

lithium aluminum hydride to the 4-hydroxy derivative which, in turn, was hydrolyzed and dehydrated to yield (-)-*trans*-10 β -methyl- $\Delta^{3,6}$ -hexalin-2-one. The crude product was hydrogenated over platinum according to the procedure of Djerassi and Marshall²⁰ to yield (+)-*trans*-10 β -methyldecalin-2-one (92% pure by v.p.c.), $[\alpha]_D^{25} +40^\circ$ (c 2.0, CHCl₃) [lit.²¹ $[\alpha]_D +33^\circ$ (c 1.14, CHCl₃)].

(+)-10 β -Methyl- $\Delta^{1(9)}$ -octalin-2-one (VI).—The 92% pure, optically active decalone was brominated following the method used for its antipode²⁰ and (+)-*trans*-3-bromo-10 β -methyldecalin-2-one was obtained as colorless needles after recrystallization from aqueous acetone: m.p. 135.0–136.5°, $[\alpha]_D^{25} +18^\circ$ (c 2.0, CHCl₃) [for antipode lit.²⁰ m.p. 137–139°, $[\alpha]_D -21^\circ$ (CHCl₃)]. The bromo ketone was dehydrobrominated with collidine and the mixture of Δ^3 - and $\Delta^{1(9)}$ -enones was separated by the procedure of Djerassi and Marshall.²⁰ The crude $\Delta^{1(9)}$ -enone was used directly in the next reaction.

(-)-8,8,10 β -Trimethyl- $\Delta^{1(9)}$ -octalin-2-one (III).—The above $\Delta^{1(9)}$ -enone was methylated, reduced, and then oxidized according to the published procedures⁹ and the product was distilled, b.p. 119–120° (0.3 mm.) [lit.⁹ b.p. 129–130° (10 mm.)]. V.p.c. analysis, in comparison with optically inactive material, showed the product to be more than 95% pure. Professor C. Djerassi kindly determined the O.R.D. curve of this material in methanol (c 0.12) at 25°: $[\theta]_{589} -115^\circ$, $[\theta]_{253} -2580^\circ$, $[\theta]_{300} +3920^\circ$, $[\theta]_{284} +3850^\circ$.

(21) R. Riniker, J. Kalvoda, D. Arigoni, A. Furst, O. Jeger, A. M. Gold, and R. B. Woodward, *J. Am. Chem. Soc.*, **76**, 313 (1954).

Methyl 2,6-Anhydro-3,4-di-*O*-methyl- α -D-mannoside. An Intramolecular Nucleophilic Displacement of Mesylate with Inversion

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Recent publications from this laboratory have described reactions of carbohydrate mesyloxy groups with various nucleophilic reagents.^{2,3} Reaction of methyl 2-*O*-mesyl-3,4,6-tri-*O*-methyl- α -D-glucoside with aqueous sodium hydroxide,² methanolic sodium methoxide, or sodium methoxide in dimethyl sulfoxide (DMSO)³ gave only products resulting from nucleophilic attack at sulfur in the mesyloxy group. No evidence for nucleophilic displacement of the mesyloxy group, involving Walden inversion, could be detected.

Selective demesylation of methyl 2,6-di-*O*-mesyl-3,4-di-*O*-methyl- α -D-glucoside⁴ made available methyl 2-*O*-mesyl-3,4-di-*O*-methyl- α -D-glucoside (1) and it was postulated that this compound might be induced to undergo an intramolecular displacement of the mesyloxy group resulting in a new 2,6-anhydro sugar.

