tion from ether gave the analytical sample of 3β,17β-dihydroxy-Δ⁵-estrene monohydrate as fine short needles, m.p. 165.0–165.8°, $[\alpha]^{25}D$ +11.7°, M_D +33.5 (*c* 1.0, chf.).

Anal. Calcd. for $C_{18}H_{28}O_2 \cdot H_2O$: C, 73.43; H, 10.27. Found: C, 73.29; H, 10.28.

DETROIT 1, MICHIGAN

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

1,5-Anhydro-D-altritol[1]

BY EMMANUEL ZISSIS AND NELSON K. RICHTMYER

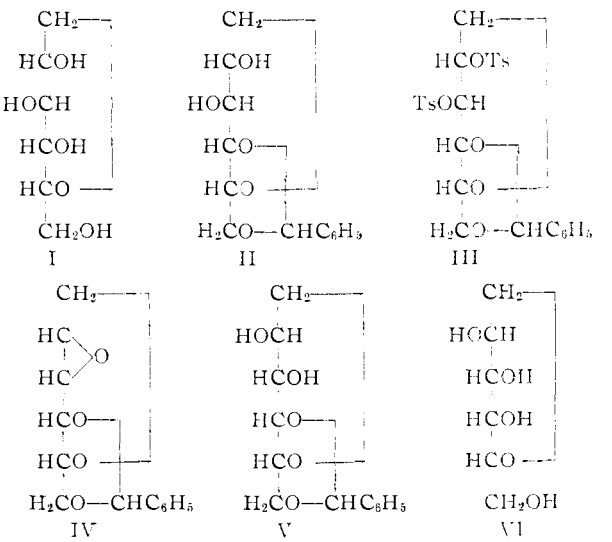
RECEIVED APRIL 29, 1955

1,5-Anhydro-D-glucitol (polygalitol) has been transformed, through a sequence of reactions involving carbon atoms 2 and 3, to the new 1,5-anhydro-D-altritol. The same anhydrohexitol has been obtained, though in very small yield, by lithium aluminum hydride reduction of the sirupy acetobromo compound prepared by the action of hydrogen bromide on α-D-altropyranose pentaacetate.

1,5-Anhydro-D-glucitol (polygalitol) and 1,5-anhydro-D-mannitol (styracitol) occur in nature and also have been synthesized by several methods in the laboratory; 1,5-anhydro-D-galactitol and 1,5-anhydro-D-talitol have been obtained synthetically.[2] Ness and Fletcher[3] have recently prepared both the 1,5-anhydro-D- and L-gulitols, the former by the lithium aluminum hydride reduction of sirupy tetra-*O*-acetyl-D-gulopyranosyl bromide and the latter by the similar reduction of tetra-*O*-benzoyl-β-D-fructopyranosyl bromide (with accompanying Walden inversion of configuration at carbon 2 of the fructose molecule).

We have synthesized the new 1,5-anhydro-D-altritol by application of the same sequence of reactions to 1,5-anhydro-D-glucitol (I) that had been effective earlier in the transformation of methyl α-D-glucopyranoside to methyl α-D-altropyranoside.[4] Thus, the first steps were the preparation of 1,5-anhydro-4,6-*O*-benzylidene-D-glucitol (II) and its 2,3-di-*O*-*p*-tolylsulfonyl derivative (III). Reaction of III with methanolic sodium methoxide in chloroform solution resulted in the elimination of both tosyl groups and the formation of an ethylene oxide ring; by analogy with the glycoside studies, the compound is presumed to have the D-allitol configuration IV. Hydrolytic opening of the ethylene oxide ring was accomplished by boiling with caustic potash and the resulting principal product was the desired 1,5-anhydro-4,6-*O*-benzylidene-D-altritol (V). Simple acid hydrolysis removed the benzylidene group and 1,5-anhydro-D-altritol (VI) was obtained as stout prisms melting at 127–129° and showing $[\alpha]^{20}D$ +28.4° in water.[5] The compound was characterized further through preparation of its crystalline tetraacetate and tetrabenzoate. Its reaction with periodate was in complete harmony with the 1,5-anhydro-D-hexitol structure.

