Carbohydrate Research
Elsevier Publishing Company, Amsterdam
Printed in Belgium

HYDROGENOLYSIS OF CYCLIC AND ACYCLIC ORTHOESTERS OF CARBOHYDRATES WITH LITHIUM ALUMINUM HYDRIDE–ALUMINUM TRICHLORIDE*

S. S. BHATTACHARJEE** AND P. A. J. GORIN

National Research Council of Canada, Prairie Regional Laboratory, Saskatoon, Saskatchewan (Canada)

(Received May 20th, 1969; in revised form, June 24th, 1969)

ABSTRACT

Several cyclic and acyclic carbohydrate orthoesters have been hydrogenolyzed with 1:1 lithium aluminum hydride–aluminum trichloride, and the mechanisms of the reaction have been studied. Generally, cyclic orthoesters are cleaved *via* cyclic carbonium-ion intermediates that are stereospecifically attacked by the reducing species, giving cyclic acetals in good yield. One example is the cleavage of both diastereoisomers of 1,2-*O*-(1-methoxyethylidene)-3,4,6-tri-*O*-methyl-β-D-mannopyranose to 1,2-*O*-ethylidene-3,4,6-tri-*O*-methyl-β-D-mannopyranose having an *exo* *O*-ethylidene proton. Cleavage of carbohydrate acyclic orthoesters with the reagent is less specific. Acyclic methyl orthoesters were formed simultaneously by the action of methyl orthoformate and a trace of acid on 1,2:3,5-di-*O*-methylene-α-D-glucofuranose (**20**). After removal of the contaminating formic ester of **20**, the remainder was hydrogenolyzed with the reagent to **20** and the two methylene acyclic acetals **24** and **25** in the ratios of 5:10:3 (w/w/w).

INTRODUCTION

Eliel[1–3] and Brown[4–11] and their co-workers have investigated the reductive cleavage, with lithium aluminum hydride–aluminum trichloride, of 1,3-dioxolanes, 1,3-dioxanes, 1,3-oxathiolanes, and *O*-tetrahydropyran-2-yl and *O*-tetrahydrofuran-2-yl derivatives to ethers. We have extended these studies to carbohydrate derivatives, and have shown that the reagent has utility in the synthesis of *O*-benzyl and *O*-methyl derivatives from cyclic *O*-benzylidene and *O*-methylene acetals, respectively[12,13]. It was also found that cyclic orthoesters of sugars can be cleaved to cyclic acetals, and that the mechanism of cleavage of this type of derivative was of interest[12]. 1,2-*O*-Isopropylidene-3,5,6-*O*-orthoformyl-α-D-glucofuranose was converted by $LiAlH_4$–$AlCl_3$ (1:1) into 1,2-*O*-isopropylidene-3,5-*O*-methylene-α-D-glucofuranose; and, when $LiAlD_4$–$AlCl_3$ (1:1) was used, specific labeling with deuterium at C-2

*Issued as NRCC No. 10975.
**N.R.C. Postdoctorate Fellow, 1967–1969.

took place in the 1,3-dioxane ring. On changing the ratio of $LiAlD_4$ to $AlCl_3$ to 1:3, a small proportion of 1,2-*O*-isopropylidene-5,6-*O*-methylene-α-D-glucofuranose was formed, and this was also specifically labeled with deuterium at C-2 of the 1,3-dioxolane ring. Only one stereoisomer was formed on conversion of 1,2-*O*-isopropylidene-3,5,6-*O*-orthoacetyl-α-D-glucofuranose into 3,5-*O*-ethylidene-1,2-*O*-isopropylidene-α-D-glucofuranose; but, as this is the thermodynamically stable isomer, it is not known with certainty whether it was formed directly or arose under the reaction conditions from the thermodynamically unstable isomer. Because only one of two possible diastereoisomers was formed in each of these reactions, it was decided to conduct a systematic investigation of the hydrogenolysis products of cyclic and acyclic orthoesters, from both a synthetic and a mechanistic point of view.

RESULTS AND DISCUSSION

The orthoesters hydrogenolyzed to acetals with $LiAlH_4$–$AlCl_3$ were as follows: (*a*) 5-membered cyclic orthoesters that were the diastereoisomers of 1,2-*O*-(1-methoxyethylidene)-3,4,6-tri-*O*-methyl-β-D-mannopyranose (**1** and **2**), 1,2-*O*-(methoxybenzylidene)-3,5-di-*O*-methyl-β-D-arabinofuranose (**5**), 3-*O*-methyl-1,2,5-*O*-orthobenzoyl-β-D-arabinofuranose (**8**), mixed 2,3:5,6-di-*O*-(methoxymethylene)-D-mannose isomers, and mixed methyl 2,3:5,6-di-*O*-(methoxymethylene)-α-D-mannofuranoside isomers (**15**); (*b*) compounds containing a 6-membered, cyclic orthoester: the isomeric methyl 2,3:4,6-di-*O*-(methoxymethylene)-α-D-mannopyranosides; and (*c*) acyclic orthoesters obtained by treating 1,2:3,5-di-*O*-methylene-α-D-glucofuranose (**20**) with methyl orthoformate–hydrogen chloride.