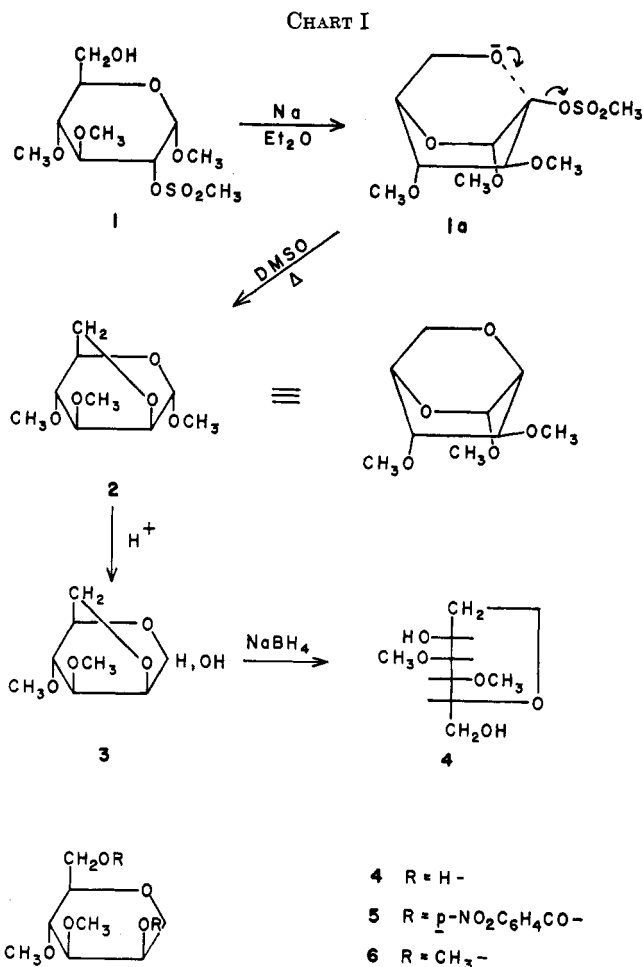
Treatment of 1 with excess sodium methoxide in refluxing anhydrous methanol failed to show any reaction. When 1 was treated with 1.1 equiv. of potassium *t*-butoxide in anhydrous DMSO at 70°, thin layer chromatography indicated a slow reaction and the formation of a small amount of a compound running faster than 1. After 20 hr. the mixture contained a

(1) National Academy of Sciences—National Research Council Visiting Scientist Resident Research Associate.

(2) A. K. Mitra, D. H. Ball, and L. Long, Jr., *J. Org. Chem.*, **27**, 160 (1962).

(3) D. H. Ball, E. D. M. Eades, and L. Long, Jr., *J. Am. Chem. Soc.*, **86**, 3579 (1964).

(4) R. C. Chalk, F. W. Parrish, and L. Long, Jr., in preparation.



small amount of this product together with a large amount of unchanged starting material and some methyl 3,4-di-*O*-methyl- α -D-glucoside.

To decrease demesylation due to intermolecular reaction with alkoxide ion, the 6-sodio salt was prepared by treatment of 1 with sodium in ether and the condensation was carried out at 85° at high dilution in DMSO.

The fast-running product was isolated by ether extraction and column chromatography as a clear sirup which crystallized after distillation. This compound was shown to be the expected methyl 2,6-anhydro-3,4-di-*O*-methyl- α -D-mannoside (2) by a series of reactions which ruptured the 1,5 ring and left the 2,6 ring intact (see Chart I). Mild acid hydrolysis removed the glycosidic methyl group and the resulting 2,6-anhydro-D-mannose derivative 3 was reduced with sodium borohydride to an anhydrohexitol derivative, 2,6-anhydro-3,4-di-*O*-methyl-D-mannitol, preferably called 1,5-anhydro-3,4-di-*O*-methyl-D-mannitol (4). This compound crystallized and also gave a crystalline di-*p*-nitrobenzoate (5).

Methylation of 4 gave a tetramethyl derivative which was shown to be 1,5-anhydro-2,3,4,6-tetra-*O*-methyl-D-mannitol (6) by comparison of its physical properties with those of an authentic sample prepared by methylation of styracitol (1,5-anhydro-D-mannitol).

The only previously reported 2,6-anhydro sugar derivative, methyl 2,6-anhydro- α -D-altrose, was prepared by Rosenfeld, Richtmeyer, and Hudson.⁵

(5) D. A. Rosenfeld, N. K. Richtmeyer, and C. S. Hudson, *J. Am. Chem. Soc.*, **70**, 2201 (1948).

