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Note

Effects of the trichloromethyl group in displacement reactions of some 3-*O*-tosyl-1,2-*O*-trichloroethylidene-α-D-galacto- and -gluco-furanose derivatives

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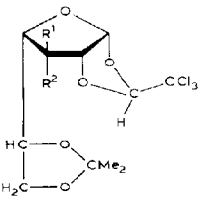
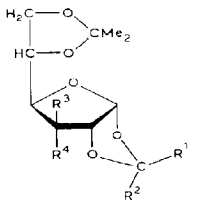
Previous investigations[2,3] have shown that the nucleophilic displacement reactions of the 3-*O*-tosyl derivative of 1,2:5,6-di-*O*-isopropylidene-α-D-gluco-furanose with charged nucleophiles are very slow (*e.g.*, the reaction with azide in *N,N*-dimethylformamide is complete only after 15 days at 115°). This is attributed to the repulsion of the approaching nucleophile by the lone-pair electrons of the 1,2-*O*-isopropylidene ring-oxygens and also to steric hindrance by the *endo*-methyl group of the same ring[3]. The effect of trichloromethyl groups in similar reactions is now considered.



1 R^1 = OH, R^2 = H
2 R^1 = OAc, R^2 = H
7 R^1 = OTs, R^2 = H
10 R^1 = H, R^2 = N_3



3 R^1 = CCl_3, R^2 = R^4 = H, R^3 = OH
4 R^1 = CCl_3, R^2 = R^4 = H, R^3 = OAc
5 R^1 = R^4 = H, R^2 = CCl_3, R^3 = OH
6 R^1 = R^4 = H, R^2 = CCl_3, R^3 = OAc
8 R^1 = CCl_3, R^2 = R^4 = H, R^3 = OTs
9 R^1 = R^4 = H, R^2 = CCl_3, R^3 = OTs
11 R^1 = CCl_3, R^2 = R^3 = H, R^4 = N_3

*Trichloroethylidene Acetals, Part II. For Part I, see ref. 1.

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Reaction of 5,6-*O*-isopropylidene-3-*O*-tosyl-1,2-*O*-trichloroethylidene-α-D-galactofuranose (**7**) with sodium azide in *N*,*N*-dimethylformamide at ~115° gave the *gulo*-azide **10** in reasonable yield after 24 h. Similar reaction of 5,6-*O*-isopropylidene-3-*O*-tosyl-1,2-*O*-trichloroethylidene-α-D-glucofuranose (**8**, *S*-isomer) produced the *allo*-azide **11**. The replacements of the tosyl groups in these reactions were relatively fast, probably because of the strong inductive effect of the trichloromethyl group which weakens the polar repulsions of the ring oxygens by decreasing their electron densities. Also, the *endo* acetal-protons of compounds **7** and **8** do not sterically hinder the approach of the nucleophile. However, an *endo* trichloromethyl group can sterically hinder the approaching nucleophile as it is considerably larger than a methyl group. The polar repulsion of the charged nucleophile by the chlorine atoms can also inhibit the reaction. The foregoing arguments suggest that the tosyl group of 5,6-*O*-isopropylidene-3-*O*-tosyl-1,2-*O*-trichloroethylidene-α-D-glucofuranose (**9**, *R*-isomer) would be unreactive in the displacement reaction with azide ions. This was, in fact, the case, and no azide formation was observed after treatment for 3 days at 115° with *N*,*N*-dimethylformamide containing sodium azide. The use of hexamethylphosphoric triamide as solvent at 115° for 46 h followed by column chromatography of the product mixture, using toluene–methanol (9:1), gave **9** and a very small proportion of the azido derivative **10** mixed with **9**, as indicated by the fragment ions at m/z 358 ($M^+ - CH_3$) and 256 ($M^+ - CCl_3$) in the mass spectrum. In the mass spectra of **1**–**11**, the most intense ion (m/z 101) is formed by rupture of the C-4–C-5 bond. The other characteristic fragments, $M^+ - CH_3$, $M^+ - CCl_3$, ($M - CCl_3$)$^+$ – acetone, and $(M - 15)^+$ – acetic acid, are observed in all of the spectra.

