The Reduction of Chlorodeoxy Sugars by Tributyltin Hydride

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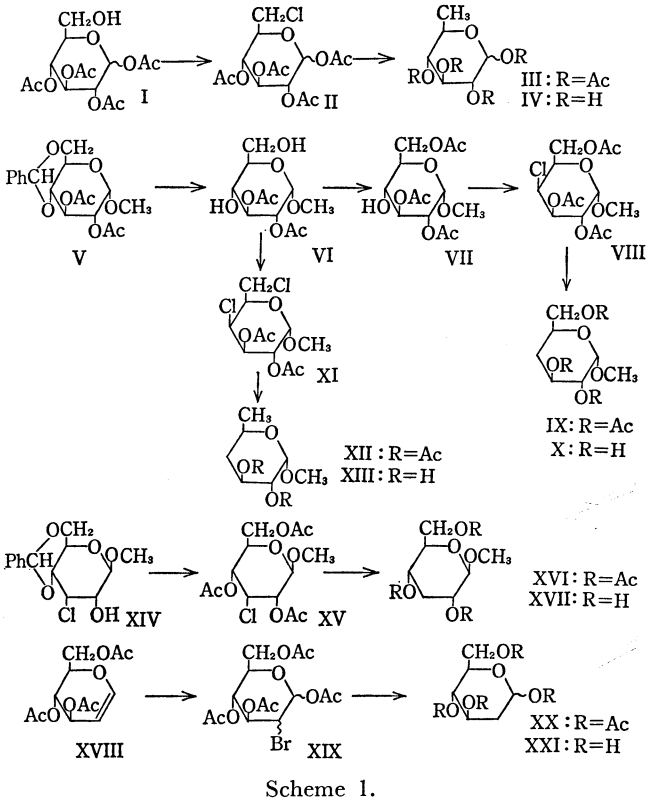
(Received July 23, 1971)

Acetylated chlorodeoxy sugars were prepared by the use of sulfuryl chloride. These chlorodeoxy sugars were then successfully reduced to deoxy sugars by the use of tri-*n*-butyltin hydride. α,α′-Azobis-isobutyronitrile, which has been known to be an effective radical initiator, was found to be indispensable for the reaction.

The deoxy sugars, long known as the components of many natural products, form an important class of carbohydrates. There have been many reports on the synthesis of deoxy sugars.[1] The reduction of deoxyhalo-sugars is one of the most important methods, and various effective reducing agents have been employed for this purpose. Lithium aluminum hydride or Raney nickel are excellent reagents, but they are not suitable for the reduction of sugar derivatives labile to alkali. To find milder reduction conditions, the present authors have investigated organotin hydride as a reducing agent of deoxyhalo sugars. Trialkyltin hydride[2] has recently been used for the selective reduction of organic halides. As reported in the previous paper,[3] we were successful in obtaining the 4′-deoxymaltose derivative in a fairly good yield by using organotin hydride and it was found that scarcely any by-product was produced during the course of the reaction. Therefore, this reagent will be useful for the synthesis of deoxy sugars. Jennings and Jones established that sulfuryl chloride could be used for the preparation of chlorodeoxy sugars.[4] We prepared *O*-acetylated chlorodeoxy sugars using this reagent. These *O*-acetyl-chlorodeoxy sugars were successfully converted to deoxy sugars by the use of organotin hydride under mild conditions. The structure of the deoxy sugars synthesized were confirmed by the NMR method and by gas-liquid chromatography. The reaction courses of the preparation of the deoxy sugars are represented in Scheme 1, while the retention times of the deoxy sugars thus obtained are summarized in Table 1.



Scheme 1.

TABLE 1. RETENTION TIMES (min) OF DEOXY SUGARS

Methyl 2-deoxy-arabinohexopyranoside	6.8
Methyl 3-deoxy-ribohexopyranoside	6.1
Methyl 4-deoxy-xylohexopyranoside	7.8 8.6
Methyl 6-deoxy-glucopyranoside	8.5 9.0

Gas chromatography was carried out at 185°C. Other conditions are described in the text.

