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Note

2-Acetamido-2-deoxy-3,6:4,5-di-*O*-isopropylidene-D-glucose diethyl dithioacetal and its single-crystal X-ray analysis

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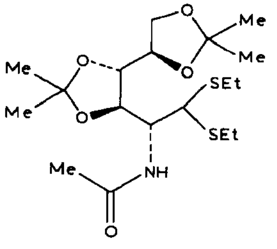
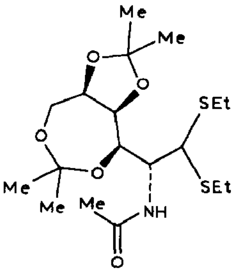
Recently, we prepared 2-acetamido-2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-glucose diethyl dithioacetal (**1**) by use of a modified procedure of Benzing and Perry[1,2]. In addition to **1** (>80% yield), we obtained a minor compound **2** having an unusual bicyclo[5.3.0]di-*O*-isopropylidene structure*. We report herein the isolation and characterization of **2**.



1



2

The two compounds **1** and **2** were easily distinguishable by thin-layer chromatography. Attempted fractional crystallization from hexane resulted in a mixture of crystals (needles and prisms) containing the two compounds. These were readily separated by flash chromatography[4] and then crystallized from hexane. The major compound was confirmed to be the desired product **1** by its physical and spectroscopic properties. The minor product (2–5% yield) was demonstrated to be an isomer of **1** by its spectroscopic data and microanalysis. In order to determine the structure and absolute configuration of the minor product, a single-crystal X-ray analysis was performed.

The crystal used for the X-ray analysis was formed in an acetone–hexane mixture and contained an undetermined amount of acetone. Due to the disordered

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*Since the completion of this manuscript, the isolation of compounds having the same *cis*-fused 3,6:4,5-di-*O*-isopropylidene residue obtained by acetalation of D-mannitol, has been reported[3].

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state of the acetone molecules in the crystal, the X-ray analysis could not confirm unequivocally the identity of this solvent nor specify its stoichiometry in the empirical formula. However, the presence of acetone in the sample was firmly established by ^{1}H-n.m.r. spectroscopy.

The crystal data are summarized in Table I. The intensity data were measured with a Hilger–Watts diffractometer (Ni-filtered CuKα radiation, θ–2θ scans, pulse-height discrimination). The size of the crystal used for data collection was approximately 0.06 × 0.20 × 0.65 mm; the data were corrected for absorption. Of the 1960 independent reflections for θ <57°, 1518 were considered to be observed [I >2.5σ(I)]. The intensities of the five standard reflections decreased by ~18% over a period of three days of data collection, probably due to the loss of acetone from the crystal.

The structure of **2** was solved by a multiple-solution procedure[5], and was refined by full-matrix least squares. In the final refinement, anisotropic thermal parameters were used for the nonhydrogen atoms. The positions of the hydrogen atoms were calculated and were included in the structure factor calculations, but their parameters were not refined. From several difference maps, six major peaks, all of which were more than 3.5 Å away from the main molecule, were interpreted as atoms of disordered acetone molecules. The assignments of carbon–oxygen scattering curves and occupancy parameters to these peaks were tentative and proved to be unsatisfactory. As a result, efforts to extract from these peaks a reasonable and meaningful structure resembling that of an acetone molecule failed. The number of variables was 255. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$, with $w = [\sigma^2(F_o) + (0.0004)F_o^2]^{-1}$. The final discrepancy indices are $R = 0.048$ and $wR = 0.046$ for the 1518 observed reflections. The final difference map has no peaks greater than ±0.2 eÅ^{-3}.

The absolute configuration of **2** was confirmed by the anomalous scattering of the sulfur atom and was established by refining both enantiomers. The values used for the anomalous components of the sulfur scattering factors were $\Delta F' = 0.310$ and $\Delta F'' = 0.580$. The final weighted R values were 0.0462 for the configuration

TABLE I

CRYSTAL DATA FOR COMPOUND **2**[a]

Formula	$C_{18}H_{33}NO_5S_2 \cdot (C_3H_6O)_x$
Space Group	$P2_122_1$
a	9.403(11) Å
b	9.823(9) Å
c	27.37(3) Å
Z	4
$d_{(calc.)}$	1.224 g · cm^{-3}
μ(CuKα)	21.3 cm^{-1}

[a] Atomic coordinates, bond lengths, bond angles, and selected torsion angles of **2** are available as supplementary material.