In the n.m.r. spectrum of the *gulo*-azide **10**, the signal for H-1 was a doublet ($J_{1,2}$ 3.8 Hz), as expected, but H-2 gave a multiplet. Decoupling of H-1 from H-2 gave a three-line pattern, which suggested either long-range or a virtual coupling. Long-range coupling is possible only if the furanoid ring exists in an extremely puckered $^3T_2$ conformation, where H-2 and H-4 can be part of a planar-W arrangement. In such a conformation, however, the 5,6-ring comes very close to the 1,2-ring, causing great steric interaction. Hence, additional splittings (~2 Hz) of the H-2 signal are more likely to be a result of virtual coupling. Conformational analysis[3] of 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose showed that coupling constants for H-1,2, H-2,3, and H-3,4 are ~4, ~6, and ~6 Hz, respectively, indicative of a preferred ($E_0 \rightleftharpoons {}^1T_0 \rightleftharpoons {}^1E$) conformation. For compound **10** in $CDCl_3$, the values $J_{1,2}$ 3.8, $J_{2,3}$ 5.4 Hz were obtained; the remainder of the spectrum was too complex to assign. The spectrum of **10** in CCl_4 (10%, 0.5 mL) containing benzene (16 drops) showed the H-2 signal as a quartet with $J_{1,2}$ 4.0, $J_{2,3}$ 5.4 Hz. The signal for H-3 was identified by removing the coupling with H-2, and $J_{3,4}$ 6.0 Hz was found. In the spectrum of the *allo*-azide **11**, the H-1, H-2, and H-3 signals were identified as a doublet and two quartets, respectively, by spin-decoupling experiments. The values $J_{1,2}$ 4.0, $J_{2,3}$ 4.8, and $J_{3,4}$ 8.6 Hz obtained are in agreement with the reported coupling-constants for 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose[4].

EXPERIMENTAL

T.l.c. was performed on Kieselgel (Merck, 7731), and column chromatography on Kieselgel (Merck, 7734). Melting points are uncorrected. N.m.r. spectra (in $CDCl_3$ unless otherwise stated) and mass spectra were recorded with Varian-T 60 and Jeol J.M.S.-D 100 instruments, respectively. Optical rotations were determined with a Perkin–Elmer 141 polarimeter

5,6-O-Isopropylidene-1,2-O-trichloroethylidene-α-D-glucofuranose (**3**, *S-isomer*). — A solution of 1,2-*O*-trichloroethylidene-α-D-glucofuranose (gluco-α-chloralose, *S*-isomer)[5] (10 g) in *N,N*-dimethylformamide (50 mL) was stirred with acetone (50 mL) and conc. hydrochloric acid (1 mL) at room temperature for 24 h. The neutralised (with dilute sodium hydroxide) solution was evaporated *in vacuo*, to give a syrup that afforded crystals of **3** (8.5 g, 75%), m.p. 176–178° (from methanol), $[\alpha]_D^{19}$ −8° (*c* 2.4, chloroform) (Found: C, 37.63; H, 4.16; Cl, 30.38. $C_{11}H_{15}Cl_3O_6$ calc.: C, 37.79; H, 4.32; Cl, 30.42%).

Acetylation of **3** gave **4** (95%), m.p. 68–69° (from ethanol), $[\alpha]_D^{19}$ −33.5° (*c* 2.4, chloroform) (Found: C, 39.81; H, 4.27; Cl, 26.98. $C_{13}H_{17}Cl_3O_7$ calc.: C, 39.87; H, 4.37; Cl, 27.16%). N.m.r. data: δ 6.19 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 4.88 (d, 1 H, $J_{2,3}$ 0 Hz, H-2), 5.36 (d, 1 H, $J_{3,4}$ 2.0 Hz, H-3). 4.00–4.40 (m, 4 H, H-4,5,6,6'), 2.12 (s, 3 H, OAc), 1.28, and 1.35 (6 H, 2 Me).

