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THE CHLOROACETYL GROUP IN SYNTHETIC CARBOHYDRATE CHEMISTRY

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ABSTRACT

A number of *O*-chloroacetyl derivatives of D-glucose have been prepared. They crystallize with ease, and, as the chloroacetyl group can be removed with facility by treatment with thiourea to yield the parent carbohydrate derivative, they serve as valuable tools in synthetic carbohydrate chemistry. To illustrate this, we have prepared 1-*O*-benzoyl-β-D-glucopyranose by reductive debenzylation of benzyl 2,3,4,6-tetra-*O*-(chloroacetyl)-β-D-glucopyranoside followed by benzoylation, and removal of the chloroacetyl groups with thiourea. An alternative route was by chromium trioxide oxidation of benzyl 2,3,4,6-tetra-*O*-(chloroacetyl)-β-D-glucopyranoside to 1-*O*-benzoyltetra-*O*-(chloroacetyl)-β-D-glucopyranose, followed by removal of the chloroacetyl groups with thiourea.

INTRODUCTION

The preparation of 1-*O*-acylaldoses has been hampered by the fact that the blocking groups employed on the carbohydrate moiety have to be of such a nature that their removal does not involve treatment either with acid or alkali. This drawback was overcome by Schmidt and co-workers[1–4] in their preparation of the 1-*O*-galloyl and 1-*O*-(*p*-hydroxybenzoyl) derivatives of D-glucose. These workers used 2,3,4,6-tetra-*O*-benzyl-D-glucose and condensed it with the appropriately blocked acid chloride; removal of the benzyl groups from the resulting 1-*O*-acyl-D-glucose derivative was then effected by hydrogenolysis. Similarly, Tejima and Fletcher[5] prepared the four possible 1-*O*-benzoyl-L-arabinoses by benzoylation of the appropriate anomer of tri-*O*-benzyl-L-arabino-pyranose or -furanose; benzyl groups in the resulting product were then cleaved by hydrogenolysis in the presence of palladium. These authors studied the rate of conversion of 1-*O*-benzoyl-β-L-arabino-pyranose and -furanose into the corresponding 2-*O*-benzoylaldose by aqueous pyridine. They also found that 1-*O*-benzoyl-α-L-arabino-pyranose and -furanose show no tendency to rearrange under these conditions. Schmidt and co-workers[1–3] had found that the 1-*O*-acyl group of 1-*O*-acyl-D-glucoses readily migrates to O-2; this is an example

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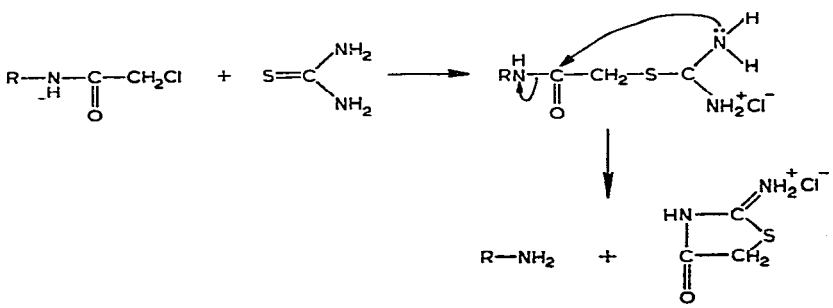
of the same general phenomenon, predicted by Lemieux and Brice[6], namely, that the 1-*O*-acylaldoses can be divided into two classes: those having the 2-hydroxyl group *cis* to the 1-*O*-acyl group, and those having the *trans* arrangement. The former class shows a facile rearrangement of the acyl group from O-1 to O-2. Glaudemans and Fletcher observed a corresponding O-1 to O-2 acyl migration of the *p*-nitrobenzoyl group[7] in the arabinofuranose series.