We have synthesized 1,5-anhydro-D-altritol also by the procedure described by Ness, Fletcher and Hudson[2c,3]; the reaction of α-D-altropyranose pentaacetate[4c] with hydrogen bromide in glacial acetic acid, followed by reduction of the resulting sirup with lithium aluminum hydride, afforded the desired substance, which was identified through its crystalline tetrabenzoate. In contrast to the excellent yields of 1,5-anhydrohexitols obtained from the pentaacetates of D-glucose, D-mannose and L-rhamnose,[2c] our product was isolated in only a 1.5% over-all yield[6]; this was sufficient to confirm the structure assigned on the basis of its original synthesis, but hardly useful, without considerable improvement, for preparative work.



The rotations of the optically active polyhydric alcohols in water are relatively low; in ammonium molybdate and particularly in acidified molybdate solutions, however, these values may be greatly

(1) Presented in part before the Division of Carbohydrate Chemistry at the Cincinnati Meeting of the American Chemical Society, April 1, 1955.

(2) (a) See the review by L. F. Wiggins, *Advances in Carbohydrate Chem.*, **5**, 191 (1950); (b) H. G. Fletcher, Jr., L. H. Koehler and C. S. Hudson, THIS JOURNAL, **71**, 3679 (1949); (c) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **72**, 4547 (1950); (d) W. A. Bonner and J. E. Kahn, *ibid.*, **73**, 2241 (1951); W. A. Bonner, *ibid.*, **73**, 2659 (1951); (e) H. G. Fletcher, Jr., and H. W. Diehl, *ibid.*, **74**, 3175 (1952).

(3) R. K. Ness and H. G. Fletcher, Jr., *ibid.*, **75**, 2619 (1953).

(4) (a) G. J. Robertson and C. F. Griffith, *J. Chem. Soc.*, 1193 (1935); (b) G. J. Robertson and W. Whitehead, *ibid.*, 319 (1940); (c) N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **63**, 1727 (1941).

(5) In agreement with the generalization of H. G. Fletcher, Jr., and C. S. Hudson [THIS JOURNAL, **71**, 3682 (1949)], the molecular rotation of 1,5-anhydro-D-altritol (+4660) lies well between the molecular rotations of methyl α-D-altropyranoside (+24,430) [reference 4c] and methyl β-D-altropyranoside (−6410) [R.E. Reeves, THIS JOURNAL, **72**, 1499 (1950)]. See also ref. 3, footnote 14, for additional support of this generalization.

(6) *Cf.* ref. 3, in which 1,5-anhydro-4,6-*O*-benzylidene-D-gulitol was obtained in 10% yield from methyl α-D-gulopyranoside tetraacetate.

and characteristically enhanced; and their measurements under standardized conditions can be useful in deciding whether a new polyol is an optically active or *meso* form, in characterizing and identifying polyols, and in testing the purity of polyols.[7] The rotations of 1,5-anhydro-D-altritol and several other representative anhydrohexitols have now been measured under the same conditions, but did not differ markedly from their corresponding rotations in water; the results are shown in Table I.

TABLE I

ROTATIONS OF SOME ANHYDROHEXITOLS

Compound	$[\alpha]^{20}D$ in H_2O (*c* 1–2)	$[\alpha]^{20}D$ in 5% molybdate (*c* 0.40)	$[\alpha]^{20}D$ in acidified molybdate (*c* 0.32)
1,5-Anhydro-D-altritol	+28.4°	+31.4°	+26.6°
1,5-Anhydro-D-glucitol	+42.5[a]	+41.9	+40.5
1,5-Anhydro-D-mannitol	−50.6[a]	−51.5	−48.3
1,5-Anhydro-D-galactitol	+76.6[b]	+80.3	+77.7
1,4-Anhydro-D-galactitol	−18.0[c]	−20.3	−21.1

[a] N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **65**, 64 (1943). [b] H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **70**, 310 (1948). [c] R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **73**, 3742 (1951).

Experimental

1,5-Anhydro-D-glucitol (= Polygalitol) (I).—Starting material for the transformations described below was obtained by the reductive desulfurization of phenyl or *p*-tolyl 1-thio-β-D-glucopyranoside tetraacetate with Raney nickel, followed by catalytic deacetylation of the resulting product.[8] However, the procedure involving the reduction and simultaneous deacetylation of tetraacetyl-α-D-glucopyranosyl bromide with lithium aluminum hydride, as developed later in this Laboratory,[2c] is now recommended for the preparation of 1,5-anhydro-D-glucitol.

