6.15–3, 5.37–3, 4.95–1, 4.41–3, 4.11–3, 3.47–2, 3.32–5, 2.95–5, 2.61–5, 2.53–5, 2.46–5, 2.35–4, 2.20–5, 2.12–5.

Crystallization of the monohydrate from hot abs. methanol yielded the anhydrous form; m.p. 155°, $[\alpha]^{26}D$ −145° (*c* 4, water) in agreement with those (155° and −146°) cited by LaForge and Hudson.[2] X-Ray diffraction data[13,14]: 6.15–2, 5.61–1, 5.01–1, 4.23–5, 3.93–2, 3.44–4, 3.22–5, 3.20–5, 2.77–4, 2.56–5, 2.48–5.

(11) Laura C. Stewart, N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **71**, 3533, footnote 21 (1949).

(12) We are indebted to Dr. N. K. Richtmyer of the National Institutes of Health, Bethesda, Maryland, for an authentic sample of sedoheptulosan monohydrate.

(13) Interplanar spacing, Å.; λ, 1.5418 Å.; film exposure, 1.8 hr. Acknowledgment is made to Prof. P. M. Harris and Messrs. A. Mishkin and H. B. Wood for assistance in obtaining these data.

(14) Relative intensity, estimated visually; 1 = strongest line.

COLUMBUS 10, OHIO RECEIVED NOVEMBER 9, 1951

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

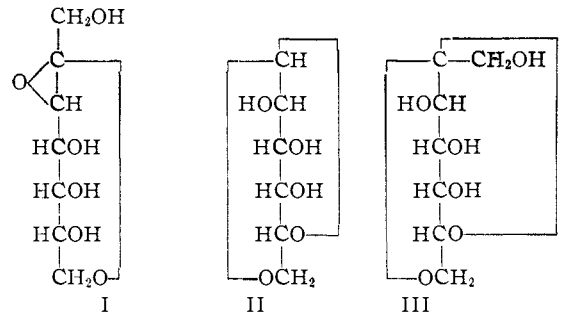
Some Reactions and Derivatives of Sedoheptulosan

BY W. T. HASKINS,[1] RAYMOND M. HANN[2] AND C. S. HUDSON

The behavior of sedoheptulosan and of tetramethylsedoheptulosan toward periodate oxidation has been studied; the molecular weight of sedoheptulosan and the position of the equilibrium between sedoheptulose and sedoheptulosan in acid have been confirmed; and crystalline isopropylidene, dimethylene, tetratosyl and tetrabenzoyl derivatives of sedoheptulosan have been described.

The experiments described in this paper were carried out several years ago and although they did not distinguish between the two most probable formulas for sedoheptulosan they did furnish valuable information leading to the definitive proofs of structure for that compound that are elaborated in the following paper.[3]

In 1938 one of us,[4] assuming the correctness of the experimental observations that had been reported from other laboratories, showed that sedoheptulosan must be regarded as possessing the unusual structure I, with one of its rings having an ethylene oxide form and the other a septanoid form. Shortly afterwards it was found[5] that D-altrosan, which is formed under acidic conditions from D-altrose in the same way that sedoheptulosan is formed from sedoheptulose (= D-altroheptulose), has a 1,6-anhydro ring and a normal pyranose ring as shown in formula II. Accordingly, it seemed desirable either to obtain a confirmatory proof of structure I for sedoheptulosan or to secure evidence of its possible formulation as III, analogous to that of D-altrosan (II). To this end we subjected sedoheptulosan to periodate oxidation[6]; the consumption of two molecular equivalents of oxidant and the liberation of one molecular equivalent of formic acid and no formaldehyde was in agreement with either I or III. Further oxidation of the dialdehyde with bromine water yielded a dibasic acid whose crystalline calcium salt had the composition $C_6H_6CaO_7 \cdot 3H_2O$. Unfortunately, neither the dialdehyde nor the dibasic acid appeared to be hydrolyzable to fragments whose identification would enable us to decide between formulas I and III for sedoheptulosan.