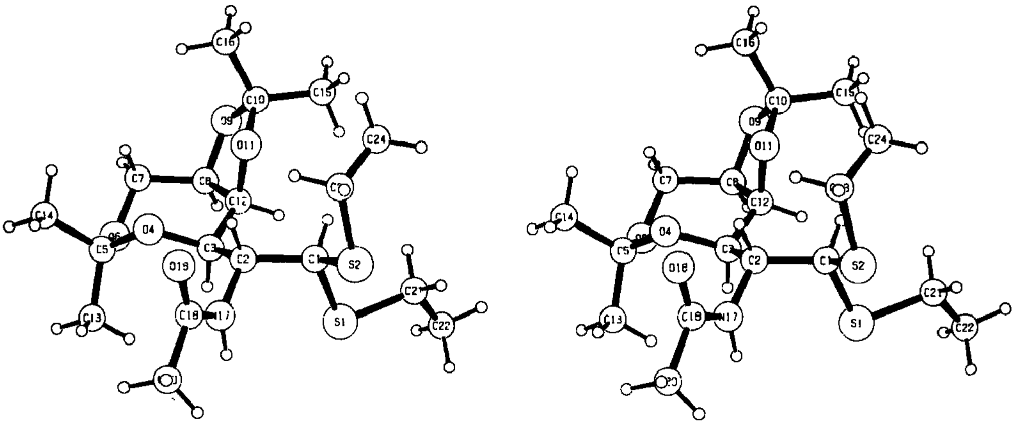

Fig. 1. Stereoscopic diagram of compound **2**.

shown and 0.0554 for its antipode. Thus, by Hamilton's test[6], the configuration shown corresponds to the absolute configuration (Fig. 1)*.

This X-ray analysis showed that the five-membered ring of **2** (C-8–O-9–C-10–O-11–C-12) adopts the conformation of an "envelope" with C-12 at the "tip of the flap" and the other four atoms forming a plane (all four atoms less than 0.04Å from the plane). The seven-membered ring (C-3–O-4–C-5–O-6–C-7–C-8–C-12) adopts a conformation with O-4–C-7–C-8–C-12 in a plane (all four atoms less than 0.05Å from it) and the other three atoms on the same side of this plane. The dihedral angle between these two planes is 62°. In this conformation, both the bonds of the bulkiest substituents in the five-membered ring (*i.e.*, C-3 attached to C-12) and in the seven-membered ring (*i.e.*, C-2 attached to C-3) are pseudo-equatorial.

In our experience, the formation of **1** and **2** occurred when the reaction was performed at room temperature or below (reaction time of 90 min or less). When the reaction was performed at reflux temperature for 1 h, only **1** was obtained in 90% yield. This is consistent with the observation that, under similar experimental conditions**, **1** was not converted into **2**. On the other hand, **2** was slowly converted into **1** at room temperature under these conditions (**2** could still be detected after 3 h), whereas, at reflux, it was completely converted into **1** in less than 15 min.

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*Tables of atomic parameters, anisotropic thermal parameters, bond lengths, bond angles, and selected torsion angles are deposited with, and can be obtained from, Elsevier Science Publishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/341/*Carbohydr. Res.*, 152 (1986) 274–278.

Addition of 0.04 mL of conc. sulfuric acid to a solution of 100 mg of either pure **1 or **2** in 3:1 2,2-dimethoxypropane–acetone (8 mL) with magnetic stirring.

EXPERIMENTAL

General. — Melting points were taken on a Thomas Model 40 Micro Hot Stage melting point apparatus and are uncorrected. I.r. spectra were recorded with a Digilab FTS 14 spectrometer and mass spectra with a Varian MAT CH5 spectrometer. ^{1}H-N.m.r. spectra were recorded with a Varian XL-200 spectrometer and are reported downfield from the signal of internal SiMe$_4$. U.v. spectra were recorded with a Cary-14 spectrophotometer. Silica gel 60 (230–400 mesh), EM Reagents, were used for flash chromatography. Silica gel 60 F-254 precoated plates (layer thickness 0.25 mm), EM Reagents, were used for t.l.c. The solvents used for both flash chromatography and t.l.c. were: (*A*) 9:1 (v/v) benzene–methanol, (*B*) 2:3 (v/v) acetone–hexane, and (*C*) 3:17 (v/v) acetone–hexane. Spots on t.l.c. plates were detected by treating the plates with I$_2$ vapor.

