Carbohydrate Research, 111 (1983) 319–324
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Note

Regioselective isopropylidenation of 2-acetamido-2-deoxy-D-xylose diethyl dithioacetal*

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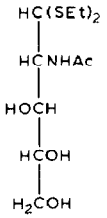
(Received March 8th, 1982; accepted for publication, May 26th, 1982)

In connection with other studies, we needed an acyclic 2-acetamido-2-deoxy-D-xylose derivative having HO-4 and -5 blocked and HO-3 free. Since HO-4 and -5 are bound to two adjacent carbon atoms, regioselective acetal formation, such as isopropylidenation, seemed the simplest way to accomplish this goal. Unlike the acetalation of alditols and sugar dithioacetals[1–5], isopropylidenation of acyclic sugar derivatives has been much less studied. Although it is known, with reasonable certainty, that isopropylidenation favors the formation of five-membered rings, probably owing to steric reasons, the dependence of regioselectivity and the extent of isopropylidenation of alditols and sugar dithioacetals upon the nature of the acid catalyst has not been elucidated. The results of our studies on the regioselective isopropylidenation of 2-acetamido-2-deoxy-D-xylose diethyl dithioacetal (**1**) are reported in this paper.

2-Acetamido-2-deoxy-D-xylose diethyl dithioacetal (**1**) was obtained by acid-catalyzed hydrolysis of 2-acetamido-2-deoxy-3,4-*O*-isopropylidene-D-xylose diethyl dithioacetal (**2**), which had been synthesized from 2-acetamido-2-deoxy-3,4-*O*-isopropylidene-D-glucose diethyl dithioacetal according to the procedure of Wolfrom and Winkley[6]. Isopropylidenation of **1** with 1:1 (v/v) anhydrous acetone–2,2-dimethoxypropane, in the presence of concentrated sulfuric acid, afforded, in 90% yield, the 3,4-*O*-isopropylidene derivative **2** as the only product of the reaction. The position of the isopropylidene group was established by comparing the product of isopropylidenation with authentic material obtained from 2-acetamido-2-deoxy-3,4-*O*-isopropylidene-D-glucose diethyl dithioacetal by periodate oxidation, followed by sodium borohydride reduction[6]. Acetylation of **2** with acetic anhydride–pyridine gave the monoacetate **3**; the comparison of its n.m.r. spectrum with that of **2** not only helped in the interpretation of the n.m.r. spectrum of **2**, but gave additional proof for the

*Taken, in part, from the Ph.D. thesis of Peter Hagel. This work was supported, in part, by grant CA-15482 from the National Cancer Institute, U.S. Public Health Service.

position of the isopropylidene group in **2**. It has been observed that acetylation shifts the signals of H_2-5 of **2** (δ 3.77–3.72, unresolved multiplet) downfield by ~0.5 p.p.m. [δ 4.24 and 4.23 for H- and H′-5].



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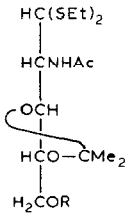

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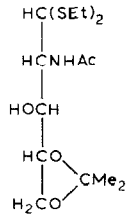
3 R = Ac



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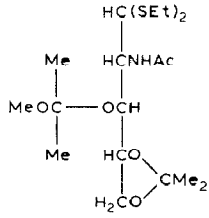

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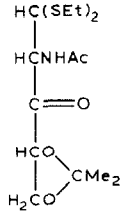