The 1-*O*-acylaldoses found in Nature all seem (presumably, for this reason) to have the 1,2-*trans* configuration: stevioside in *Stevia rebaudiana* Bertoni[8], asiaticoside from *Centella asiatica*[9], periplanetin in the insect *Periplaneta americana* L.[10], 1-*O*-galloyl-β-D-glucopyranose in Chinese rhubarb[11], and a number of 1-*O*-acyl-D-glucuronic acids in urine[12]. Zenk[13] found that, in the leaves of *Colchicum neapolitanum* Ten., indole-3-acetic acid seems to be linked through its carboxyl group to C-1 of β-D-glucose; this compound was subsequently synthesized by Keglević and Porkony[14], who condensed 2,3,4,6-tetra-*O*-benzyl-D-glucosyl chloride with the silver salt of indole-3-acetic acid, and subsequently removed the blocking groups by hydrogenolysis.

Our interest was in finding a procedure to protect the hydroxyl groups in carbohydrates in ways other than by benzylation, so that they might be removed under mild, neutral conditions; this would permit the facile preparation of 1-*O*-acylaldoses.

In 1968, Masaki and co-workers[15] found that an *N*-chloroacetyl group can readily be removed by treatment with thiourea, to form the amine and the pseudothiohydantoin.



Fontana and Scoffone[16] confirmed the observations and extended them to include *O*-chloroacetyl derivatives. We have now investigated the use of this protecting group in carbohydrate reactions.

RESULTS AND DISCUSSION

In a study of the conditions of *O*-(chloroacetyl)ation, we initially esterified 1,2,4,6-tetra-*O*-acetyl-β-D-glucopyranose[17] in ether solution, containing a small proportion of pyridine, by adding chloroacetyl chloride in ether while the mixture was cooled in ice. After the reaction was complete, the product was isolated by successively

washing the solution with ice water, aqueous acid, and sodium hydrogen carbonate solution, and evaporating, to yield crystalline 1,2,4,6-tetra-*O*-acetyl-3-*O*-(chloroacetyl)-β-D-glucopyranose (**1**). From this compound, the chloroacetyl group could readily be removed by treatment with thiourea in methanol. Because one of us had observed that 1,2,4,6-tetra-*O*-benzoyl-β-D-glucopyranose[18] (**2**) displays lower reactivity towards bulky substituent groups[19] than the corresponding acetyl derivative[20], we turned next to the chloroacetylation of **2**, which proved to be an exceptionally facile reaction. The resulting 1,2,4,6-tetra-*O*-benzoyl-3-*O*-(chloroacetyl)-β-D-glucopyranose (**3**) could be obtained from the reaction mixture directly, without resort to column chromatography. De(chloroacetylation) of **3** with thiourea in benzene–methanol at the reflux temperature regenerated **2**.

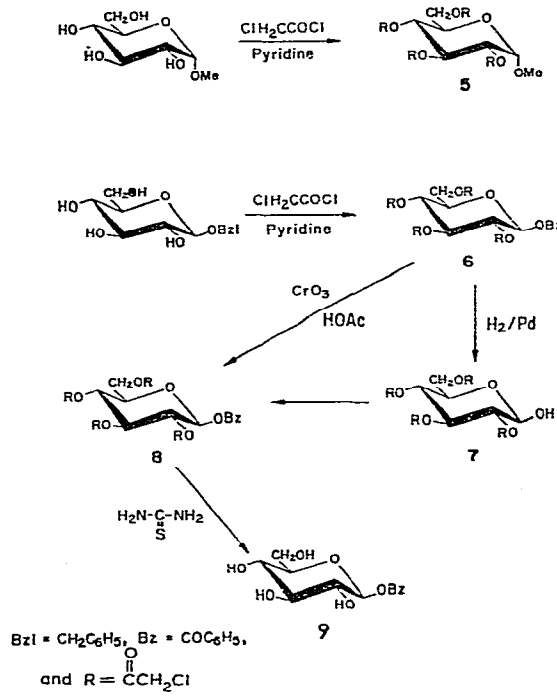
When a suspension of D-glucose in dichloromethane containing chloroacetyl chloride was cooled in ice and triethylamine was added, a violent reaction occurred, without the formation of (chloroacetyl)ated D-glucose. Treatment of D-glucose with chloroacetic anhydride and pyridine also failed, in our hands, to yield the fully substituted derivative desired. Aware of the fact that the fully substituted trifluoroacetyl derivatives of methyl α-D-glucopyranoside and polysubstituted trifluoroacetyl derivatives of alditols and aldoses are unstable[21], we turned next to the chloroacetylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, to see if a diol could be thus derivatized. The product, methyl 4,6-*O*-benzylidene-2,3-di-*O*-(chloroacetyl)-α-D-glucopyranoside (**4**), was crystalline, and could readily be de(chloroacetyl)ated with thiourea in benzene–methanol. The benzylidene group was unstable under these conditions, and methyl α-D-glucopyranoside was formed almost exclusively.