5,6-O-Isopropylidene-1,2-O-trichloroethylidene-α-D-glucofuranose (**5**, *R-isomer*). — Isopropylidenation of 1,2-*O*-trichloroethylidene-α-D-glucofuranose (gluco-α-chloralose, *R*-isomer)[5] (10 g), as in the preparation of **3**, gave a syrupy product which crystallised at 0° to give **5** (8 g, 71%), m.p. 101–102° (from methanol–water), $[\alpha]_D^{19}$ +15.5° (*c* 5, methanol) (Found: C, 37.68; H, 4.34; Cl, 30.46%. Calc.: as for **3**).

Acetylation of **5** gave **6** (80%), m.p. 175° (from ethanol–water), $[\alpha]_D^{19}$ −4° (*c* 2, chloroform) (Found: C, 39.90; H, 4.30; Cl, 27.10%. Calc.: as for **4**). N.m.r. data: δ 6.05 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.68 (d, 1 H, $J_{2,3}$ 0 Hz, H-2), 5.42 (d, 1 H, $J_{3,4}$ 3.0 Hz, H-3), 4.62 (q, 1 H, $J_{4,5}$ 8.0 Hz, H-4), 3.83–4.46 (3 H, H-5,6,6'), 2.12 (s, 3 H, OAc), 1.34, 1.44 (6 H, 2 Me), and 5.30 (s, 1 H, CCl_3CH).

5,6-O-Isopropylidene-3-O-tosyl-1,2-O-trichloroethylidene-α-D-galactofuranose (**7**). — A solution of compound **1**[1] (10 g) in pyridine (100 mL) was stirred with toluene-*p*-sulphonyl chloride (12 g) at room temperature for 16 h. The reaction mixture was poured into ice–water, and the resulting solid crystallised to give **7** (7.5 g, 52%), m.p. 89–91° (from methanol–water), $[\alpha]_D^{19}$ −5° (*c* 4, chloroform) (Found: C, 43.00; H, 4.27; Cl, 20.94; S, 6.25. $C_{18}H_{21}Cl_3O_8S$ calc.: C, 42.91; H, 4.20; Cl, 21.11; S, 6.36%). N.m.r. data: δ 6.21 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 4.90 (d, 2 H, H-2,3), 3.66–4.33 (m, H-4,5,6,6'), 5.65 (s, 1 H, CCl_3CH), 1.38, 1.45 (s, 6 H, 2 Me), 2.40 (s, 3 H, *Me*-Ar), 7.38 (d, 2 H, J_{ortho} 7.6 Hz, Ph), and 7.83 (d, 2 H, J_{ortho} 7.6 Hz, Ph); in CCl_4: δ 6.20 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 4.87 (d, 1 H, $J_{2,3}$ 0 Hz, H-2), and 4.96 (d, 1 H, $J_{3,4}$ 1.8 Hz, H-3).

5,6-O-Isopropylidene-3-O-tosyl-1,2-O-trichloroethylidene-α-D-glucofuranose

(**8**, S-*isomer*). — Compound **3** (10 g) was tosylated as in the previous experiment, but at 50° for 36 h. The gummy product that separated on pouring the reaction mixture into water was taken up in chloroform. Evaporation of the solvent and crystallisation of the residue gave **8** (6.2 g, 43%), m.p. 116–117° (from methanol–water), $[\alpha]_D^{19}$ −67° (*c* 1.9, chloroform) (Found: C, 42.95; H, 4.20; Cl, 20.90; S, 6.16%. Calc.: as for **7**). N.m.r. data: δ 6.23 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.20 (d, 1 H, $J_{2,3}$ ~0 Hz, H-2), 4.90 (s, 1 H, $J_{3,4}$ 0.5 Hz, H-3), 3.83–4.15 (4 H, H-4,5,6,6'), 5.60 (s, 1 H, CCl_3CH), 1.15, 1.20 (s, 6 H, 2 Me), 2.45 (3 H, *Me*-Ar), 7.33 (d, 2 H, J_{ortho} 7.8 Hz, Ph), and 7.83 (d, 2 H, J_{ortho} 7.8 Hz, Ph).

