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The Reduction of Acetylated Glycopyranosyl Bromides to 1,5-Anhydroglycitols with Lithium Aluminum Hydride. 1,5-Anhydro-L-rhamnitol

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Since the discovery in nature of polygalitol² and styracitol³ and the recognition of these substances as anhydrides of the sugar alcohols (or glycitols), considerable attention has been given to the synthesis of 1,5-anhydroglycitols. The most obvious and attractive path involves the replacement of the halogen of acylohalogen sugars with hydrogen and indeed it was evidently with this object in mind that E. Fischer and K. Zach⁴ in 1913 treated tetraacetyl- α -D-glucopyranosyl bromide with zinc dust and acetic acid. The product which they obtained, however, was not the expected derivative of D-glucitol but triacetyl-D-glucal, a singularly pregnant discovery in itself. It remained for Zervas⁵ in 1930 to devise a synthesis for 1,5-anhydroglycitols; catalytic hydrogenation of tetraacetyl-2-hydroxy-D-glucal, a compound previously obtained by Maurer and Mahn⁶ through the dehydrobromination of tetraacetyl- α -D-glucopyranosyl bromide, gave styracitol. Although subsequently applied in a variety of other series, this synthetic method proved of limited value since (aside from the laboriousness of the process) carbon atom 2 becomes asymmetric and its configuration in the 1,5-anhydride must be proved. Thus, from Zervas' synthesis it was not evident whether styracitol was 1,5-anhydro-D-mannitol or 1,5-anhydro-D-glucitol.

A method for the synthesis of 1,5-anhydroglycitols of unequivocal configuration was introduced by Richtmyer, Carr and Hudson⁷ who reductively desulfurized with Raney nickel both tetraacetyl-1-thio- β -D-glucose and octaacetyl- β , β -di-D-glucopyranosyl disulfide to 1,5-anhydro-D-glucitol (polygalitol) tetraacetate. Application of this method to more readily accessible 1-thio sugar derivatives, such as the xanthates and thioglycosides,⁸ has made available a considerable number of 1,5-anhydroglycitols of known configuration. However, none of the 1-thio derivatives is as readily accessible as the acetohalogen sugars (from which, indeed, the majority of them are prepared) and attention was therefore turned to the original aim

of Fischer and Zach, the direct reduction of tetraacetyl- α -D-glucopyranosyl bromide.

Since lithium aluminum hydride has been shown to reduce acid halides to alcohols⁹ as well as alkyl halides to hydrocarbons¹⁰ it is reasonable to predict that acylohalogen sugars, where the halogen is intermediate in character between an alkyl halide and an acid halide, will similarly be reduced to an anhydroglycitols. Such has now been shown to be the case. Reaction of tetraacetyl- α -D-glucopyranosyl bromide with lithium aluminum hydride in anhydrous ether solution readily gave 1,5-anhydro-D-glucitol, the acetyl groups having been removed as would be expected from the known action of this reagent on esters.⁹ Subsequent experiments showed that isolation of the acetohalogen compound was unnecessary; reaction of D-glucopyranose pentaacetate with hydrogen bromide in glacial acetic acid solution was carried out in the usual manner, the reaction mixture was diluted with ether, freed of acid, dried, and treated directly with an ethereal solution of lithium aluminum hydride. In this fashion 1,5-anhydro-D-glucitol was obtained in 67% yield from β -D-glucopyranose pentaacetate. α -D-Mannopyranose pentaacetate¹¹ was similarly converted to 1,5-anhydro-D-mannitol (styracitol) in 74% yield.

This new method of synthesizing 1,5-anhydroglycitols has been applied to the L-rhamnose series. An ethereal solution of triacetyl- α -L-rhamnopyranosyl bromide (II), prepared from β -L-rhamnopyranose tetraacetate (I) was treated with lithium aluminum hydride to give in 87% yield a new, crystalline anhydroglycitols, 1,5-anhydro-L-rhamnitol (III). The structure of the substance was confirmed through quantitative periodate oxidation; as expected of a tetrahydropyran structure it was found to consume two moles of oxidant with the simultaneous formation of one mole of formic acid.

