100 mg.) of amorphous solid. Attempts to crystallize this salt from a variety of solvents were not successful.

A small portion of this material, when treated with hot acid or base at room temperature, gave a compound with chromatographic properties identical with pinitol phosphate. There was no chromatographic evidence for the formation of two isomers.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

The Preparation and Characterization of Di-O-benzylidene-(−)-inositol

BY ELIE A. SHNEOUR AND CLINTON E. BALLOU

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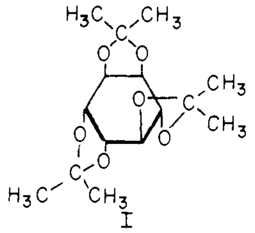
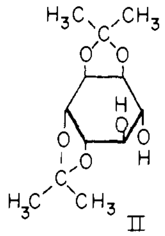
A crystalline di-O-benzylidene-(−)-inositol (V) has been obtained from (−)-inositol when it was treated with benzaldehyde and fused zinc chloride. Lead tetraacetate oxidation of V gave amorphous 2,3:4,5-di-O-benzylidene-L-*manno*-hexodiose (VI) which was characterized as the bis-phenylhydrazone and the bis-*p*-nitrophenylhydrazone; VI was converted to 2,3:4,5-di-O-benzylidene-L-mannitol by reduction. On treatment with ethanethiol, VI yielded the crystalline tetraethyl tetrathioacetal of L-*manno*-hexodiose.

(+)-Inositol[1] and (−)-inositol[2] are readily acetonated in the presence of acetone and zinc chloride under anhydrous conditions at room temperature, yielding a mixture of products consisting mainly of the tri-O-isopropylidene (I) and of the di-O-isopropylidene (II) derivatives. The tri-O-isopropylidene derivative I can be partially hydrolyzed to yield II and some mono-O-isopropylidene-inositol (III).[2]



I



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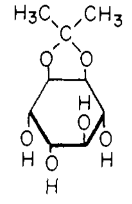
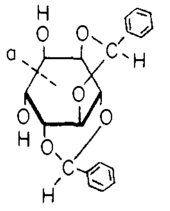
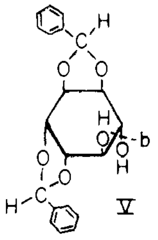


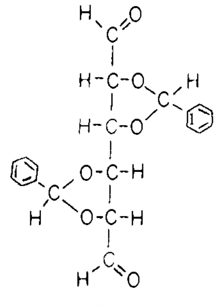
III



IV



V



VI

According to the modified Hann–Hudson rules for acetal and ketal substitutions, outlined by Barker and Bourne,[3] benzaldehyde derivatives of (+)- or (−)-inositol might be expected to take the (1,3) ring configuration (IV) rather than the (1,2) configuration (V). We have now demonstrated that the reaction of (−)-inositol with benzaldehyde and zinc chloride results in the formation of a di-O-benzylidene derivative. This substance reacts readily with lead tetraacetate, consuming one mole, with the formation of a dialdehyde VI. Treatment of the di-O-benzylidene-L-*manno*-hexodiose (VI) with ethanethiol gives a thioacetal derivative which is enantiomorphic with D-*manno*-hexodiose tetraethyl tetrathioacetal.[1] The reduction of VI gave a dibenzylidene hexitol which yielded L-mannitol on removal of the benzylidene groups. Examination of structures IV and V shows that the only possible combination of benzylidene substituents which would allow fission at (b) to yield L-mannitol involves two *cis*-(1,2) cyclic acetals in positions 1,2 and 3,4 of the (−)-inositol ring. Should the di-O-benzylidene compound have been of structure IV with oxidative splitting at (a), the resulting hexitol would have been D-iditol.

The benzylidene derivatives offer certain advantages as intermediates over the isopropylidene derivatives because the benzylidene radical can be removed readily by catalytic hydrogenation with a palladium catalyst in a neutral medium. The preparation and isolation of free dialdehydes may thus be facilitated.

Experimental

1,2:3,4-Di-O-benzylidene-(−)-inositol.—(−)-Inositol from the demethylation of quebrachitol[4] was treated as follows. Finely ground fused zinc chloride (50 g.) was added to anhydrous benzaldehyde (150 ml.) with mechanical stirring. After a few minutes the mixture became opaque and partially solidified. With continued stirring the viscosity decreased rapidly. After 20 minutes, finely

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[1] C. E. Ballou and H. O. L. Fischer, THIS JOURNAL, **75**, 3673 (1953).

