Carbohydrate Research, 32 (1974) 370–374
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Note

Isopropylidene derivatives of D-xylose diethyl dithioacetal

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(Received June 22nd, 1973; accepted September 17th, 1973)

Three reports[1–3] describe the reaction of acetone with D-xylose dialkyl dithioacetals in the presence of different catalysts. We required derivatives of D-xylose diethyl dithioacetal (**1**) for synthetic purposes and investigated the products of the reaction with acetone when anhydrous zinc chloride, copper sulfate, or phosphorus pentaoxide were used as catalysts. A small amount of 2,4:3,5-di-*O*-isopropylidene-D-xylose diethyl dithioacetal[2] (**3**) was isolated when anhydrous zinc chloride was used as a catalyst. Controlled hydrolysis of this compound gave 2,4-*O*-isopropylidene-D-xylose diethyl dithioacetal[2] (**6**). 3,4-*O*-Isopropylidene-D-xylose diethyl dithioacetal (**4**), identified from its n.m.r. spectrum in deuterated dimethyl sulfoxide, was also isolated. The primary hydroxyl group appeared as a triplet and the secondary hydroxyl group as a doublet, both signals disappearing when the spectrum was determined after the addition of a drop of deuterium oxide.

When the reaction of **1** with acetone was catalyzed with phophorus pentaoxide, the only product was 2,3:4,5-di-*O*-isopropylidene-D-xylose diethyl dithioacetal[2] (**2**) (Table I) and not the isomeric 2,4:3,5-di-*O*-isopropylidene compound (**3**) as Dalley *et al.*[3] had claimed. Furthermore, these authors[3] claimed that the diisopropylidene compound that they isolated gave, upon methylation, 3,5-*O*-isopropylidene-2,4-di-

TABLE I

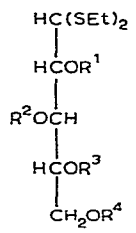
YIELDS (%) OF COMPOUNDS FORMED BY THE REACTION OF D-XYLOSE DIETHYL DITHIOACETAL (**1**) WITH ACETONE

Derivatives of **1**	*Reaction time (h)*[a]					
	4[b]	*12*[b]	*8*[c]	*24*[c]	*120*[c]	*1*[d]
2,3;4,5-Di-*O*-isopropylidene (**2**)	18	25	11	32	52	100
2,4;3,5-Di-*O*-isopropylidene (**3**)	8	12	1	2	2	
3,4-*O*-Isopropylidene (**4**)	14	2	25	24	12	
4,5-*O*-Isopropylidene (**5**)	60	61	63	42	34	

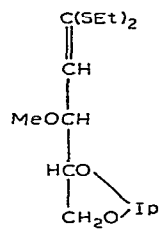
[a]At room temperature; compound **1** (2.0 g) and acetone (30 ml). [b]Anhydrous zinc chloride (3.0 g). [c]Anhydrous copper sulfate (5.0 g). [d]Phosphorus pentaoxide (2.0 g) (Ref. 3).

O-methyl-D-xylose diethyl dithioacetal. Attempted methylation of **2** with dimethyl sulfate and potassium hydroxide in tetrahydrofuran gave unchanged **2**. However, when **2** was first treated with potassium hydroxide in boiling tetrahydrofuran and then with dimethyl sulfate, the product was 1,2-dideoxy-1,1-bis(ethylthio)-4,5-*O*-isopropylidene-3-*O*-methyl-D-*threo*-pent-1-enitol (**7**).

Treatment of **2** with silver oxide and methyl iodide gave a large number of products. It was suspected that the silver oxide removed the dithioacetal group, and further reaction at C-1 could result in the formation of an aldonic ester or dimethyl acetal. 2,3,4,5-Tetra-*O*-methyl-D-xylose diethyl dithioacetal (**8**) was selected as a model compound to study the action of methyl iodide and silver oxide at C-1 exclusively. G.l.c. analysis of the reaction product showed the presence of methyl 2,3,4,5-tetra-*O*-methyl-D-xylonate (**9**) and 2,3,4,5-tetra-*O*-methyl-D-xylose dimethyl acetal (**11**) as the main products. It was also shown that two of the main components formed during methylation of the diisopropylidene compound (**2**) were the corresponding methyl D-xylonate and the dimethyl acetal.



