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SYNTHESIS OF DEOXY AND AMINODEOXY SUGARS BY WAY OF CHLORODEOXY SUGARS*

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ABSTRACT

Chlorodeoxy sugars, readily prepared by the reaction of sulfuryl chloride with carbohydrates containing free hydroxyl groups, have been shown to be valuable intermediates in the synthesis of deoxy and aminodeoxy sugars. Hydrogenation of methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside (**1**) over Raney nickel in the presence of triethylamine results in a selective dechlorination at the secondary position to give methyl 6-chloro-4,6-dideoxy α-D-*xylo*-hexopyranoside (**2**).

INTRODUCTION

For several years, there has been considerable interest in deoxyhalo sugars, not only because of their potential intrinsic value in biochemistry or pharmacology, but also because of their utility in the synthesis of other rare sugars, such as deoxy and aminodeoxy sugars[2]. Most of the chemical reactions of deoxyhalo sugars that have been reported have involved iodo or bromo derivatives. Work in this laboratory has centered on the synthesis and reactions of chlorodeoxy sugars. These sugars have been prepared mainly by the reaction of sulfuryl chloride with carbohydrates containing free hydroxyl groups. The reaction has been shown[3] to give fully substituted derivatives containing both chlorodeoxy and chlorosulfate groups. The chlorodeoxy groups are formed by bimolecular displacement by chloride ion of certain of the chlorosulfonyloxy groups[4]. It is often possible to predict the reactivity of a chlorosulfonyloxy group by a consideration of the steric and polar factors affecting the formation of the transition state[5], in the manner summarized by Richardson[6] for nucleophilic replacement reactions of sulfonic esters of carbohydrate derivatives. Thus, it has been found that the presence of a vicinal axial substituent or a *β-trans*-axial substituent on a pyranoid ring inhibits replacement of a chlorosulfonyloxy group; also, a chlorosulfate group at C-2 has been observed to be deactivated to nucleophilic substitution by chloride ion.

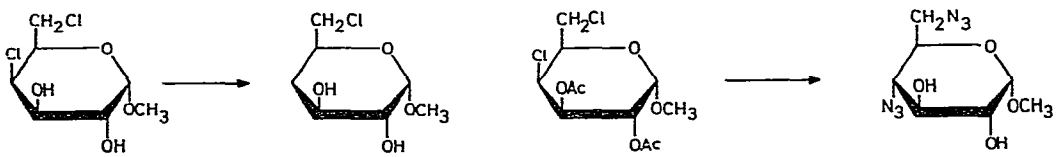
The ready availability of chlorodeoxy sugars by reaction of sugars with sulfuryl chloride, and by other methods[2b], should make these compounds valuable inter-

*Dedicated to Professor F. Micheel in celebration of his 70th birthday. Part III in the series "Synthesis and Reactions of Chlorodeoxy Sugars". For a preliminary communication, see Ref. 1.

mediates in the synthesis of other sugar derivatives. This potential utility has been, however, up until now relatively unexplored. We have previously used chlorodeoxy sugars in the preparation of 4,6-dideoxy-D-*xylo*-hexose[7] and 4,6-dideoxy-3-*O*-methyl-D-*xylo*-hexose (D-chalcose)[8], and some displacements of primary chloro groups in carbohydrate derivatives have been reported by other workers[9]. The displacement with azide ion of chloro groups in hexopyranosides at C-6 and at ring carbons has already been communicated[1]. In the present paper, details of the displacement reactions with azide ion are described, and the utility of chlorodeoxy sugars in the synthesis of deoxy sugars is demonstrated further.

RESULTS AND DISCUSSION

The deoxy sugars are an important class of carbohydrates that occur quite widely in Nature. Several different methods have been employed for the synthesis of deoxy sugars[10]. The merits of using chlorodeoxy sugars as intermediates are well illustrated by the ready synthesis[7] of 4,6-dideoxy-D-*xylo*-hexose in an overall yield of 65% from the commercially available methyl α-D-glucopyranoside. The synthetic route involved the preparation of methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside (**1**) by using sulfuryl chloride, followed by hydrogenation of **1**, in the presence of potassium hydroxide, over a W-4 Raney nickel catalyst prepared by the procedure described by Pavlic and Adkins[11]. Occasionally, the reduction of compound **1** was accompanied by the formation of side-products. In an effort to obviate this difficulty, the reduction was attempted by substituting other bases for potassium hydroxide. With barium carbonate, even after 24 h, less than a 5% yield of a reduced product was obtained. The use of triethylamine, however, led to a selective, reductive dechlorination at C-4 to give methyl 6-chloro-4,6-dideoxy-α-D-*xylo*-hexopyranoside (**2**), and an explanation for the observed selectivity is being sought.