The diastereoisomer of the 1,2-(1-methoxyethylidene) acetal of 3,4,6-tri-*O*-acetyl-β-D-mannopyranose, having an *exo* methoxyl group[14], was considered as a substrate. Since treatment with lithium aluminum hydride in the initial stages of the hydrogenolysis reaction would cause deacetylation and formation of a difficultly soluble intermediate, the hydroxyl groups were protected by conversion into the 3,4,6-trimethyl ether (**1**) by successive deacetylation and *O*-methylation. Hydrogenolysis of the trimethyl ether with $LiAlH_4$–$AlCl_3$ gave one diastereoisomer of 1,2-*O*-ethylidene-3,4,6-tri-*O*-methyl-β-D-mannopyranose (**4**), as shown by proton magnetic resonance (p.m.r.) spectroscopy; this compound has a C–CH_3 signal at τ 8.51, compared with τ 8.65 for its diastereoisomer (20% of the mixture) formed on equilibration with $CDCl_3$–HCl. By analogy with the findings of Perlin[15] on the relative C–CH_3 chemical shifts of the diastereoisomers of 3,4,6-tri-*O*-acetyl-1,2-*O*-(methoxyethylidene)-β-D-mannopyranose, the hydrogenolysis product should contain an *endo* C–CH_3 group.

Hydrogenolysis of a diastereoisomeric mixture of the 1,2-*O*-(1-methoxyethylidene)-3,4,6-tri-*O*-methyl-β-D-mannopyranoses (**1** and **2**) (prepared from mixed 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-methoxyethylidene)-β-D-mannopyranoses[16] gave the same 1,2-*O*-ethylidene-3,4,6-tri-*O*-methyl-β-D-mannopyranose (**4**), having an *endo* C–CH_3, as was obtained from the pure orthoacetate. This is significant, since it means that

both reactions have a common carbonium-ion intermediate (3) which is attacked by the hydrogen of the reducing species to form a 1,2-*O*-ethylidene group having an *exo*-hydrogen atom. The hydrogenolysis reaction bears a similarity to that reported by Buchanan and Edgar[17], who prepared fluoroborate salts by treatment of a mixture of the methyl β-L-arabinopyranoside 3,4-(ethyl orthoacetates) with boron trifluoride, and then reduced this mixture with lithium borohydride to the diastereoisomeric methyl 3,4-*O*-ethylidene-β-L-arabinopyranosides. The ratio of the isomers containing the *endo* and *exo* C–CH_3 groups was 9:1, and it is possible that some acetal equilibration had occurred.

A series of reactions similar to that described for the β-D-mannopyranose series was conducted with two β-D-arabinofuranose derivatives. 2,3,5-Tri-*O*-benzoyl-1,2-*O*-(methoxybenzylidene)-β-D-arabinofuranose has an *exo*-OCH_3 group, as it is prepared by the action of methanol on 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl bromide in the presence of 2,6-lutidine[18], a reaction that has been used by Mazurek and Perlin[14] to prepare the *exo* OCH_3 isomer of 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-methoxyethylidene)-β-D-mannopyranose from 3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl bromide. The β-D-arabinofuranose derivative was converted into 1,2-*O*-(methoxybenzylidene)-3,5-di-*O*-methyl-β-D-arabinofuranose (5), which was cleaved with $LiAlH_4$–$AlCl_3$ to a single diastereoisomer of 1,2-*O*-benzylidene-3,5-di-*O*-methyl-β-D-arabinofuranose (7). The stereochemistry is uncertain on the basis of the chemical shift of its benzylic proton (τ 3.98), which is virtually the same as that of its stereoisomer

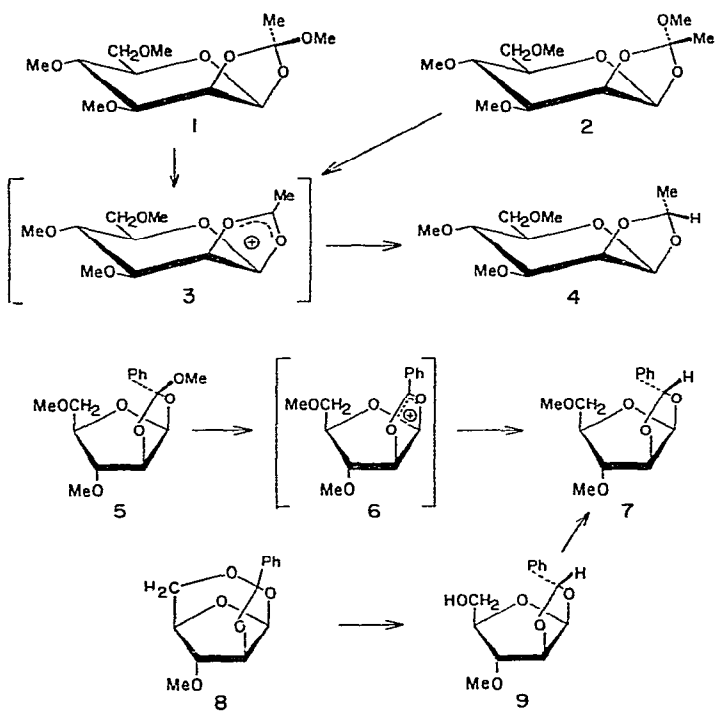
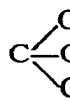


Fig. 1. Mechanism of cleavage of cyclic orthoesters with $LiAlH_4$–$AlCl_3$.