1 $R^1 = R^2 = R^3 = R^4 = H$
2 R^1, $R^2 = R^3$, $R^4 = Ip$
3 R^1, $R^3 = R^2$, $R^4 = Ip$
4 $R^1 = R^4 = H$; R^2, $R^3 = Ip$
5 $R^1 = R^2 = H$; R^3, $R^4 = Ip$
6 $R^2 = R^4 = H$; R^1, $R^3 = Ip$
8 $R^1 = R^2 = R^3 = R^4 = Me$



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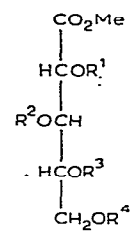
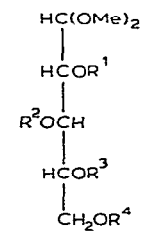


9 $R^1 = R^2 = R^3 = R^4 = Me$
10 R^1, $R^2 = R^3$, $R^4 = Ip$



11 $R^1 = R^2 = R^3 = R^4 = Me$
12 R^1, $R^2 = R^3$, $R^4 = Ip$

EXPERIMENTAL

Solutions were evaporated at 40° under diminished pressure. Melting points were determined on a Fisher–Johns apparatus and are uncorrected. N.m.r. spectra were recorded on a Varian T-60, tetramethylsilane was used as an internal standard, and chemical shifts are quoted in p.p.m. Mass spectra were determined with a Hitachi RMU7. G.l.c. analysis were performed on a Bendix gas chromatograph 2600 with a 6-ft. column of 10% EGSS-X on gas-chrom P (Applied Science Labs., State College, Pa.), at 200° with nitrogen carrier gas. Reaction mixtures were acetylated with pyridine and acetic anhydride prior to g.l.c. analysis. Column chromatography was performed with Silica Gel (60–200 mesh, Baker).

Reaction of D-*xylose diethyl dithioacetal* (**1**) *with acetone and zinc chloride.* — D-Xylose diethyl dithioacetal[4] (22.8 g), acetone (300 ml), and anhydrous zinc chloride (30.0 g) were stirred for 2 h at room temperature. Ether (300 ml) was added, followed

by addition of a solution of anhydrous potassium carbonate (40.0 g) in water (40 ml). The zinc carbonate was removed and washed with ether. The filtrate was dried over sodium sulfate and evaporated to give a syrup (21.0 g). Ethyl acetate and petroleum ether (40–60°) were added and the solution was kept at −10°. 4,5-*O*-Isopropylidene-D-xylose diethyl dithioacetal[2] (**5**, 9.3 g) mixed with some starting material crystallized. The mother liquors were evaporated and the syrup (9.5 g) was distilled at 0.01 mmHg through a column (15 cm) filled with glass helices. Three fractions were collected: (a) b.p. 105–108° (2.0 g), (b) b.p. 108–124° (3.0 g), and (c) b.p. 124–126° (3.0 g). Fractions (a) and (b) crystallized partly and 90 mg of a crystalline compound (**2**), m.p. 108–109° (recrystallized from hexane) was isolated from fraction (a) by the addition of petroleum ether (40–60°); $[\alpha]_D^{21}$ +48° (*c* 0.6, chloroform); n.m.r. data (chloroform-*d*): δ 1.12 (6-proton triplet, *J* 7.8 Hz, SCH_2CH_3), 1.48 [12-proton singlet, $C(CH_3)_2$], 2.73 (4-proton quartet, *J* 7.8 Hz, SCH_2CH_3), and 4.28–3.70 (6-proton complex).

Fraction (c) was applied to a column of silica gel with 1:19 methanol–benzene as eluent and gave 4,5-*O*-isopropylidene-D-xylose diethyl dithioacetal[2] (**5**) (30%), m.p. 76–77°; 2,4-*O*-isopropylidene-D-xylose diethyl dithioacetal[2] (**6**) (8%), m.p. 117–118°; and 3,4-*O*-isopropylidene-D-xylose diethyl dithioacetal (**4**) (50%), syrup; $[\alpha]_D^{20}$ +45° (*c* 1.48, chloroform); n.m.r. data (dimethyl sulfoxide-d_6): δ 1.07 (6-proton triplet, *J* 7.8 Hz, SCH_2CH_3), 1.18 [6-proton singlet, $C(CH_3)_2$], 2.68 (4-proton quartet, *J* 7.8 Hz, SCH_2CH_3), 4.22–3.34 (6-proton complex), 4.76 (1-proton triplet, *J* 5.5 Hz, CH_2OH), and 5.0 (1-proton doublet, *J* 7.8 Hz, CHOH) (the two last-named signals disappeared on addition of a drop of deuterium oxide).

Anal. Calc. for $C_{12}H_{24}O_4S_2$: C, 48.65; H, 8.11. Found: C, 48.55; H, 8.00.