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Isopropylidenation of **1** with 1:1 (v/v) anhydrous acetone–2,2-dimethoxypropane in the presence of copper(II) sulfate* gave 2-acetamido-2-deoxy-4,5-*O*-isopropylidene-D-xylose diethyl dithioacetal (**4**) as a colorless syrup in 72% yield. As a minor product of this reaction, 2-acetamido-2-deoxy-4,5-*O*-isopropylidene-3-*O*-(1-methoxy-1-methylethyl)-D-xylose diethyl dithioacetal (**5**) was isolated in crystalline form in 7% yield. The structure of the 4,5-*O*-isopropylidene derivative **4** was ascertained both by n.m.r. spectroscopy and by oxidation with 2:1 (v/v) dimethyl sulfoxide–acetic anhydride, which afforded 2-acetamido-2-deoxy-4,5-*O*-isopropylidene-D-xylos-3-ulose diethyl dithioacetal (**6**) as a colorless syrup in 85% yield. The n.m.r. spectrum of **6** unequivocally proved the location of the carbonyl group and, thus, the position of the isopropylidene group in the parent sugar **4** (*vide infra*).

The structure of **5** was deduced on the basis of its n.m.r. spectrum. The formation of mixed acetals has previously been reported[7–9], but in the majority of cases the primary rather than the secondary hydroxyl group was involved.

The isopropylidenation of **1** with 2-methoxypropene in anhydrous acetone in the presence of anhydrous copper(II) sulfate afforded the 4,5-*O*-isopropylidene derivative **4** in 74% yield, **5** being isolated in only 3% yield, but a small proportion of starting material (~7%) remained. A significant advantage of 2-methoxypropene over 2,2-dimethoxypropane as a reagent for isopropylidenation of vicinal diols is the much shorter reaction time (~1/6 times). It should be noted that the prolonged reaction times favor the formation of **5**. Thus, isopropylidenation of **1** for 25 h afforded the 4,5-*O*-isopropylidene derivative **4** in only 45% yield, whereas the 3-*O*-(1-methoxy-1-methylethyl) derivative **5** was isolated in 39% yield.

For all acetonation studies described herein, anhydrous copper(II) sulfate was prepared by drying crystalline copper(II) sulfate pentahydrate in a crucible over an

*With anhydrous copper(II) sulfate as the catalyst, the isopropylidenation of **1** did not take place in either anhydrous acetone (in the course of 24 h) or in 2,2-dimethoxypropane alone.

open flame (Bunsen burner) until the top layer became completely white. The anhydrous copper(II) sulfate obtained under these conditions was not homogeneous, as the bottom layer was brown and the top layer white. All isopropylidenations just described were performed with the top layer of anhydrous copper(II) sulfate. When the bottom layer was used as catalyst, the 4,5-*O*-isopropylidene derivative **4** was isolated in only 34%, the 3,4-*O*-isopropylidene derivative **2** in 39%, and the 3-*O*-(1-methoxy-1-methylethyl) derivative **5** in 21% yield. The most likely reason for the loss in regioselectivity is the high acidity of the bottom layer of anhydrous copper(II) sulfate (pH 1.74 of the 0.5M aqueous solution) when compared with that of the top layer (pH 4.59 of the 0.5M aqueous solution). Therefore, the 4,5-*O*-isopropylidene derivative **4** is most probably the primary product of isopropylidenation also when the bottom layer of anhydrous copper(II) sulfate was used as the catalyst, but owing to the presence of mineral acid (possibly formed by decomposition of copper sulfate by overheating) **4** was isomerized into the 3,4-*O*-isopropylidene derivative **2**.

These results suggest that, in the case of alditols, or acyclic sugar derivatives, or both, isopropylidenation occurs for steric reasons, first at the chain terminal(s), involving the primary hydroxyl group(s) and, then, if the catalyst (such as a Brønsted acid) is capable of reversing the acetalation, the end product(s) are thermodynamically controlled. If, however, the catalyst is incapable of reversing the acetalation [as is the case with copper(II) sulfate], the product formation is kinetically controlled.

EXPERIMENTAL

General. — Melting points are uncorrected. Optical rotations were determined with a Cary 60 spectropolarimeter for solutions in a 1.0-cm cell. Infrared spectra were recorded with a Perkin–Elmer infrared spectrophotometer Model 267, and n.m.r. spectra of chloroform-*d* solutions with Bruker WM-360 and Varian T-60 spectrometers with tetramethylsilane as the internal standard. Silica gel (<0.08 mm) used for all column chromatography was obtained from E. Merck (Darmstadt, W. Germany).

