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Note

An easy synthesis of *muco*-inositol

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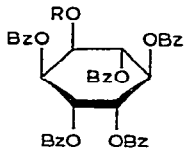
muco-Inositol (**6**) is one of the rarer cyclitols. It has not been found in Nature, but its D-1-*O*-methyl derivative occurs in many gymnosperms and a few angiosperms[1]. It has the same configuration as gammexane: there are three axial hydroxyl groups in each of its two (equivalent) chair forms. It was suggested[2] that it would occur preponderantly in a boat or twist form; an X-ray crystallographic investigation, however, found it to exist, in the crystal, in the chair form[3], and the n.m.r. spectrum in aqueous solution also indicated preponderance of the chair form[4].

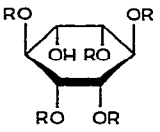
The first synthesis[5] of *muco*-inositol has never been published in detail. Since then, several syntheses have been published[6,7], none of which is particularly convenient. We now describe a synthesis in which every step is readily carried out in high yield; the starting material is quebrachitol* (L-2-*O*-methyl-*chiro*-inositol), which occurs widely in the vegetable kingdom, particularly in the rubber tree (*Hevea brasiliensis*)[8]. An unusual feature of the synthesis is that it uses the methyl group as a protecting group: this is replaced by a tosyl group on the carbon atom which has to be inverted.

The pentabenzoate (**1**) of quebrachitol was oxidized with chromium trioxide in acetic acid[9], converting the methyl into a formyl group (see **2**). Whistler and Roberts[10] stated that a formyl group can be removed in the presence of acetyl groups by treatment with piperidine, but we found this method unsuccessful because migration of benzoyl groups occurred. However, the formyl group was readily removed by treatment with methanolic hydrochloric acid, giving **3**. (After completion of this work, a similar, selective deformylation was described[11].) The free hydroxyl group of the pentabenzoate **3** was then tosylated, the tosyl compound (**4**) solvolyzed in *N*,*N*-dimethylformamide[7], and 1,2,3,4,6-penta-*O*-benzoyl-*muco*-inositol (**5**) obtained

*The authors would be pleased to provide small quantities of crude quebrachitol to interested workers.



1 R = OMe
2 R = OCHO
3 R = H
4 R = OTs



5 R = Bz
6 R = H

in good yield. It is not necessary to purify each intermediate during the synthesis of *muco*-inositol (**6**), obtained by debenzoylation of **5**.

Surprisingly, the penta-*O*-benzoyl-*muco*-inositol (**5**) proved to be optically active. The solvolysis reaction that produced it is generally regarded[7,12] as proceeding through a cyclic, benzoxonium ion intermediate, and, as this ion would be symmetrical, the product should be racemic. Apparently, in this case, part or all of the reaction proceeds by direct displacement, without participation of the neighboring, *trans*-benzoyloxy group; such an occurrence has been observed before[12], and it has been suggested[7] that it may always accompany the reaction occurring by acyl participation. The optical purity of our pentabenzoyl-*muco*-inositol is not known, and hence, the extent of the direct displacement cannot be estimated.

The same reaction-sequence applied to pinitol (D-3-*O*-methyl-*chiro*-inositol) would furnish *allo*-inositol. Only the first three steps (benzoylation, oxidation, and deformylation) were carried out, because the rest of the sequence is obvious, as the pentaacetate of L-3-*O*-tosyl-*chiro*-inositol had already been converted into *allo*-inositol[7].

EXPERIMENTAL

L-*1,3,4,5,6-Penta*-O-*benzoyl-2*-O-*methyl*-chiro-*inositol* (**1**). — To finely powdered quebrachitol (6.1 g) (United States Rubber Company) in a flask equipped with a stirrer and a reflux condenser was added a hot mixture of benzoyl chloride (40 mL) and pyridine (80 mL), and the mixture was stirred for 6 h at 80–90°, and cooled. Ice and sodium hydrogencarbonate (25 g) were added, followed by chloroform (300 mL), the mixture was stirred and shaken, and the organic layer was separated, successively washed with water, dilute hydrochloric acid, and water, and evaporated, to give 20 g (89%) of the product which, after recrystallization from ethanol, had m.p. 106–109°, $[\alpha]_D^{23}$ −111° (*c* 1.14, chloroform); ^{1}H-n.m.r. data (Varian A60A, $CDCl_3$): δ 8.3–7.2 (Bz), 6.2–6.1 (5 H), 4.18 (dd, $J_{1,2}$ 2, $J_{2,3}$ 10 Hz, H-2), and 3.50 (Me).

Anal. Calc. for $C_{42}H_{34}O_{11}$: C, 70.6; H, 4.8. Found: C, 70.5; H, 4.6.

L-*1,3,4,5,6-Penta*-O-*benzoyl-2*-O-*formyl*-chiro-*inositol* (**2**). — Compound **1** (5.0 g) was added to a stirred suspension of chromium trioxide (12.0 g) in acetic acid (120 mL) at room temperature. The mixture was stirred for 3 h, filtered, and the filtrate poured into chloroform (400 mL). The solution was washed successively

with water, saturated sodium hydrogencarbonate solution, and water, dried (Na_2SO_4), treated with charcoal, and evaporated, to give 4.56 g (89%) of a white solid. From ethanol–water, it separated as an amorphous solid, m.p. 110–120°, $[\alpha]_D^{23}$ −79° (*c* 2.55, chloroform); ^{1}H-n.m.r. data: δ 8.3–7.2 (Bz) and 6.3–6.1 (7 H, ring-H and CHO).