On the basis of the isorotation hypothesis and the molecular rotations of methyl α -L-mannopyranoside, methyl α -L-rhamnopyranoside and 1,5-anhydro-L-mannitol (Table I), the specific rotation of 1,5-anhydro-L-rhamnitol may be calculated

(1) Senior Research Fellow, National Institutes of Health, 1948-1950.

(2) M. Chodat, *Arch. sci. phys. et nat.*, [3] 18, 228 (1887); [3] 19, 290 (1888); [3] 20, 593 (1888).

(3) Y. Asahina, *Arch. Pharm.*, 245, 325 (1907); 247, 157 (1909).

(4) E. Fischer and K. Zach, *Sitzber. kgl. preuss. Akad. Wiss.*, 16, 311 (1913).

(5) L. Zervas, *Ber.*, 63, 1689 (1930).

(6) K. Maurer and H. Mahn, *ibid.*, 60, 1316 (1927).

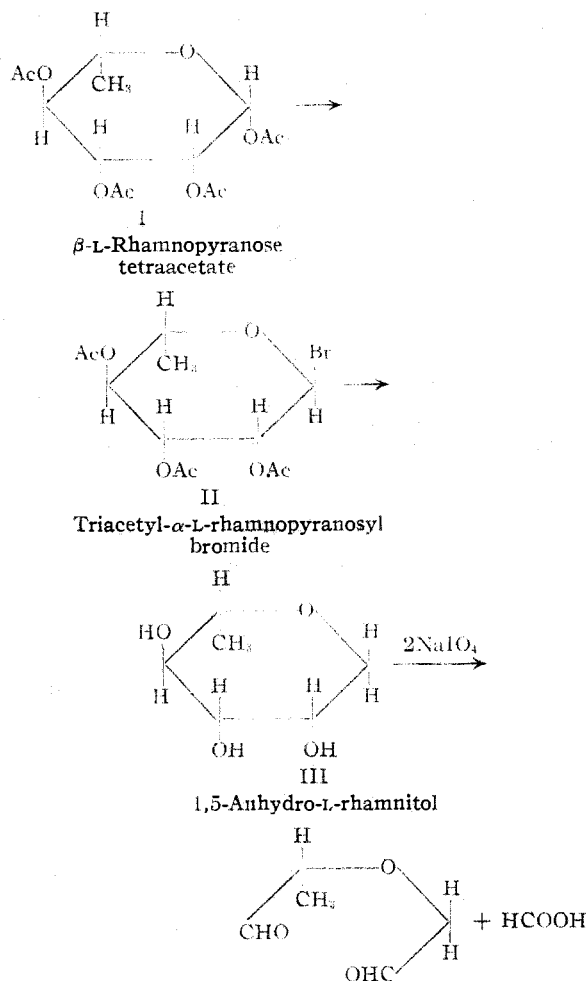
(7) N. K. Richtmyer, C. J. Carr and C. S. Hudson, *THIS JOURNAL*, 68, 1477 (1943).

(8) For a general review of this topic see H. G. Fletcher, Jr., and N. K. Richtmyer, *Advances in Carbohydrate Chem.*, 5, 1 (1950).

(9) R. F. Nystrom and W. G. Brown, *THIS JOURNAL*, 69, 1197 (1947).

(10) R. F. Nystrom and W. G. Brown, *ibid.*, 70, 3738 (1948).

(11) This substance, which may be obtained through the acetylation of methyl α -D-mannopyranoside tetraacetate in 59% yield [R. M. Hann and C. S. Hudson, *ibid.*, 56, 2465 (1934)] may even more conveniently be prepared by the sulfuric acid-catalyzed acetylation of methyl α -D-mannopyranoside (62% yield), a compound which, in turn, is readily available from the very inexpensive ivory nut meal [C. S. Hudson, "Organic Syntheses," Coll. Vol. 1, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 371]. This improved preparation is described in the experimental section.



as $(4,240 + 8,340) \div 148 = +85^\circ$. A specific rotation in water of $+83.8^\circ$ was found for the pure substance.