*2-Acetamido-2-deoxy-*D*-xylose diethyl dithioacetal* (**1**). — To a cooled (ice bath) round-bottom flask containing 2-acetamido-2-deoxy-3,4-*O*-isopropylidene-D-xylose diethyl dithioacetal[6] **2** (657 mg; 1.95 mmol) was added ice-cold, concentrated hydrochloric acid (0.75 mL), and the mixture was stirred for 15 min (the material dissolved slowly over a period of 10 min). Lead carbonate (3 g) was added, followed by water (15 mL), and stirring continued for another 10 min. The precipitate (lead carbonate and lead dichloride) was filtered off, and the residue extracted with ethanol (10-mL portions). The filtrate and extracts were combined and evaporated to dryness. The residue (a syrup together with some inorganic material) was chromatographed on silica gel (10 g). Elution with 6:1 (v/v) benzene–methanol gave pure **1** (399 mg; 69%), a colorless and chromatographically homogeneous syrup that crystallized after some time. Recrystallization from acetone–ether–petroleum ether gave the analytical sample, m.p. 56°, $[\alpha]_D^{27}$ −11.6° (*c* 1.06, chloroform); $\nu_{max}^{CHCl_3}$ 3400 (amide NH),

3360 (H-bonded OH), and 1650 cm^{-1} (amide C=O); ^{1}H-n.m.r.: δ 6.78 (d, 1 H, $J_{2,NH}$ 9.16 Hz, NH), 4.68 (br. s, 1 H, OH), 4.51 (br. s, 1 H, OH), 4.27 (br. s, 1 H, OH), 4.23–4.19 (m, 2 H), 4.08 (d, 1 H, $J_{1,2}$ 7.63 Hz, H-1), 3.75 (br. s, 1 H), 3.61 (br. s, 2 H), 2.76–2.59 (m, 4 H, 2 SCH_2CH_3), 2.06 (s, 3 H, $NHCOCH_3$), and 1.26 and 1.25 (2 t, 6 H, J 7.31 Hz, 2 SCH_2CH_3).

Anal. Calc. for $C_{11}H_{23}NO_4S_2$: C, 44.42; H, 7.79. Found: C, 44.20; H, 7.81.

*2-Acetamido-2-deoxy-3,4-*O*-isopropylidene-*D*-xylose diethyl dithioacetal* (**2**). — To a solution of **1** (75 mg, 0.25 mmol) in 1:1 (v/v) anhydrous acetone–2,2-dimethoxypropane (1 mL) was added conc. sulfuric acid (one drop) with stirring, and the mixture kept at room temperature for 1 h, at which time t.l.c. (1:2, v/v, benzene–ethyl acetate) indicated the disappearance of starting material and the presence of only one product (R_F 0.23). The mixture was poured into saturated aqueous sodium hydrogencarbonate solution, stirred for 5 min, and evaporated to dryness *in vacuo*. The solid residue was extracted with chloroform. After evaporation of chloroform *in vacuo*, the residue was chromatographed on silica gel (5 g). Elution with 1:1 (v/v) benzene–ethyl acetate gave chromatographically homogeneous **2** (76 mg, 90%) as a colorless syrup, $[\alpha]_D^{27}$ −1.6° (*c* 2.27, chloroform); $\nu_{max}^{CHCl_3}$ 3420 (NH and OH) and 1670 cm^{-1} (amide C=O); ^{1}H-n.m.r.: δ 6.21 (d, 1 H, $J_{NH,2}$ 8.79 Hz, NH), 4.54 (dd, 1 H, $J_{3,4}$ 7.57, $J_{2,3}$ 0.98 Hz, H-3), 4.28 (ddd, 1 H, $J_{1,2}$ 7.33, $J_{2,NH}$ 8.79, $J_{2,3}$ 0.98 Hz, H-2), 3.97 (d, 1 H, $J_{1,2}$ 7.33 Hz, H-1), 3.77–3.72 (m, 3 H, H-4, -5, and H-5′), 2.71–2.61 (m, 4 H, 2 SCH_2CH_3), 2.07 (s, 3 H, $NHCOCH_3$), 1.43 and 1.42 [2 s, 6 H, $C(CH_3)_2$], and 1.27 and 1.26 (2 t, 6 H, J 7.32 Hz, 2 SCH_2CH_3).