1,5-Anhydro-2,3,4,6-tetra-*O*-benzoyl-D-glucitol.—A mixture of 2 g. of 1,5-anhydro-D-glucitol, 15 ml. of benzoyl chloride and 25 ml. of pyridine was heated on the steam-bath for 15 minutes, cooled, and then a small piece of ice added to destroy the excess of benzoyl chloride. The mixture was poured onto cracked ice, and the resulting sirup, after being washed several times with water by decantation, was dissolved in ethanol; the product (5.2 g.) crystallized when the solution was allowed to concentrate in the refrigerator. Several recrystallizations from ethanol furnished clusters of needles with m.p. 100–102° and $[\alpha]^{20}D$ +43.4° in chloroform (*c* 1.1).

Anal. Calcd. for $C_{34}H_{28}O_9$: C, 70,34; H, 4.86. Found: C, 70.04; H, 4.96.

1,5-Anhydro-4,6-*O*-benzylidene-D-glucitol (II).—A mixture of 48.7 g. of 1,5-anhydro-D-glucitol, 300 ml. of benzaldehyde and 75 g. of freshly fused zinc chloride was shaken mechanically until a clear solution was obtained (3 hours) and then left 5 days at room temperature. The solution was stirred dropwise into 1500 ml. of ice-water and the mixture stored overnight in the refrigerator. The aqueous portion was decanted and the residual magma was kept cold and stirred with several 100-ml. portions of *n*-pentane to remove most of the benzaldehyde. The crystalline residue was filtered, washed with water and pentane, and dried in the air; wt. 49 g. Recrystallization from 150 ml. of absolute ethanol yielded 28.7 g. (38%) of benzylidene compound with m.p. 154–163°. Two additional recrystallizations raised the m.p. to 164–165°; the needles showed $[\alpha]^{20}D$ −21.2° in chloroform (*c* 0.5). Oxidation of the compound with sodium metaperiodate consumed 1 molar equivalent of oxidant, produced neither acid nor formaldehyde, and was complete within 2.5 hours at 20°.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 62.02; H, 6.10.

1,5-Anhydro-4,6-*O*-benzylidene-2,3-di-*O*-*p*-tolylsulfonyl-D-glucitol (III).—The reaction of 28.7 g. of 1,5-anhydro-4,6-*O*-benzylidene-D-glucitol with 120 g. (5.5 molar equivalents) of *p*-toluenesulfonyl chloride in 350 ml. of dry pyridine for 7 days at room temperature furnished a nearly quantitative yield of the ditosyl compound. The product crystallized from acetone as fine needles with m.p. 185–189° and $[\alpha]^{20}D$ −48.5° in chloroform (*c* 1.5). From a mixture of chloroform and *n*-pentane two types of crystals appeared to deposit simultaneously—clusters of fine needles and large prismatic needles; melting points, mixed melting points and analyses, however, indicated that the difference was only in the crystal habit.

Anal. Calcd. for $C_{27}H_{28}O_9S_2$: C, 57.84; H, 5.03; S, 11.44. Found (crystals from acetone): C, 57.85, 57.93, 58.10; H, 4.87, 5.26, 4.94; S, 11.05, 11.73, 11.28; (mixed crystals from chloroform–pentane): C, 57.84; H, 5.30; S, 11.10.

In a preliminary tosylation in which double the theoretical amount of *p*-toluenesulfonyl chloride was allowed to react with compound II only overnight, a small amount of a monotosyl derivative also was isolated. It separated from chloroform–pentane as flat prisms with m.p. 175–179°. By analogy with the monotosylation product from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside,[4a] our substance is presumed to be **1,5-anhydro-4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-D-glucitol.**

Anal. Calcd. for $C_{20}H_{22}O_7S$: C, 59.10; H, 5.46; S, 7.89. Found: C, 59.13; H, 5.40; S, 7.61.

1,5:2,3-Dianhydro-4,6-*O*-benzylidene-D-allitol (IV) (or -mannitol?).—To a cold solution of 28.4 g. of 1,5-anhydro-4,6-*O*-benzylidene-2,3-di-*O*-*p*-tolylsulfonyl-D-glucitol in 400 ml. of chloroform was added 200 ml. of 3 *N* methanolic sodium methoxide and the homogeneous reaction mixture was kept for 3 days at 5° and then 6 days at room temperature. About 500 ml. of water was added and the chloroform layer and several chloroform extracts of the aqueous layer were combined, washed with water, dried with anhydrous sodium sulfate, and concentrated to a crystalline mass. The crude product, filtered and washed with ether, weighed 11.5 g. Recrystallization from chloroform–pentane gave 7.0 g. with m.p. 120–128° and a second crop of 3.8 g. with m.p. 112–124° (total, 91%). For analysis the first portion was recrystallized further from ethanol and then from chloroform–pentane; the resulting clusters of prismatic needles melted at 129–130° and showed $[\alpha]^{20}D$ +35.0° in chloroform (*c* 0.5).

