was distilled twice and had the following physical constants: n^{25}_D 1.4521, $[\alpha]^{25}_D$ −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.

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[18] W. Freudenberg and J. T. Sheehan [*J. Am. Chem. Soc.*, **62**, 558 (1940)] reported n^{25}_D 1.4520 and $[\alpha]^{25}_D$ −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 Hess[2] 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, $[\alpha]^{28}_D$ +86.3° (chloroform), is very similar to that of the anhydro sugar isolated by Hess, $[\alpha]^{20}_D$ +90.8° (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 chromotographic 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

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[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.

[2] K. Hess and F. Neumann, *Ber.*, **68**, 1360 (1935).

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

[4] J. Kops, Ph.D. Thesis, State University College of Forestry at Syracuse University, Syracuse, N. Y., June 1965.

[5] C. T. Bishop and F. P. Cooper, *Can. J. Chem.*, **40**, 224 (1962).

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Jeanloz[7] involved the separation of the desired compound from other methylated galactosides.

The preparation of these methylated sugars through the anhydro sugar intermediate may, however, be a more general method. It appears, for example, that minor modification of the Hess synthesis *via* the furanosides could also lead to 2,3,6-tri-O-methyl-L-idose, and other methylated polysaccharides could serve as convenient starting materials.

Experimental Section

1,4-Anhydro-2,3,6-tri-O-methyl-D-galactose. A. 2,3,6-Tri-O-methyl-D-glucose.—Commercial highly methylated methyl cellulose (200 g., Dow MC 568) with a methoxyl content of 41.5% (theoretical 45.6%) was hydrolyzed according to Denham and Woodhouse[8] in 4 l. of concentrated hydrochloric acid. The resulting reddish syrup (205 g.) was dissolved in acetone, and dry ethyl ether was added to precipitate most of the syrup. The precipitated and soluble materials were extracted separately with boiling dry benzene to recover the 2,3,6-tri-O-methyl-D-glucose. The compound crystallized upon evaporation of the benzene. By repeated extractions with benzene (without attempting a quantitative recovery of the compound), 68 g. (30%) of 2,3,6-tri-O-methyl-D-glucose was recovered: m.p. 122–123°, $[\alpha]^{25}\mathrm{D}$ 62.1° (*c* 2.0, chloroform) and +68° (*c* 1.1, water); lit.[9,10,11] m.p. 122–123°, $[\alpha]\mathrm{D}$ +64 to +70° (water).

B. **Methyl 2,3,6-Tri-O-methyl-D-glucoside.**—The 2,3,6-tri-O-methyl-D-glucose (60 g.) was added to 1200 ml. of anhydrous methanol containing 1% hydrogen chloride and refluxed for 16 hr. in the presence of some Drierite.[2] The solution was neutralized with anhydrous ammonia gas and the solvent and excess ammonia were then evaporated. Extraction of the residue with anhydrous ethyl ether yielded 62 g. of colorless oil. Distillation on a 16-in. spinning-band column gave 41 g. (73%) of colorless oil: b.p. 84–86° (0.08 mm.), $n^{20}\mathrm{D}$ 1.4559, $[\alpha]^{24}\mathrm{D}$ +14.2 → +79.3° (0.8 *N* MeOH–HCl); lit. b.p. 115–118° (0.5 mm. of Hg), $n\mathrm{D}$ 1.4590, $[\alpha]\mathrm{D}$ +72° (methanol),[12] $[\alpha]\mathrm{D}$ +80.6° (1% MeOH–HCl).[18]

C. **Methyl 2,3,6-Tri-O-methyl-4-O-tosyl-D-glucoside.**—The methyl 2,3,6-tri-O-methyl-D-glucoside (30.7 g.) was dissolved in 60 ml. of anhydrous pyridine, 29.8 g. of *p*-toluenesulfonyl chloride was added and the solution kept for 4 days at room temperature. After the work-up described by Hess,[2] 45.8 g. (90%) remained of a light yellow syrup, $[\alpha]^{28}\mathrm{D}$ 22.8° (*c* 5.8, chloroform), lit.[2] $[\alpha]^{17}\mathrm{D}$ 20.1° (chloroform). The infrared spectrum showed essentially no hydroxyl absorption.