We now applied this procedure to the preparation of fully chloroacetylated aldosides. Methyl α-D-glucopyranoside readily yielded crystalline methyl 2,3,4,6-tetra-*O*-(chloroacetyl)-α-D-glucoside (**5**); similarly benzyl β-D-glycopyranoside was converted into benzyl 2,3,4,6-tetra-*O*-(chloroacetyl)-β-D-glucoside (**6**). From compound **6**, two routes were now open for the preparation of 1-*O*-benzoyl-β-D-glucopyranose (**9**). Reductive debenzylation of **6** with hydrogen over palladium did not affect the chloroacetyl groups, and yielded 2,3,4,6-tetra-*O*-(chloroacetyl)-β-D-glucopyranose (**7**) as a crystalline material. Benzoylation of **7** in pyridine* gave a mixture of the anomers of 1-*O*-benzoyltetra-*O*-(chloroacetyl)-D-glucopyranose, from which the β-D anomer (**8**) was isolated by fractional recrystallization. De(chloroacetyl)ation of **8** to give **9** proceeded without difficulty.

Publication by Angyal and James[22] of a method for the oxidation of *O*-methyl derivatives of carbohydrates to formates prompted us to study a second route for the preparation of **8**, namely oxidation of **6** with chromium trioxide in glacial acetic acid to yield crystalline **8**. Treatment of compound **8** with thiourea in ethanol–

*Although no difficulty has been encountered in using pyridine as a catalyst in these (chloroacetyl)-ation reactions, Dr. M. F. Dolan and one of us (C.P.J.G.) have since observed, in the preparation of the *N*-(chloroacetyl) derivative of sphingosine, that, on prolonged standing, pyridine reacts with the *N*-chloroacetyl group, apparently to form a quaternized pyridinium compound. This interference can be obviated by the use of 2,6-lutidine, which does not so react.

chloroform gave 1-*O*-benzoyl-β-D-glucopyranose (**9**), identical with **9** synthesized by an independent route[23].



EXPERIMENTAL

1,2,4,6-Tetra-O-acetyl-3-O-(chloroacetyl)-β-D-glucose (**1**). — 1,2,4,6-Tetra-*O*-acetyl-β-D-glucopyranose[17] (300 mg) was dissolved in ether (100 ml) containing pyridine (0.3 ml). The solution was cooled in ice, chloroacetyl chloride (0.3 ml) in ether (5 ml) was added dropwise, and the mixture was kept for 4 h at room temperature. It was diluted with ether, successively washed with ice–water (twice), aqueous M hydrochloric acid, and saturated aqueous sodium hydrogen carbonate, dried (sodium sulfate), and evaporated. The residual syrup was dissolved in warm ethanol; cooling caused crystallization, to give 215 mg (58.8%) of **1**, m.p. 117–119°, $[\alpha]_D^{20}$ +3.1° (*c* 1.0, chloroform).

Anal. Calc. for $C_{16}H_{21}ClO_{11}$: C, 45.24; H, 4.97; Cl, 8.36. Found: C, 45.35; H, 4.83; Cl, 8.41.