(< 35% of the mixture), formed on $CDCl_3$–HCl equilibration. However, it seems likely that the benzylidene proton is *exo*, as the intermediate carbonium-ion (**6**) would be more readily approached by the reducing agent from this side. As the 1,2-*O*-(methoxybenzylidene)-3,5-di-*O*-methyl-β-D-arabinofuranose having an *endo* OCH_3 orthoester group was not available as a hydrogenolysis substrate, a stereochemically analogous compound, namely, 3-*O*-methyl-1,2,5-orthobenzoyl-β-D-arabinofuranose (**8**) was used; this was prepared by methylation of 1,2,5-*O*-orthobenzoyl-β-D-arabinofuranose[18]. Hydrogenolysis of **8** with $LiAlH_4$–$AlCl_3$ gave 1,2-*O*-benzylidene-3-*O*-methyl-β-D-arabinofuranose (**9**), which was converted by methylation into 1,2-*O*-benzylidene-3,5-di-*O*-methyl-β-D-arabinofuranose (**7**), identical (by p.m.r. spectroscopy) with the compound prepared by hydrogenolysis of 1,2-*O*-(methoxybenzylidene)-3,5-di-*O*-methyl-β-D-arabinofuranose (**5**).

A noticeable feature of the above series of reactions is the selective, hydrogenolytic cleavage of the C-2–oxygen bonds that are external to the 1,3-dioxolane rings; this behavior is presumably due to the lower free-energies of the five-membered, cyclic carbonium-ions as compared with other possibilities. Two other examples of transformation of the 5-membered, cyclic orthoester to a 5-membered, cyclic acetal were noted. Firstly, D-mannose was treated with methyl orthoformate–HCl to give a crude orthoester mixture from which a di-*O*-(methoxymethylene)-D-mannose derivative was isolated; it was substituted in the 2,3:5,6-positions, because spin-decoupling experiments showed that it contained a free hydroxyl group on C-1. Hydrogenolysis gave 2,3:5,6-di-*O*-methylene-D-mannose (**12**) containing a trace of 2,3:5,6-di-*O*-methylene-D-mannitol (**13**) (combined yield, 40%). Secondly, methyl α-D-mannofuranoside (**14**) was dissolved in methyl orthoformate–HCl to give a syrup from which a crystalline stereoisomer of methyl 2,3:5,6-di-*O*-(methoxymethylene)-α-D-mannofuranoside (**15**) was isolated. The crude orthoester mixture was hydrogenolyzed to syrupy methyl 2,3:5,6-di-*O*-methylene-α-D-mannofuranoside (**16**) in 28% yield. (The product was identical with the compound formed by the action of sodium hydride and dichloromethane on methyl α-D-mannofuranoside in *N*,*N*-dimethylformamide.) In these two hydrogenolyses, there is a tendency for preponderance of the cyclic, carbonium-ion intermediate, as the yields are higher than 11% (the yield that would be obtained were the cleavage of the  bonds of the orthoesters random).

A lower yield of *O*-methylene acetal was obtained on hydrogenolysis of a 6-membered *O*-(methoxymethylene) ring. Methyl α-D-mannopyranoside (**10**) was converted into orthoester derivatives. Hydrogenolysis of the crude product gave methyl 2,3:4,6-di-*O*-methylene-α-D-mannopyranoside (**11**) in 17% yield. In each of these three examples, the yield of sugar orthoester is low, due to incomplete substitution of the available hydroxyl groups by action of methyl orthoformate–HCl and, probably, also, the formation of formic esters (see later).

Although cyclic methylene acetals are relatively stable to hydrogenolysis conditions, they can undergo further cleavage[4,12,13]. Prolonged hydrogenolysis of

methyl 2,3:5,6-di-*O*-methylene-α-D-mannofuranoside (**16**) gave a mixture from which syrupy methyl 6-*O*-methyl-2,3-*O*-methylene-α-D-mannofuranoside (**17**; 9% yield) and crystalline methyl 5-*O*-methyl-2,3-*O*-methylene-α-D-mannofuranoside (**18**; 4.5% yield) were isolated. A further fraction (12% yield) was treated with sodium periodate to give periodate-resistant methyl 2,6-di-*O*-methyl-α-D-mannofuranoside (**19**), identified by conversion with methanolic hydrogen chloride into the corresponding pyranoside derivative, the g.l.c. characteristics of which are known[13]. The periodate-oxidized material is probably a polyhydric alcohol containing hydroxyl groups on C-4 and C-5; this could arise *via* cleavage of the C-1 to furanose-ring-oxygen bond of one of the partially hydrogenolyzed products, such as methyl 2,6-di-*O*-methyl-α-D-mannofuranoside or methyl 6-*O*-methyl-2,3-*O*-methylene-α-D-mannofuranoside.

