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SELECTIVE REDUCTION OF SUGAR IODIDES AND *p*-TOLUENESULFONATES WITH SODIUM CYANOBOROHYDRIDE

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ABSTRACT

Methyl 2-azido-3,4-di-*O*-benzyl-2,6-dideoxy-6-iodo-α-D-altropyranoside (**6**) and the corresponding 6-*p*-tolylsulfonyloxy compound (**5**) were prepared as model compounds that have both an iodine atom (or a *p*-tolylsulfonyloxy group) and an azido group. Compound **6** smoothly underwent selective reduction with sodium cyanoborohydride in hexamethylphosphoramide, yielding methyl 2-azido-3,4-di-*O*-benzyl-2,6-dideoxy-α-D-altropyranoside (**7**) in good yield. In contrast, **5** resisted reduction, but could also be directly converted into **7** when it was treated in the same solvent with a mixture of sodium iodide and sodium cyanoborohydride.

INTRODUCTION

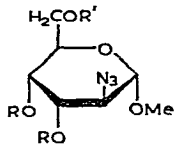
Procedures widely used for the synthesis of ω-deoxyaldoses include reduction of the corresponding ω-iodo or ω-*p*-tolylsulfonyloxy derivatives. Various reducing agents, such as zinc dust and acetic acid, Raney nickel and hydrogen, sodium amalgam, and lithium aluminum hydride have been used for the reduction[1,2]. As all these reagents also reduce the azido group, they cannot be used for the syntheses of azido ω-deoxyaldoses from the corresponding ω-iodo or ω-*p*-tolylsulfonyloxy derivatives of azido sugars. Consequently, reduction at the ω-position of a sugar derivative has hitherto had to precede the introduction of the azido group into the molecule.

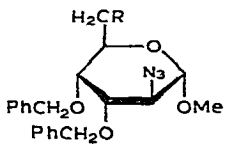
We now describe a new pathway developed for the preparation of azido ω-deoxyaldoses that entails reductive removal of the iodine atom or the *p*-tolylsulfonyloxy group from the ω-carbon atom of a correspondingly substituted azido sugar without affecting the azido group.

RESULTS AND DISCUSSION

With the aim of obtaining model compounds to be tested for the selective reduction, a series of preparations was performed. Methyl 2-azido-2-deoxy-α-D-altropyranoside[3] (**1**) was tritylated with an equivalent amount of trityl chloride, giving the 6-*O*-trityl derivative (**2**). The two hydroxyl groups of **2** were benzylated with

benzyl chloride and potassium hydroxide, in order to increase the solubility in organic solvents. The resulting 3,4-di-*O*-benzyl derivative (**3**) was treated with aqueous acetic acid to afford the *O*-detritylated compound (**4**). *p*-Toluenesulfonylation of **4** in the usual way gave methyl 2-azido-3,4-di-*O*-benzyl-2-deoxy-6-*O*-*p*-tolylsulfonyl-α-D-altropyranoside (**5**), which was then treated with sodium iodide in hexamethylphosphoramide to yield methyl 2-azido-3,4-di-*O*-benzyl-2,6-dideoxy-6-iodo-α-D-altropyranoside (**6**). Compounds **5** and **6** were used as test compounds for the selective reduction.





1 R = R' = H
2 R = H, R' = Tr
3 R = $PhCH_2$, R' = Tr
4 R = $PhCH_2$, R' = H
5 R = $PhCH_2$, R' = Ts

6 R = I
7 R = H

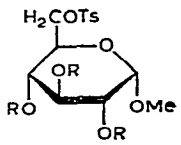
Several examples[4–9] in carbohydrate chemistry have shown that the azido group resists reduction by sodium borohydride at low temperature. On the other hand, it has been reported that organic halogen compounds and *p*-tolylsulfonyloxy compounds could be reduced at 25–45° with sodium borohydride if dimethyl sulfoxide was used as the solvent[10]. Therefore, we attempted to reduce **5** and **6** in dimethyl sulfoxide with sodium borohydride at room temperature. However, this attempt failed, because the azido group was reduced under these reaction conditions*.

Recently, cyanohydridoborate anion has been reported to reduce a wide variety of organic functional groups with remarkable selectivity[11–15]. According to Hutchins and co-workers[14], sodium cyanoborohydride ($NaBH_3CN$) in hexamethylphosphoramide provides a selective system for the reductive removal of bromo, iodo, and *p*-tolylsulfonyloxy groups in the presence of such sensitive moieties as epoxide, ketone, and aldehyde groups. In order to examine the applicability of this reducing method to the carbohydrates, simple test-compounds were prepared. Methyl 6-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside[16] (**8**) was permethylated by Kuhn's method[17], giving methyl 2,3,4-tri-*O*-methyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (**9**). Treatment of **9** with sodium iodide afforded methyl 6-deoxy-6-iodo-2,3,4-tri-*O*-methyl-α-D-glucopyranoside (**10**).