1,5-Anhydro-L-rhamnitol was characterized as the triacetate and tribenzoate, both crystalline derivatives. The specific rotation of the triacetate, calculated from the data in Table I is $(13,900 - 310) \div 274 = +49.6^\circ$; a rotation of $+48.1^\circ$ in chloroform was found. 1,5-Anhydro-L-rhamnitol tribenzoate would likewise be expected to have a rotation of $(87,400 + 45,600) \div 460 = +289^\circ$ which may be compared with a measured value of $+279^\circ$ in chloroform.

Experimental¹²

1,5-Anhydro-D-glucitol from β-D-Glucopyranose Pentaacetate.—To 23.75 g. of β-D-glucopyranose pentaacetate was added 25 ml. of a chilled 30% solution of hydrogen bromide in glacial acetic acid; solution was complete within ten to twenty minutes. After two hours at room temperature, ether was added and the organic layer washed successively with ice water and cold, saturated sodium bicarbonate solution. After drying with sodium sulfate,

(12) Melting points were measured with a calibrated Anschütz-type thermometer completely immersed in the bath liquid. Rotations are specific rotations for the D line of sodium at 20°; concentration is expressed in g. of substance per 100 ml. of solution.

the ether solution of tetraacetyl-α-D-glucopyranosyl bromide was added slowly (thirty minutes) with mechanical stirring and protection from atmospheric moisture to 350 ml. of ca. 1.8 M lithium aluminum hydride solution in ether. Thirty minutes later, 400 ml. of water was cautiously added; the ether layer formed was devoid of optical activity and therefore discarded. The aqueous layer was filtered to remove aluminum hydroxide, deionized by passage through the cation exchange resin Amberlite IR-120¹³ and the anion exchange resin Duolite A-4¹⁴ and concentrated *in vacuo* (65° bath) to a sirup. Crystallization from 125 ml. of absolute ethanol afforded 6.68 g. (67%) of material melting at 141–143°. Further recrystallization from twenty parts of hot absolute alcohol gave 6.13 g. of 1,5-anhydro-D-glucitol showing a rotation of $+42.8^\circ$ in water (*c*, 2.14) and melting at 142–143° either alone or in admixture with authentic material. A melting point of 142–143° and a rotation in water of $+42.3^\circ$ (*c*, 0.844) have been reported¹⁵ previously for 1,5-anhydro-D-glucitol.

α-D-Mannopyranose Pentaacetate from Methyl α-D-Mannopyranoside.—Forty grams of pure, powdered methyl α-D-mannopyranoside was added to a freshly prepared mixture of 268 ml. of acetic anhydride and 5.4 ml. of concentrated sulfuric acid which had previously been cooled in an ice-salt-bath. After four hours agitation at approximately 0°, solution was essentially complete and the reaction mixture was left at room temperature overnight. It was then poured on chipped ice and the resulting mixture agitated (with a stream of air) until the ice had melted. Five 50-ml. portions of chloroform served to extract the product; the combined extracts were washed successively with water, aqueous sodium bicarbonate and water, dried over sodium sulfate and concentrated *in vacuo* at 45–50°. The resulting clear, colorless sirup was dissolved in 50 ml. of absolute ethanol and reconcentrated *in vacuo*; after repetition of this process the sirup was dissolved in 100 ml. of ether, the solution cooled to 5°, treated with 25 ml. of isopentane and seeded. After four days at 5° the α-D-mannopyranose pentaacetate thus obtained amounted to 49.4 g. (62%) and melted at 73–74°. Recrystallization from 16 parts of 30% aqueous methanol and then from 5.5 parts of *n*-butanol gave material with the same melting point and a rotation of $+55.2^\circ$ in chloroform (*c*, 2.2). Levene and Tipson¹⁶ reported a melting point of 74° for this substance and a rotation in chloroform of $+56.6^\circ$.

