SOME ACETALS OF METHYL 2-DEOXY-2-HALOGENO-α-D-ALTROPYRANOSIDE AND THEIR REACTIONS WITH LITHIUM ALUMINIUM HYDRIDE

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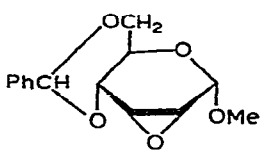
ABSTRACT

Methyl 4,6-*O*-benzylidene-2-deoxy-2-halogeno-α-D-altropyranosides undergo facile, acid-catalysed, acetal migrations to give methyl 3,4-*O*-(*R*)- and -(*S*)-*O*-benzylidene-2-deoxy-2-halogeno-α-D-altropyranosides. Whereas reduction of methyl 3,4-*O*-(*R*)-benzylidene-2-chloro-2-deoxy-6-*O*-toluene-*p*-sulphonyl-α-D-altropyranoside with lithium aluminium hydride affords methyl 3,4-*O*-(*S*)-benzylidene-2,6-dideoxy-α-D-*ribo*-hexopyranoside, similar reduction of the corresponding 2-deoxy-2-iodo derivative affords only methyl 2,3,6-trideoxy-α-D-*erythro*-hex-2-enopyranoside.

INTRODUCTION

In 1968, Lemieux and his co-workers showed that methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**1**) was converted, in high yield (95%), into methyl 4,6-*O*-benzylidene-2-deoxy-2-iodo-α-D-altropyranoside (**2**) on treatment with sodium iodide, sodium acetate, and acetic acid in acetone[1]. We have found it difficult to obtain reproducibly high yields from this reaction or from a corresponding reaction in which methyl 4,6-*O*-benzylidene-2-chloro-2-deoxy-α-D-altropyranoside (**5**) was prepared by treatment of **1** with lithium chloride, and now report that, in both cases, facile acetal migration occurs to give methyl 3,4-*O*-benzylidene-2-deoxy-2-halogeno-α-D-altropyranosides.



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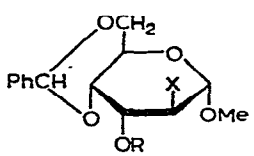
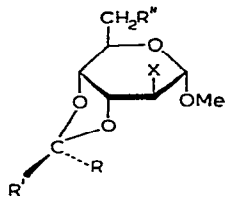


2 X=I, R=H
2a X=I, R=Ts
5 X=Cl, R=H

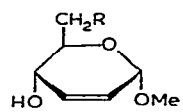
DISCUSSION

Both methyl 4,6-*O*-benzylidene-2-deoxy-2-iodo-α-D-altropyranoside (**2**, 65%) and methyl 3,4-*O*-(*R*)-benzylidene-2-deoxy-2-iodo-α-D-altropyranoside (**3**, 20%),

which was characterised as its crystalline acetate (**3a**), were isolated from the reaction of **1** with sodium iodide under the conditions described by Lemieux and his co-workers[1]. From a number of similar experiments, it was found that the relative proportions of **2** and **3** varied with reaction time and work-up conditions, and that much higher yields of **2** could be obtained. Reaction times in excess of 1 h favoured the formation of **3**, and in prolonged reactions methyl 3,4-*O*-(*S*)-benzylidene-2-deoxy-2-iodo-α-D-altropyranoside (**4**), m.p. 100°, could also be obtained. That **4** was the thermodynamically more-stable form of methyl 3,4-*O*-benzylidene-2-deoxy-2-iodo-α-D-altropyranoside was demonstrated when it was shown that **3** rearranged into **4** when stored in benzene containing toluene-*p*-sulphonic acid at room temperature. Equilibration of **3** and **4** with **2** also occurred. The configurational assignments to **3** and **4** were based on the n.m.r. spectroscopic method of Foster and his co-workers[2] who showed that benzylic protons in dioxolane derivatives resonate at higher field when opposed by only protons at C-4 and C-5 than when one or both of the *cis* C-4 and C-5 positions are substituted. In **3**, the benzylic proton resonated at 5.8 p.p.m. and in **4** at 6.16 p.p.m.