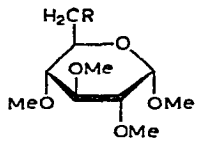
Unexpectedly, there was no reaction when **9** was treated with sodium cyanoborohydride in hexamethylphosphoramide for several hours at 70°. From this result, the *p*-toluenesulfonate group of the carbohydrate derivative seemed to be less reactive with this reductant than that of simple alkyl esters (such as dodecyl *p*-toluenesulfonate,

*With **6**, only, a trace of desired product (**7**) was detected by thin-layer chromatography.

which is readily converted into dodecane under the same reaction conditions[14]). In contrast to **9**, however, **10** proved to react with this reducing agent, although the rate of the reaction was not high. When **10** was heated overnight at 70° with sodium cyanoborohydride, it gave the known methyl 6-deoxy-2,3,4-tri-*O*-methyl-α-D-glucopyranoside[18,19] (**11**) and a small proportion of an unidentified product. After chromatography and vacuum distillation of the mixture, pure **11** was obtained in 31% yield.



8 R = H
9 R = Me



10 R = I
11 R = H

The selective reduction of the azido sugars **5** and **6** was then investigated by reference to the preliminary experiments with **9** and **10**. Compound **6** was treated with sodium cyanoborohydride in hexamethylphosphoramide under the same conditions as for **10**, yielding a single product which moved more slowly than **6** in thin-layer chromatography (t.l.c.). The presence of the azido group in the product was indicated by its infrared (i.r.) spectrum, which had a sharp absorption band at 2100 cm^{-1}. Furthermore, its n.m.r. spectrum had a doublet at δ 1.23, which was assigned to the protons of the 6-methyl group. On the basis of these spectroscopic data and the results of the elemental analyses, the product was methyl 2-azido-3,4-di-*O*-benzyl-2,6-dideoxy-α-D-altropyranoside (**7**). The yield of **7** was ~80% after purification by chromatography.

In view of the similarity of **5** to **9**, inertness of the *p*-toluenesulfonate **5** on attempted reduction with sodium cyanoborohydride was expected. This was indeed the case when **5** was treated at 70° with the reducing agent. When the temperature was raised to 100° and the time was extended to 20 h, compound **5** gave a complex mixture, including several unidentified products, unchanged **5**, and a negligible proportion of **7**. Direct conversion of **5** into **7** could, however, be realized when **5** was treated at 70° with a mixture of sodium iodide and sodium cyanoborohydride in hexamethylphosphoramide. The yield of **7** was 60% (on the basis of **5** used), which is higher than the total yield of the two steps of reactions **5** → **6** → **7**, as purification of iodide **6** by chromatography decreased its yield.

In conclusion, sodium cyanoborohydride in hexamethylphosphoramide is a useful system for the selective removal of an ω-iodo or ω-*p*-tolylsulfonyloxy group of correspondingly substituted azido sugars.

EXPERIMENTAL

Materials. — Commercially available hexamethylphosphoramide (HMPA) was purified by distillation *in vacuo*, and used as the solvent for all reductions and

substitutions*. Sodium cyanoborohydride was purified according to the literature[13]. Kieselgel 60 (E. Merck, Darmstadt) was used for all column chromatography.

General methods. — All melting points are uncorrected. Specific rotations were measured with a Perkin–Elmer Model 141 polarimeter and a 1-dm tube. The i.r. spectra were recorded with a Shimadzu IR-27G infrared spectrometer. The n.m.r. spectra were recorded at 100 MHz with a Varian HA-100D spectrometer for solutions in chloroform-*d* (with tetramethylsilane as the internal standard).

*Methyl 2-azido-2-deoxy-6-*O*-trityl-α-*D*-altropyranoside* (**2**). — Chlorotriphenylmethane (17 g) was added to a solution of **1** (11.6 g) in dry pyridine (240 ml), and the mixture was kept for three days at room temperature. The mixture was poured into water, and the resulting mixture was extracted with chloroform. The extract was washed with water, dried (sodium sulfate), and evaporated *in vacuo* to afford a syrup which was chromatographed on silica gel with 7:1 (v/v) benzene–ethyl ether as the eluant. The product was recrystallized from isopropyl alcohol; yield 16.2 g (57%); m.p. 136–137°, $[\alpha]_D^{24}$ +20° (*c* 1.48, ethyl acetate); ν_{max}^{KBr} 3400 (OH), 2100 (N_3), 1600, and 1495 cm^{-1} (phenyl).