Hydrolysis of 2,4:3,5-di-O-isopropylidene-D-xylose diethyl dithioacetal (**3**). — Compound **3** (40 mg), methanol (3 ml) and M hydrochloric acid (0.2 ml) were kept at room temperature. Progress of the hydrolysis was monitored by t.l.c. in 1:19 methanol–benzene. The reaction mixture was neutralized after 1.5 h with Dowex 45 (OH^-) and evaporated to give a solid. Column chromatography in 1:19 methanol–benzene of this solid gave the starting material, m.p. 108–109° (11 mg) and 2,4-*O*-isopropylidene-D-xylose diethyl dithioacetal (**6**, 15 mg), m.p. and mixed m.p. with an authentic sample 117–118°.

1,2-Dideoxy-1,1-bis(ethylthio)-4,5-O-isopropylidene-3-O-methyl-D-threo-pent-1-enitol (**7**). — A mixture of **1** (1.0 g), powdered potassium hydroxide (5.0 g), and anhydrous tetrahydrofuran (15 ml) was heated under reflux with stirring for 3 h. Dimethyl sulfate (4 ml) was slowly added to the dark solution and heating continued for 3 h. A concentrated ammonia solution (5 ml) was added to decompose the excess of dimethyl sulfate. The product (0.85 g) was isolated as a syrup by extraction with chloroform and water. The syrup was applied to a column of silica gel with 1:39 methanol–benzene as the eluent to give a pure syrup, $[\alpha]_D^{25}$ −18° (*c* 1.63, chloroform); i.r. datum: ν_{max}^{film} 1578 cm^{-1} (>C=CH); n.m.r. data (chloroform-*d*): δ 1.30 (6-proton triplet, *J* 7.8 Hz, SCH_2CH_3), 1.45 [6-proton doublet, *J* 3.5 Hz, $C(CH_3)_2$], 2.80 (4-proton quartet, *J* 7.8 Hz, SCH_2CH_3), 3.36 (3-proton singlet, OCH_3), 3.50–4.66

(4-proton complex), and 5.80 (1-proton doublet, J 7.3 Hz, H-1); m.s.: 292 (M^+), 277 ($M^+ - CH_3$), 260 ($M^+ - CH_3OH$).

Anal. Calc. for $C_{13}H_{24}O_3S_2$: C, 53.38; H, 8.21. Found: C, 53.42; H, 8.18.

*2,3,4,5-Tetra-*O*-methyl-*D*-xylose diethyl dithioacetal* (**8**). — A mixture of **1** (2.0 g), powdered potassium hydroxide (10.0 g), tetrahydrofuran (20 ml), and dimethyl sulfate (10 ml) was stirred overnight at room temperature. The product was isolated and purified as just described to give a pure syrup (1.60 g), $[\alpha]^{25}$ +6° (*c* 1.41, chloroform); n.m.r. data (chloroform-*d*): δ 1.30 (6-proton triplet, J 7.8 Hz, SCH_2CH_3), 2.73 (4-proton quartet, J 7.8 Hz, SCH_2CH_3), 3.40, 3.50, 3.57, 3.64 (3-proton singlets, OCH_3), and 3.65–4.23 (6-proton complex).

Anal. Calc. for $C_{13}H_{28}O_4S_2$: C, 50.00; H, 8.97. Found: C, 50.10; H, 8.86.

Methylation of **8**. — Compound **8** (1.0 g) and methyl iodide (10 ml) were heated under reflux with stirring. Silver oxide (3.0 g) was added in small portions over a period of 12 h. The product was extracted with chloroform and the solution evaporated to a syrup. The syrup was methylated two times more in the same manner; i.r. datum: ν_{max}^{film} 1735 cm^{-1} (C=O ester); g.l.c. (155°): 2,3,4,5-tetra-*O*-methyl-D-xylose dimethyl acetal (**11**) (45%, 4.2 min), methyl 2,3,4,5-tetra-*O*-methyl-D-xylonate (**9**) (9%, 6.6 min), and three other unidentified components (12%, 1.0 min; 21%, 1.7 min; and 13%, 2.6 min).