1,2,4,6-Tetra-O-acetyl-β-D-glucose from **1**. — A solution of **1** (200 mg) in warm methanol (20 ml) was treated with thiourea (40 mg), and then stirred for 24 h at room temperature. T.l.c. (silica gel, 1:1 benzene–ether) then revealed ~80% conversion, so the solvent was evaporated, and the residue extracted with ether. The extracts were combined and evaporated, and the product was placed on a column of silica gel. Elution with 4:1 benzene–acetone yielded one major fraction, which was evaporated

to a syrup and triturated with benzene–hexane to give 1,2,4,6-tetra-*O*-acetyl-β-D-glucopyranose (70 mg, 42.6%); m.p. and mixed m.p. 126–127°; lit.[17] m.p. 127°.

1,2,4,6-Tetra-O-*benzoyl-3*-O-(*chloroacetyl*)-β-D-*glucose* (**3**). — Benzoyl chloride (6.3 ml) was added to dry pyridine (25 ml), and the solution was cooled in ice. 3-*O*-Benzyl-D-glucose (3.15 g) was added batchwise during 20 min, and the solid mixture was kept at room temperature for several days and then processed in the usual way, to yield 1,2,4,6-tetra-*O*-benzoyl-3-*O*-benzyl-β-D-glucose (6.43 g, 80.0%); m.p. 209–210°, $[\alpha]_D^{20}$ 0° (*c* 0.8, chloroform).

Anal. Calc. for $C_{41}H_{34}O_{10}$: C, 71.71; H, 4.99. Found: C, 71.52; H, 4.75.

To a solution of this product (3.0 g) in *p*-dioxane (200 ml) was added palladium chloride (1 g), and the compound was hydrogenated for 24 h. The suspension was treated with Duolite A-4 anion-exchange resin, and filtered, and the filtrate was evaporated to a syrup. This was dissolved in hot ethanol, and the solution was cooled, giving compound **2** (1.9 g, 73%); m.p. 183–185°, $[\alpha]_D^{20}$ +9.2° (*c* 1.25, chloroform); lit.[18] m.p. 179–180°, $[\alpha]_D^{21}$ +8.7° (*c* 1, chloroform).

A solution of **2** (100 mg) in a mixture of benzene (20 ml), acetone (3 ml), and pyridine (0.2 ml) was cooled in ice, and chloroacetyl chloride (0.25 ml) was added dropwise. The reaction mixture was kept at room temperature until starting material was undetectable by t.l.c. on silica gel (4:1 benzene–ether). Ether was added, and the solution was successively washed with ice–water, ice-cold aqueous hydrochloric acid, and ice-cold aqueous sodium hydrogen carbonate, dried (sodium sulfate), and evaporated to a syrup which was dissolved in a small volume of benzene. On addition of ethanol, compound **3** (86 mg, 77.0%) was deposited; m.p. 210°, $[\alpha]_D^{20}$ +5.25° (*c* 2.5, chloroform).

Anal. Calc. for $C_{36}H_{29}ClO_{11}$: C, 64.23; H, 4.34; Cl, 5.26. Found: C, 63.90; H, 4.52; Cl, 5.44.

1,2,4,6-Tetra-O-*benzoyl*-β-D-*glucopyranose from* **3**. — A solution of thiourea (30 mg) in methanol (5 ml) was added to a solution of **3** (70 mg) in 2:1 benzene–methanol (15 ml). The mixture was boiled under reflux for 12 h, cooled, shaken with IRC-50 cation-exchange resin (1 g) for one min, the suspension filtered, and the resin washed with methanol. The filtrate and washings were combined, shaken with Duolite A-4 anion-exchange resin, and the suspension was filtered. The filtrate was dried, and evaporated to a thin syrup which was placed on a column of silica gel. Elution with 4:1 benzene–ether gave a major fraction, which was crystallized from methanol at 5° to yield 40 mg (64.5%) of 1,2,4,6-tetra-*O*-benzoyl-β-D-glucose; m.p. and mixed m.p. 183°.

