Carbohydrate Research, 142 (1985) 132–134
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

(±)-1,2:4,5-Di-*O*-isopropylidene-*myo*-inositol

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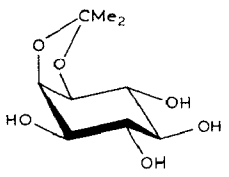
(Received January 12th, 1985; accepted for publication, March 22nd, 1985)

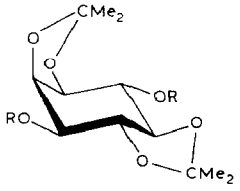
We have described[1] a preparation of (±)-1,2-*O*-isopropylidene-*myo*-inositol (**1**), and we now describe a modified method which allows direct crystallisation of the product and avoids the need to distil off the reaction solvent (methyl sulphoxide). We have used **1**, readily available by this method, for the preparation of the previously undescribed 1,2:4,5-di-*O*-isopropylidene derivative (**2**) of *myo*-inositol.

Treatment of **1** with 2,2-dimethoxypropane in acetone containing an acid catalyst caused a rapid conversion into soluble isopropylidene derivatives, and crystalline **2** was isolated by chromatography of the products on alumina. Compound **2** gave the known[2] 1,4-di-*O*-benzyl-*myo*-inositol (**6**) on benzylation and subsequent acid hydrolysis; **2** also gave a crystalline acetate **4**, the ^{1}H-n.m.r. spectrum of which supported the assigned structure.

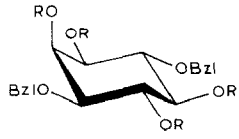
The dibenzoate (**5**) of **2** was highly crystalline and had a low solubility in pyridine and *N*,*N*-dimethylformamide, and could be used to isolate **2** from the



1



2 R = H
3 R = Bn
4 R = Ac
5 R = Bz



6 R = H
7 R = Ac

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0008-6215/85/$ 03.30

above mixture of products (see Experimental). The conversion **5**→**2** was effected with boiling methanolic sodium hydroxide or lithium aluminium hydride in tetrahydrofuran. Compound **2** has been used in the synthesis[3] of 1,2,4-tri-*O*-benzyl-*myo*-inositol.

EXPERIMENTAL

General methods. — ^{1}H-N.m.r. spectra (internal Me_4Si) were recorded with a Bruker WH-270 spectrometer. T.l.c. was carried out on silica gel G (Merck).

*(±)-1,2-*O*-Isopropylidene*-myo-*inositol*[1] (**1**). — A mixture of *myo*-inositol (50 g), dry methyl sulphoxide (160 mL), 2,2-dimethoxypropane (85 mL), and toluene-*p*-sulphonic acid monohydrate (500 mg) was stirred at 100° until a clear solution was obtained (~30 min). The solution was then cooled and triethylamine (5 mL) and ethanol (200 mL) were added, followed by ether (1 L). The mixture was stirred at 20° for 4 h. The crystalline product was collected, washed with ether–methanol (5:1, 200 mL) and then ether, and dried to give **1** (20 g, 32%), m.p. and mixture m.p. 182–184°.

Methanol (500 mL) and conc. hydrochloric acid (50 mL) were added to the filtrate and, after 2 h at 20°, the *myo*-inositol (33 g) was recovered by filtration.

*(±)-1,2:4,5-Di-*O*-isopropylidene*-myo-*inositol* (**2**). — (*a*) A mixture of **1** (20 g), dry acetone (400 mL), 2,2-dimethoxypropane (100 mL), and toluene-*p*-sulphonic acid monohydrate (2 g) was stirred at 50° for 1 h; only a small amount of solid then remained. Triethylamine (10 mL) was added to the cooled solution, the solid (~1.2 g) was removed, sodium hydrogencarbonate (2 g) was added to the filtrate, the solvent was evaporated, and the products were extracted from the residue with dichloromethane. T.l.c. (ether) showed a major product(s) (R_F 0.3) with only small amounts of less-polar materials. The crude product was eluted from a column of basic alumina (250 g) with ether–methanol (19:1), which removed the less-polar products and then gave **2** which crystallised on trituration with ether. Recrystallisation from ethyl acetate gave **2** (5 g, 21%), m.p. 171–173° (Found: C, 55.00; H, 7.93. Calc. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75%).