I II III

Other experiments described below have confirmed the monomeric molecular weight of sedoheptulosan and the position of its equilibrium with sedoheptulose under acidic conditions as first announced by its discoverers, LaForge and Hudson,[7] many years ago. Crystalline isopropylidene, dimethylene, tetratosyl and tetrabenzoyl derivatives of sedoheptulosan have been prepared and characterized.

Experimental

Oxidation of Sedoheptulosan by Periodic Acid Followed by Hypobromite.—The reaction of sedoheptulosan with sodium periodate will be discussed in the following paper.[3] For its reaction with periodic acid, 7.7 g. of sedoheptulosan in 300 ml. of water was mixed with 134 ml. (2.1 molecular equivalents) of 0.628 *M* periodic acid. After standing at 25° for 1 hour the reaction mixture was neutralized to phenolphthalein by the addition of aqueous calcium hydroxide.

(1) National Microbiological Institute, National Institutes of Health.

(2) Deceased April 30, 1949.

(3) J. W. Pratt, N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **74**, 2200 (1952); see also *ibid.*, **73**, 1876 (1951).

(4) C. S. Hudson, *ibid.*, **60**, 1241 (1938).

(5) N. K. Richtmyer and C. S. Hudson, *ibid.*, **62**, 961 (1940).

(6) A preliminary announcement of this reaction was reported by N. K. Richtmyer, *Advances in Carbohydrate Chem.*, **1**, 52 (1945).

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

The precipitated salts were removed by filtration and the filtrate was concentrated *in vacuo* to a thick sirup that was extracted with several 25-ml. portions of absolute ethanol and the filtered extracts concentrated *in vacuo* to remove the solvent. The residual sirup was dissolved in 500 ml. of water, 40 g. of calcium carbonate and 8.5 ml. of bromine were added, and the mixture was allowed to stand for 18 hours at 25°. Excess bromine was removed by aeration, the bromide ions by shaking with silver carbonate, and, following a filtration, the silver ions were precipitated with hydrogen sulfide. The clear, colorless, filtered solution was concentrated *in vacuo* to about 25 ml. and upon the addition of an equal volume of ethanol the calcium salt began to crystallize. After several days the salt was filtered, washed with ethanol, and allowed to dry at room temperature; it weighed 9.0 g. (79%). Upon recrystallization from aqueous alcohol it formed fine needles; the air-dried material had the composition of a trihydrate and an $[\alpha]^{20}D$ value of +43.5° in water (*c* 0.88). A solution of 4.0 g. of the hydrated salt in 20 ml. of water was freed from calcium ions by the addition of a slight excess of sulfuric acid and the calcium sulfate precipitated with ethanol. The filtered solution was concentrated to a sirup that was then made up to a volume of 50 ml. with *N* sulfuric acid. The rotation of the liberated dibasic acid under these conditions was estimated as $[\alpha]^{20}D$ +24° (*c* 5.4).

Anal. Calcd. for $C_6H_6CaO_7 \cdot 3H_2O$: C, 25.35; H, 4.26; Ca, 14.10; H_2O, 19.0. Found: C, 25.46; H, 4.28; Ca, 14.19; H_2O, 18.6.

Behavior of Tetramethylsedoheptulosan toward Periodic Acid.—The methylation of sedoheptulosan with methyl iodide and silver oxide as described by Hibbert and Anderson[8] yielded a product with m.p. 52–53° and $[\alpha]^{20}D$ −145° in water (*c* 0.84); their values were m.p. 48–49° and $[\alpha]^{20.5}D$ −137° in water (*c* 1.14).

Anal. Calcd. for $C_{11}H_{20}O_6$: C, 53.21; H, 8.12; CH_3O, 50.00. Found: C, 53.26; H, 8.09; CH_3O, 49.89.

If tetramethylsedoheptulosan contained an ethylene oxide ring as in formula I, it might hydrolyze slowly in periodic acid solution and liberate a pair of contiguous hydroxyl groups that would then be oxidized by that reagent. Experiment showed, however, that in such a solution kept at 25° for 6 days none of the oxidant was consumed.

