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FORMATION OF THE BUTYLIDENE ACETALS OF α-CHLORALOSE

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ABSTRACT

The acid-catalysed reaction of α-chloralose[1] (**1**, 1,2-*O*-trichloroethylidene-α-D-glucofuranose, the isomer having m.p. 190–195°) with butyraldehyde gave two stereoisomeric, crystalline 5,6-*O*-butylidene-1,2-*O*-trichloroethylidene-α-D-glucofuranoses (**2** and **3**). The structures of **2** and **3** were identified by chemical and spectroscopic means. The formation of the 3,5-acetal (**11**) was not observed in the direct butylidenation of α-chloralose, but **11** could be synthesised by indirect routes. The butylidene acetal ring of **11** was hydrolysed much more readily than the butylidene group of **2** or **3**.

INTRODUCTION

Levene and Raymond[2] reported that, under kinetically controlled conditions (*e.g.*, sodium sulphate catalyst; reaction time, 30 min at 140–150°), 1,2-*O*-isopropylidene-α-D-glucofuranose reacted with benzaldehyde to afford 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose, whereas prolonged reaction (5 h) gave the thermodynamic product, 5,6-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose. These results imply that the 1,2:5,6-diacetal is more stable than the 1,2:3,5 structure, although the latter includes a six-membered acetal ring which most probably possesses a chair conformation. The use[2] of zinc chloride as catalyst at room temperature and at 100° was claimed to give the 3,5-acetal, a somewhat surprising result since, at 100°, the thermodynamically stable 5,6-acetal would be the expected product. We now report on an analogous reaction, namely that of butyraldehyde (chosen because it affords more-stable acetal rings than benzaldehyde) with 1,2-*O*-trichloroethylidene-α-D-glucofuranose (α-chloralose).

RESULTS AND DISCUSSION

The reaction of α-chloralose (**1**) with butyraldehyde in *N*,*N*-dimethylformamide at room temperature, in the presence of conc. hydrochloric acid as catalyst, gave the

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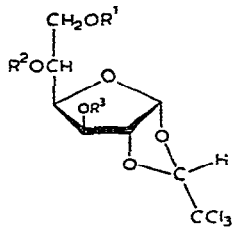
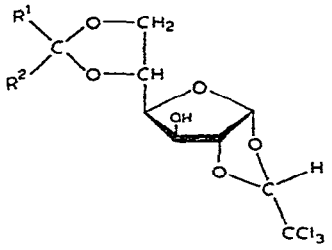
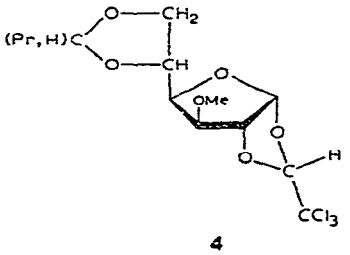
diastereoisomeric 5,6-butylidene acetals **2** and **3**, but no other products (t.l.c.). The syrupy product mixture obtained after reaction for 24 h was fractionated by chromatography on silica gel to give the diastereoisomeric 5,6-*O*-butylidene-1,2-*O*-trichloroethylidene-α-D-glucofuranoses **2** {m.p. 122–123°, $[\alpha]_D^{23}$ +14.5° (chloroform)} and **3** {m.p. 94–96°, $[\alpha]_D^{23}$ +12.5° (chloroform)}.



1 $R^1 = R^2 = R^3 = H$
5 $R^1 = Bz; R^2 = R^3 = H$
6 $R^1 = R^2 = H; R^3 = Me$
7 $R^1 = R^2 = Ac; R^3 = Me$
8 $R^1 = Bz; R^2 = R^3 = Ac$



2 $R^1 = H; R^2 = Pr$
3 $R^1 = Pr; R^2 = H$



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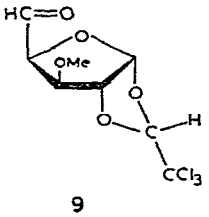

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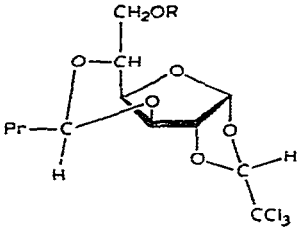