Anal. Calc. for $C_{14}H_{27}NO_4S_2$: C, 49.82; H, 8.06; N, 4.15; S, 19.00. Found: C, 49.92; H, 8.29; N, 4.00; S, 18.84.

*2-Acetamido-5-*O*-acetyl-2-deoxy-3,4-*O*-isopropylidene-*D*-xylose diethyl dithioacetal* (**3**). — Acetic anhydride (0.5 mL) was added to a pyridine solution (1 mL) of **2** (49 mg, 0.15 mmol). The solution was kept at room temperature for 14 h, and then an excess of methanol was added with stirring, and the reaction mixture was kept for another 15 min at room temperature. After evaporation *in vacuo*, a yellow syrup was obtained that was chromatographed on silica gel (3 g). Elution with 2:1 (v/v) benzene–ethyl acetate yielded a chromatographically homogeneous, colorless syrup (51 mg, 92%), which crystallized eventually, m.p. 66°. After two recrystallizations from hexane–ether, the analytical sample (36 mg) was obtained as long, white needles, m.p. 66.5°, $[\alpha]_D^{27}$ +12.5° (*c* 2.09, chloroform); $\nu_{max}^{CHCl_3}$ 3420 (NH), 1740 (acetate C=O), and 1680 cm^{-1} (amide C=O); ^{1}H-n.m.r.: δ 6.12 (d, 1 H, $J_{2,NH}$ 9.55 Hz, NH), 4.51 (dd, 1 H, $J_{2,3}$ 0.98, $J_{3,4}$ 8.55 Hz, H-3), 4.30 (ddd, 1 H, $J_{2,NH}$ 9.55, $J_{2,3}$ 0.98, $J_{1,2}$ 7.08 Hz, H-2), 4.24 (d, 1 H, $J_{4,5}$ 5.13 Hz, H-5), 4.23 (d, 1 H, $J_{4,5'}$ 4.15 Hz, H-5′), 3.96 (d, 1 H, $J_{1,2}$ 7.08 Hz, H-1), 3.87 (ddd, 1 H, $J_{3,4}$ 8.55, $J_{4,5}$ 5.13, $J_{4,5'}$ 4.15 Hz, H-4), 2.72–2.63 (m, 4 H, 2 SCH_2CH_3), 2.12 (s, 3 H, $OCOCH_3$), 2.07 (s, 3 H, $NHCOCH_3$), 1.44 and 1.43 [2 s, 6 H, $C(CH_3)$], and 1.27 (t, 6 H, J 7.32 Hz, 2 SCH_2CH_3).

Anal. Calc. for $C_{16}H_{29}NO_5S_2$: C, 50.63; H, 7.70; N, 3.69; S, 16.90. Found: C, 50.50; H, 7.87; N, 3.65; S, 16.70.