Recently Meyer zu Reckendorf has reported⁶ the preparation of a 2,6-imino derivative of methyl α -D-altropyranoside. Both of these compounds were prepared by reactions involving displacement of a primary tosyloxy group at C-6 by attack from anionoid forms of hydroxyl or amino groups at C-2 of D-altrose derivatives without configurational inversion. These ring closures were effected with relatively mild nucleophilic reagents, sodium acetate in absolute ethanol⁶ and sodium hydroxide in aqueous Methyl Cellosolve.⁵ In our case it was necessary to employ a dipolar aprotic solvent, DMSO, and preferable to preform the anionic form at C-6 in order to achieve the displacement of the secondary mesyloxy group at C-2 with inversion. This reaction, and presumably the others described above leading to 2,6 rings, must occur *via* the boat configuration 1a of the pyranose ring in order to achieve the correct stereochemistry.

The reaction we describe appears to be the first example of displacement of a ring secondary sulfonyloxy group by attack from the anionic form of the primary hydroxyl at C-6. Recently a large number of 2',5'- and 3',5'-anhydro derivatives of the pentose nucleosides have been reported.⁷⁻⁹ All of these are derived from displacement of sulfonyloxy groups on the 5' or primary position by attack of anionoid forms of the respective ring secondary hydroxyls. However, reactions have been described⁷⁻⁹ in which ring secondary sulfonyloxy groups in pentose nucleosides have been displaced with inversion by an intramolecular attack of an anionoid form derived from the 2-keto group of the pyrimidine moiety giving rise to 2,2'- and 2,3'-anhydro derivatives.

An example of participation by the primary hydroxyl at C-6 in the opening of the 2,3-anhydro ring during acid hydrolysis of methyl 2,3-anhydro-D-hexopyranosides has been recently reported.¹⁰ The reaction gives predominantly the 3,6-anhydro derivative by ring opening at C-3 and there is no evidence reported for opening at C-2 to give a 2,6-anhydro derivative.

Experimental Section^{11,12}

Methyl 2,6-Anhydro-3,4-di-O-methyl- α -D-mannoside (2).—To a solution of methyl 2-O-mesyloxy-3,4-di-O-methyl- α -D-glucoside (1, 2.4 g., 7.95 mmoles) in anhydrous ether (100 ml.) was added 50% sodium in paraffin dispersion (0.42 g., 9.1 mmoles) and the solution was refluxed for 2 hr. Anhydrous dimethyl sulfoxide

(DMSO,¹³ 600 ml.) was added and the solution was stirred at 85° overnight. The cooled solution was poured into ice-water (3500 ml.) and the mixture was extracted continuously with ether for 48 hr. Evaporation of the dried (Na_2SO_4) ether extract gave an oil containing DMSO. T.l.c. (ether) showed a major product, running faster than starting material, which gave a distinctive red-brown color with the spray reagent. Smaller amounts of starting material and demesyloxy product were also evident. Fractionation of the residue on a column of silica gel (300 g.) using ether as eluent gave the major product, methyl 2,6-anhydro-3,4-di-O-methyl- α -D-mannoside (2, 0.776 g., 47.5%) as a clear sirup which crystallized after distillation. Recrystallization from ether-hexane gave white prisms, m.p. 37–38.5°, $[\alpha]^{25}_D + 52^\circ$ (*c* 2.0, carbon tetrachloride). V.p.c. showed a single peak, R_V (TMG),¹⁴ 0.72, on an Apiezon L column at 183°.

Anal. Calcd. for $\text{C}_9\text{H}_{16}\text{O}_5$: C, 52.94; H, 7.90; mol. wt., 204.2. Found: C, 53.03; H, 7.89; mol. wt., 204.8 (by vapor pressure lowering), 204 (by mass spectrometry).

2,6-Anhydro-3,4-di-O-methyl-D-mannose (3).—Methyl 2,6-anhydro-3,4-di-O-methyl- α -D-mannoside (2, 0.40 g.) was treated with 1 *N* hydrochloric acid at 60° for 2 hr. and the solution was then passed down a column of Amberlite IR-45 (OH⁻) resin. Evaporation of the effluent gave a yellow sirup (0.31 g.), $[\alpha]^{25}_D - 31.7^\circ$ (*c* 1.89, chloroform). T.l.c. (acetone) showed only one component running slower than starting material. The n.m.r. spectra of the sirup as solutions in D_2O and CDCl_3 were consistent with a mixture of the α and β anomers of 2,6-anhydro-3,4-di-O-methyl-D-mannose (3).