Methyl 4,6-O-*benzylidene-2,3-di*-O-(*chloroacetyl*)-α-D-*glucoside* (**4**). — To a solution of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (500 mg) in 4:1 ether–acetone (40 ml) and pyridine (0.7 ml) was added chloroacetyl chloride (0.7 ml) in acetone (10 ml). The mixture was kept at room temperature for 0.5 h, diluted with ether, and processed as described for compound **2**. The resulting, thin syrup was dissolved in ether, and hexane was added to faint turbidity, causing crystallization of compound **4** (430 mg, 53.6%); m.p. 147–148°, $[\alpha]_D^{20}$ +65.4° (*c* 1.0, chloroform).

Anal. Calc. for $C_{18}H_{20}Cl_2O_8$: C, 49.66; H, 4.65; Cl, 16.20. Found: C, 49.56; H, 4.82; Cl, 16.51.

Methyl α-D-glucopyranoside from **4**. — A solution of **4** (270 mg) in 1:5 benzene–methanol (30 ml) was treated with thiourea (100 mg) in methanol at room temperature. T.l.c. on silica gel (3:1 benzene–acetone) showed that a product moving at the same rate as authentic methyl 4,6-*O*-benzylidene-α-D-glucopyranoside was formed, but that it decomposed to such an extent that it was never present as more than 10–20% of the total material. After three days, the mixture contained almost exclusively a compound having the same R_F value as authentic methyl α-D-glucopyranoside; the presence of benzaldehyde was evidenced by its odor. The mixture was diluted with methanol, and treated with ion-exchange resins as described for compound **3**. The resulting syrup was purified by column chromatography on silica gel with 3:1 ether–methanol as the eluant. From the major fraction was isolated methyl α-D-glucopyranoside (50 mg, 41.5%), m.p. 165–168°; lit.[24] m.p. 166°.

*Methyl 2,3,4,6-tetra-*O-(*chloroacetyl*)-α-D-*glucoside* (**5**). — A suspension of methyl α-D-glucopyranoside (10 g) in acetone (100 ml) was cooled in a Dry Ice–acetone bath, and pyridine (25 ml) was added. A solution of chloroacetyl chloride (25 ml) in ether (25 ml) was added slowly, while cold ether (total, 300 ml) was added simultaneously. The mixture was then allowed to warm to room temperature, and filtered. The clear, yellow filtrate was successively washed with ice–water, aqueous hydrochloric acid, ice–water, and half-saturated, ice-cold, aqueous sodium hydrogen carbonate solution, dried, filtered, and evaporated to a thick, yellow syrup which crystallized. The crystals were collected (8 g, 31.0%), and recrystallized from chloroform–petroleum ether to give pure **5** (5 g), m.p. 95–97°, $[\alpha]_D^{20}$ +106° (*c* 2.0, chloroform).

Anal. Calc. for $C_{15}H_{18}Cl_4O_{10}$: C, 36.03; H, 3.60; Cl, 28.4. Found: C, 36.13; H, 3.60; Cl, 28.4.

*Benzyl 2,3,4,6-tetra-*O-(*chloroacetyl*)-β-D-*glucoside* (**6**). — A suspension of benzyl β-D-glucopyranoside (2.0 g) in acetone (50 ml) and pyridine (6 ml) was cooled in a Dry Ice–acetone bath. A solution of chloroacetyl chloride (6 ml) in cold ether (20 ml) was added dropwise, and, after the addition was complete, cold ether (250 ml) was added, and the mixture was allowed to warm to room temperature. The mixture was then processed as described for compound **5**, the resulting, thick syrup was dissolved in chloroform, and ligroin was added to slight turbidity, causing the crystallization of impure **6** (2.8 g). This was recrystallized from chloroform–hexane to yield pure **6** (2.0 g, 44.8%); m.p. 81–83°, $[\alpha]_D^{20}$ −33° (*c* 2.0, chloroform).

Anal. Calc. for $C_{12}H_{21}Cl_4O_{10}$: C, 43.60; H, 3.84; Cl, 24.5. Found: C, 43.58; H, 4.07; Cl, 24.7.