Results and Discussion

Among the various tri-alkyltin hydrides, we chose tri-*n*-butyltin hydride because of its high reactivity and ease of preparation. The compound was stable at room temperature under a nitrogen atmosphere. During the course of this study, we found two important facts. The reduction of chlorodeoxy sugars by organotin hydride was unsuccessful if α,α′-azobis-isobutyronitrile was not present, also. By the addition of a small amount of the latter compound, though reduction proceeded smoothly under mild conditions. Menapace[5] proposed a radical mechanism for the reduction by the use of organotin hydride; in accordance with this proposal, the reduction of chlorodeoxy sugars also needed a radical initiator. The other point concerned the nature of the blocking groups of hydroxyls. We attempted to reduce methyl 4,6-*O*-benzylidene-3-chloro-3-deoxy-β-D-allopyranoside (XIV)[6] without success, in spite of the co-existence of α,α′-azobis-isobutyronitrile. On the other hand, the reduction of methyl 3-chloro-3-deoxy-

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2,4,6-tri-*O*-acetyl-β-D-allopyranoside (XV) proceeded smoothly. The reduction of methyl 4,6-dichloro-4,6-dideoxy-2,3-di-*O*-acetyl-α-D-galactopyranoside (XI) at 60°C gave methyl 4-deoxy-6-chloro-6-deoxy-2,3-di-*O*-acetyl-α-D-xylohexopyranoside[7] as the main product. The reactivity of primary and secondary halogenide agreed with the data presented by Menapace.[5] The yield of the reduction of each chlorodeoxy sugars was over 85%, and the separation of the product from the reaction mixture was complete and easy.

Experimental

General Methods. All the melting points are uncorrected. The nuclear magnetic resonance spectra were recorded at 60 MHz in chloroform-*d*, with tetramethylsilane as the internal standard. Thin-layer chromatography (tlc) was performed with silica gel G (Merck). The spots were detected by spraying with 5% sulfuric acid in methanol and by subsequent heating at 150°C. A Shimadzu gas chromatograph model GC-4A equipped with a 0.3×300 cm column of 5% SE-30 on chromosorb W (80—100 mesh) was employed. A sample was methanolyzed in a sealed glass tube with 1 N hydrogen chloride in methanol at 100°C for 2 hr. After the methanolysate had been dried up *in vacuo*, the residue was trimethylsilylated.[8]

Tri-n-*butyltin Hydride.* This reagent was prepared by the thermal decomposition of tri-*n*-butyltin formate according to the method of Okawara and Ohara.[9]

1,2,3,4-Tetra-O-*acetyl*-D-*glucopyranose (I).* Compound I was prepared by the detritylation of 6-*O*-trityl-1,2,3,4-tetra-*O*-acetyl-D-glucopyranose according to the method of Helferich and Klein.[10]

6-Chloro-6-deoxy-1,2,3,4-tetra-O-*acetyl*-D-*glucopyranose (II).* Compound I (14.5 g) was dissolved in 100 m*l* of anhydrous pyridine, and the solution was cooled in an ice-water bath. Into this solution was then stirred sulfuryl chloride (4.5 m*l*) and the mixture was kept at 4—5°C overnight. The excess sulfuryl chloride was destroyed by a few drops of water, and the mixture was extracted with chloroform (3×150 m*l*). The chloroform extracts were washed with water, 5% aqueous sulfuric acid, and finally with water. Evaporation *in vacuo* gave a reddish residue, which was decolorized with Norit A. Crystallization occurred in absolute methanol, and recrystallization in the same solvent gave 11.5 g of colorless needles. Mp 113—115°C, $[\alpha]_D = +113°$ (*c* 0.51, chloroform). Found: C, 45.43; H, 5.17; Cl, 9.87%. Calcd for $C_{14}H_{19}O_9Cl$: C, 45.85; H, 5.22; Cl, 9.67%.