1 2 3 4

In contrast to this dechlorination, treatment of methyl 4,6-dichloro-4,6-dideoxy-2,3-di-*O*-methyl-α-D-galactopyranoside with lithium aluminum hydride in boiling tetrahydrofuran gave methyl 4-chloro-4,6-dideoxy-2,3-di-*O*-methyl-α-D-galactopyranoside[12,*]. Another recent example of a selective dehalogenation in the carbo-

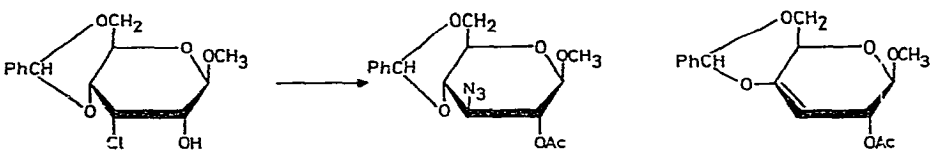
*When methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside (**1**) was treated with lithium aluminum hydride in boiling ethyl ether, even after 68 h, only the presence of starting material and a faster moving component was revealed by thin-layer chromatography (t.l.c)[12]; the latter component was visualized only when a periodate–permanganate spray reagent had reacted for 1 h, and was, presumably, a 3,6-anhydro derivative.

hydrate field has been reported by Hanessian and Plessas[13]. Catalytic hydrogenation of methyl 4-*O*-benzoyl-3-bromo-2,6-dichloro-2,3,6-trideoxy-α-D-mannopyranoside over palladium-on-carbon in the presence of barium carbonate gave methyl 4-*O*-benzoyl-6-chloro-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside. The presence of a bromine atom at C-3 apparently leads to the selective reduction of the C-2 and C-3 halogen atoms, in preference to the C-6 chlorine atom, since in a precursor, methyl 3,4-*O*-benzylidene-2,6-dichloro-2,6-dideoxy-α-D-altropyranoside, the two chlorine atoms were inert to catalytic hydrogenation.

A demonstration of the utility of the selective dechlorination procedure with triethylamine as base is provided by the ready synthesis of a 4-deoxyhexose. Thus, treatment of methyl 2,3-di-*O*-acetyl-6-chloro-4,6-dideoxy-α-D-*xylo*-hexopyranoside (prepared by acetylation of **2** with acetic anhydride–pyridine) with sodium acetate in *N*,*N*-dimethylformamide gave, in 90% yield, methyl 2,3,6-tri-*O*-acetyl-4-deoxy-α-D-*xylo*-hexopyranoside, which can be readily converted into 4-deoxy-D-*xylo*-hexose. The triacetate has been prepared previously[14] by catalytic hydrogenation of methyl 3,4-anhydro-α-D-galactoside and acetylation of the product. In the present work, a second, although less convenient, synthesis of the triacetate has been achieved also from methyl 6-*O*-triphenylmethyl-α-D-glucopyranoside[15]. Treatment of this compound with sulfuryl chloride with subsequent dechlorosulfation gave a syrup, which on hydrogenation over W-4 Raney nickel, followed by acetylation of the reduced product, yielded methyl 2,3,6-tri-*O*-acetyl-4-deoxy-α-D-*xylo*-hexopyranoside. The synthesis of 4-deoxy-D-*xylo*-hexose has been reported by other workers[16].

The direct replacement of sulfonyloxy groups in carbohydrate molecules by azide ion has proved to be a valuable method for the preparation of azidodeoxy sugars[17]. In the present work, chloro groups have similarly been shown to be susceptible to nucleophilic displacement by azide ion. A particular advantage of using chlorodeoxy sugars prepared by the sulfuryl chloride reaction, however, is that, with both the formation of the chlorodeoxy sugar and displacement of the chloro groups proceeding by an S_N2 mechanism, the configuration of the azidodeoxy sugar is the same as that of the starting unsubstituted sugar. The displacement reactions were performed in *N*,*N*-dimethylformamide at 120–130° with a twofold excess of sodium azide. Methyl 2,3-di-*O*-acetyl-4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside[12] (**3**) (prepared by way of a sulfuryl chloride reaction with methyl α-D-glucopyranoside) gave, after 12 h, a syrupy product, which was *O*-deacetylated to give crystalline methyl 4,6-diazido-4,6-dideoxy-α-D-glucopyranoside[18] (**4**) in 90% yield. With methyl 4,6-*O*-benzylidene-3-chloro-3-deoxy-β-D-allopyranoside[4,19] (**5**) (prepared by the reaction of sulfuryl chloride with methyl 4,6-*O*-benzylidene-β-D-glucopyranoside), a crystalline product was isolated after 1 h, and was shown to consist of two components (t.l.c.). A separation of the components could not be achieved by crystallization or by preparative t.l.c. The product was treated, therefore, with acetic anhydride–pyridine to give, in 60% yield, methyl 2-*O*-acetyl-3-azido-4,6-*O*-benzylidene-3-deoxy-β-D-glucopyranoside (**6**). Compound **6** could be converted into methyl 3-acetamido-2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-β-D-glucopyranoside[20] by hydrogenation over Adams'