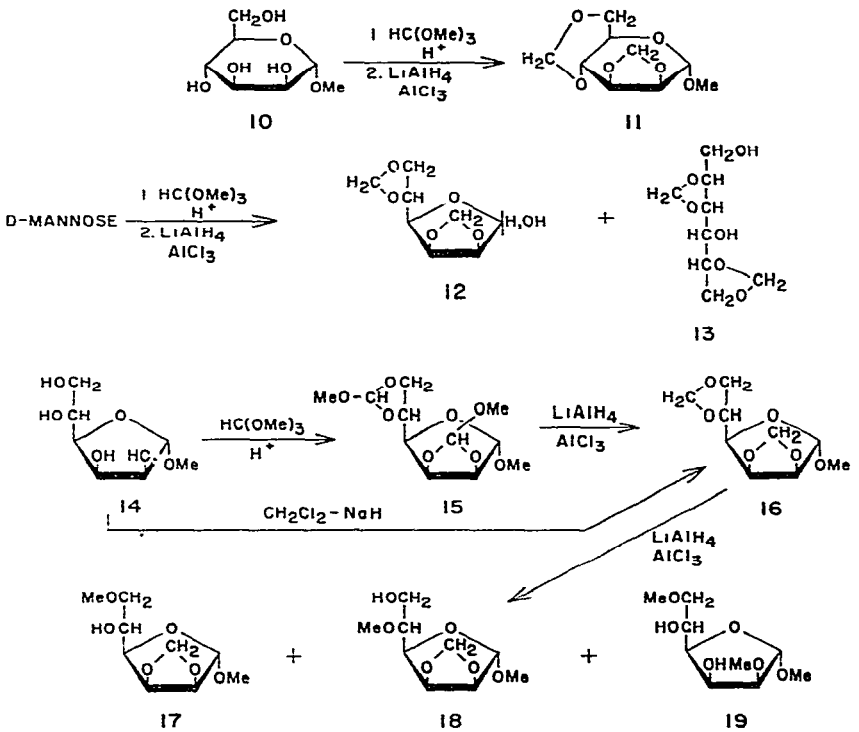


Fig. 2. Conversion of D-mannose derivatives into cyclic methylene acetals by successive treatment with methyl orthoformate–HCl and $LiAlH_4$–$AlCl_3$.

Acyclic orthoformic esters were prepared by treating 1,2:3,5-di-*O*-methylene-α-D-glucofuranose (**20**) with methyl orthoformate in the presence of a trace of acid. The product contained some formic ester, as it showed infrared absorption at 1720 cm^{-1}; it was treated with methanolic sodium methoxide, and the resulting 1,2:3,5-di-*O*-methylene-α-D-glucofuranose was removed by repeatedly washing a chloroform solution of the product with water. The resulting orthoesters were

hydrogenolyzed with $LiAlH_4$–$AlCl_3$, and the product was fractionated by column chromatography on silicic acid. 6-*O*-(Methoxymethyl)-1,2:3,5-di-*O*-methylene-α-D-glucofuranose (**24**) was eluted initially (25% yield), and was identified by its p.m.r. spectrum. The next fraction (7.5% yield) contained a crystalline compound which had a molecular weight, carbon and hydrogen analysis, and p.m.r. spectrum corresponding to 6,6'-*O*-methylenebis(1,2:3,5-di-*O*-methylene-α-D-glucofuranose) (**25**). 1,2:3,5-Di-*O*-methylene-α-D-glucofuranose (**20**) was also isolated. The ratio (w/w/w) of 6-*O*-(methoxymethyl)-1,2:3,5-di-*O*-methylene-α-D-glucofuranose (**24**), a product of high molecular weight (**25**), and 1,2:3,5-di-*O*-methylene-α-D-glucofuranose (**20**) isolated from the column was 10:3:5. Since the unresolvable mixture of orthoesters obtained by treatment of 1,2:3,5-di-*O*-methylene α-D-glucofuranose could contain **21**, **22**, and **23**, little can be deduced on the pathway of hydrogenolysis of the acyclic orthoester. For example, **21** or **22** can give rise to **24**, and **25** could be formed from either **21** or **23**. However, hydrogenolysis proceeds only to acyclic *O*-methylene derivatives, and further conversion into methyl ethers does not occur; this behavior is also a characteristic of cyclic *O*-methylene acetals[12].

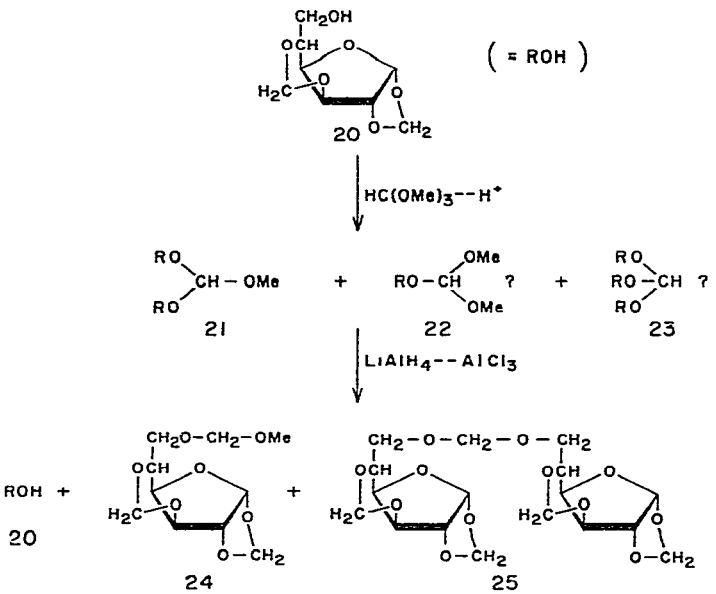
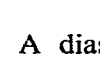
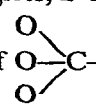


Fig. 3. Cleavage of acyclic orthoesters of 1,2:3,5-di-*O*-methylene-α-D-glucofuranose with $LiAlH_4$–$AlCl_3$.