D. **2,3,6-Tri-O-methyl-4-O-tosyl-D-glucose.**—The methyl 2,3,6-tri-O-methyl-4-O-tosyl-D-glucose (44.3 g.) was hydrolyzed for 12 hr. at reflux temperature in 1100 ml. of a mixture of water–dioxane (1:1) containing 5 g. of hydrogen chloride per 100 ml. of solvent mixture. This optimum hydrolysis time was established by determining the rate of formation of methanol in the reaction mixture by gas–liquid chromatography (6-ft. 20% Carbowax 20M on firebrick, 85°) similar to the technique used by Sarkanen.[14] The mixture was neutralized with sodium carbonate and extracted with benzene and the extract was evaporated to dryness. The residue was dissolved in benzene, the solution washed with water, and the benzene was evaporated after drying over anhydrous sodium sulfate. The yield was 28.5 g. (64%), $[\alpha]^{28}\mathrm{D}$ 42.9° (*c* 5.9, chloroform), lit.[2] $[\alpha]^{20}\mathrm{D}$ 51.3° (chloroform). The infrared spectrum showed only weak hydroxyl absorption.

E. **1,4-Anhydro-2,3,6-tri-O-methyl-D-galactose.**—The 2,3,6-tri-O-methyl-4-O-tosyl-D-glucose (22.5 g., 0.0598 mole) was dissolved in 1125 ml. of anhydrous isopropyl alcohol. Then 254 ml. of a solution was added containing 0.0598 mole of sodium isopropoxide in anhydrous isopropyl alcohol and after a short time sodium tosylate started to precipitate. The reaction mixture was then stirred at room temperature for 18 hr. after which 0.8 ml. of water was added and the stirring continued for 5 min. more. A stream of carbon dioxide was passed through the solution and the solution was then dried over anhydrous magnesium sulfate. The isopropyl alcohol was evaporated *in vacuo;* the residue was extracted with petroleum ether (b.p. 40–60°). Simple vacuum distillation of the brown oil which remained after evaporation of the petroleum ether yielded 2.7 g. (22%) of a colorless oil, b.p. 75–76° (0.17 mm.). This material was found to be at least 95% pure by gas–liquid chromatography [3-ft. 10% poly(ethyleneglyxol succinate), 190°]. Several fractions prepared as described above were combined and distilled on a 16-in. spinning-band column. From 10.8 g. of crude material, 6.9 g. of very pure fractions was obtained, b.p. 71–72° (0.18 mm.). Analyses by gas–liquid chromatography showed no impurities and the compound exhibited a single symmetrical peak [3-ft. 10% poly(ethyleneglycol succinate), 6-ft. 20% Carbowax 20M, and 6-ft. 20% silicone SE 52, all on firebrick, 180°]. When these fractions were stored at −15° one of them crystallized. Upon seeding, all the other fractions crystallized. After recrystallization from ethyl ether–petroleum ether, 3.5 g. of crystals was recovered, m.p. 36–37°, $[\alpha]^{25}\mathrm{D}$ 86.3° (*c* 2.1, chloroform).

Anal.[15] Calcd. for $C_9H_{16}O_5$: C, 52.93; H, 7.91; OCH_3, 45.6. Found: C, 52.89; H, 7.81; OCH_3, 45.5.

F. **Conversion of the Anhydro Sugar to 2,3,6-Tri-O-methyl-D-galactono-1,4-lactone.**—The anhydro sugar (0.1 g.) was refluxed for 0.5 hr. in 1% hydrochloric acid after which the solution was neutralized with silver carbonate. After filtration and treatment of the filtrate with Amberlite IR-120 cation-exchange resin, the water was evaporated *in vacuo*. The residue was oxidized with bromine–water as described by Hough and Jones.[16] The resulting crystals were recrystallized from ethyl ether–petroleum ether: m.p. 98–99°, $[\alpha]^{23}\mathrm{D}$ −39.7° (*c* 1.0 initial value, water); lit. m.p. 97–99°,[16-21] $[\alpha]\mathrm{D}$ −38 to −40° (initial value, water).[16,19,20] The infrared spectrum exhibited the strong absorption at 5.6 μ which is characteristic for a γ-lactone. It has recently been reported that, when the galactonic acid is completely converted into the lactone, the following values are obtained[7]: m.p. 100–101°, $[\alpha]\mathrm{D}$ −29° → −18° (after 12 days in water). A melting point in this range was also reported by Haworth in one case.[22] However, the melting point range 97–99° and an initial rotation of −38 to −40° is generally obtained for preparations carried out as described above.