*5,6-O-Isopropylidene-3-O-tosyl-1,2-O-trichloroethylidene-α-*D*-glucofuranose* (**9**, R-*isomer*). — A solution of compound **5** (10 g) was tosylated as described for **1**, but at room temperature for 36 h. Isolation of the product as described for **8** gave **9** (6 g, 41%), m.p. 98–100° (from ethanol–water), $[\alpha]_D^{19}$ −48° (*c* 3.95, chloroform) (Found: C, 43.05; H, 4.23; Cl, 21.00; S, 6.12%. Calc.: as for **7**). N.m.r. data: δ 6.11 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 5.04 (d, 1 H, $J_{2,3}$ 0 Hz, H-2), 4.96 (d, 1 H, $J_{3,4}$ 2.0 Hz, H-3), 4.50 (q, 1 H, $J_{4,5}$ 6.4 Hz, H-4), 3.83–4.25 (m, 3 H, H-5,6,6'), 5.30 (s, 1 H, CCl_3CH), 1.19 (s, 6 H, 2 Me), 2.49 (s, 3 H, *Me*-Ar), 7.34 (d, 2 H, J_{ortho} 7.4 Hz, Ph), and 7.84 (d, 2 H, J_{ortho} 7.4 Hz, Ph).

*3-Azido-3-deoxy-5,6-O-isopropylidene-1,2-O-trichloroethylidene-α-*D*-gulofuranose* (**10**, S-*isomer*). — A solution of compound **7** (5 g) in *N*,*N*-dimethylformamide (60 mL) was stirred at 115° with sodium azide (5.2 g) under a nitrogen stream for 24 h. T.l.c. (toluene–acetone, 9:1) showed a product and a small proportion of starting compound. The solvent was partly evaporated *in vacuo* and the reaction mixture was poured into water (250 mL). Extraction with chloroform (6 × 50 mL) gave a syrupy product that contained a trace of **7**. Three successive crystallisations at 0° gave pure **10** (2.2 g, 59%), m.p. 111–112° (from methanol–water), $[\alpha]_D^{19}$ +117° (*c* 0.6, chloroform) (Found: C, 35.27; H, 3.75; Cl, 28.00; N, 11.20. $C_{11}H_{14}Cl_3N_3O_5$ calc.: C, 35.27; H, 3.77; Cl, 28.39; N, 11.22%). N.m.r. data: δ 6.83 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 5.11 (m, 1 H, $J_{2,3}$ 5.4 Hz, H-2), 3.56–4.33 (m, 5 H, H-3,4,5,6,6'), 5.78 (s, 1 H, CCl_3CH), 1.35, and 1.41 (s, 6 H, 2 Me); in CCl_4–benzene: δ 5.86 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 4.70 (q, 1 H, $J_{2,3}$ 5.4 Hz, H-2), 3.46 (q, $J_{3,4}$ 6.0 Hz, H-3), and 5.76 (s, 1 H, CCl_3CH).

*3-Azido-3-deoxy-5,6-O-isopropylidene-1,2-O-trichloroethylidene-α-*D*-allofuranose* (**11**, S-*isomer*). — A solution of compound **4** (5 g) was treated with sodium azide as described above. Three crystallisations of the product gave **11** (1.9 g, 51%), m.p. 125–126° (from methanol–water), $[\alpha]_D^{19}$ +6° (*c* 1.85, chloroform) (Found: C, 35.30; H, 3.75; Cl, 28.32; N, 11.10%. Calc. as for **10**). N.m.r. data: δ 6.13 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.11 (q, 1 H, $J_{2,3}$ 4.8 Hz, H-2), 3.68 (q, 1 H, $J_{3,4}$ 8.6 Hz, H-3), 3.93–4.33 (m, 4 H, H-4,5,6,6'), 5.75 (s, 1 H, CCl_3CH), 1.41, and 1.52 (s, 6 H, 2 Me).

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