catalyst and acetylation of the reduced product. Also isolated from the acetylation of the original mixture was a crystalline compound which was assigned the structure of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-β-D-*erythro*-hex-3-enopyranoside (**7**) by i.r. and n.m.r. spectroscopy; the same compound could be obtained, as the sole product, by heating the chlorodeoxy sugar **5** in *N*,*N*-dimethylformamide at reflux temperature with sodium benzoate, followed by treatment of the mixture with acetic anhydride-pyridine. The displacement of the chloro group in compound **5** with azide ion has also been achieved by other investigators[19]. In that work, however, the formation of an unsaturated derivative was not reported.



The displacement of chloro groups in sugars and reduction of the resultant azido derivatives constitutes a convenient, high-yielding procedure for synthesis of amino sugars.

EXPERIMENTAL

General methods — Melting points were determined on a Fisher–Johns melting-point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 141 automatic polarimeter at 23 ±2°. I.r. spectra were recorded with a Beckman-IR5A spectrophotometer. N.m.r. spectra were recorded at 60 MHz in chloroform-*d* with tetramethylsilane as the internal standard. Thin-layer chromatography (t.l.c.) was performed with Silica Gel G as the adsorbent. The developed plates were air-dried, sprayed with 5% ethanolic sulfuric acid, and heated at ~150°. Sugars containing a chlorosulfate group were detected by spraying with aniline–pyridine–butyl alcohol (1:2:7)[21].

Methyl 6-chloro-4,6-dideoxy-α-D-xylo-*hexopyranoside* (**2**). — A solution of methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside[7] (**1**, 1 g) in absolute ethanol (30 ml) containing triethylamine (1.3 ml) and W-4 Raney nickel catalyst[11] (2 g) was subjected to a hydrogen pressure of 45 lb/sq.in for 30 h. The filtered solution was neutralized with 2M hydrochloric acid and concentrated to a residue, which was partitioned between chloroform and water. The dried ($MgSO_4$) chloroform solution was concentrated to a residue which crystallized from ethyl acetate. Fractionation on silica gel, with 5% methanol in ethyl acetate as eluent, and then recrystallization from ethyl acetate–petroleum ether (b.p. 60–80°) gave compound **2** as colorless needles (*ca.* 90%), m.p. 110–111°, $[\alpha]_D$ +165° (*c* 1.02, methanol).

Anal. Calc. for $C_7H_{13}ClO_4$: C, 42.8; H, 6.6; Cl, 18.1. Found: C, 42.7; H, 6.5; Cl, 18.2.

Methyl 2,3,6-tri-O-acetyl-4-deoxy-α-D-xylo-hexopyranoside. — Compound **2** was treated with acetic anhydride–pyridine in the usual manner to give methyl 2,3-di-*O*-acetyl-6-chloro-4,6-dideoxy-α-D-*xylo*-hexopyranoside (85%), m.p. 41–45°, $[\alpha]_D$ +153° (*c* 1.85, chloroform). A stirred mixture of this compound (1 mmole), sodium acetate (2 mmoles), and dry *N,N*-dimethylformamide was maintained at 130° for 48 h. The solvent was removed under reduced pressure, and the residue was partitioned between chloroform and water. The dried ($MgSO_4$) chloroform solution was concentrated to a residue, which was recrystallized from ethyl acetate–petroleum ether (b.p. 60–80°) to give methyl 2,3,6-tri-*O*-acetyl-4-deoxy-α-D-*xylo*-hexopyranoside (80%), m.p. 76–77°, $[\alpha]_D$ +134° (*c* 1.01, chloroform); lit.[14], m.p. 74°, $[\alpha]_D$ +135° (*c* 0.9, chloroform). The tri-*O*-acetyl derivatives was prepared also from methyl 6-*O*-triphenylmethyl-α-D-glucopyranoside[15]. Treatment of this compound with sulfuryl chloride, with subsequent dechlorosulfation as described for **1**, gave a syrup, which on hydrogenation for 4 h over W-4 Raney nickel in the presence of potassium hydroxide[7,8], followed by acetylation of the reduced product with acetic anhydride–pyridine, gave methyl 2,3,6-tri-*O*-acetyl-4-deoxy-α-D-*xylo*-hexopyranoside (overall yield, 15%).