*2,3,4,6-Tetra-*O-(*chloroacetyl*)-D-*glucopyranose* (**7**). — To a solution of **6** (1 g) in 2:1 benzene–ether (50 ml) was added palladium black (500 mg), and the suspension was hydrogenated for 12 h. The catalyst was removed by filtration, and the filtrate was evaporated to a thick syrup. On addition of ether, it deposited crystalline **7** (500 mg,

59.2%), m.p. 104–106°, $[\alpha]_D^{20}$ +24.0° (*c* 1, chloroform), $[\alpha]_D^{20}$ +24.5 (initial) → +72.5° (constant; 240 min; *c* 1, in chloroform containing 1 drop of pyridine per ml).

Anal. Calc. for $C_{14}H_{16}Cl_4O_{10}$: C, 34.54; H, 3.30; Cl, 29.20. Found: C, 34.47; H, 3.12; Cl, 29.02.

1-O-Benzoyl-2,3,4,6-tetra-O-(chloroacetyl)-β-D-glucopyranose (**8**). — *Method A.* To a solution of compound **7** (900 mg) in 1:1 benzene–ether (50 ml) were added pyridine (3 ml) and benzoyl chloride (3 ml), and the mixture was heated for ~4 h at 50°. The mixture was cooled, ether was added, and the solution was successively washed with ice–water (twice), aqueous hydrochloric acid, and aqueous sodium hydrogen carbonate, dried, and evaporated to a syrup which was placed on a column of silica gel. The major fraction was eluted with 4:1 benzene–ether. From benzene–hexane, ~500 mg of crystalline material was obtained, but t.l.c. (4:1 benzene–ether) showed this to be a mixture of anomers, the α anomer moving slightly faster than the β anomer without really separating from it. The mixture was dissolved in hot methanol, and nucleated with authentic 1-*O*-benzoyltetra-*O*-(chloroacetyl)-β-D-glucopyranose*, to yield pure **8** (125 mg, 11.6%), m.p. 113–114°, $[\alpha]_D^{20}$ −15.6° (*c* 1, chloroform).

Method B. Compound **6** (1 g) was dissolved in glacial acetic acid (20 ml), chromium trioxide (2.3 g, predried over phosphorus pentaoxide *in vacuo* for 4 h at 60°) was added, and the mixture was stirred overnight at room temperature. Cold chloroform was added, and the mixture was successively washed with ice-water and saturated aqueous sodium hydrogen carbonate. The organic layer was dried over sodium sulfate, decolorized with charcoal, and filtered, and the filtrate was evaporated *in vacuo* to a syrup which was dissolved in ether; hexane was added, and the solution was kept overnight at +5°, affording crystals. Recrystallization from hot ethanol gave pure **8** (360 mg, 35.4%), m.p. 113–114°, $[\alpha]_D^{20}$ −17.8° (*c* 1, chloroform).

Anal. Calc. for $C_{21}H_{20}Cl_4O_{11}$: C, 42.73; H, 3.41; Cl, 24.04. Found: C, 42.68, H, 3.35, Cl, 24.06.

When treated with sodium methoxide in methanol, compound **8** yielded a glucose (t.l.c. with 6:1 ether–ethanol).

1-O-Benzoyl-β-D-glucopyranose (**9**). — To a solution of **8** (300 mg) in 1:8 chloroform–ethanol (~40 ml) was added thiourea (200 mg), and the suspension was stirred for 24 h at 35°, concentrated, and passed through a column of Amberlite IR-120 (H^+) cation-exchange resin. The column was washed with methanol, and the eluate and washings were combined and evaporated to a syrup, which was placed on a column of silica gel. The fraction desired was eluted with 6:1 ether–methanol; this eluate was evaporated to a syrup, which was dissolved in ether–chloroform. Nucleation with authentic 1-*O*-benzoyl-β-D-glucopyranose[23] caused crystallization, yielding pure **9** (20 mg, 14%), m.p. and mixed m.p. 188–189°, $[\alpha]_D^{20}$ −28° (*c* 0.5, water); lit.[23] m.p. 191–192°, $[\alpha]_D$ −27° (water).

*Obtained by oxidation of benzyl tetra-*O*-(chloroacetyl)-β-D-glucopyranoside with chromium trioxide; see method B.

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