3 R = Ph, R' = H, R" = OH, X = I
3a R = Ph, R' = H, R" = OAc, X = I
3b R = Ph, R' = H, R" = OTs, X = I
3c R = Ph, R' = H, R" = Cl, X = I
4 R = H, R' = Ph, R" = OH, X = I



8 R = H
9 R = OTs
11 R = Cl

6 R = Ph, R' = H, R" = OH, X = Cl
6a R = Ph, R' = H, R" = H, X = Cl
6b R = Ph, R' = H, R" = H, X = H
6c R = Ph, R' = H, R" = OTs, X = Cl
7 R = H, R' = Ph, R" = OH, X = Cl
10 R = R' = CH_3, R" = OH, X = I
10a R = R' = CH_3, R" = OTs, X = I
10b R = R' = CH_3, R" = Cl, X = I

It was more difficult to obtain high yields of methyl 4,6-*O*-benzylidene-2-chloro-2-deoxy-α-D-altropyranoside (**5**) by treatment of **1** with lithium chloride than it was to obtain **2** from the corresponding reaction with sodium iodide, since the former reaction required a longer reaction time. Optimal yields of **5** were obtained with a reaction time of 2 h and with a large excess of lithium chloride. Longer reaction times resulted in the formation of the 3,4-*O*-benzylidene isomer **6** with possibly trace amounts of **7**. In one reaction, a small proportion of methyl 2-chloro-2-deoxy-3,4-*O*-isopropylidene-α-D-altropyranoside was also detected.

Presumably the driving force for these facile rearrangements in which 4,6-*O*-benzylidene derivatives are converted into 3,4-*O*-benzylidene derivatives is the magnitude of the non-bonded interactions in the former compounds. The n.m.r. data for the 3,4(*R*)- and 3,4(*S*)-benzylidene derivatives are consistent with conformations in which non-bonded interactions are minimised. It must be pointed out, however, that methyl 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-α-D-altropyranoside, like

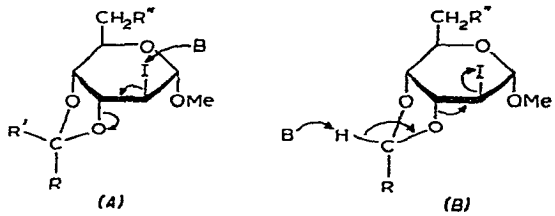
methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-altropyranoside[4] and 1,2,3,4,6-penta-*O*-acetyl-α-D-altropyranose[3], exists in the normal $^4C_1$ chair form.

In an attempt to obtain chemical proof of the structure of **3**, the 6-*O*-toluene-*p*-sulphonyl derivative (**3b**) was treated with lithium aluminium hydride, with the expectation that the product would be methyl 3,4-*O*-(*R*)-benzylidene-2,6-dideoxy-α-D-*ribo*-hexopyranoside (**6b**). In practice, no trace of **6b** was obtained, and the only products isolated were benzyl alcohol and methyl 2,3,6-trideoxy-α-D-*erythro*-hex-2-enopyranoside (**8**). Although the reaction was complete within a few minutes of the addition of **3b** to lithium aluminium hydride in ether at room temperature, the 6-*O*-toluene-*p*-sulphonyl derivative **9** could be isolated from the reaction mixture immediately after the addition.

Reduction of the 2-chloro derivative **6c** with lithium aluminium hydride, in contrast to the reductions of the corresponding 2-iodo derivatives but in agreement with the results of similar reductions of 2,6-dichloro-2,6-dideoxy-α-D-altropyranoside[5], afforded methyl 3,4-*O*-(*S*)-benzylidene-2,6-dideoxy-α-D-*ribo*-hexopyranoside (**6b**) as the preponderant product. Whereas elimination in **3b** occurred more rapidly than reduction of the 6-*O*-toluene-*p*-sulphonyl substituent, in **6c** reduction of the 6-*O*-toluene-*p*-sulphonyl group occurred rapidly, the reduction of the 2-chloro substituent requiring prolonged treatment with lithium aluminium hydride in boiling ether. Although **6b** was the preponderant product from the reduction of **6c** (or **6a**) with lithium aluminium hydride, other products were also formed in small quantities. However, there was no evidence (n.m.r., t.l.c.) for the formation of the unsaturated derivative **8**.