Methyl 4,6-diazido-4,6-dideoxy-α-D-glucopyranoside (**4**). — A stirred mixture of methyl 2,3-di-*O*-acetyl-4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside (1 mmole) [prepared[12] by acetylation (acetic anhydride–pyridine) of methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside (**1**)], sodium azide (4 mmoles), and dry *N,N*-dimethylformamide was maintained at 130° for 12 h. The solvent was removed under reduced pressure, and the residue was partitioned between chloroform and water. The chloroform solution was dried over anhydrous sodium sulfate and concentrated to leave a syrupy product which was de-esterified by treatment with ethanolic sodium ethoxide[18] to give methyl 4,6-diazido-4,6-dideoxy-α-D-glucopyranoside (**4**) (90%), m.p. 85–87°, $[\alpha]_D$ +108° (*c* 1.05, chloroform); lit.[18], m.p. 86–88°, $[\alpha]_D$ +110° (*c* 1.18, chloroform).

Methyl 4,6-O-benzylidene-3-chloro-3-deoxy-β-D-allopyranoside (**5**). — Compound **5** was prepared from methyl 4,6-*O*-benzylidene-β-D-glucopyranoside by the method of Jennings and Jones[4], except that the time of treatment with sulfuryl chloride was extended to 10 h. By this procedure, a crystalline product was obtained, which on recrystallization from ether–petroleum ether (b.p. 60–80°) gave colorless prisms (94%), m.p. 129–130°, $[\alpha]_D$ −30° (*c* 1.05, methanol). Jennings and Jones[4] reported $[\alpha]_D$ −30° (*c* 1.05, methanol) for syrupy **5**. Hanessian and Plessas[19] have recently obtained **5** in crystalline form, m.p. 129–131°, $[\alpha]_D$ −24° (*c* 1.0, chloroform).

Anal. Calc. for $C_{14}H_{17}ClO_5$: C, 55.9; H, 5.7; Cl, 11.8. Found: C, 55.6; H, 5.8; Cl, 11.7.

Reaction of methyl 4,6-O-benzylidene-3-chloro-3-deoxy-β-D-allopyranoside (**5**) *with sodium azide.* — Compound **5** (1 mmole) was treated, with stirring, with sodium azide (2 mmoles) in dry *N,N*-dimethylformamide at 130° for 1 h. T.l.c. [petroleum ether (b.p. 60–80°)–ether, 2:1 (v/v)] showed the presence of two components. The products were isolated, as described for **4**, to yield a crystalline material; a separation of the components could not be achieved by crystallization or by preparative t.l.c. The

material was treated with acetic anhydride–pyridine, and the products were isolated in the usual manner. Two crystalline acetates were obtained by fractional crystallization. One of the compounds (60%) was methyl 2-*O*-acetyl-3-azido-4,6-*O*-benzylidene-3-deoxy-β-D-glucopyranoside (**6**), m.p. 107–109°, $[\alpha]_D$ −81° (*c* 1.15, chloroform). Hydrogenation of compound **6** over Adams' catalyst and acetylation of the reduced product gave crystalline methyl 3-acetamido-2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-β-D-glucopyranoside, m.p. 286–287°, $[\alpha]_D$ −77° (*c* 1.03, chloroform); lit.[20], m.p. 276–277°, $[\alpha]_D$ −96° (*c* 1.06, chloroform). The other crystalline compound isolated from the acetylation of the original mixture was methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-β-D-*erythro*-hex-3-enopyranoside (**7**), m.p. 130–131°, $[\alpha]_D$ −164° (*c* 1.05, chloroform); λ_{max}^{Nujol} 5.78 (OAc), 5.91 μm (C=C); n.m.r. data: τ 5.33 (1-proton doublet, $J_{1,2}$ 4 Hz, H-1), 4.67 (1-proton quartet, vinylic H).

Anal. Calc. for $C_{16}H_{18}O_6$: C, 62.7; H, 5.9. Found: C, 62.3; H, 6.0.

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