1,5-Anhydro-D-mannitol from α-D-Mannopyranose Pentaacetate.—An ether solution of tetraacetyl-α-D-mannopyranosyl bromide was prepared from 23.75 g. of α-D-mannopyranose pentaacetate by the same procedure as that employed in the preparation of the ether solution of tetraacetyl-α-D-glucopyranosyl bromide above. The reaction of the tetraacetyl-α-D-mannopyranosyl bromide with 350 ml. of ca. 1.8 M lithium aluminum hydride in ether was carried out in a manner similar to that used in the preparation of 1,5-anhydro-D-glucitol. During the concentration of the deionized aqueous solution, the product began to crystallize; from 100 ml. of absolute alcohol 6.69 g. (66.9%) of 1,5-anhydro-D-mannitol, which melted at 155–157° and rotated in water -49.8° (*c*, 2.13), was obtained. The compound gave no depression of melting point when mixed with an authentic sample of 1,5-anhydro-D-mannitol (styracitol). The mother liquor, after concentration, afforded an additional 0.75 g. (7.5%) of material melting at 153–155°. Hockett and Conley¹⁷ reported the melting point of styracitol as 154–155° and its specific rotation in water as -50.9° .

1,5-Anhydro-L-rhamnitol (III) from β-L-Rhamnopyranose Tetraacetate (I).—Starting with 14.6 g. of β-L-

(13) A product of the Resinose Products and Chemical Co., Washington Square, Philadelphia 5, Pa.

(14) A product of Chemical Process Co., 901 Spring St., Redwood City, California.

(15) H. G. Fletcher, Jr., *THIS JOURNAL*, **69**, 706 (1947).

(16) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **90**, 89 (1931).

(17) R. C. Hockett and Maryalice Conley, *THIS JOURNAL*, **66**, 464 (1944).

TABLE I^a
COMPARISON OF SOME MOLECULAR ROTATIONS IN THE L-RHAMNOSE AND L-MANNOSE SERIES

	Mol. wt.	$[\alpha]^{20}_D$, (H ₂ O)	$[M]^{20}_D$	Difference
Methyl α -L-mannopyranoside	194	-79.2	-15,380	4,240
Methyl α -L-rhamnopyranoside	178	-62.5	-11,140	
1,5-Anhydro-L-mannitol	164	+50.9 ^b	+ 8,340	4,060
1,5-Anhydro-L-rhamnitol	148	+83.8 ^c	+12,400	
(CHCl ₃)				
Methyl α -L-mannopyranoside tetraacetate	362	-49.1	-17,790	-310
Methyl α -L-rhamnopyranoside triacetate	304	-59.4	-18,100	
1,5-Anhydro-L-mannitol tetraacetate	332	+42.0 ^e	+13,900	-700
1,5-Anhydro-L-rhamnitol triacetate	274	+48.1	+13,200	
Methyl α -L-mannopyranoside tetrabenzoate	611	+66.3 ^d	+40,500	45,600
Methyl α -L-rhamnopyranoside tribenzoate	490	+175.8 ^d	+86,100	
1,5-Anhydro-L-mannitol tetrabenzoate	581	+150.4 (17°) ^e	+87,400	40,600
1,5-Anhydro-L-rhamnitol tribenzoate	460	+279	+128,000	

^a Various rotational values reported for compounds of the D-series are here listed as of the L-series, the appropriate change in sign being made. Unless otherwise credited, the data were obtained either through the present research or from the tables by F. J. Bates and Associates, "Polarimetry, Saccharimetry and the Sugars," U. S. Govt. Printing Office, Washington, D. C., 1942. ^b R. C. Hockett and Maryalice Conley, *THIS JOURNAL*, **66**, 464 (1944). ^c H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **71**, 3682 (1949). ^d W. T. Haskins, R. M. Hann and C. S. Hudson, *ibid.*, **68**, 628 (1946). ^e Y. Asahina, *Arch. Pharm.*, **247**, 157 (1909).