Synthesis and separation of **1** *and* **2**. — 2-Acetamido-2-deoxy-D-glucose diethyl dithioacetal (15 g, 45.8 mmol) was added with magnetic stirring to a mixture of 2,2-dimethoxypropane (60 mL) and acetone (20 mL). Conc. H$_2$SO$_4$ (0.37 mL) was added to this mixture, followed by stirring at room temperature for 90 min. The mixture was then partitioned between saturated aqueous NaHCO$_3$ solution (100 mL), water (300 mL), and ethyl acetate (2 × 400 mL). The ethyl acetate layers were in turn washed with water (400 mL) and saturated aqueous NaCl solution (400 mL), combined, and dried (MgSO$_4$); t.l.c. showed the presence of both **1** and **2** [R_F (*A*) **1**, 0.43, **2**, 0.35; (*B*) **1**, 0.47, **2**, 0.39]. After filtration and concentration, the resulting oil was separated by flash chromatography on silica gel (400 g) in solvent *C* (4 L), followed by solvent *B* (1.5 L), collecting 250 mL per flask. Flasks 9–12 and 13–19 were combined and concentrated to give **1** and **2**, respectively.

2-Acetamido-2-deoxy-3,4:5,6-di-O-isopropylidene-D-glucose diethyl dithioacetal (**1**). — Crystallized from hexane in two crops as colorless prisms (15.5 g, 83% yield), m.p. 67–68°, $[\alpha]_D^{25}$ −36.69° (*c* 2.04, methanol); lit.[1] m.p. 65–66° $[\alpha]_D$ −35.7° (*c* 2.1, methanol); lit.[2] m.p. 66–67°, $[\alpha]_D^{21}$ −36.0° (*c* 2.25, methanol); λ_{max}^{MeOH} 238 nm (sh, ε 700); ν_{max}^{KBr} 3310, 1650, and 1510 cm^{-1}; ^{1}H-n.m.r. (CDCl$_3$): δ 1.26 (t, 3 H, *J* 4 Hz), 1.28 (t, 3 H, *J* 4 Hz), 1.34 (s, 3 H), 1.40 (s, 3 H), 1.42 (s, 3 H), 1.46 (s, 3 H), 2.04 (s, 3 H), 2.70 (q, 4 H, *J* 4 Hz), 3.57 (m, 1 H), 3.98 (m, 2 H), 4.12 (m, 2 H), 4.55 (dd, 1 H, *J* 4 and 5 Hz), 4.67 (d, 1 H, *J* 4 Hz), and 6.07 (d, 1 H, *J* 4 Hz); m.s. (rel. intens.): *m/z* 407 (M$^+$, 2), 348 (39), 214 (20), 135 (100), 114 (25), 101 (20), 43 (52), and 28 (38).

Anal. Calc. for C$_{18}$H$_{33}$NO$_5$S$_2$: C, 53.04; H, 8.16; N, 3.44; S, 15.73. Found: C, 52.99; H, 7.94; N, 3.45; S, 15.48.

2-Acetamido-2-deoxy-3,6:4,5-di-O-isopropylidene-D-glucose diethyl dithioacetal (**2**). — Crystallized from hexane as white needles (0.42 g, 2.3% yield), m.p. 133–133.5°, $[\alpha]_D^{25}$ −59.01° (*c* 0.93, methanol); λ_{max}^{MeOH} 240 nm (sh, ε 430); ν_{max}^{KBr} 3315, 1654, and 1544 cm^{-1}; ^{1}H-n.m.r. (CDCl$_3$): δ 1.26 (t, 3 H, *J* 4 Hz), 1.27 (t, 3 H, *J* 4 Hz), 1.30 (s, 3 H), 1.37 (s, 3 H), 1.41 (s, 3 H), 1.45 (s, 3 H), 2.02 (s, 3 H), 2.70 (m, 4 H), 3.43 (m, 1 H), 3.72 (m, 1 H), 4.02 (d, 1 H, *J* 4 Hz), 4.12 (m, 2 H), 4.50 (m, 2 H), and 5.95 (br d, 1 H, *J* 5 Hz); m.s. (rel. intens.): *m/z* 407 (M^+, 5), 378 (30), 348 (45), 214 (75), 202 (30), 177 (32), 176 (100), 172 (66), 156 (83), 147 (32), 135 (91), 114 (57), 100 (46), 96 (33), 59 (41), 57 (53), and 43 (42).

Anal. Calc. for $C_{18}H_{33}NO_5S_2$: C, 53.04; H, 8.16; N, 3.44; S, 15.73. Found: C, 53.24; H, 7.94; N, 3.46; S, 15.59.

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