1,4-Anhydro-2,3-di-O-methyl-L-arabinose. A. Isolation of Wood Xylan.—The xylan was extracted, as previously described,[23] from trembling aspen sapwood, which has an open-cell structure with easily accessible linear xylan. From 1300 g. of extractive-free wood meal there was recovered 141 g. (9.2%) of fluffy gray-white powder.

B. **Methylation of Xylan.**—The xylan (30 g.) was methylated three times with dimethyl sulfate according to standard methods.[23,24] The yield was 29.6 g. of fluffy white powder, $[\alpha]^{25}\mathrm{D}$ −63° (*c* 1.1, chloroform), lit.[23] $[\alpha]\mathrm{D}$ −67° (*c* 2.0, chloroform).

C. **Methyl 2,3-Di-O-methyl-D-xyloside.**—The methylated xylan (50 g.) was refluxed for 20 hr. in 2150 ml. of 0.8 *N* methanolic hydrogen chloride containing some Drierite.[23] The solution was then neutralized with anhydrous ammonia gas. The solvent was evaporated and the residue was extracted with ethyl ether. After this was dried over anhydrous sodium sulfate, the ether was evaporated and 53 g. of an orange oil was obtained. Following a simple vacuum distillation, this material was distilled on a 16-in. spinning-band column and 28.1 g. (52%) distilled over between 74 and 76° at 0.35 mm.: $[\alpha]^{28}\mathrm{D}$ +64.2°

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(c 2.1, methanol), n^{20}_{D} 1.4568; lit.[25] $[\alpha]_D$ +61.8° (methanol), n_D 1.4581.

D. Methyl 2,3-Di-O-methyl-4-O-tosyl-D-xyloside.—The procedure is similar to that used for the preparation of the corresponding D-glucose derivative. The methyl 2,3-di-O-methyl-D-xyloside (21.5 g.) was allowed to react with 25.7 g. of tosyl chloride in 45 ml. of pyridine for 3 days. The yield was 36.0 g. (93%) of light brown syrup, $[\alpha]^{28}_D$ 20.95° (c 6.2, chloroform). The infrared spectrum indicated no hydroxyl absorption.

E. 2,3-Di-O-methyl-4-O-tosyl-D-xylose.—The procedure is the same as that used for the preparation of the corresponding glucose derivative. The methyl 2,3-di-O-methyl-D-xyloside (35.3 g.) was hydrolyzed for 12 hr. in 900 ml. of a mixture of water–dioxane (1:1) containing 5 g. of hydrogen chloride per 100 ml. of solvent mixture. The yield was 19.1 g. (57%) of dark brown syrup, $[\alpha]^{28}_D$ 25.1° (c 6.9, chloroform). The infrared spectrum indicated appreciable hydroxyl absorption.

F. 1,4-Anhydro-2,3-di-*O*-methyl-D-arabinose.—The procedure is the same as that used for the preparation of the corresponding D-galactose derivative. The 2,3-di-O-methyl-4-O-tosyl-D-xylose (18.8 g., 0.0565 mole) was dissolved in 940 ml. of anhydrous isopropyl alcohol and allowed to react with 0.0565 mole of sodium isopropoxide in 240 ml. of isopropyl alcohol. A simple vacuum distillation yielded 4.86 g. (54%) of a colorless oil, b.p. 61–63° (0.6 mm.). This material was found to be at least 95% pure in the two isomeric anhydro sugars by gas–liquid chromatography [3-ft. 10% poly(ethyleneglycol succinate), 190°]. Several crude fractions prepared as described above were combined and distilled on a 16-in. spinning-band column. The distillate (10.8 g., b.p. 49–50° at 0.22 mm.) was better than 99% pure in the two isomers as analyzed by gas–liquid chromatography (3-ft. 10% poly(ethyleneglycol succinate), 6-ft. 20% Carbowax 20M, and 6-ft. 20% silicone SE 52, all on firebrick, 180°). The last traces of impurities were removed by preparative gas–liquid chromatography (20-ft. 20% QF-1 on Chromosorb P, 180°). The product showed $[\alpha]^{29}_D$ 128.5° c 3.5, chloroform), d^{25} 1.18.