Anal. Calc. for $C_{42}H_{32}O_{12}$: C, 69.2; H, 4.4. Found: C, 69.4; H, 4.3.

L-*1,3,4,5,6-Penta*-O-*benzoyl*-chiro-*inositol* (**3**). — A solution of compound **2** (4.0 g) in 0.05M methanolic hydrogen chloride (100 mL) was boiled under reflux for 80 min and was then evaporated to dryness. The residue (3.63 g, 94%), which contained only traces of the starting material (t.l.c.), was crystallized from methanol, and then melted at 120–130°, $[\alpha]_D^{23}$ −140° (*c* 1.14, chloroform); ^{1}H-n.m.r. data: δ 8.1–7.2 (Bz), 6.2–5.7 (m, 5 H), 4.67 (dd, $J_{1,2}$ 2, $J_{2,3}$ 8 Hz, H-2), and 3.2 (broad s, OH).

Anal. Calc. for $C_{41}H_{32}O_{11}$: C, 70.3; H, 4.6. Found: C, 70.8; H, 4.1.

L-*1,3,4,5,6-Penta*-O-*benzoyl*-2-O-*tosyl*-chiro-*inositol* (**4**). — To a solution of the pentabenzoate **3** (3.5 g) in anhydrous pyridine (60 mL) was added *p*-toluenesulfonyl chloride (10 g). After 24 h, 5 g of the chloride was added, and the solution was heated on a steam-bath for 24 h, cooled, poured into ice–water, and the resulting precipitate (3.2 g, 90%) collected by filtration. Recrystallized from methanol, it had m.p. 195–200°, $[\alpha]_D^{23}$ −103° (*c* 1.57, chloroform); ^{1}H-n.m.r. data: δ 8.2–6.9 (Bz), 6.3–5.8 (m, 5 H), 5.45 (dd, $J_{1,2}$ ~2, $J_{2,3}$ 8 Hz, H-2), and 2.24 (Me).

Anal. Calc. for $C_{48}H_{38}SO_{13}$: C, 67.4; H, 4.5. Found: C, 67.7; H, 4.4.

L-*1,2,3,4,6-Penta*-O-*benzoyl*-muco-*inositol* (**5**). — Compound **4** (3.0 g) was heated under reflux with *N*,*N*-dimethylformamide (90 mL) and water (2.5 mL) for 48 h, the mixture evaporated under diminished pressure at 70–80°, the brown residue dissolved in benzene, and the solution treated with decolorizing charcoal, successively washed with dilute sulfuric acid, a saturated solution of sodium hydrogencarbonate, and water, and evaporated. The residue crystallized on trituration with methanol; after recrystallization from ethanol, compound **5** (2.20 g, 90%) had m.p. 190–200°, $[\alpha]_D^{23}$ −43° (*c* 1.55, chloroform); ^{1}H-n.m.r. data: δ 8.2–7.1 (Bz), 6.3–6.0 (m, 5 H), and 4.7 (broad, H-5).

Anal. Calc. for $C_{41}H_{32}O_{11}$: C, 70.3; H, 4.6. Found: C, 70.7; H, 4.4.

muco-*Inositol* (**6**). — The pentabenzoate **5** (1.0 g) was dissolved in methanol (100 mL), sodium (0.5 g) was added, and the solution was boiled under reflux for 2 h, cooled, and evaporated. The residue was dissolved in aqueous acetic acid (1 mL), and the solution was washed with chloroform, treated with charcoal, and evaporated. The residue was crystallized from water–ethanol, to give *muco*-inositol (0.23 g, 91%), m.p. 265–275°, identical with an authentic sample (by n.m.r. spectroscopy and paper electrophoresis[13]).

Reaction sequence starting with pinitol. — By following the methods just described, pinitol was successively converted into D-1,2,4,5,6-penta-*O*-benzoyl-3-*O*-methyl-*chiro*-inositol (**7**), m.p. 138–140° (from ethanol), $[\alpha]_D^{23}$ +47° (*c* 1.0, chloroform) (lit.[14] m.p. 97°, $[\alpha]_D$ +32°); D-1,2,4,5,6-penta-*O*-benzoyl-3-*O*-formyl-*chiro*-

inositol (**8**), m.p. 110–112° (from ethanol–water), $[\alpha]_D^{23}$ +85° (*c* 1.0, chloroform); and D-1,2,3,5,6-penta-*O*-benzoyl-*chiro*-inositol (**9**), m.p. 95–100°, $[\alpha]_D^{23}$ +43° (*c* 1.0, chloroform).

Anal. For **7**: Calc. for $C_{42}H_{34}O_{11}$: C, 70.6; H, 4.8. Found: C, 70.9; H, 4.8. For **8**: Calc. for $C_{42}H_{32}O_{12}$: C, 69.2; H, 4.4. Found: C, 69.4; H, 4.6. For **9**: Calc. for $C_{41}H_{32}O_{11}$: C, 70.3; H, 4.6. Found: C, 70.4; H, 4.8.

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