2-Acetamido-2-deoxy-4,5-O-isopropylidene-D-xylose diethyl dithioacetal (**4**) *and 2-acetamido-2-deoxy-4,5-O-isopropylidene-3-O-(1-methoxy-1-methylethyl)-D-xylose diethyl dithioacetal* (**5**). — (*a*). Compound **1** (75 mg, 0.25 mmol) was dissolved in 1:1 (v/v) 2,2-dimethoxypropane–anhydrous acetone (1 mL), and anhydrous copper(II) sulfate (200 mg) was added to the solution. The mixture was stirred vigorously for 11 h at room temperature, at which point t.l.c. (1:2, v/v, benzene–ethyl acetate) indicated complete disappearance of the starting material, and the presence of one major (R_F 0.31) and one minor (R_F 0.43) product. The mixture was filtered, and the residue washed with acetone (3 10-mL portions). Solid sodium hydrogencarbonate (~200 mg) was added to the combined filtrate, and the acetone evaporated *in vacuo*. The resulting, thick syrup (containing solid sodium hydrogencarbonate) was dried in high vacuum for 2 h, and then chromatographed on silica gel (5 g). Elution with 1:1 (v/v) benzene–ethyl acetate gave **4** as the major reaction-product, as a chromatographically homogeneous, colorless syrup (61 mg, 72%), $[\alpha]_D^{27}$ −8.3° (*c* 3.14, chloroform); $\nu_{max}^{CHCl_3}$ 3530 (H-bonded OH), 3420 (amide NH), and 1670 cm^{-1} (amide C=O); ^{1}H-n.m.r.: δ 6.24 (d, 1 H, $J_{2,NH}$ 7.08 Hz, NH), 4.17 (dd, 1 H, $J_{3,OH}$ 2.93, $J_{3,4}$ 8.30 Hz, H-3), 4.10 (d, 1 H, $J_{5,5'}$ 8.55 Hz, H-5), 4.05 (dd, 1 H, $J_{1,2}$ 5.13, $J_{2,NH}$ 7.08 Hz, H-2), 3.99 (dd, 1 H, $J_{3,4}$ 8.30, $J_{4,5'}$ 5.62 Hz, H-4), 3.96 (d, 1 H, $J_{1,2}$ 5.13 Hz, H-1), 3.77 (dd, 1 H, $J_{4,5'}$ 5.62, $J_{5,5'}$ 8.55 Hz, H-5'), 2.98 (d, 1 H, $J_{3,OH}$ 2.93 Hz, OH), 2.75–2.56 (m, 4 H, 2 SCH_2CH_3), 2.04 (s, 3 H, $NHCOCH_3$), 1.46 and 1.36 [2 s, 6 H, $C(CH_3)_2$], and 1.27 and 1.26 (2 t, 6 H, *J* 7.32 Hz, 2 SCH_2CH_3).

Anal. Calc. for $C_{14}H_{27}NO_4S_2$: C, 49.82; H, 8.06; N, 4.15; S, 19.00. Found: C, 49.56; H, 8.04; N, 4.35; S, 18.84.

The minor product (**5**) was isolated as a white, crystalline material (7 mg, 7%), m.p. 60–62°. Owing to its instability, this product was not characterized by microanalysis and optical rotation, which require extended drying in high vacuum. The ^{1}H-n.m.r. spectrum was in full accord, however, with the proposed structure: δ 6.11 (d, 1 H, $J_{2,NH}$ 9.52 Hz, NH), 4.53 (d, 1 H, $J_{3,4}$ 8.55 Hz, H-3), 4.33 (dd, 1 H, $J_{2,NH}$ 9.52, $J_{1,2}$ 6.84 Hz, H-2), 3.96 (d, 1 H, $J_{1,2}$ 6.84 Hz, H-1), 3.80 (ddd, 1 H, $J_{3,4}$ 8.55, $J_{4,5}$ 5.62, $J_{4,5'}$ 4.64 Hz, H-4), 3.59 (dd, 1 H, $J_{4,5}$ 5.62, $J_{5,5'}$ 10.25 Hz, H-5), 3.52 (dd, 1 H, $J_{4,5'}$ 4.64, $J_{5,5'}$ 10.25 Hz, H-5'), 3.22 (s, 3 H, OCH_3), 2.75–2.64 (m, 4 H, 2 SCH_2CH_3), 2.05 (s, 3 H, $NHCOCH_3$), 1.44 and 1.42 [2 s, 6 H, $C(CH_3)_2$], 1.36 [s, 6 H, $CH_3O(CH_3)_2CO$], and 1.27 and 1.26 (2 t, 6 H, *J* 7.33 Hz, 2 SCH_2CH_3).