By analogy with the work of Lemieux and his co-workers[1], who showed that chloride ion in pyridine caused elimination in toluene-*p*-sulphonyl derivatives of iodohydrins (*e.g.* **2a**), and because reduction of vicinal iodo compounds with lithium aluminium hydride gives olefins by a similar route[6], the most likely mechanism for elimination is as illustrated in (*A*). However, if this were the mechanism, similar elimination should have taken place when **3b** was treated with pyridine hydrochloride in pyridine. In fact, the only product isolated from this reaction was the 6-chloro derivative **3c**. The alternative, elimination mechanism (*B*) was precluded because PhCHDOH and not $PhCD_2OH$ was isolated following treatment of **3b** with lithium aluminium deuteride, and because the 3,4-*O*-isopropylidene derivative **10a** also afforded **8** on treatment with lithium aluminium hydride. Consequently, it is necessary to postulate that the elimination reaction between **3b** and similar derivatives with lithium aluminium hydride is facilitated by co-ordination of aluminium with either O-3 or O-4. Evidence in support of such a co-ordination effect was provided when methyl 6-chloro-2,6-dideoxy-2-iodo-3,4-*O*-isopropylidene-α-D-altropyranoside (**10b**) was converted into methyl 6-chloro-2,3,6-trideoxy-α-D-*erythro*-hex-2-enopyranoside (**11**) by treatment with methylmagnesium iodide in ether at room temperature.

However, if co-ordination effects are important in elimination reactions caused by Grignard reagents or metal hydrides, some indication that the above concept is a gross over-simplification is provided by a comparison of the reactions of these



reagents with the 4,6-*O*-benzylidene derivative **2** and with the 3,4-acetal derivatives. Treatment of **2** with lithium aluminium hydride afforded a trace of methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (<3%), in addition to a preponderance of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside, and with Grignard reagents **2** afforded mixtures of 4,6-*O*-benzylidene-1,2-dideoxy-D-*ribo*-hex-1-enopyranose and methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside[7]. Since, in the 4,6- and 3,4-acetals, the 1-*O*-substituent bears the same geometrical relationship to the 2-iodo substituent as does the 3-*O*-substituent, it is difficult to explain why both the 4,6- and 3,4-acetals underwent elimination reactions with lithium aluminium hydride to give 2,3-enes, whereas Grignard reagents converted the 4,6-benzylidene derivative **2** into a 1,2-ene and converted the 3,4-acetal **10b** into the 2,3-ene **11**.

EXPERIMENTAL

Thin-layer chromatography (to which R_F values refer) was performed on microscope slides coated with Silica Gel G (Merck), and column chromatography was performed with Silica Gel (Merck) of particle size 0.05–0.2 mm. Products from all reactions were purified, after normal work-up, by chromatography over silica gel and characterised by their n.m.r. spectra. N.m.r. spectra were measured with a JEOL-JNM-4H-100 n.m.r. spectrometer at 100 MHz with deuteriochloroform as solvent and with tetramethylsilane as an internal standard. Chemical shifts are expressed as δ values in p.p.m. and coupling constants are in Hz. Light petroleum refers to the fraction with b.p. 40–60°.

*Reaction of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-*D*-allopyranoside* (**1**) *with sodium iodide.* — Treatment of **1** (2.64 g) with sodium iodide, sodium acetate, and acetic acid, under essentially the conditions described by Lemieux and his co-workers[1], afforded **2** (2.6 g, 65%), R_F 0.5 (ether–light petroleum 1:1), and methyl 3,4-*O*-(*R*)-benzylidene-2-deoxy-2-iodo-α-D-altropyranoside (**3**; 0.8 g, 20%), R_F 0.2 (ether–light petroleum 1:1). N.m.r. data (δ) for **3**: benzylic H, 5.8; H-1, 5.02; H-3, 4.48; H-4, 4.25; OMe, 3.35; $J_{1,2}$ 6; $J_{2,3}$ 8.9; $J_{3,4}$ 6.8; $J_{4,5}$ 8. Compound **3** afforded an acetate (**3a**), m.p. 105° (from ethanol), $[\alpha]_D^{20}$ −36.5° (*c* 1, chloroform) (Found: C, 44.2; H, 4.4. $C_{16}H_{19}O_6$ calc.: C, 43.8; H, 4.4%). N.m.r. data (δ): benzylic H, 5.88; H-1, 5.12; H-3, 4.56; H-4, 4.2; OMe, 3.40; $J_{1,2}$ 6; $J_{2,3}$ 9; $J_{3,4}$ 6.7; $J_{4,5}$ 9.8.

The toluene-*p*-sulphonate (**3b**) had m.p. 87–88° (from ethanol). N.m.r. data (δ): benzylic H, 5.72; H-1, 4.93; H-3, 4.44; $-C_6H_4Me$, 2.30; OMe, 3.26; $J_{1,2}$ 6; $J_{2,3}$ 8.9; $J_{3,4}$ 6.8.