The Molecular Weight of Sedoheptulosan.—A 0.4829-g. sample of pure sedoheptulosan depressed the freezing point of 9.975 g. of water 0.475°. The calculated molecular weight for $C_7H_{12}O_6$ is 192; found, 190. LaForge and Hudson[7] found 175. This verification of the molecular weight definitely excludes the possibility that sedoheptulosan is a dimolecular anhydride similar to the non-reducing diheterolevulosans and difructose anhydrides that are formed by the action of acids on D-fructose and inulin.[9]

Isopropylidenesedoheptulosan.—A suspension of 2.0 g. of finely powdered sedoheptulosan in 20 ml. of acetone containing 0.2 ml. of concentrated sulfuric acid was shaken for 24 hours; the character of the crystalline material changed from the original granular form to small, rod-like prisms. The product was recovered by filtration and washed free of acid with acetone; the yield was 2.4 g. (quantitative). It was recrystallized from 30 parts of methanol, forming clusters of elongated prisms melting at 226–227° and showing $[\alpha]^{20}D$ −124° in water (*c* 0.88). It is soluble in water, pyridine, dioxane, hot methanol and hot ethanol, and only slightly soluble in acetone, ether, petroleum ether, cold methanol and cold ethanol.

Anal. Calcd. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.95. Found: C, 51.77; H, 6.95.

Dimethylenesedoheptulosan.—A solution of 10 g. of sedoheptulosan in a mixture of 10 ml. of concentrated hydrochloric acid and 10 ml. of 37% aqueous formaldehyde was concentrated in a vacuum desiccator containing calcium chloride, sodium hydroxide and a beaker of concentrated sulfuric acid. After seven days the dark-colored, crystalline magma was stirred with 25 ml. of methanol, cooled to 5°, and filtered. The crude product was extracted with 175 ml. of boiling methanol and the hot extract, after filtration through a layer of activated carbon, gave a nearly colorless solution from which was deposited on cooling 4.1 g. (36%) of long, stiff needles. The dimethylene compound, after recrystallization from 30 parts of methanol, melted at 183–184° and showed $[\alpha]^{20}D$ −131° in water (*c* 0.86). It is soluble in water, dioxane, pyridine, hot methanol and hot ethanol, and nearly insoluble in ether, petroleum ether, cold methanol and cold ethanol.

Anal. Calcd. for $C_9H_{12}O_6$: C, 50.00; H, 5.60. Found: C, 50.19; H, 5.57.

Tetratosylsedoheptulosan.—To an ice-cold solution of 5.0 g. of sedoheptulosan in 50 ml. of pyridine was added 21.8 g. (4.4 molecular equivalents) of *p*-toluenesulfonyl chloride. After standing at 25° for 5 days the reaction mixture was poured into 500 ml. of ice-water and the fine, flocculent precipitate filtered and washed with water. The crude product, which was slightly sticky, was recrystallized by dissolving it in 2 parts of acetone and adding 10 parts of ether; the clusters of fine needles (18.4 g., 87%) then melted at 96–97° and showed $[\alpha]^{20}D$ −73.0° in chloroform (*c* 0.84). Tetratosylsedoheptulosan is very soluble in acetone, chloroform, pyridine, dioxane and methyl cellosolve, moderately soluble in hot methanol and hot ethanol, and nearly insoluble in ether, petroleum ether, cold methanol and cold ethanol.

Anal. Calcd. for $C_{35}H_{36}O_{14}S_4$: C, 51.97; H, 4.49; S, 15.85. Found: C, 51.82; H, 4.57; S, 15.80.

Tetratosylsedoheptulosan did not react with sodium iodide in acetone solution when heated for 65 hours at 100° in a sealed container, or in acetonylacetone when heated for 48 hours at 80°; at 130° the acetonylacetone reaction mixture became very dark and while 1 molecular equivalent of sodium *p*-toluenesulfonate was isolated at the end of 96 hours, 60% of the original tetratosylsedoheptulosan was recovered, indicating some deep-seated decomposition of a portion of the material.