(*b*). To a solution of **1** (100 mg, 0.34 mmol) in 20:3 (v/v) anhydrous acetone–2-methoxypropene (3.14 mmol) (total 2.3 μL) was added anhydrous copper(II) sulfate (200 mg). The mixture was stirred for 2 h at room temperature, when t.l.c. (1:2, v/v, benzene–ethyl acetate) indicated the presence, in addition to traces of starting material, of one major product (R_F 0.30) and a very small proportion of a less polar, minor product (R_F 0.46). The mixture was filtered and the precipitate washed with acetone (2 10-mL portions). Solid sodium hydrogencarbonate was added (~200 mg), and the combined filtrates were evaporated *in vacuo*. The residue was chromatographed on silica gel (5 g). Elution with 1:1 (v/v) benzene–ethyl acetate gave **5** (4 mg, 3%) identified by comparison with authentic **5** (t.l.c. in three

different solvent systems: 1:2, v/v, benzene–ethyl acetate; 9:1, v/v, benzene–methanol, and 1:1, v/v, hexane–acetone). The second fraction (85 mg, 74%), obtained as a colorless syrup, was chromatographically and spectroscopically identical with **4**. Starting material (7 mg, 7%) was eluted with 6:1 (v/v) benzene–methanol.

*2-Acetamido-2-deoxy-4,5-O-isopropylidene-*D*-xylos-3-ulose diethyl dithioacetal* (**6**). — A solution of **4** (38 mg, 0.11 mmol) in 2:1 (v/v) dimethyl sulfoxide–acetic anhydride (0.5 mL) was kept at room temperature for 16 h, when t.l.c. (2:1, v/v, benzene–ethyl acetate) indicated the absence of starting material and the presence of only one product (R_F 0.62). The mixture was evaporated in high vacuum (bath temperature, 60°), and the resulting yellowish syrup chromatographed on silica gel (2 g). Elution with 40:1 (v/v) benzene–methanol gave chromatographically homogeneous **6** (32 mg, 85%) as a colorless syrup, $[\alpha]_D^{27}$ +90.9° (*c* 1.15, chloroform); $\nu_{max}^{CHCl_3}$ 3410 (amide NH), 1723 (keto C=O), and 1673 cm^{-1} (amide C=O); ^{1}H-n.m.r.: 6.15 (d, 1 H, $J_{2,NH}$ 8.79 Hz, NH), 5.49 (dd, 1 H, $J_{2,NH}$ 8.79, $J_{1,2}$ 4.64 Hz, H-2), 4.65 (dd, 1 H, $J_{4,5}$ 7.56, $J_{4,5'}$ 5.85 Hz, H-4), 4.56 (d, 1 H, $J_{1,2}$ 4.64 Hz, H-1), 4.23 (dd, 1 H, $J_{4,5}$ 7.56, $J_{5,5'}$ 8.79 Hz, H-5), 4.17 (dd, 1 H, $J_{4,5'}$ 5.86, $J_{5,5'}$ 8.79 Hz, H-5'), 2.77–2.63 (m, 4 H, 2 SCH_2CH_3), 2.07 (s, 3 H, $NHCOCH_3$), 1.50 and 1.42 [2 s, 6 H, $C(CH_3)_2$], and 1.31 and 1.27 (2 t, 6 H, *J* 7.32 Hz, 2 SCH_2CH_3).

Anal. Calc. for $C_{14}H_{25}NO_4S_2$: C, 50.12; H, 7.51. Found: C, 50.12; H, 7.62.

ACKNOWLEDGMENT

The authors are greatly indebted to Dr. Charles W. DeBrosse for recording the 360-MHz ^{1}H-n.m.r. spectra.

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