Elution with methanol gave other di-*O*-isopropylidene derivative(s) which were not investigated.

The 3,6-dibenzoate (**5**) of **2** had m.p. 328–330° (from *N,N*-dimethylformamide, 10 mg/mL) (Found: C, 66.61; H, 6.03. Calc. for $C_{26}H_{28}O_8$: C, 66.65; H, 6.02%).

(*b*) A mixture of *myo*-inositol (50 g), *N,N*-dimethylformamide (200 mL), 2,2-dimethoxypropane (150 mL), and toluene-*p*-sulphonic acid monohydrate (1 g) was stirred at 100° for 2 h, when only a trace of solid remained. Triethylamine (10 mL) was added to the cooled solution, the solid was removed, toluene (25 mL) was added to the filtrate, and the low-boiling solvents were evaporated at 40°. Pyridine (150 mL) was added to the *N,N*-dimethylformamide solution followed by benzoyl chloride (200 mL) dropwise with stirring and cooling during 15 min. After a further

2 h, the solid was collected and washed successively with pyridine, water, acetone, and ether to give **5** (34 g, 26%). A mixture of **5** (10 g), sodium hydroxide (4 g), and methanol (250 mL) was heated under reflux for 30 min. The resulting clear solution was cooled, neutralised with solid carbon dioxide, diluted with water (200 mL), and evaporated to dryness. The residue was extracted with dichloromethane to give **2** (5.2 g, 94%) identical with the material described in (*a*).

*(±)-3,6-Di-*O*-benzyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol* (**3**). — Compound **2** was treated with an excess of benzyl bromide and sodium hydride in *N,N*-dimethylformamide at 20°, and the product was isolated in the usual way to give **3**, m.p. 153–155° [from light petroleum (b.p. 60–80°)] (Found: C, 71.20; H, 7.53. Calc. for $C_{26}H_{32}O_6$: C, 70.89; H, 7.32%).

*(±)-1,4-Di-*O*-benzyl-*myo*-inositol* (**6**). — A solution of **3** in 80% acetic acid was kept at 100° for 15 min, cooled, and diluted with water. The product was collected and recrystallised from ethanol (10 mg/mL) to give **6**, m.p. 205–207°; lit.[2] m.p. 203–204° (Found: C, 67.01; H, 6.80. Calc. for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71%).

The tetra-acetate (**7**) of **6** had m.p. 131–133° (from ethanol); lit.[2] m.p. 128–130° (Found: C, 63.51; H, 5.95. Calc. for $C_{28}H_{32}O_{10}$: C, 63.62; H, 6.10%).

*(±)-3,6-Di-*O*-acetyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol* (**4**). — Conventional treatment of **2** with acetic anhydride–pyridine gave **4**, m.p. 230–232° [from ethyl acetate–light petroleum (b.p. 60–80°)] (Found: C, 55.62; H, 6.95. Calc. for $C_{16}H_{24}O_8$: C, 55.80; H, 7.03%). ^{1}H-N.m.r. data: δ 1.33, 1.43, 1.47, 1.59 (4 s, 2 CMe_2), 2.14, 2.19 (2 s, 2 Ac), 3.49 (dd, J 9.2 and 11.3 Hz, H-5), 4.15 (m, H-1,4), 4.61 (t, J 4.6 Hz, H-2), 5.12 (dd, J 4.1 and 10.8 Hz, H-3), 5.29 (dd, J 11.2 and 6.7 Hz, H-6) (*cf.* n.m.r. data[4] for 3,6-di-*O*-acetyl-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol).

ACKNOWLEDGMENT

We thank Dr. J. Feeney and Mr. M. Searle for the n.m.r. spectra.

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