10 R = Bz
11 R = H

The n.m.r. spectra of **2** and **3** were complex, but triplets at τ 5.00 and 5.11, respectively, for the butylidene acetal proton were present and indicated the presence of five-membered butylidene acetal rings[3–5]. Other signals for **2** were τ 3.90 (d, *J* 4 Hz, H-1), 4.72 (s, $CCl_3 \cdot CH$), and 5.32 (d, H-2); and for **3**, τ 3.90 (d, *J* 4 Hz, H-1) and 4.70 (s, $Cl_3C \cdot CH$). The hydroxyl signal appeared as a doublet (*J* 3 Hz) for **2** and a broad singlet for **3**; both signals were concentration-dependent.

In the mass spectra of **2** and **3**, the most-intense peak was at *m/e* 115, indicating fission between C-4 and C-5.

Methylation of an equimolar mixture of **2** and **3** gave a syrupy mixture of diastereoisomeric 5,6-*O*-butylidene-3-*O*-methyl-1,2-*O*-trichloroethylidene-α-D-glucofuranoses (**4**), which was stable towards conc. hydrochloric acid in ethanol–water at 50° for 4 h. Addition of trifluoroacetic acid and further heating cleaved the butylidene

acetal and gave syrupy **6**, which was characterised as the acetate **7**. Sodium periodate reacted readily with **6** to give syrupy **9**, which was characterized as the 2,4-dinitrophenylhydrazone. Thus, the foregoing reaction of chloralose with butyraldehyde did not involve any rearrangement.

The acetals **2** and **3** were the sole products when *N*,*N*-dimethylformamide was used as reaction solvent together with conc. hydrochloric acid as catalyst and a reaction time of 3 h at 60°, or with 5M hydrochloric acid at room temperature.

The 3,5-acetal was obtained indirectly. Selective benzoylation of α-chloralose gave the 6-benzoate **5**, which was characterised as the 3,5-diacetate **8**. The structure of **8** was confirmed by n.m.r. spectroscopy. Reaction of **5** with butyraldehyde gave crystalline 6-*O*-benzoyl-3,5-*O*-butylidene-α-chloralose (**10**), the mass spectrum of which did not contain a peak at *m/e* 115. The removal of the benzoyl group from **10** gave the syrupy 3,5-acetal **11** of α-chloralose, which was hydrolysed easily to α-chloralose (**1**) when trichloroacetic acid or trifluoroacetic acid was added to its solution in chloroform at room temperature. When the hydrolysis conducted in deuteriochloroform containing a trace of trifluoroacetic acid was monitored by n.m.r. spectroscopy, no new butylidene-acetal proton signal appeared which would be indicative[6] of acetal migration.

The foregoing results indicate that the 1,2:5,6-di-*O*-alkylidene-α-D-glucofuranose contains a more-stable arrangement of the acetal rings than does the 1,2:3,5 isomer. This result was somewhat unexpected, as molecular models of the 1,2:3,5-acetal show that the 3,5-ring can adopt a chair conformation with equatorial propyl and hydroxymethyl groups. However, this structure contains *trans* carbon–oxygen bonds and therefore lacks the stabilising influence of the gauche effect[7,8].

EXPERIMENTAL

Optical rotations were determined at 23° with a Perkin–Elmer 141 polarimeter. T.l.c. was performed on silica gel (precoated plates) with ether–light petroleum (9:1) unless otherwise stated. N.m.r. spectra were determined for solutions in $CDCl_3$ at 100 MHz (Varian HA-100) with Me_4Si as internal standard. Mass spectra (70 eV) were obtained with an A.E.I. MS-12 instrument.

The reaction of butyraldehyde with α-chloralose. — A solution of α-chloralose (6 g) in *N*,*N*-dimethylformamide (50 ml) was mixed with butyraldehyde (5 ml) and conc. hydrochloric acid (0.3 ml). After 24 h, t.l.c. showed that most of the starting material had reacted. The solution was neutralized with Amberlite IR-45(HO^-) resin, a little aqueous NH_3 was added, and the solution was concentrated to give the syrupy mixture of acetals. This mixture was eluted from a column (160 × 2.5 cm) of silica gel (300 g) with ether–light petroleum (9:1) to give, first, 5,6-*O*-butylidene-1,2-*O*-trichloroethylidene-α-D-glucofuranose-*I* (**2**, 2.2 g, 31%), m.p. 122–123°, $[\alpha]_D^{23}$ +14.5° (*c* 1.2, chloroform) (Found: C, 40.3; H, 4.6; Cl, 29.4. $C_{12}H_{17}Cl_3O_6$ calc.: C, 39.6; H, 4.7; Cl, 29.2%).