rhamnopyranose tetraacetate (m. p. 97.5-99°) and 20 ml. of the hydrogen bromide-glacial acetic acid solution, an ether solution of triacetyl- α -L-rhamnopyranosyl bromide was made by the procedure employed for the corresponding glucose derivative. This solution was added over a period of thirty minutes to 200 ml. of ca. 1.8 M lithium aluminum hydride in ether. The product was separated from the reaction mixture by the process used for 1,5-anhydro-D-glucitol. Concentration of the deionized aqueous solution *in vacuo* (80° bath) left a sirup. The addition of 100 ml. of absolute alcohol and reconcentration of the solution yielded a solid which, crystallized from 30 ml. of absolute alcohol, weighed 4.96 g. (76.1%) and melted at 122-124°. Treatment of the mother liquor with carbon and concentration to a volume of about 5 ml. gave an additional 0.72 g. (11.0%) of material melting at 121-123°. After treatment of the first fraction with carbon, one recrystallization from 7.5 parts of 2:1 absolute alcohol-pentane and another one from 2.5 parts of methanol afforded large, clear prisms which melted at 123-124° and rotated in water +83.8° (c, 0.97).

Anal. Calcd. for C₈H₁₂O₄: C, 48.64; H, 8.16. Found: C, 48.72; H, 8.33.

Oxidation of 1,5-Anhydro-L-rhamnitol with Sodium Metaperiodate.—Using the technique of Jackson and Hudson,¹⁸ the 1,5-anhydro-L-rhamnitol (0.0794 g.) was dissolved in a few ml. of water, treated with 5.0 ml. of 0.48 M sodium metaperiodate solution and the solution diluted to 25.0 ml. with water. After twenty-four hours at room temperature a 5.0 ml. sample was titrated for formic acid and residual oxidant. On a molal basis the anhydride consumed 2.01 moles of oxidant and liberated 1.01 moles of formic acid.

1,5-Anhydro-L-rhamnitol Triacetate.—1,5-Anhydro-L-rhamnitol (1.45 g.) was acetylated with acetic anhydride and pyridine at 95° for two hours. After removal of the excess reactants, the sirupy product was distilled at 100-130° (3-4 mm. pressure); seed crystals were first obtained by chilling an alcoholic solution of the substance in a Dry Ice-acetone-bath. The distillate was crystallized from a mixture of absolute alcohol and pentane at -10°. A second fraction obtained subsequently raised the yield to 0.96 g. (36%) of material melting at 60-62°. Recrystallization from seventeen parts of 1:2 absolute alcohol-

pentane at -10° gave a product which melted at 61-62° and showed a rotation in chloroform of +48.1° (c, 1.26).

Anal. Calcd. for C₁₂H₁₈O₇: C, 52.55; H, 6.62. Found: C, 52.53; H, 6.59.

1,5-Anhydro-L-rhamnitol Tribenzoate.—1,5-Anhydro-L-rhamnitol (0.506 g.) was benzoylated with benzoyl chloride in pyridine in the usual manner to give a product which crystallized from 80 ml. of methanol as prisms (1.40 g., 88.9%) melting at 168-170°. Recrystallization from six parts of 1:2 ethyl acetate-pentane and then from methanol gave large, clear prisms melting at 169-170° and rotating in chloroform +279° (c, 0.98).

Anal. Calcd. for C₂₇H₂₄O₇: C, 70.42; H, 5.25. Found: C, 70.61; H, 5.36.

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Summary

β -D-Glucopyranose pentaacetate was converted to tetraacetyl- α -D-glucopyranosyl bromide and the reduction of the latter with lithium aluminum hydride afforded 1,5-anhydro-D-glucitol (polygalitol) in high yield.

α -D-Mannopyranose pentaacetate has similarly been converted to tetraacetyl- α -D-mannopyranosyl bromide, which was reduced with lithium aluminum hydride to 1,5-anhydro-D-mannitol (sty-racitol).

By the same general process the new anhydride, 1,5-anhydro-L-rhamnitol, has been prepared from β -L-rhamnopyranose tetraacetate. Its structure has been confirmed by periodate oxidation and it has been further characterized as its tetraacetate and tetrabenzoate.

An improved method for the preparation of α -D-mannopyranose pentaacetate has been described.

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