[2] S. J. Angyal and C. G. MacDonald, *J. Chem. Soc.*, 686 (1952).

[3] S. A. Barker and E. J. Bourne, *ibid.*, 906 (1952).

[4] Quebrachitol (100 g.) was refluxed with 47% hydriodic acid (250 ml.) for two hours, using an air condenser. The hot solution was poured in boiling absolute ethanol (1600 ml.) and the (−)-inositol crystallized immediately. After 12 hours at 5°, the (−)-inositol was collected on a funnel, washed thoroughly with absolute ethanol and dried *in vacuo* at 80°. The yield was 92.5 g. (99%) and the product melted at 235–237°.

powdered (−)-inositol (20 g.) was added and the mixture was shaken mechanically for 22 hours. The resulting clear solution was poured slowly into rapidly stirred water (1500 ml.), and the stirring was continued for 30 minutes during which crystallization of the product occurred. The water was decanted and the crystals were washed successively with water (1500 ml.) for 5 minutes, with petroleum ether (1000 ml.) for 5 minutes and again with water (1500 ml.) for one hour. The crystals were collected by suction and dried over phosphorus pentoxide for a week, and at 60° for two hours. The product weighed 25 g. (89% for a di-O-benzylidene compound) and melted at 152–155°. It was recrystallized from isopropyl alcohol (200 ml.), the filtered crystals were washed with petroleum ether (200 ml.) and air-dried for a week. The yield was 23 g. of a product melting at 158–159.5°, with sintering at 155° and showing $[\alpha]^{25}\mathrm{D}$ +6.0° (*c* 1, chloroform).

Anal. Calcd. for $C_{20}H_{14}O_6$ (356.4): C, 67.4; H, 5.62. Found: C, 67.3; H, 5.79.

Oxidation of the di-O-benzylidene-(−)-inositol with periodic acid in 95% ethanol was complete after 5 hours with a net uptake of one mole of periodate per mole of the di-O-benzylidene compound.

2,3:4,5-Di-O-benzylidene-L-*manno*-hexodiose.—Finely powdered di-O-benzylidene-(−)-inositol (5 g.) was suspended in dry thiophene-free benzene (100 ml.) and one mole equivalent of lead tetraacetate (6.2 g.) was added. The solid was triturated with a glass rod to ensure complete reaction. The solution was tested for excess oxidant at 30-minute intervals with starch–iodide paper.

After 9 hours, a small amount of the inositol derivative (0.2 g.) was added to consume the remaining excess of the lead tetraacetate. The mixture was then filtered to remove insoluble lead salts and the filtrate was concentrated *in vacuo* to give a white amorphous friable solid (5.0 g.). This was purified by dissolving it in dry benzene and reprecipitating it by the addition of petroleum ether to opalescence. After standing overnight at 5°, the precipitate was collected by suction and dried in air. It weighed 4.4 g. (87%) and melted at 106–108° with sintering at 104°. The material is insoluble in water, slightly soluble in ethanol and very soluble in acetone and chloroform. In chloroform, it showed $[\alpha]^{25}\mathrm{D}$ +142°, which slowly changed to a constant value of $[\alpha]^{25}\mathrm{D}$ +122° after 3 days. No microscopic physical changes in the product were noticeable after six weeks in an evacuated desiccator containing calcium chloride. Repeated attempts at crystallization have failed.

2,3:4,5-Di-O-benzylidene-L-mannitol.—2,3:4,5-Di-O-benzylidene-L-*manno*-hexodiose (1 g.) and sodium borohydride (0.112 g.) were suspended in cold 95% ethanol (200 ml.) and shaken until complete solution was effected, then the solution was allowed to stand at room temperature for two hours. The solution was filtered with Celite and the solvent was distilled off *in vacuo*. The residue was extracted with chloroform and the chloroform solution washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was dissolved in 95% ethanol (20 ml.) to which water was added to opalescence and the solution allowed to stand at 5° overnight. The resulting crystal platelets were collected and dried. They weighed 0.7 g. (70%) and melted at 120–127°. Two further recrystallizations gave 0.2 g. with m.p. 139–141° and $[\alpha]^{20}\mathrm{D}$ +50.0° (*c* 1, ethanol).