1,5-Anhydro-3,4-di-O-methyl-D-mannitol (4).—Sirupy 3 (0.22 g.) was dissolved in water (8 ml.) and a solution of sodium borohydride (0.2 g.) in water (8 ml.) was added dropwise with stirring. T.l.c. (acetone) indicated complete reaction after 1 hr. Excess borohydride was destroyed by addition of a few drops of glacial acetic acid and the solution was freed from cations by passage down a column of Amberlite IR-120 (H⁺) resin. Concentration of the aqueous effluent afforded a solid residue, and borate ions were removed by repeated evaporation with methanol leaving a clear sirup (0.20 g.). The sirup was chromatographed on a column of silica gel (25 g.) with acetone as eluent giving pure 1,5-anhydro-3,4-di-O-methyl-D-mannitol (4, 0.17 g.) which crystallized. Recrystallization from ether gave white prisms, m.p. 80–80.5°, $[\alpha]^{25}_D - 16.3^\circ$ (*c* 2.7, chloroform).

Anal. Calcd. for $\text{C}_8\text{H}_{16}\text{O}_6$: C, 50.00; H, 8.37. Found: C, 50.09; H, 8.39.

Treatment of 4 with 2.5 equiv. of *p*-nitrobenzoyl chloride in boiling pyridine followed by pouring into water afforded a solid residue which was collected by filtration and washed with 0.1 *N* sodium hydroxide and water. Recrystallization from ethanol gave pale yellow crystals of 1,5-anhydro-3,4-di-O-methyl-2,6-di-O-*p*-nitrobenzoyl-D-mannitol (5), m.p. 146.5–147.5°, $[\alpha]^{25}_D - 37.6^\circ$ (*c* 2.1, chloroform).

Anal. Calcd. for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_{11}$: C, 53.87; H, 4.52; N, 5.71. Found: C, 53.90; H, 4.53; N, 5.91.

1,5-Anhydro-2,3,4,6-tetra-O-methyl-D-mannitol (6).—To a solution of 4 (0.10 g.) in anhydrous redistilled tetrahydrofuran (10 ml.) was added sodium hydride powder¹⁵ (50 mg.) and methyl iodide (2 ml.), and the mixture was stirred at room temperature. T.l.c. (acetone) showed that reaction was complete in 2 hr. giving one product having the same R_f value as authentic 1,5-anhydro-2,3,4,6-tetra-O-methyl-D-mannitol. Methanol was added dropwise to destroy the excess sodium hydride and removal of solvents gave a solid residue. Extraction with ether and concentration of the extracts gave a sirupy residue 6 (70 mg.) which was purified by distillation at 12 mm. (bath temperature 100°), $[\alpha]^{25}_D - 39.6^\circ$ (*c* 2.12, ethanol). V.p.c. showed a single component, R_V (TMG), 0.83, on an Apiezon L column at 183°.

A sample of 1,5-anhydro-2,3,4,6-tetra-O-methyl-D-mannitol was prepared by methylation of styrcitol¹⁶ (1,5-anhydro-D-mannitol) by the procedure of Kuhn, *et al.*¹⁷ The sirupy product

(13) DMSO was dried and distilled over Linde 13X Molecular Sieves.

(14) R_V (TMG) is the relative retention volume compared with methyl 2,3,4,6-tetra-O-methyl- α -D-glucoside (TMG) as standard. On an Apiezon L column, 6 ft. \times 0.25 in. at 183°, helium flow rate 170 cc. min.⁻¹, TMG had a retention time of 18 min.

(15) A 55% oil dispersion of sodium hydride was washed with anhydrous ether under an atmosphere of dry nitrogen to remove the oil.

(16) The authors wish to thank Dr. H. G. Fletcher, Jr., for a sample of styrcitol.

(17) R. Kuhn, H. Trischmann, and L. Löw, *Angew. Chem.*, **67**, 32 (1955).