Further elution gave 5,6-*O*-butylidene-1,2-*O*-trichloroethylidene-α-D-gluco-

furanose-*II* (3, 1.5 g, 21%), m.p. 94–96°, $[\alpha]_D^{23}$ +12.5° (*c* 1.6, chloroform) (Found: C, 40.3, H, 4.7; Cl, 29.3%).

Methylation and hydrolysis of the butylidene-α-chloraloses. — A solution of a crude, equimolar mixture (6 g) of **2** and **3** in *N,N*-dimethylformamide (75 ml) was treated with silver oxide (15 g) and methyl iodide (20 ml) for 24 h. The usual work-up procedure[5] gave the methylated product **4**, a solution of which in ethanol–water (1:1, 100 ml) containing conc. hydrochloric acid (0.3 ml) and trifluoroacetic acid (0.5 ml) was kept at 65° for 5 h. T.l.c. then indicated almost complete hydrolysis. The solution was concentrated, and extracted with a little light petroleum to remove any unhydrolysed acetal. The aqueous phase was concentrated and a solution of the syrupy residue in chloroform was neutralised, dried, and concentrated to give syrupy 3-*O*-methyl-1,2-*O*-trichloroethylidene-α-D-glucofuranose (**6**, 3 g, 53%), $[\alpha]_D^{23}$ −13° (*c* 0.8, chloroform) (Found: C, 34.8; H, 4.0; Cl, 32.4. $C_9H_{13}Cl_3O_6$ calc.: C, 33.4; H, 4.0; Cl, 32.9%). N.m.r. data: τ 3.94 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.28 (d, 1 H, $J_{2,3}$ ~0 Hz, H-2), 5.94 (d, 1 H, $J_{3,4}$ 3 Hz, H-3), 5.48 (q, 1 H, $J_{4,5}$ 8 Hz, H-4), 6.00–6.40 (m, 4 H, H-5 and -CH_2OH), 7.10 (d, 1 H, $J_{HO,H}$ 7 Hz, OH), 6.53 (s, 3 H, OMe), 4.73 (s, 1 H, $CCl_3 \cdot CH$).

Conventional acetylation (pyridine–acetic anhydride) of **6** gave the 5,6-diacetate **7**, m.p. 87–89° (from ethanol–ether), $[\alpha]_D^{23}$ +6° (*c* 1.5, chloroform) (Found: C, 38.3; H, 4.4; Cl, 25.9. $C_{13}H_{17}Cl_3O_8$ calc.: C, 38.3; H, 4.2; Cl, 26.1%). N.m.r. data: τ 3.95 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.28 (d, 1 H, $J_{2,3}$ ~0 Hz, H-2), 6.10 (d, 1 H, $J_{3,4}$ 3 Hz, H-3), 5.24 (q, 1 H, $J_{4,5}$ 8 Hz, H-4), 4.78 (m, 1 H, $J_{5,6}$ 2, $J_{5,6'}$ 4 Hz, H-5), 5.42 (q, 1 H, $J_{6,6'}$ 13 Hz, H-6), 5.36 (q, 1 H, H-6'), 6.60 (s, 3 H, OMe), 7.90, 7.96 (6 H, 2 Ac), 4.69 (s, 1 H, $CCl_3 \cdot CH$).