Tetrabenzoylsedoheptulosan.—To an ice-cold solution of 1.0 g. of sedoheptulosan in 10 ml. of pyridine was added 5.0 ml. of benzoyl chloride. After standing at 25° for 24 hours the mixture was poured on 50 g. of crushed ice, thereby precipitating a thick gum that crystallized slowly while standing at 5° for several days. The product (3.2 g., quantitative) was recrystallized from 40 parts of 95% ethanol, forming lustrous, pointed plates that melted at 165–166° and showed $[\alpha]^{20}D$ −188° in chloroform (*c* 0.84). The tetrabenzoate is soluble in chloroform, acetone, ether and pyridine, and nearly insoluble in water and petroleum ether.

Anal. Calcd. for $C_{35}H_{28}O_{10}$: C, 69.07; H, 4.64; C_6H_5CO, 69.1. Found: C, 69.09; H, 4.69; C_6H_5CO, 69.4.

Upon debenzoylation catalytically with sodium methoxide it yielded sedoheptulosan of m.p. 154–155° and $[\alpha]^{20}D$ −146° in water (*c* 0.72).

The Equilibrium between Sedoheptulose and Sedoheptulosan in Acid Solution.—The equilibrium mixture was shown by LaForge and Hudson[7] to contain approximately 20% of the sugar and 80% of its anhydride, based on the copper reduction values of the solutions obtained by heating sirupy sedoheptulose or the crystalline sedoheptulosan in 1% hydrochloric acid until equilibrium was established. In a new study of this equilibrium we have confirmed these figures, both from equilibria established at 20° and at steam-bath temperature, by preparing and isolating crystalline tetrabenzoylsedoheptulosan from the mixture; this was possible because from crystalline sedoheptulosan the tetrabenzoate was obtained in quantitative yield, and the procedure may be employed as a means of estimating the amount of sedoheptulosan present in the equilibrium solutions.

Thus, a solution of 2.534 g. of sedoheptulosan ($[\alpha]^{20}D$ −146° in water) was made up to 25 ml. with 10% aqueous sulfuric acid and the rotation measured in a 1-dm. all-glass tube at 20°. The initial rotation, $[\alpha]^{20}D$ −147° (calculated as sedoheptulosan), changed to the equilibrium rotation, $[\alpha]^{20}D$ −134°, within 260 hours and remained unchanged for an additional 740 hours. The solution was then diluted with 500 ml. of water, neutralized with aqueous barium hydroxide, filtered to remove the precipitated barium sulfate, and the filtrate concentrated *in vacuo* to a dry sirup. The sirup was dissolved in 25 ml. of pyridine and 10 ml. of benzoyl chloride added; after standing at 25° for 18 hours the mixture was poured into 100 ml. of ice-water and the precipitated crystalline product recovered by filtra-

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

(9) For a review article, see E. J. McDonald, *Advances in Carbohydrate Chem.*, **2**, 253 (1946); see also M. L. Wolfrom and M. G. Blair, THIS JOURNAL, **70**, 2406 (1948) and M. L. Wolfrom, W. W. Binkley, W. L. Shilling and H. W. Hilton, *ibid.*, **73**, 3553 (1951).

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.

BETHESDA 14, MARYLAND RECEIVED NOVEMBER 16, 1951

[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]

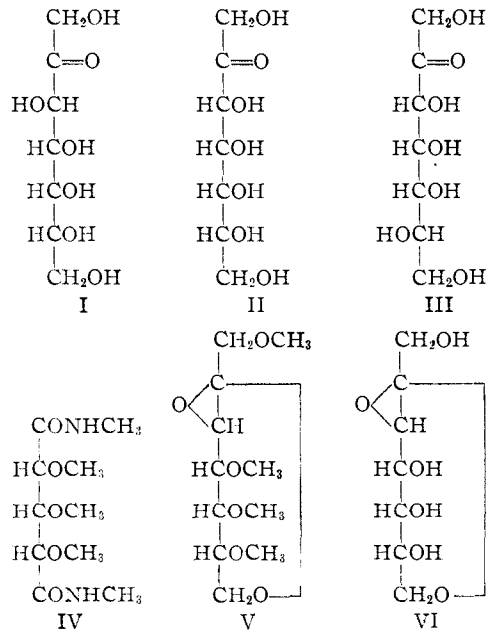
BY JAMES W. PRATT, NELSON K. RICHTMYER AND C. S. HUDSON

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).