Anal. Calc. for $C_{26}H_{27}N_3O_5$: C, 67.66; H, 5.90; N, 9.11. Found: C, 67.76; H, 5.95; N, 9.21.

*Methyl 2-azido-3,4-di-*O*-benzyl-2-deoxy-6-*O*-trityl-α-*D*-altropyranoside* (**3**). — A mixture of **2** (9 g), powdered potassium hydroxide (17 g), and benzyl chloride (40 ml) was vigorously stirred for 3 h at 100°, cooled, poured into water, and extracted with ethyl ether. The extract was washed with water, dried (sodium sulfate), and evaporated *in vacuo* (<1 torr), giving a syrup which was chromatographed on silica gel with 7:1 (v/v) hexane–ethyl acetate as the eluant; yield 11.5 g (92%); $[\alpha]_D^{16}$ +45° (*c* 1.11, chloroform); ν_{max}^{film} 2100 (N_3), 1600, and 1495 cm^{-1} (phenyl).

Anal. Calc. for $C_{40}H_{39}N_3O_5$: C, 74.86; H, 6.13; N, 6.55. Found: C, 74.79; H, 6.29; N, 6.67.

*Methyl 2-azido-3,4-di-*O*-benzyl-2-deoxy-α-*D*-altropyranoside* (**4**). — Water (72 ml) was added in portions to a solution of **3** (9.8 g) in glacial acetic acid (168 ml); the mixture was heated for 3 h at 80°, cooled, and evaporated to dryness *in vacuo*. The residue was triturated with a small volume of methanol, and the suspension filtered. The filtrate was evaporated *in vacuo*, and the residue was chromatographed on silica gel with 8:1 (v/v) benzene–ethyl ether as the eluant to afford syrupy **4**; yield 5.4 g (89%); $[\alpha]_D^{17}$ +94° (*c* 1.09, chloroform); ν_{max}^{film} 3500–3450 (OH), 2100 (N_3), and 1500 cm^{-1} (phenyl).

Anal. Calc. for $C_{21}H_{25}N_3O_5$: C, 63.14; H, 6.31; N, 10.52. Found: C, 62.83; H, 6.33; N, 10.63.

*Methyl 2-azido-3,4-di-*O*-benzyl-2-deoxy-6-*O*-p-tolylsulfonyl-α-*D*-altropyranoside* (**5**). — *p*-Toluenesulfonyl chloride (3.5 g) was added to a solution of **4** (4.8 g) in dry pyridine (100 ml). The mixture was kept for two days at room temperature, poured

*Purification of HMPA is mandatory, as HMPA of commercial grade often contains chloride ions (which may cause unexpected substitutions).

into water, and extracted with chloroform. The extract was successively washed with dilute sulfuric acid and water, dried (sodium sulfate), and evaporated *in vacuo*, to afford **5** as a syrup which was chromatographed on silica gel with 4:1 (v/v) hexane–ethyl acetate as the eluant; yield 4.2 g (63%); $[\alpha]_D^{25}$ +70° (*c* 0.88, chloroform); ν_{max}^{film} 2100 (N_3), 1600, 1495 (phenyl), 1360, and 1175 cm^{-1} (SO_2).

Anal. Calc. for $C_{28}H_{31}N_3O_7S$: C, 60.75; H, 5.64; N, 7.59; S, 5.79. Found: C, 60.55; H, 5.41; N, 7.61; S, 5.79.

*Methyl 2-azido-3,4-di-*O*-benzyl-2,6-dideoxy-6-iodo-α-*D*-altropyranoside* (**6**). — Sodium iodide (700 mg) was added to a solution of **5** (900 mg) in hexamethylphosphoramide (16 ml). The mixture was heated for 3 h at 70°, with stirring, diluted with water, and extracted with ethyl ether. The extract was washed with water, dried (sodium sulfate), and evaporated *in vacuo* to a syrup which was chromatographed on silica gel with 6:1 (v/v) hexane–ethyl acetate as the eluant; yield 260 mg (32%)*; $[\alpha]_D^{18}$ +70° (*c* 1.13, chloroform); ν_{max}^{film} 2100 (N_3) and 1500 cm^{-1} (phenyl).

Anal. Calc. for $C_{21}H_{24}IN_3O_4$: C, 49.52; H, 4.75; I, 24.92; N, 8.25. Found: C, 50.08; H, 4.55; I, 24.51; N, 8.16.