Anal. Calcd. for $C_{20}H_{22}O_6$ (358.4): C, 67.0; H, 6.20. Found: C, 66.7; H, 6.4.

L-Mannitol.—2,3:4,5-Di-O-benzylidene-L-mannitol (0.5 g.) was dissolved in 95% ethanol (25 ml.), a suspension of previously reduced palladium chloride-on-carbon (0.5 g.) was added, and the mixture shaken with hydrogen gas at atmospheric pressure and room temperature to constant volume. The hydrogen uptake was 103 ml. (theoretical for 4 mole equivalents, 125 ml.) in 105 minutes. The catalyst was centrifuged out, washed with water and the combined supernatants were distilled *in vacuo*. The residue was recrystallized from water with 95% ethanol added to opalescence. The yield was 230 mg. (92%) of a product that melted at 161–162.5° and showed $[\alpha]^{20}\mathrm{D}$ 0° in water. The melting point of a mixture with an authentic sample of L-mannitol was 162–163.5°. Reported for L-mannitol is m.p. 163–164° and $[\alpha]^{20}\mathrm{D}$ −2° in water. By the above reactions, structure IV would lead to D-iditol with a reported m.p. of 73.5° and $[\alpha]^{20}\mathrm{D}$ +3.5° (water).[5]

2,3:4,5-Di-O-benzylidene-L-*manno*-hexodiose Bis-phenylhydrazone.—2,3:4,5-Di-O-benzylidene-L-*manno*-hexodiose (0.435 g.) was dissolved in absolute ethanol (25 ml.), phenylhydrazine (0.5 ml.) was added and the solution refluxed for one hour. The solution was allowed to stand at 5° overnight, and the crystals thus formed were collected, and when dried weighed 300 mg. After successive recrystallizations from methanol (30 ml.) and absolute ethanol (20 ml.), the dry crystals weighed 195 mg. (26%) and melted with decomposition at 182–183°, after sintering at 176°.

Anal. Calcd. for $C_{32}H_{30}O_4N_4$ (534.6): N, 10.5. Found: N, 9.57.

2,3:4,5-Di-O-benzylidene-L-*manno*-hexodiose Bis-*p*-nitrophenylhydrazone.—2,3:4,5-Di-O-benzylidene-L-*manno*-hexodiose (350 mg.) was dissolved in absolute ethanol (25 ml.), to which 2 mole equivalents of *p*-nitrophenylhydrazine (306 mg.), dissolved in glacial acetic acid (10 ml.), were added. The solution was shaken for 5 minutes and water (50 ml.) was added. Crystallization occurred immediately, and the crystals were collected and twice recrystallized from acetone with water added to opalescence. The yield was 200 mg. (44%) of crystals melting at 211–212.5°, with slight sintering at 208°.

Anal. Calcd. for $C_{32}H_{28}O_8N_6$ (624.6): N, 13.4. Found: N, 13.3.

L-*manno*-Hexodiose Tetraethyl Tetrathioacetal.—Finely divided 2,3:4,5-di-O-benzylidene-L-*manno*-hexodiose (1.0 g.) was suspended in cold concentrated hydrochloric acid (15 ml.), and ethanethiol (5 ml.) was added. The mixture was shaken for 5 minutes and allowed to stand for 5 minutes. Ice-water (50 ml.) was then added and the mixture shaken for 5 minutes. The crystals thus formed were collected on a Büchner funnel, and washed successively with ice-water (50 ml.) twice, and with petroleum ether (50 ml.) twice. The air-dried crystals weighed 760 mg. (75%). After two recrystallizations from absolute ethanol (10 ml.) to which water was added to turbidity, the crystals were collected and washed with petroleum ether. The beautiful white needles weighed 450 mg. (44%), melted at 110–111° and showed $[\alpha]^{25}\mathrm{D}$ +26.9° (*c* 1, ethanol). Ballou and Fischer[1] reported m.p. 109–111° and $[\alpha]^{21}\mathrm{D}$ −24.2° (*c* 1, ethanol) for the D-*manno*-hexodiose tetraethyl tetrathioacetal derivative.

Anal. Calcd. for $C_{14}H_{30}O_4S_4$ (390.1): C, 43.2; H, 7.7; S, 32.8. Found: C, 42.8; H, 8.1; S. 32.7.

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(5) R. L. Lohmar and R. M. Goepp, *Adv. in Carbohydrate Chem.*, **4**, 211 (1949).