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.55; H, 5.83.

1,5-Anhydro-4,6-*O*-benzylidene-D-altritol (V).—Five grams of the once-recrystallized dianhydro compound IV was refluxed for 48 hours with 300 ml. of 4% aqueous potassium hydroxide in a silver flask. The reaction mixture was cooled, filtered from a small amount (0.5 g.) of unchanged ditosyl compound that had been a contaminant in the anhydro compound, and the filtrate extracted with three 500-ml. portions of chloroform. The chloroform solution was dried with anhydrous sodium sulfate and concentrated *in vacuo* to a sirup that crystallized readily upon the addition of ether. The product, after one recrystallization from chloroform–pentane, weighed 3.5 g. (65%); two additional recrystallizations yielded thick prisms with m.p. 125–126° and $[\alpha]^{20}D$ +1.7° in chloroform (*c* 0.5).

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.95; H, 6.63.

1,5-Anhydro-D-altritol (VI).—A 3.4-g. portion of 1,5-anhydro-4,6-*O*-benzylidene-D-altritol was heated with 30 ml. of *N* sulfuric acid for 1.5 hours on the steam-bath. The solution was cooled, extracted several times with pentane to remove the liberated benzaldehyde, neutralized with aqueous barium hydroxide, filtered, and the filtrate concentrated *in vacuo* to a sirup. The addition of ethanol and reconcentration resulted in a solid mass of crystals. The product was dissolved in hot absolute ethanol, and the solution, when cooled, deposited 1.8 g. (81%) of thick prisms melting at 127–129°; the m.p. was not changed by further recrystallizations. The rotation was $[\alpha]^{20}D$ +28.4° in water (*c* 1.2), +31.4° in 5% aqueous ammonium molybdate (*c* 0.40), and +26.6° in the acidified molybdate solution (*c* 0.32).[7]

(7) N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **73**, 2249 (1951).

(8) *Cf.* H. G. Fletcher, Jr., and N. K. Richtmyer, *Advances in Carbohydrate Chem.*, **5**, 16, 27 (1950).

Anal. Calcd. for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 43.96; H, 7.27.

Oxidation of 1,5-Anhydro-D-altritol with Sodium Metaperiodate.—A solution containing 0.2001 g. of 1,5-anhydro-D-altritol and 6.0 ml. of 0.48 *M* aqueous sodium periodate in a total volume of 25 ml. reached the constant rotation $[\alpha]^{20}D$ −9.4° (calculated as the expected dialdehyde) sometime within a week at 20°. This rotation is in good agreement with the values −9.9 and −9.7° observed for the similar oxidations of 1,5-anhydro-D-glucitol and 1,5-anhydro-D-mannitol, respectively.[9] Titrations showed the consumption of 1.95 molar equivalents of oxidant and the liberation of 0.99 molar equivalent of formic acid; the dimedone test for formaldehyde was negative.

2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-altritol.—Acetylation of 1,5-anhydro-D-altritol with acetic anhydride and fused sodium acetate gave a 75% yield of the tetraacetate: prisms, from chloroform–pentane, with m.p. 104–105° and $[\alpha]^{20}D$ −22.7° in chloroform (*c* 1.3).

Anal. Calcd. for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07; CH_3CO, 51.8. Found: C, 50.54; H, 6.23; CH_3CO, 51.5.

1,5-Anhydro-2,3,4,6-tetra-*O*-benzoyl-D-altritol.—To a solution of 0.6 g. of 1,5-anhydro-D-altritol in 10 ml. of dry pyridine was added 3 ml. of benzoyl chloride and the mixture was heated for 15 minutes on the steam-bath. A few drops of water were added and the solution was then poured onto cracked ice. The resulting sirup crystallized readily upon decantation of the aqueous layer and the addition of water. The product, filtered and washed with cold water and cold 50% ethanol, and dried in the air, weighed 2.1 g. (quantitative). The tetrabenzoate crystallized as small prisms from 95% ethanol and as thicker prisms from chloroform–pentane, melted at 176–177°, and showed $[\alpha]^{20}D$ −6.8° in chloroform (*c* 1.5).