*Methyl 2-azido-3,4-di-*O*-benzyl-2,6-dideoxy-α-*D*-altropyranoside* (**7**). — (*a*) *From* **6**. Sodium cyanoborohydride (150 mg) was added to a solution of **6** (260 mg) in hexamethylphosphoramide (4 ml). The mixture was stirred overnight at 70°, diluted with water, and extracted with ethyl ether. The extract was washed with water, dried (sodium sulfate), and evaporated *in vacuo*, giving a syrup which showed one spot in t.l.c. with 20:1 (v/v) benzene–ethyl ether as the solvent. The syrup was chromatographed on silica gel with 30:1 (v/v) benzene–ethyl ether as the eluant; yield 150 mg (77%); $[\alpha]_D^{22}$ +77° (*c* 1.39, chloroform); ν_{max}^{film} 2110 (N_3) and 1500 cm^{-1} (phenyl); n.m.r. data: δ 1.23 (3 protons, doublet, $J_{5,6}$ 7 Hz, 6-Me).

Anal. Calc. for $C_{21}H_{25}N_3O_4$: C, 65.78; H, 6.57; N, 10.96. Found: C, 65.88; H, 6.48; N, 11.10.

(*b*) *From* **5**. Sodium cyanoborohydride (400 mg) and sodium iodide (200 mg) were added to a solution of **5** (500 mg) in hexamethylphosphoramide (10 ml), and the mixture was stirred overnight at 70°, and then treated as just described, to afford **7** (190 mg; 61%).

*Methyl 2,3,4-tri-*O*-methyl-6-*O*-p-tolylsulfonyl-α-*D*-glucopyranoside* (**9**). — To a solution of **8** (12.3 g) in *N*,*N*-dimethylformamide (123 ml) were added methyl iodide (82 ml), barium oxide (20.5 g), and barium hydroxide octahydrate (8.2 g). The mixture was stirred for 5 h at room temperature, poured into ice–water, and extracted with ethyl ether. The extract was washed with water, dried (sodium sulfate), and evaporated *in vacuo* to a syrup which was chromatographed on silica gel with 5:1 (v/v) benzene–ethyl ether; yield 7.3 g (53%); $[\alpha]_D^{24}$ +101° (*c* 0.99, chloroform); ν_{max}^{film} 1600 (phenyl), 1360, and 1180 cm^{-1} (SO_2).

Anal. Calc. for $C_{17}H_{26}O_8S$: C, 52.30; H, 6.71; S, 8.21. Found: C, 52.60; H, 6.68; S, 8.23.

*Additional **6** contaminated with an impurity was separately obtained.

Methyl 6-deoxy-6-iodo-2,3,4-tri-O-methyl-α-D-glucopyranoside (**10**). — Sodium iodide (5.2 g) was added to a solution of **9** (5.3 g) in hexamethylphosphoramide (100 ml). The mixture was heated for 3 h at 70°, cooled, poured into water, and extracted with ethyl ether. The extract was washed with water, dried (sodium sulfate), and evaporated *in vacuo* to a syrup which was chromatographed on silica gel with 3:1 (v/v) cyclohexane–ethyl acetate as the eluant; yield 2.3 g (49%); $[\alpha]_D^{18}$ +122° (*c* 1.24, chloroform). The syrup crystallized; m.p. 48–50°.

Anal. Calc. for $C_{10}H_{19}IO_5$: C, 34.70; H, 5.53; I, 36.66. Found: C, 34.91; H, 5.50; I, 36.48.

Methyl 6-deoxy-2,3,4-tri-O-methyl-α-D-glucopyranoside (**11**). — Sodium cyanoborohydride (2 g) was added to a solution of **10** (2.5 g) in hexamethylphosphoramide (40 ml). The mixture was heated overnight at 70°, cooled, diluted with water, and extracted with ethyl ether. The extract was washed with water, dried (sodium sulfate), and evaporated *in vacuo* to a pale-yellow syrup which was chromatographed on silica gel with 4:1 (v/v) benzene–ethyl ether, and then distilled; b.p. 100°/2 torr; yield 500 mg (31%); $[\alpha]_D^{17}$ +153° (*c* 3.60, chloroform) [lit.[18] b.p. 95°/0.65 torr, $[\alpha]_D^{23}$ +151.1° (*c* 1.80, chloroform); lit.[19] b.p. 137–140°/13 torr, $[\alpha]_D^{12}$ +168° (*c* 1.05, methanol)]; n.m.r. data: δ 1.26 (3 protons, doublet, $J_{5,6}$ 6 Hz, 6-Me); *m/e* 220 (M^+), 189 ($M^+ - MeO$).

Anal. Calc. for $C_{10}H_{20}O_5$: C, 54.53; H, 9.15. Found: C, 54.59; H, 8.50.

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