The yields of **2** and **3** obtained by this procedure were variable, and in some experiments much higher yields of **2** were obtained.

Reaction of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (**1**) *with lithium chloride.* — A mixture of **1** (4 g), lithium chloride (40 g), sodium acetate (0.7 g), and acetic acid (22 ml) in acetone (100 ml) was boiled under reflux for 2.5 h. The mixture was diluted with ether, washed with water and aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and concentrated. The following products were obtained: (*a*) Methyl 4,6-*O*-benzylidene-2-chloro-2-deoxy-α-D-altropyranoside (**5**; 2.3 g, 48%), m.p. 102–103° (from light petroleum), R_F 0.5 (ether–light petroleum 1:1); lit.[8] m.p. 102–103.5°. (*b*) Methyl 3,4-*O*-(*R*)-benzylidene-2-chloro-2-deoxy-α-D-altropyranoside (**6**; 0.4 g, 9%), $[\alpha]_D^{20}$ +20° (*c* 3, chloroform), R_F 0.3. N.m.r. data (δ): benzylic H, 5.83; H-1, 4.78; $J_{1,2}$ 6. (*c*) Methyl 3,4-*O*-(*S*)-benzylidene-2-chloro-2-deoxy-α-D-altropyranoside (**7**, *ca.* 20 mg) R_F 0.33. (*d*) Methyl 2-chloro-2-deoxy-3,4-*O*-isopropylidene-α-D-altropyranoside, R_F 0.28. The n.m.r. spectra of the last two compounds displayed the same characteristics as the corresponding 2-deoxy-2-iodo isomers.

Conversion of **2** *into methyl 3,4-*O-(R)- *and* -(S)-*benzylidene-2-deoxy-2-iodo-α-D-altropyranoside* (**4**). — A solution of **2** (4 g) and toluene-*p*-sulphonic acid in benzene was stored at room temperature for 2 h. The solution was neutralised with Amberlite IRA-400 (OH^-) resin and concentrated. Following chromatography over silica gel in ether–light petroleum, the following products were obtained: (*a*) **2** (1.8 g), R_F 0.5. (*b*) Methyl 3,4-*O*-(*S*)-benzylidene-2-deoxy-2-iodo-α-D-altropyranoside (**4**; 0.8 g, 20%), m.p. 100° (from light petroleum b.p. 60–80°), $[\alpha]_D^{20}$ + 35° (*c* 1, chloroform) (Found: C, 42.5; H, 4.3. $C_{14}H_{17}IO_5$ calc.: C, 42.9; H, 4.4%). N.m.r. data (δ): benzylic H, 6.16; H-1, 5.07; H-2, 4.28; H-3, 4.68; H-4, 4.42; OMe, 3.42; $J_{1,2}$ 4.9; $J_{2,3}$ 7.3; $J_{3,4}$ 6.1; $J_{4,5}$ 8.6. (*c*) **3** (1 g, 25%). After 1 h, equilibration was incomplete. On storage in benzene containing toluene-*p*-sulphonic acid at room temperature, **3** was converted into **2** and **4**, and similarly **4** was converted into **2**, only a trace of **3** being apparent in this equilibration.

*Preparation of methyl 2,3,6-trideoxy-α-D-*erythro*-hex-2-enopyranoside* (**8**). — A solution of **3b** (0.65 g) in ether was added to a suspension of excess of lithium aluminium hydride in ether. An immediate, vigorous reaction took place, and after 15 min no starting material remained (t.l.c.; ether–light petroleum, 1:1). The only products detected and subsequently isolated were benzyl alcohol (R_F 0.7) and methyl 2,3,6-trideoxy-α-D-*erythro*-hex-2-enopyranoside (R_F 0.3) (**8**; 0.1 g, 60%), $[\alpha]_D^{20}$ +75° (*c* 2, chloroform). N.m.r. data (δ): H-1, 4.84; H-2, 5.90; H-3, 5.72; Me, 1.33; OMe, 3.43. $J_{1,2} = J_{1,3} = 1.9$; $J_{3,4}$ 2.7; $J_{2,3}$ 10.2. The unsaturated toluene-*p*-sulphonyl derivative **9** was isolated from the reduction product of **3b** immediately after the addition of **3b** to lithium aluminium hydride. The n.m.r. spectra of **8** and **9** were similar, apart from the presence of signals for CH_3–C_6H_4– in **9**.