6-Deoxy-1,2,3,4-tetra-O-*acetyl*-D-*glucopyranose (III).* Compound II (1.5 g) was dissolved in anhydrous toluene (10 m*l*), and to the solution were added tri-*n*-butyltin hydride (2.0 g) and α,α′-azobis-isobutyronitrile (15 mg) under a nitrogen atmosphere. The reaction was continued overnight under stirring in an oil bath kept at 80—90°C. On the evaporation *in vacuo* of the solution, crystals appeared immediately. They were washed with ligroin several times to remove the organotin compounds; subsequent recrystallization in methanol gave 1.3 g of colorless needles. Mp 141.5—142.5°C NMR data: δ1.1 (3-H d, C-CH_3), 2.0—2.1 (12-H $-COCH_3$). Found: C, 50.79; H, 6.15%. Calcd for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07%.

6-Deoxy-D-*glucopyranose (IV).* 6-Deoxy-1,2,3,4-tetra-*O*-acetyl-D-glucopyranose (III, 800 mg) was deacetylated in 0.1 M sodium methoxide in methanol. The solution was deionized with Dowex 50×8 (H^+) and dried up *in vacuo*. Crystallization cocurred in ethyl acetate, giving 380 mg of a colorless specimen. Mp 144—145°C, $[\alpha]_D^{24} = +78°$ (*c* 0.98, H_2O). A previous report[11] gave a mp of 146°C, $[\alpha]_D^{20} + 70°$. Found: C, 43.42; H, 7.23%. Calcd for $C_6H_{12}O_5$: C, 43.90; H, 7.37%.

*Methyl 4,6-*O-*Benzylidene-2,3-di-*O-*acetyl-α-*D-*glucopyranoside (V).* Compound V was prepared from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside by acetylation with acetic anhydride and pyridine. Mp 108—109°C, $[\alpha]_D = +170°$ (*c* 0.5, chloroform). Found: C, 58.88; H, 6.04%, Calcd for $C_{18}H_{22}O_8$: C, 59.01; H, 6.05%.

Methyl 2,3,-*Di*-O-*acetyl-α-*D-*glucopyranoside (VI).* Compound V (17 g) was dissolved in 80% aqueous acetic acid (200 m*l*) and the solution was kept at 60°C for 2 hr. On the evaporation *in vacuo* of the solution, a syrupy product remained which showed a single spot on thin-layer chromatography.

*Methyl 2,3,6-Tri-*O-*acetyl-α-*D-*glucopyranoside (VII).* Compound VI (6.0 g) was dissolved in a mixture of pyridine (25 m*l*) and chloroform (15 m*l*), after which the solution was cooled in a dry ice-acetone bath. Acetic anhydride (2.25 m*l*) was then added carefully to the solution, and it was kept at −20°C for 24 hr. Subsequent evaporation *in vacuo* gave a syrupy residue, which was put on a silica-gel column; the column was then eluted with ethylacetate-toluene (1 : 1). Methyl 2,3,6-tri-*O*-acetyl-α-D-glucopyranoside (VII) was separated; it showed a single spot on tlc. Yield, 4.2 g.

*Methyl 4-Chloro-4-deoxy-2,3,6-tri-*O-*acetyl-α-*D-*galactopyranoside (VIII).* Compound VII (1.6 g) was dissolved in anhydrous pyridine (20 m*l*) and to this solution was added, drop by drop, sulfuryl chloride (0.7 m*l*) under cooling in an ice-water bath. The mixture was kept at room temperature overnight. The excess sulfuryl chloride was destroyed by the addition of a few drops of water, the reaction mixture was extratced with chloroform (3×50 m*l*), and the extracts were washed with 5% aqueous sulfuric acid and then with water. Evaporation *in vacuo* gave a reddish syrup, which was decolorized in methanol with Norit A. Crystallization occurred in ethanol-ligroin, and recrystallization in the same solvent gave 1.1 g of colorless needles. Mp 80—81°C, $[\alpha]_D^{24} = +180.7°$ (*c* 0.65, chloroform). Found: C, 46.11; H, 5.66; Cl, 10.67%. Calcd for $C_{13}H_{19}O_8Cl$: C, 46.09; H, 5.65; Cl, 10.47%.