EXPERIMENTAL

P.m.r. spectra were recorded with a Varian 100-MHz spectrometer, with tetramethylsilane as the internal standard; chemical shifts are recorded as τ values. Hydrogenolyses with lithium aluminum hydride–aluminum trichloride were conducted with a 1:1 molar ratio of the two reagents by the procedure described previously[12],

except that the reaction mixture was decomposed by means of cold, dilute, aqueous potassium carbonate solution. G.l.c. was performed with a column (0.25 in × 12 ft) of 2% neopentyl glycol succinate on Chromosorb W, at 190° and a helium pressure of 36 lb.in^{-2}. Evaporations were performed under diminished pressure. I.r. spectra were recorded with a Perkin–Elmer Model 21 spectrometer. Paper chromatography was conducted on Whatman No. 1 filter paper with 40:11:19 (v/v) butyl alcohol–ethanol–water. T.l.c. was performed on plates of Silica Gel G with detection by use of a 50% sulfuric acid spray, and charring.

Hydrogenolysis of 1,2-O-(1-methoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranoses. — 3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-methoxyethylidene)-*β*-D-mannopyranose (200 mg), containing an *exo* OCH_3 group[14], was deacetylated with sodium methoxide in methanol, and the product was methylated with Purdie's reagents to give 1,2-*O*-(1-methoxyethylidene)-3,4,6-tri-*O*-methyl-*β*-D-mannopyranose[19] (**1**) (150 mg); $[\alpha]_D^{25}$ −1.4° (*c* 0.5, ethanol) and p.m.r. signals ($CDCl_3$) at τ 4.63 (doublet, *J* 2.5 Hz, anomeric H), τ 6.44, 6.47, 6.62, 6.70 (4 singlets, 4 OMe), τ 8.30 (singlet, CH_3 of ). A diastereoisomeric mixture[16] of tri-*O*-acetyl-*β*-D-mannopyranose 1,2-(methyl orthoacetates) consisting of 55% of the *exo* and 45% of the *endo* OCH_3 compound was similarly converted into the trimethyl ethers[19] (**1** and **2**), $[\alpha]_D^{25}$ −8° (*c* 1.0, ethanol); p m.r. signals ($CDCl_3$) at τ 4.63 (doublet, *J* 2.5 Hz, anomeric H), τ 4.86 (doublet, *J* 2.5 Hz, anomeric H), τ 6.44 (2 superimposed singlets, 2 OCH_3), τ 6.46 (2 superimposed singlets, 2 OCH_3), τ 6.57, 6.62, 6.65, 6.70 (4 singlets, 4 OCH_3), τ 8.30, 8.48 (2 singlets, 2 of ).

Each of the two preparations of trimethyl ethers was hydrogenolyzed for 45 min with 1.1 molar equivalents of $LiAlH_4$–$AlCl_3$, giving products in 65–75% yields. In each case, one stereoisomer of 1,2-*O*-ethylidene-3,4,6-tri-*O*-methyl-*β*-D-mannopyranose (**4**) was obtained, and this could be separated from other, minor components (20–25%) by chromatography on silicic acid with elution with 8:1 (v/v) chloroform–acetone. The product gave p.m.r. signals ($CDCl_3$) at τ 4.74 (quartet, *J* 5 Hz, CH of *O*-ethylidene), τ 4.84 (doublet, *J* 2.5 Hz, anomeric H), τ 6.46, 6.48, 6.63 (3 singlets, 3 OCH_3), and τ 8.51 (doublet, *J* 5 Hz, CH_3 of *O*-ethylidene). The two products had the same g.l.c. retention-time, and $[\alpha]_D^{25}$ +4° (*c* 0.5, ethanol).

Equilibration of **4** with 0.1% of hydrogen chloride in $CDCl_3$ gave a diastereoisomeric mixture. The new diastereoisomer was detected by the p.m.r. signal of its —CCH_3 group (20% of the total C—CH_3 signals; doublet at τ 8.65).

Hydrogenolysis of 1,2-O-(methoxybenzylidene)-3,5-di-O-methyl-β-D-arabinofuranose (endo *Ph group*) (**5**) *and 3-O-methyl-β-D-arabinofuranose 1,2,5-orthobenzoate* (**8**). — 2,3,5-Tri-*O*-benzoyl-*α*-D-arabinofuranosyl bromide was treated with methanol in the presence of 2,6-lutidine, and the product was debenzoylated to give 1,2-*O*-(methoxybenzylidene)-*β*-D-arabinofuranose having an *exo* OCH_3 group[18]. This

compound was methylated with Purdie's reagents, and the resulting 1,2-*O*-(methoxybenzylidene)-3,5-di-*O*-methyl-β-D-arabinofuranose (**5**) had $[\alpha]_D^{25} - 10°$ (*c* 0.5, chloroform), and p.m.r. signals (in CCl_4) at τ 2.40–2.80 (multiplet, 15 aromatic protons), τ 4.01 (doublet, *J* 4 Hz, anomeric H), τ 6.68, 6.94, 6.96 (three singlets, three OCH_3).

Hydrogenolysis of **5** (300 mg) with 1 molar equivalent of $LiAlH_4$–$AlCl_3$ for 45 min gave a syrup (210 mg) which had a p.m.r. spectrum containing one *O*-benzylidene proton (at τ 3.98) of 1,2-*O*-benzylidene-3,5-di-*O*-methyl-β-D-arabinofuranose (**7**). Slower-moving, minor contaminants, detectable by t.l.c. with 2:1 (v/v) chloroform–acetone were removed by chromatography on silicic acid with 2:1 (v/v) chloroform–acetone. The product had $[\alpha]_D^{25}$ +7° (*c* 1.0, ethanol). The original reaction-product and the purified product gave the same p.m.r. signals ($CDCl_3$); τ 1.90–2.80 (multiplet, 15 aromatic protons), τ 3.98 (singlet, *O*-benzylidene proton), τ 4.06 (doublet, *J* 4 Hz, anomeric H), τ 6.56, 6.58 (two singlets, 2 OCH_3).