Periodate oxidation of 3-O-methyl-α-chloralose. — A solution of **6** (1.7 g) in ethanol–water (1:1) was treated with a solution of sodium periodate (1 g) in water (10 ml) overnight. Extraction of the solution with ether and removal of the solvent gave syrupy 3-*O*-methyl-1,2-*O*-trichloroethylidene-D-*xylo*-pentodialdose (**9**, 1.3 g), which was characterised as the 2,4-dinitrophenylhydrazone (85%), m.p. 175–177° (from ethanol), $[\alpha]_D^{23}$ −3° (*c* 1.2, chloroform) (Found: C, 36.0; H, 3.0; Cl, 22.6; N, 12.1. $C_{14}H_{13}Cl_3N_4O_8$ calc.: C, 35.6; H, 2.8; Cl, 22.5; N, 11.9%). N.m.r. data: τ 3.83 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.16 (d, 1 H, $J_{2,3}$ ~0 Hz, H-2), 5.89 (d, 1 H, $J_{3,4}$ 4 Hz, H-3), 4.75 (q, 1 H, $J_{4,5}$ 7 Hz, H-4), 2.58 (d, 1 H, H-5), 6.06 (s, 3 H, OMe), 4.66 (s, 1 H, $CCl_3 \cdot CH$), 2.20 (d, 1 H, J_{ortho} 9 Hz, Ph), 1.72 (q, 1 H, J_{meta} 2 Hz, Ph), 0.96 (d, 1 H, Ph), −1.04 (s, 1 H, NH).

Selective benzoylation of α-chloralose. — To a solution of α-chloralose (2.9 g) in pyridine (40 ml), benzoyl chloride (1.4 g) was added at −10°. The solution was kept at −5° for 3 h and then at room temperature overnight; it was then poured into ice–water, and the syrup which separated was extracted with ether. Concentration of the ether solution gave 6-*O*-benzoyl-1,2-*O*-trichloroethylidene-α-D-glucofuranose (**5**, 1.3 g), m.p. 166–168° (from ether–light petroleum) (Found: C, 43.7; H, 3.3; Cl, 25.4. $C_{15}H_{15}Cl_3O_7$ calc.: C, 43.5; H, 3.7; Cl, 25.7%).

The 3,5-diacetate of **5** had m.p. 120–122°. N.m.r. data: τ 3.88 (d, 1 H, $J_{1,2}$

4 Hz, H-1), 5.33 (d, 1 H, $J_{2,3}$ ~0 Hz, H-2), 4.42 (d, 1 H, $J_{3,4}$ 3 Hz, H-3), 5.02 (q, 1 H, $J_{4,5}$ 10 Hz, H-4), 4.69 (m, $J_{5,6}$ 2, $J_{5,6'}$ 5 Hz, H-5), 5.20 (q, 1 H, $J_{6,6'}$ 12.5 Hz, H-6), 5.74 (q, 1 H, H-6'), 7.92, 8.00 (2 s, 6 H, 2 Ac), 4.69 (s, 1 H, $CCl_3 \cdot CH$), 1.95–2.80 (m, Bz).

6-O-Benzoyl-3,5-O-butylidene-1,2-O-trichloroethylidene-α-D-glucofuranose (**10**). — A mixture of **5** (5 g), ethyl ether (75 ml), butyraldehyde (2 ml), and conc. sulphuric acid (1 ml) was stirred overnight at room temperature, then filtered, washed with aqueous sodium hydrogen carbonate, and concentrated. The syrupy residue was extracted with boiling light petroleum, from which was deposited **10** (1.5 g), m.p. 67–68° (Found: C, 48.7; H, 4.8; Cl, 23.1. $C_{19}H_{21}Cl_3O_7$ calc.: C, 48.8; H, 4.5; Cl, 22.7%). N.m.r. data: τ 3.80 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 4.70 (s, 1 H, $CCl_3 \cdot CH$), 8.20–9.10 (m, Pr), 1.90, 2.60 (m, Bz).

3,5-O-Butylidene-1,2-O-trichloroethylidene-α-D-glucofuranose (**11**). — Compound **10** (1 g) was debenzoylated with triethylamine in methanol. T.l.c. (toluene–methanol, 9:1) of the resulting, syrupy product showed a single spot of **11**, $[\alpha]_D^{25}$ +44.5° (*c* 2, chloroform) (Found: C, 40.2; H, 4.6; Cl, 28.7. $C_{12}H_{17}Cl_3O_6$ calc.: C, 39.6; H, 4.7; Cl, 29.2%). N.m.r. data: τ 3.76 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 4.65 (s, 1 H, $CCl_3 \cdot CH$), 5.5 (t, 1 H, *J* 5 Hz, PrC*H*), 8.2, 9.1 (m, Pr).

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