(6) W. Meyer zu Reckendorf, *Chem. Ber.*, **98**, 93 (1965).

(7) J. P. Horwitz, J. Chua, J. A. Urbanski, and M. Noel, *J. Org. Chem.*, **28**, 942 (1963).

(8) I. L. Doerr, J. F. Codington, and J. J. Fox, *ibid.*, **30**, 467 (1965).

(9) J. F. Codington, J. L. Doerr, and J. J. Fox, *ibid.*, **30**, 476 (1965).

(10) J. G. Buchanan and J. Conn, *J. Chem. Soc.*, 201 (1965).

(11) Infrared and n.m.r. spectra consistent with the proposed structures were obtained for all new compounds. Infrared spectra were recorded on a Perkin-Elmer InfraCORD spectrophotometer. The n.m.r. spectra were recorded at 60 Mc. on a Varian Model A-60 spectrometer. Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Optical rotations were measured with an ETL-NPL automatic polarimeter (The Bendix Corporation, Cincinnati, Ohio). Molecular weights were determined in chloroform solution with a vapor pressure osmometer (Mechrolab, Inc., Mountain View, Calif.). Ascending thin layer chromatography (t.l.c.) was performed on 0.25-mm. layers of silica gel G prepared according to Stahl, (distributed by Brinkmann Instruments, Inc., Great Neck, N. Y.) and the plates were sprayed successively with a 1% solution of α -naphthol in ethanol and with 10% sulfuric acid and were then heated. Silica gel, grade 950, 60–200 mesh, from the Davison Co., Baltimore 3, Md., was used without pretreatment for column chromatography. Vapor phase chromatography (v.p.c.) was carried out using a Perkin-Elmer vapor fractionator, Model 154. Solvents were removed under reduced pressure.

(12) The authors wish to thank F. H. Bissett for the n.m.r. spectra and C. DiPietro for the microanalyses.

was distilled twice and had the following physical constants: n_D^{25} 1.4521, $[\alpha]_D^{25}$ -40.2° (c 2.49, ethanol).¹⁸ V.p.c. on Apiezon L at 183° gave R_v (TMG) 0.83.

Comparison of the infrared and n.m.r. spectra of this compound with those obtained from 6 identified the latter as 1,5-anhydro-2,3,4,6-tetra-*O*-methyl-*D*-mannitol.

(18) W. Freudenberg and J. T. Sheehan [*J. Am. Chem. Soc.*, **62**, 558 (1940)] reported n_D^{25} 1.4520 and $[\alpha]_D^{25}$ -36.5° (no solvent).

Syntheses of

1,4-Anhydro-2,3,6-tri-*O*-methyl-*D*-galactose and 1,4-Anhydro-2,3-di-*O*-methyl-*L*-arabinose

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Recent studies on anhydro sugar addition polymerization have shown that 1,4-anhydro sugar derivatives under the influence of Lewis acid catalysts will produce high molecular weight polymers.¹ In connection with these studies 1,4-anhydro-2,3,6-tri-*O*-methyl-*D*-galactose and 1,4-anhydro-2,3-di-*O*-methyl-*L*-arabinose have been synthesized.

There has been considerable controversy in the literature over the existence and possible structure of 1,4-anhydro sugars obtained *via* internal displacement reactions. Hess was led to believe^{2,3} that the reaction of 2,3,6-tri-*O*-methyl-4-*O*-tosyl-*D*-glucose with alkoxide ion resulted in inversion on C-5 rather than on C-4 yielding a 1,4-anhydro sugar with *L*-ido configuration instead of the *D*-galacto configuration which should be expected in view of the present-day knowledge of the stereochemistry of displacement reactions.

As summarized elsewhere,⁴ the data on the 1,4-anhydro sugar (and the reducing sugar thereof) prepared by Hess appear in the light of recent data to agree somewhat better with the *D*-galacto configuration and this configuration has in fact been confirmed by the present investigation.