Anal. Calcd. for $C_{34}H_{28}O_9$: C, 70.34; H, 4.86. Found: C, 70.34; H, 4.88.

1,5-Anhydro-2,3,4,6-tetra-*O*-benzoyl-D-altritol from α-D-Altropyranose Pentaacetate.—To 7.4 g. of α-D-altropyranose pentaacetate[4c] in 100 ml. of glacial acetic acid was added 100 ml. of a 30% solution of hydrogen bromide in glacial acetic acid. The solution quickly reached a constant rotation of about $[\alpha]^{20}D$ +150° (calculated as the expected acetobromo compound) and after 3 hours at room temperature it was poured onto cracked ice and the mixture extracted with chloroform. The chloroform solution was washed successively with water, aqueous bicarbonate, and water, dried with sodium sulfate, and concentrated *in vacuo*. The resulting sirup was dissolved in 400 ml. of anhydrous ether and added dropwise to a well-stirred suspension of 14 g. of lithium aluminum hydride in 600 ml. of ether. The reaction mixture was left overnight at 20° and then refluxed for 1 hour; excess lithium aluminum hydride was decomposed by the cautious addition of ethyl acetate, followed by water. The coagulated precipitate was filtered and washed with water, and the aqueous solution was deionized and concentrated to a sirup that weighed only 0.2 g. Benzoylation of the sirup produced 0.15 g. of a crystalline product that was identified by m.p., mixed m.p. and rotation as 1,5-anhydro-2,3,4,6-tetra-*O*-benzoyl-D-altritol.

Acknowledgment.—The authors wish to thank Dr. Hewitt G. Fletcher, Jr., and Dr. Robert K. Ness for the samples of 1,4- and 1,5-anhydro-D-galactitols and Dr. William C. Alford and his associates of this Institute's microanalytical laboratory for carrying out the microanalyses.

BETHESDA 14, MARYLAND

(9) N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **65**, 64 (1943).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY]

Periodate Oxidation of Hexose Phosphates[1]

BY MARTIN MORRISON, GEORGE ROUSER[2] AND ELMER STOTZ

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The products of periodate oxidation of several sugar phosphates were investigated by paper chromatography. The results show that the oxidation occurs with the sugars in their ring forms. Those sugars with the phosphate on carbon 6 yield derivatives of the biologically important D-glyceraldehyde-3-phosphate, which have been shown to be active with triosephosphate dehydrogenase.

Recent studies have indicated that the hemiacetal carbon atoms of carbohydrates are oxidized by periodate to yield a formic acid ester.[3] The investigations to be reported were designed to determine whether this is a more general reaction that might be specifically applicable to the phosphate esters of carbohydrates. It has been shown that under the conditions employed, the carbohydrate moiety is oxidized in the ring form. The carbonyl carbon atom is then a hemi-acetal and is oxidized by periodate to yield an ester. The periodate oxidation of D-glucose-6-phosphate, fructose-6-phosphate and hexose diphosphate yield derivatives of D-glyceraldehyde-3-phosphate, the latter being an important intermediate of carbohydrate metabolism.

In order to follow the products of the periodate reaction, paper chromatographic techniques were employed. Figure 1 shows the paper chromatographic movement in the picric acid solvent[4] of α-glycerol phosphate (α-GP), glucose-6-phosphate (G6P), fructose-6-phosphate (F6P), fructose-1,6-diphosphate (HDP) and glucose-1-phosphate (G1P) and the products obtained from these compounds by periodate oxidation. The glycerol phosphate preparation contained some β-glycerol phosphate that moves just behind the α-glycerol phosphate and does not react with periodate. The product of α-glycerol phosphate oxidation is shown in Fig. 1 with an R_f value of about 0.36. It is evident that the hexose-6-phosphates do not produce the same glycolaldehyde phosphate as would be expected if the compounds reacted in the straight chain form. The sugar phosphates must, therefore, react in the ring form. The following products would be expected from the periodate oxidation of the four sugar phosphates tested. It will be noted that all four products are different, and that three of these compounds are car-

(1) This work was supported in part by the Damon Runyon Fund.

(2) U. S. Public Health Post-Doctoral Fellow.

(3) M. Morrison, A. C. Kuyper and J. M. Orten, THIS JOURNAL, **75**, 1502 (1953).

(4) C. S. Hanes and F. A. Isherwood, *Nature*, **164**, 1107 (1949).