Methylation of 1,2,5-*O*-orthobenzoyl-β-D-arabinofuranose[18] with Purdie's reagents gave the 3-methyl ether (**8**) which (from ether) had m.p. 126–128° and $[\alpha]_D^{25}$ −26.4° (*c* 0.5, ethanol).

Anal. Calc. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.14; H, 5.78.

It gave p.m.r. signals ($CDCl_3$) at τ 2.3–2.75 (multiplet, 15 aromatic H), τ 3.96 (doublet, *J* 4 Hz, anomeric H), τ 6.58 (singlet, OCH_3). Hydrogenolysis of the 3-methyl ether **8** (100 mg) with 1 molar equivalent of $LiAlH_4$–$AlCl_3$, as already described, gave syrupy 1,2-*O*-benzylidene-3-*O*-methyl-β-D-arabinofuranose (**9**) (75 mg), which was homogeneous on t.l.c. with 8:1 (v/v) chloroform–acetone. The compound showed p.m.r. signals (in methyl sulfoxide-d_6) at τ 2.15–2.40 (multiplet, 15 aromatic protons), τ 3.67 (singlet, *O*-benzylidene proton), τ 3.71 (doublet, anomeric H), τ 4.70 (triplet, primary hydroxyl), and τ 6.30 (singlet, OCH_3). Methylation of **9** with Purdie's reagents gave 1,2-*O*-benzylidene-3,5-di-*O*-methyl-β-D-arabinofuranose (**7**) with a p.m.r. spectrum and $[\alpha]_D^{25}$ [+7° (*c* 0.5, ethanol)] identical with those of the known compound.

Synthesis of O-*methylene*-D-*mannose derivatives* via *cyclic orthoesters.* — *A. Methyl 2,3:4,6-di-*O-*methylene-*α-D-*mannopyranoside* (**11**). A mixture of methyl α-D-mannopyranoside (**10**) (2 g), dry *N,N*-dimethylformamide (2 ml), methyl orthoformate (3 ml), and 4 drops of 3% methanolic hydrogen chloride was shaken for 40 min. Chloroform (20 ml) and anhydrous potassium carbonate were added, and the mixture was shaken and filtered. The filtrate was evaporated to a syrup (600 mg), which was treated with 2.5 molar equivalents of $LiAlH_4$–$AlCl_3$ for 1 h. The crude reaction product (400 mg) was chromatographed on a column of silicic acid with 2:1 (v/v) chloroform–acetone as the eluant. The initial fraction (100 mg) crystallized from methanol; it had m.p. 138°, and was identical by p.m.r. spectrum, g.l.c. retention-time, and mixed m.p. with methyl 2,3:4,6-di-*O*-methylene-α-D-mannopyranoside[12] (**11**).

*B. 2,3:5,6-Di-*O-*methylene-*D-*mannose* (**12**) *and 2,3:5,6-di-*O-*methylene-*D-*mannitol* (**13**). D-Mannose (2 g) was added to dry *N,N*-dimethylformamide (2 ml), methyl orthoformate (3 ml), *p*-toluenesulfonic acid (20 mg), and Drierite (1 g), and the

mixture was shaken for 4 h (until complete dissolution of the sugar had occurred). Chloroform (25 ml) and anhydrous potassium carbonate were added, and the mixture was shaken for a few minutes, filtered, and the filtrate evaporated to dryness in the presence of a trace of potassium carbonate. The product was treated with sodium methoxide in methanol (to remove any ester groups that might have been present). Extraction of an aqueous solution of the product with ether, followed by evaporation, gave a syrup, a portion of which crystallized from chloroform–hexane (20% yield). The resulting 2,3:5,6-di-*O*-(methoxymethylene)-D-mannose had m.p. 107–109° and $[\alpha]_D^{25}$ +27.7° (*c* 1.3, ethanol).

Anal. Calc. for $C_{10}H_{16}O_8$: C, 45.45; H, 6.10. Found: C, 44.98; H, 5.78.

P.m.r. signals ($CDCl_3$): τ 4.24, 4.26 (2 singlets, 2 orthoester protons), τ 4.61 (doublet, *J* 2 Hz, anomeric H), τ 6.70, 6.73 (2 singlets, 2 OCH_3), τ 7.01 (doublet, *J* 2 Hz, secondary OH). A spin-decoupling experiment, with H-1 as the reference proton, showed that the free hydroxyl group was on C-1.

Hydrogenolysis of the crystalline derivative (100 mg) with 2.5 molar equivalents of $LiAlH_4$–$AlCl_3$ gave essentially one product (75 mg), as shown by t.l.c. After purification of the mixture by column chromatography on silicic acid with 2:1 (v/v) chloroform–acetone, the p.m.r. spectrum of the purified material (50 mg) corresponded to that for a 2,3:5,6-di-*O*-methylenemannose (such as **12**) contaminated by approximately 20% of a 2,3:5,6-di-*O*-methylenemannitol (such as **13**). It reduced Fehling solution, and, on hydrolysis with 0.5M sulfuric acid for 15 h at 100°, a mannose with a trace of a mannitol could be detected by paper chromatography.