*Methyl 4-Deoxy-2,3,6-tri-*O-*acetyl-α-*D-*xylohexopyranoside (IX).* Compound VIII (580 mg) was mixed with toluene (10 m*l*), tri-*n*-butyltin hydride (600 mg), and α,α′-azobis-isobutyronitrile (10 mg), and the reaction was continued overnight under a nitrogen atmosphere in an oil bath kept at 80°C. The reaction mixture was then dired up *in vacuo*, and a residual syrup was crystallized in ligroin. Recrystallization in the same solvent gave 453 mg of colorless crystals. Mp 74—75°C, $[\alpha]_D^{25} = +133.2°$. One previous report[7] gave a mp of 76—77°C, $[\alpha]_D + 134°$, and another[12] a mp of

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74°C $[\alpha]_D$+135° (*c* 0.52, chloroform), Found: C, 50.79; H, 6.41%. Calcd for $C_{13}H_{20}O_8$: C, 51.31; H, 6.62%.

Methyl 4-Deoxy-α-D-xylohexopyranoside (X). Compound IX (300 mg) was deacetylated with 0.1 M sodium methoxide in methanol. Crystallization occurred in ethyl acetate, giving 160 mg of a colorless specimen. Mp 91—93°C, $[\alpha]_D^{25}$=+175.2° (*c* 1.0, water) Found: C, 47.32; H, 7.91%. Calcd for $C_7H_{14}O_5$: C, 47.18; H, 7.92%.

Methyl 4,6-Dichloro-4,6-dideoxy-2,3-di-O-acetyl-α-D-galactopyranoside (XI). Methyl 2,3-di-*O*-acetyl-α-D-glucopyranoside (VI, 5.5 g) was dissolved in anhydrous pyridine (65 m*l*) and the solution was cooled in an ice-water bath. To the solution sulfuryl chloride (5.1 m*l*) was then added and it was kept at 4°C overnight. The reddish-colored reaction solution was extracted with chloroform (7×50 m*l*), and the extracts were washed with water, 5% aqueous sulfuric acid, and finally with water. Evaporation *in vacuo* gave a syrup, which was then decolorized in methanol with Norit A. Crystallization in ethanol-ligroin gave 4.2 g of a colorless specimen. Mp, 103.5—105°C; $[\alpha]_D^{25}$=+162.9° (*c* 0.5, chloroform). Found: C, 42.07; H, 5.09; Cl, 22.55%. Calcd for $C_{11}H_{16}O_6Cl_2$: C, 41.92; H, 5.11; Cl, 22.50%.

Methyl 4,6-Dideoxy-2,3-di-O-acetyl-α-D-xylohexopyranoside (XII). Compound XI (1 g) was mixed with anhydrous toluene (20 m*l*), tri-*n*-butyltin hydride (2.8 g), and α,α′-azobis-isobutyronitrile (10 mg), and the mixture was refluxed overnight. Evaporation *in vacuo* gave 780 mg of a colorless syrup, which was purified by silica-gel column chromatography. The syrup thus obtained showed a single spot on tlc. NMR data: δ 1.1 (3-H, d, C-CH_3) 2.0—2.1 (6-H -$COCH_3$), 3.2 (3-H -OCH_3).

Methyl 4,6-Dideoxy-α-D-xylohexopyranoside (XIII). The deacetylation of Compound XII with sodium methoxide gave a colorless syrup, which crystallized on standing. Yield, 450 mg; mp, 106—108°C, $[\alpha]_D^{28}$=+168° (*c* 0.8, methanol). A previous report[13] gave a mp of 107—109°C, $[\alpha]_D$+171° (*c* 1.0 methanol). Found: C, 51.69 H, 8.61%.

Methyl 4,6-O-Benzylidene-3-chloro-3-deoxy-β-D-allopyranoside (XIV). Compound XIV was prepared from methyl 4,6-*O*-benzylidene-β-D-glucopyranoside according to the method of Jennings and Jones.[6] Crystallization occurred in ligroin-benzene. Mp 125.5—127°C, $[\alpha]_D^{25}$=−47° (*c* 1.02, chloroform). Found: C, 56.06; H, 5.74; Cl, 11.81%. Calcd for $C_{14}H_{17}O_5Cl$: C, 55.91; H, 5.70; Cl, 11.79%.