*2,3,4,5-Tetra-*O*-methyl-*D*-xylose dimethyl acetal* (**11**). — 2,3,4,5-Tetra-*O*-methyl-D-xylose diethyl dithioacetal (**8**, 1.0 g), methanol (15 ml), and cadmium carbonate (7.0 g) were treated with a solution of mercuric chloride (3.5 g) in methanol (10 ml). The solution was stirred and heated under reflux for 5 h. The reaction mixture was filtered and the residue on the filter washed repeatedly with chloroform. The filtrate was washed successively with water, 10% potassium iodide solution, and water and dried over sodium sulfate. The solution was evaporated to a crude syrup (0.89 g), which was purified on a column of silica gel with 1:99 methanol–benzene as the eluent, $[\alpha]_D^{25}$ +10° (*c* 4.76, chloroform); n.m.r. data (chloroform-*d*): δ 3.40 and 3.44 (3-proton singlets, OCH_3), 3.54 (11-proton broad singlet, OCH_3 and other protons), and 4.46 (1-proton doublet, J 6.0 Hz, H-1).

Anal. Calc. for $C_{11}H_{24}O_6$: C, 52.40; H, 9.52. Found: C, 52.32; H, 9.63.

*Methyl 2,3,4,5-tetra-*O*-methyl-*D*-xylonate* (**9**). — 2,3,4,5-Tetra-*O*-methyl-D-xylose diethyl dithioacetal (**8**, 0.50 g), acetone (10 ml), water (2 ml), cadmium carbonate (3.0 g), and mercuric chloride (1.5 g) were stirred for 2 h at 30° and then heated under reflux for 0.5 h. The solution was treated as described for **11** to give a syrup (0.30 g); i.r. datum: ν_{max}^{film} 1720 cm^{-1} (CHO). The crude syrup, water (10 ml), and calcium carbonate (0.6 g) were stirred at room temperature and treated dropwise with bromine. When the bromine color persisted for 0.5 h, the solution was extracted with chloroform and the extracts rejected. The solution was acidified and extraction with chloroform, followed by evaporation gave a syrup (0.15 g). This was treated with diazomethane in ether to give the methyl ester (0.13 g). The ester was applied to a column of silica gel with 1:99 methanol–benzene as the eluent to give a pure syrup, $[\alpha]_D^{25}$ +27° (*c* 0.70, chloroform); i.r. datum: ν_{max}^{film} 1740 cm^{-1} (C=O ester); n.m.r. data

(chloroform-*d*): δ 3.44, 3.46, 3.50 and 3.54 (3-proton singlets, OCH_3), 3.84 (3-proton singlet, CO_2CH_3), and 3.54–4.06 (5-proton complex).

Anal. Calc. for $C_{10}H_{20}O_6$: C, 50.88; H, 4.07. Found: C, 50.76; H, 4.00.

Methylation of 2,3:4,5-di-O-isopropylidene-D-xylose diethyl dithioacetal (**2**). — This was performed as described for **8** with silver oxide and methyl iodide; g.l.c. data (160°): 2,3:4,5-di-*O*-isopropylidene-D-xylose dimethyl acetal (**12**) (11%, 4.2 min); methyl 2,3:4,5-di-*O*-isopropylidene-D-xylonate (**10**) (47%, 6.5 min); and four other major unidentified components (7%, 1.5 min; 10%, 5.7 min; 9%, 9.5 min; and 11%, 13.9 min).

2,3:4,5-Di-O-isopropylidene-D-xylose dimethyl acetal (**12**). — This compound was prepared from 2,3:4,5-di-*O*-isopropylidene-D-xylose diethyl dithioacetal (**2**) (1.0 g) by the procedure described for **11**, syrup; $[\alpha]_D^{25}$ +0.5° (*c* 4.4, chloroform); n.m.r. data (chloroform-*d*): δ 1.47 [12-proton singlet, $C(CH_3)_2$], 3.50 (6-proton singlet, $C(OCH_3)_2$], and 3.92–4.50 (6-proton complex).

Anal. Calc. for $C_{13}H_{24}O_6$: C, 56.52; H, 8.69. Found: C, 56.60; H, 8.57.

Methyl 2,3:4,5-di-O-isopropylidene-D-xylonate (**10**). — This compound was prepared from 2,3:4,5-di-*O*-isopropylidene-D-xylose diethyl dithioacetal (1.0 g) as described for **9**, syrup (0.35 g), $[\alpha]_D^{25}$ +3° (*c* 1.71 chloroform); i.r. datum: ν_{max}^{film} 1740 cm^{-1} (C=O ester); n.m.r. data (chloroform-*d*): δ 1.52 [12-proton doublet, *J* 2.0 Hz, $C(CH_3)_2$], 3.86 (3-proton singlet, CO_2CH_3), and 4.00–4.64 (5-proton complex).

Anal. Calc. for $C_{12}H_{20}O_6$: C, 55.38; H, 7.69. Found: C, 55.47; H, 7.60.

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