The procedure outlined by Hess² and which he believed led to 1,4-anhydro-2,3,6-tri-*O*-methyl-*L*-idose was essentially followed. A sharp-melting crystalline anhydro sugar was isolated which was identified as 1,4-anhydro-2,3,6-tri-*O*-methyl-*D*-galactose by hydrolyzing the compound to the reducing sugar and oxidizing this to the corresponding γ -lactone with bromine-water. The hydrolysis product of the anhydro sugar exhibited on a paper chromatogram a single spot whose R_G value corresponded to that of 2,3,6-tri-*O*-methyl-*D*-galactose. The specific rotation for the anhydro sugar, $[\alpha]_D^{25}$ $+86.3^\circ$ (chloroform), is very similar to that of the anhydro sugar isolated by Hess, $[\alpha]_D^{20}$ $+90.8^\circ$ (chloroform). It is, therefore,

concluded that a 1,4-anhydro derivative of 2,3,6-tri-*O*-methyl-*D*-galactose must be sterically feasible and that Hess probably obtained this same compound, his evaluation of the molecular models notwithstanding. The oily compound obtained by Hess was not, probably, the pure isomer since the tosylation of the methyl 2,3,6-tri-*O*-methyl-*D*-glucoside leads to some tosylation at C-5 of the furanoside forms present in the glucoside mixture. The specific rotation for the glucoside used in the tosylation step in the present study indicated incomplete equilibration of the various glucosidic forms. However, since the *D*-galacto derivative could be isolated, an adequate amount of the pyranosidic forms must have been present in the glucoside mixture.

A 1,4-anhydro sugar has been obtained also from the corresponding tosylated *D*-xylose derivative. The methyl 2,3-di-*O*-methyl-*D*-xyloside intermediate was obtained by methanolysis of a linear 1,4-linked wood xylan after methylation of the free hydroxyl groups. This glycoside has been shown by Bishop and Cooper^{5,6} to consist at equilibrium of 83.6% pyranosidic and 16.4% furanosidic forms. After tosylation this composition was essentially preserved since the yield in the tosylation step was very high (93%). Since the *D*-xylopyranose derivative has the tosyloxy group attached to the asymmetric C-4, an internal displacement occurring with inversion of configuration at this carbon atom will lead to 1,4-anhydro-2,3-di-*O*-methyl-*L*-arabinose. Since the *D*-xylofuranose derivative, on the other hand, has the tosyloxy group attached to the C-5 which is not an optically active center, the internal displacement will lead to 1,4-anhydro-2,3-di-*O*-methyl-*D*-xylose.

It was not feasible, as in the case of the 1,4-anhydro-*D*-galactose derivative, to isolate a pure isomer as acrySTALLINE material. In a very pure sample of the 1,4-anhydro-2,3-di-*O*-methyl-*L*-arabinose there appeared after long standing in the cold a small amount of a crystalline material. Separation of this material, which melted at about 8° , was not attempted.

The mixture of *L*-arabinose and *D*-xylose anhydro sugar derivatives was represented by a single symmetrical peak when analyzed by gas-liquid chromatography on a number of different columns. For preparation of the pure *L*-arabinose and *D*-xylose anhydro sugars a chromatographic separation of the tosylates prior to the displacement reaction could be attempted.

The composition of the anhydro sugar mixture was found qualitatively by paper chromatography to correspond to that which should be expected on the basis of Bishop's equilibrium data.^{5,6} The mixture of reducing sugars obtained by hydrolysis of the anhydro sugar showed up as essentially two spots, one major spot whose R_G value corresponded to that of 2,3-di-*O*-methyl-*L*-arabinose and one minor spot whose R_G value was identical with that of an authentic sample of 2,3-di-*O*-methyl-*D*-xylose.

These 1,4-anhydro sugars, in addition to being interesting monomers for addition polymerization, also are convenient intermediates for preparation of the methylated sugars in pure form. A recent synthesis of 2,3,6-tri-*O*-methyl-*D*-galactose by Williams and

(1) Paper presented by J. Kops and C. Schuerch at the Fifth Cellulose Conference held May 6-7, 1965, at the State University College of Forestry, Syracuse, N. Y.; *J. Polymer Sci.*, in press.

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(3) K. Hess and K. E. Heumann, *ibid.*, **72**, 137 (1939).

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