Methyl 3-Chloro-3-deoxy-2,4,6-tri-O-acetyl-β-D-allopyranoside (XV). Compound XIV (5 g) was dissolved in 60% aqueous acetic acid (60 m*l*), and the solution was refluxed for 10 min. After cooling, the solution was dried *in vacuo*. The residual syrup was consecutively acetylated with acetic anhydride and pyridine, giving 5 g of a syrupy product.

Methyl 3-Deoxy-2,4,6-tri-O-acetyl-β-D-ribohexopyranoside (XVI). Compound XV (2.5 g) was dissolved in anhydrous toluene (30 m*l*) and reduced by placing it in tri-*n*-butyltin hydride (2.5 g) and α,α′-azobis-isobutyronitrile (20 mg) at 80°C overnight. A syrupy product crystallized from ligroin in a refrigerator. The crystals were dissolved in methanol and treated with Norit A, and recrystallization in ligroin gave 1.8 g of colorless needles. Mp 64—66°C, $[\alpha]_D^{25}$=−45.3° (c 1.07, chloroform). NMR data: δ 2.0—2.1 (9-H -$COCH_3$) 3.24 (3-H -OCH_3). Found: C, 51.20; H, 6.66%. Calcd for $C_{13}H_{20}O_8$: C, 51.31; H, 6.62%.

Methyl 3-Deoxy-β-D-ribohexopyranoside (XVII). Compound XVI was deacetylated with sodium methoxide to Compound XVII. We thus obtained, a colorless syrup which crystallized on standing for a long period. A melting-point determination failed because of the high hygroscopicity of the crystals, $[\alpha]_D^{25}$=−49.5° (*c* 1.01, water). An earlier report[14] gave $[\alpha]_D^{20}$ −46°.

3,4,6-Tri-O-acetyl-glycal (XVIII). Compound XVIII was prepared from 2,3,4,6-tetra-*O*-acetyl-glucosyl bromide by the method of Fischer.[15]

2-Bromo-2-deoxy-1,3,4,6-tetra-O-acetyl-gluco(manno)pyranose (XIX). 3,4,6-Tri-*O*-acetyl-glycal (XVIII, 6.5 g) was dissolved in dichloromethane (25 m*l*), and to this solution was added bromine in dichloromethane until a slightly red color remained. The solution was then dried *in vacuo*, the syrupy residue was instantaneously dissolved in glacial acetic acid (120 m*l*), and mercuric acetate (12 g) was added to the solution. The mixture was then kept at room temperature overnight. The excess acetic acid was removed by evaporation *in vacuo*, and the residue was extracted with chloroform (3×100 m*l*). The extracts were washed three times with aqueous potassium bromide and finally with water. The chloroform layer was dried over calcium chloride and was evaporated *in vacuo*, giving 9 g of a syrup. Found: Br, 18.98%. Calcd for $C_{14}H_{19}O_9Br$: Br, 19.43%.

2-Deoxy-1,3,4,6-tetra-O-acetyl-D-arabinohexopyranose (XX). Compound XIX (1.5 g) was dissolved in anhydrous toluene (15 m*l*), together with tri-*n*-butyltin hydride (1.5 g) and α,α′-azobis-isobutyronitrile (10 mg) under a nitrogen atmosphere. The reaction was allowed to continue for 2 hr at 50—60°C. Subsequent evaporation *in vacuo* gave a colorless syrup, which was purified by silica-gel column chromatography. A syrup highly pure on thin-layer and gas-liquid chromatography was obtained; it weighed 1.1 g but failed to crystallize.

2-Deoxy-D-arabinohexopyranose (XXI). Compound XX (500 mg) was dissolved in cold 0.1 M barium methoxide in methanol and kept overnight in a refrigerator. The solution was then neutralized by adding 0.1 M aqueous sulfuric acid, and the barium sulfate which was thus precipitated was removed by centrifugation. The supernatant was treated with Dowex 50×8 (H^+) and dried up *in vacuo*. The residual syrup was extracted with acetone and crystallized in the same solvent. Mp 139—141°C. A previous report[16] gave a mp 142—144°C. The specimen was also identified by thin-layer chromatography (*n*-BuOH : EtOH : H_2O=3 : 1 : 1).

The authors are especially indebted to the Nitto Kasei Co., Ltd., for its gift of tri-*n*-butyltin oxide.

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