*C. Methyl 2,3:5,6-di-*O*-methylene-α-D-mannofuranoside* (**16**). Methyl α-D-mannofuranoside (**14**) (500 mg) was shaken with methyl orthoformate (2.5 ml) containing 2–3 drops of 3% methanolic hydrogen chloride for 15 min. Benzene (5 ml) was then added, and the resulting solution was shaken for 15 min, diluted with benzene, stirred with anhydrous potassium carbonate, and filtered. The filtrate was evaporated to a syrup (600 mg) which partly (~30% of the total) crystallized from chloroform–hexane. The product (**15**) had m.p. 104–107°, $[\alpha]_D^{25}$ +81° (*c* 1.0, ethanol).

Anal. Calc. for $C_{11}H_{18}O_8$: C, 47.48; H, 6.52. Found: C, 47.78; H, 6.71.

The crude, syrupy mixture of orthoesters (500 mg) was hydrogenolyzed with 2.5 molar equivalents of $LiAlH_4$–$AlCl_3$ for 1 h, and the product was purified by column chromatography on silicic acid with 2:1 (v/v) chloroform–acetone. Methyl 2,3:5,6-di-*O*-methylene-α-D-mannofuranoside (**16**) (140 mg) was eluted initially, and it constituted ~50% of the product; it was homogeneous by t.l.c. and g.l.c.; p.m.r. signals ($CDCl_3$) at τ 4.96, τ 5.02, τ 5.08, τ 5.11, and τ 5.14 (5 singlets for 5 protons, anomeric H and 4 *O*-methylene protons), τ 6.70 (singlet, OCH_3). It had $[\alpha]_D^{25}$ +78° (*c* 1.3, chloroform), and was identical by g.l.c., p.m.r. spectroscopy, and $[\alpha]_D^{25}$ with material synthesized by the following procedure.

Methyl α-D-mannofuranoside (**14**) (1 g) was dissolved in dry *N*,*N*-dimethylformamide (10 ml), and sodium hydride (0.5 g) was slowly added, followed[20] by dichloromethane (1 ml). After the mixture had been shaken for 4 days, the same amounts of sodium hydride and dichloromethane were added, and the reaction was

continued for a further 2 days. Methanol was slowly added and, after 1 h, water was carefully added. The mixture was extracted with chloroform, and fractionation of the extract by column chromatography on silicic acid with 2:1 (v/v) chloroform–acetone afforded methyl 2,3:5,6-di-*O*-methylene-α-D-mannofuranoside (**16**) (330 mg) as the initial fraction.

*Hydrogenolysis of methyl 2,3:5,6-di-*O*-methylene-α-D-mannofuranoside* (**16**). — Methyl 2,3:5,6-di-*O*-methylene-α-D-mannofuranoside (**16**) (1 g) was treated with 3 molar equivalents of $LiAlH_4$–$AlCl_3$ for 8 days in the usual way. Column chromatography of the crude product on silicic acid with 2:1 (v/v) chloroform–acetone gave the following fractions.

Fraction A (600 mg) was identified as unreacted starting-material.

Fraction B (90 mg) had $[\alpha]_D^{25}$ +92° (*c* 0.5, ethanol) and contained methyl 6-*O*-methyl-2,3-*O*-methylene-α-D-mannofuranoside (**17**); p.m.r. signals ($CDCl_3$) at τ 5.02–5.08 (2 peaks, 3 protons, anomeric H and 2 *O*-methylene protons), τ 6.60, 6.72 (2 singlets, 2 OCH_3), and τ 7.16 (doublet, one secondary hydroxyl group). Spin-decoupling experiments established the positions of all of the ring protons, and also showed that the hydroxyl group was on C-5.

Fraction C (45 mg) was identified as methyl 5-*O*-methyl-2,3-*O*-methylene-α-D-mannofuranoside (**18**), which crystallized from chloroform–hexane and had m.p. 70–72° and $[\alpha]_D^{25}$ +98° (*c* 1.0, ethanol).

Anal. Calc. for $C_9H_{16}O_6$: C, 49.08; H, 7.32. Found: C, 49.34; H, 7.25.

It showed p.m.r. signals ($CDCl_3$) at τ 5.06–5.11 (3 peaks, 3 protons, anomeric H and two *O*-methylene protons), τ 6.52, 6.71 (2 singlets, 2 OCH_3). The p.m.r. spectrum obtained from a solution in methyl sulfoxide-d_6 at 70° showed a triplet[21] corresponding to a primary hydroxyl group.

Fraction D (120 mg) was treated overnight with $NaIO_4$, and the oxidized material was removed by column chromatography on silicic acid. The slow-moving component (50 mg) had $[\alpha]_D^{25}$ +96° (*c* 0.5, ethanol) and was methyl 2,6-di-*O*-methyl-α-D-mannofuranoside (**19**). It was homogeneous by g.l.c.; the retention times have already been reported[13]. It showed p.m.r. signals ($CDCl_3$) at τ 5.11 (doublet, *J* 2 Hz, anomeric H), τ 6.54, 6.62, 6.66 (3 singlets, 3 OCH_3). A solution of **19** in 3% methanolic hydrogen chloride was refluxed for 2 h, made neutral with silver carbonate, the suspension filtered, and the filtrate evaporated to a syrup whose p.m.r. spectrum and g.l.c. retention-time were identical with those of methyl 2,6-di-*O*-methyl-α-D-mannopyranoside[13].