Anal.[15] Calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.50; H, 7.57.

Paper Chromatography.—After hydrolysis of the anhydro sugars in 1% hydrochloric acid, the separation of the resulting sugars was done on Whatman No. 1 paper using a moving phase consisting of 1-butanol–water–ethanol (5:4:1) (upper layer) according to Hirst and Jones.[26] The pertinent R_G values have been compiled by Lederer.[27] 2,3-Di-O-methyl-D-xylose, 2,3,6-tri-O-methyl-D-glucose, and 2,3,4,6-tetra-O-methyl-D-glucose were used as reference compounds.

Acknowledgment.—This investigation has been supported by Research Grant GM-06168 from the Division of General Medical Sciences, National Institutes of Health.

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Preparation of 2- and 4-Substituted D-Glucose Derivatives from 1,6-Anhydro-β-D-glucopyranose[1]

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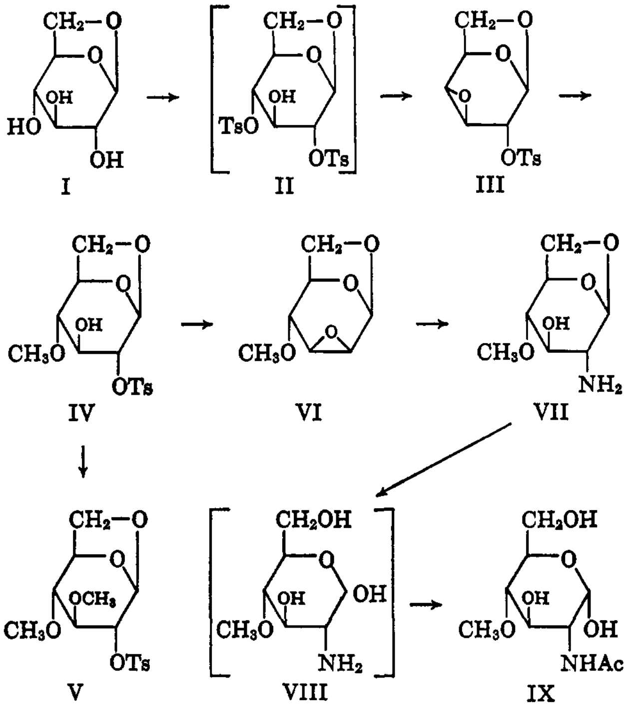
The partial esterification of 1,6-anhydro-β-D-glucopyranose (I) has been reported.[2,3] Substitution occurs predominantly at the 2- and 4-positions. Jeanloz, Rapin, and Hakomori[3] have pointed out that *p*-tolylsulfonate esters of 1,6-anhydro-β-D-glucopyranose should form epoxides useful for the preparation of derivatives of D-glucose. The molecule is made rigid by the 1,6-anhydro ring and places all hydroxyl groups in the axial position. This allows one to predict with confidence the results of opening the epoxide groups.[4–6] In addition the yields are better and the reaction products are less complicated by the selective opening. This will be the case, however, only if the 1,6-anhydro ring is preserved during the opening of the epoxide groups.

This paper reports on some 2,4-substituted compounds with the D-glucose configuration prepared *via* the diester and on the unusual action of sulfonic acid ion-exchange resins in opening the 3,4-epoxide group without splitting the 1,6-anhydro ring if the 2-position is occupied by the *p*-tolylsulfonyl group.

The diester II could possibly give two epoxides. Treatment with base has given only 1,6:3,4-dianhydro-2-*O*-*p*-tolylsulfonyl-β-D-galactopyranose (III).[2] This dianhydro compound is readily obtained from the crude ester mixture in about 50% yield from 1,6-anhydro-β-D-glucopyranose. It has also been obtained by Hann and Richtmyer from 1,6-anhydro-2,3,4-tri-*O*-*p*-tolylsulfonyl-β-D-glucopyranose.[7]



Attempts were made to open the 3,4-anhydro ring of III by methanol using both acidic and basic conditions. Reaction with sodium methoxide in methanol gave a complex mixture of products that was not investigated further. Černý, Buben, and Pacák[8] have shown that several compounds are formed when III is

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[1] Presented at the 20th Northwest Regional Meeting of the American Chemical Society, Corvallis, Ore., June 1965.

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