Reduction of **3b** with lithium aluminium deuteride afforded C_6H_5CHDOH and the 6-deuterio derivative of **8** as shown by n.m.r. Reduction of the toluene-*p*-sulphonyl derivative of **4** with lithium aluminium hydride also afforded **8**.

Methyl 2-deoxy-2-iodo-3,4-*O*-isopropylidene-6-*O*-toluene-*p*-sulphonyl-α-D-al-

tropyranoside (**10a**) {$[\alpha]_D^{20}$ +20° (*c* 2, chloroform); n.m.r. data (δ): H-1, 4.93; H-3, 4.44; $(CH_3)_2$, 1.28 and 1.42; OCH_3, 3.45; C_6H_4–CH_3, 2.44}, which was obtained as a syrup by toluene-*p*-sulphonylation of the product **10** formed by storing **2** in acetone containing toluene-*p*-sulphonic acid, also afforded **8** on reduction with lithium aluminium hydride.

*Reaction of methyl 6-chloro-2,6-dideoxy-2-iodo-3,4-*O*-isopropylidene-α-*D*-altropyranoside* (**10b**) *with methylmagnesium iodide.* — A solution in ether of **10b** (obtained by treatment of the 6-*O*-toluene-*p*-sulphonyl derivative **10a** with pyridine hydrochloride in pyridine; the use of pyridine–pyridine hydrochloride for converting primary sulphonates into chlorides has been used extensively in steroid chemistry[9]) was treated with an excess of methylmagnesium iodide in ether for 3 h at room temperature. The only product detected (R_F 0.3; t.l.c., ether–light petroleum, 1:1) and subsequently isolated had an n.m.r. spectrum consistent with the structure methyl 6-chloro-2,3,6-trideoxy-α-D-*erythro*-hex-2-enopyranoside (**11**). It had $[\alpha]_D^{20}$ +100° (*c* 4, chloroform). N.m.r. data (δ): H-1, 4.87; H-2, 5.92; H-3, 5.68; OMe, 3.45; $J_{1,2} = J_{1,3} = 1.5$; $J_{3,4}$ 2.8; $J_{2,3}$ 10.3.

*Methyl 3,4-*O*-(R)-benzylidene-6-chloro-2,6-dideoxy-2-iodo-α-*D*-altropyranoside* (**3c**). — A solution of **3** (0.4 g) and toluene-*p*-sulphonyl chloride (0.5 g) in pyridine (5 ml) was stored at room temperature overnight [the preponderant product (R_F 0.5; t.l.c., ether–light petroleum, 2:3) was **3b**]. The solution was heated at 70–80° for 5 h and worked up in the normal way to give, after chromatographic separation: (*a*) The title compound **3c** (0.25 g, 60%), m.p. 125° (from ethanol), R_F 0.7 (ether–light petroleum, 2:3) (Found: C, 40.9; H, 4.0. $C_{14}H_{16}ClIO_4$ calc.: C, 41.0; H, 3.9%); and (*b*) **3b** (0.15 g, 28%).

*Reduction of methyl 3,4-*O*-(R)-benzylidene-2-chloro-2-deoxy-6-*O*-toluene-p-sulphonyl-α-*D*-altropyranoside* (**6c**) *with lithium aluminium hydride.* — A solution of **6c** (0.4 g) and lithium aluminium hydride (0.4 g) in ether was stored at room temperature for 2 h and worked up in the normal way to give methyl 3,4-*O*-(*R*)-benzylidene-2-chloro-2,6-dideoxy-α-D-altropyranoside (**6a**, 0.2 g) as a crude syrup. N.m.r. data (δ): benzylic H, 5.86; H-1, 4.70; H-2, 4.0; H-3, 4.34; H-4, 4.5; OMe, 3.42; CH_3, 1.35. $J_{1,2}$ 5.5; $J_{2,3}$ 8; $J_{3,4}$ 6.5. Re-treatment of **6a** with lithium aluminium hydride in boiling ether for 5 h afforded methyl 3,4-*O*-(*S*)-benzylidene-2,6-dideoxy-α-D-*ribo*-hexopyranoside (**6b**; 0.2 g, 65%). N.m.r. data (δ): benzylic H, 5.80; H-1, 4.73; H-2, 2.08; H-2′, 2.33; H-3, 4.28; OMe, 3.38; CH_3, 1.30. $J_{1,2} = J_{1,2'} = 5.1$; $J_{2,2'}$ 14.0; $J_{2,3}$ 5.1; $J_{2',3}$ 6.8; $J_{3,4}$ ~6.

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