*Conversion of 1,2:3,5-di-*O*-methylene-α-D-glucofuranose* (**20**) *into* O*-methylene derivatives.* — A crude mixture (1.2 g) of orthoesters was obtained by treating 1,2:3,5-di-*O*-methylene-α-D-glucofuranose (1 g) with methyl orthoformate (10 ml) containing 5 drops of 3% methanolic hydrogen chloride; following neutralization, the solution was evaporated to dryness. The crude syrup, which showed i.r. absorption at 1720 cm^{-1}, was treated with sodium methoxide in methanol, the solution was evaporated to dryness, and the product was washed with water and then dissolved in chloroform; the solution was washed with water, and evaporated to dryness.

The resulting material (**21** and **22**) (800 mg) was free from 1,2:3,5-di-*O*-methylene-α-D-glucofuranose (by t.l.c.) and its formic ester (by i.r.). The material derived from the hydrogenolysis of the orthoester mixture (400 mg) with 1 molar equivalent of $LiAlH_4$–$AlCl_3$ was resolved into three fraction by column chromatography on silicic acid with 8:1 (v/v) chloroform–acetone.

Fraction A (100 mg), a syrup, had $[\alpha]_D^{25}+42.5°$ (*c* 1.5, ethanol) and, on the basis of its p.m.r. spectrum (CCl_4), was 6-*O*-(methoxymethyl)-1,2:3,5-di-*O*-methylene-α-D-glucofuranose (**24**); signals occurred at τ 4.16 (doublet, *J* 4 Hz, anomeric H), τ 5.06–5.12 (superimposed signals, 3 protons of *O*-methylene), τ 5.34 (doublet, *J* 5 Hz, one proton of six-membered *O*-methylene group), τ 5.46 (singlet, 2 protons of 6-*O*-substituted *O*-methylene), τ 6.70 (singlet, OCH_3).

Fraction B (30 mg) crystallized from carbon tetrachloride; m.p. 100–102°, $[\alpha]_D^{25}+49.8°$ (*c* 1.0, ethanol).

Anal. Calc. for $C_{17}H_{24}O_{12}$: C, 48.57; H, 5.76; Mol. wt. 420. Found: C, 48.87; H, 5.57; Mol. wt. 431.

Its p.m.r. spectrum was consistent with structure **25**; signals ($CDCl_3$) at τ 3.98 (doublet, *J* 4 Hz, 2 anomeric H), τ 4.95 (doublet, *J* 6 Hz, 4 five-membered *O*-methylene H), τ 4.99 (doublet, *J* 6 Hz, 2 equatorial *H* of six-membered *O*-methylene group), τ 5.18 (doublet, *J* 6 Hz, 2 axial protons of six-membered *O*-methylene group), τ 5.28 (singlet, 2 protons of *O*-methylene bridge), τ 5.53–6.30 (signals for 12 ring-protons).

Fraction C (50 mg) was identified as 1,2:3,5-di-*O*-methylene-α-D-glucofuranose (**20**) by its characteristic p.m.r. spectrum.

ACKNOWLEDGMENTS

The authors thank Mr. M. Mazurek for recording the p.m.r. spectra, and Mr. W. C. Haid for recording the infrared spectra and making the microanalytical determinations.

REFERENCES

1 E. L. Eliel, V. G. Badding, and M. N. Rerick, *J. Amer. Chem. Soc.*, 84 (1962) 2371.
2 E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Amer. Chem. Soc.*, 84 (1962) 2377.
3 E. L. Eliel, B. E. Nowak, R. A. Daignault, and V. G. Badding, *J. Org. Chem.*, 30 (1965) 2441.
4 B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, 42 (1964) 990.
5 B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, 41 (1963) 2671.
6 U. E. Diner and R. K. Brown, *Can. J. Chem.*, 45 (1967) 2547.
7 B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, 43 (1965) 1030.
8 B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, 42 (1964) 1005.
9 B. E. Leggetter, U. E. Diner, and R. K. Brown, *Can. J. Chem.*, 42 (1964) 2113.
10 U. E. Diner and R. K. Brown, *Can. J. Chem.*, 45 (1967) 1297.
11 U. E. Diner, H. A. Davis, and R. K. Brown, *Can. J. Chem.*, 45 (1967) 207.
12 S. S. Bhattacharjee and P. A. J. Gorin, *Can. J. Chem.*, 47 (1969) 1195.
13 S. S. Bhattacharjee and P. A. J. Gorin, *Can. J. Chem.*, 47 (1969) 1207.
14 M. Mazurek and A. S. Perlin, *Can. J. Chem.*, 43 (1965) 1918.
15 A. S. Perlin, *Can. J. Chem.*, 41 (1963) 399.

16 J. K. DALE, *J. Amer. Chem. Soc.*, 46 (1924) 1046.
17 J. G. BUCHANAN AND A. R. EDGAR, *Chem. Commun.*, (1967) 29.
18 N. K. KOCHETKOV, A. YA. KHORLIN, A. F. BOCHKOV, AND I. G. YAZLOVETSKIĬ, *Izv. Akad. Nauk SSSR Ser. Khim.*, (1966) 2030; *Chem. Abstr.*, 66 (1967) 95326.
19 H. G. BOTT, W. N. HAWORTH, AND E. L. HIRST, *J. Chem. Soc.*, (1930) 1395.
20 J. S. BRIMACOMBE, A. B. FOSTER, B. D. JONES, AND J. J. WILLARD, *J. Chem. Soc.*, (1967) 2404.
21 O. L. CHAPMAN AND R. W. KING *J. Amer. Chem. Soc.*, 86 (1964) 1256.

Carbohyd. Res., 12 (1970) 57–68