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Note

A simple synthesis of *cis*-inositol ☆

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cis-Inositol (1,2,3,4,5,6/-cyclohexanehexol) is an interesting compound. It readily forms strong complexes with metal cations [2,3] and with oxyacid anions, e.g., borate [4,5] because of the three *syn*-axial hydroxyl groups in either of its equivalent chair conformations. At present, however, it is not readily available. In this Note we describe a simple one-step synthesis of this cyclitol.

cis-Inositol was first isolated as one of the many products formed in the high-pressure hydrogenation of tetrahydroxyquinone over Raney nickel but its configuration was not determined [6]. It was fully characterized when obtained from the low-pressure hydrogenation over a palladium catalyst [7]. An eight-step synthesis from *myo*-inositol was [8] later published; the first of these steps is cumbersome and proceeds in low yield.

From the hydrogenation of tetrahydroxyquinone over palladium, *cis*-inositol was obtained in a yield of only 4%; four other inositols, three quercitols, one inosose, and several cyclohexane-tetrols and -triols were isolated from the mixture by lengthy and tedious chromatography [7]. Hence, this method is not well suited for the preparation of *cis*-inositol.

In order to turn the hydrogenation into a practical synthesis of *cis*-inositol, two aims had to be achieved: to improve the yield and to simplify the method of purification. The introduction of chromatography on cation-exchange resins in the calcium form [9] has solved the latter problem. *cis*-Inositol forms much stronger complexes than any of the other products and is readily separated from them by chromatography even on a small column.

☆ Cyclitols, Part XLI. For Part XL, see ref. [1].

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Tetrahydroxyquinone is rapidly hydrogenated to give hexahydroxybenzene. Further reaction with six atoms of hydrogen while the compound is adsorbed on the surface of the catalyst should give only *cis*-inositol. The other products arise from desorption of partially hydrogenated products — which are enols — from the catalyst, subsequent keto–enol rearrangements, and loss of water from dihydrobenzene derivatives [7]. Hence the yield of *cis*-inositol should be improved by increasing the surface of the catalyst (and thereby the time spent by the substrate on the catalyst surface) and by minimizing the rate of rearrangements.

In order to provide more catalyst surface, the proportion of catalyst to substrate was kept high (i.e., more palladium was used than substrate). Hydrogenation at higher temperatures resulted in extensive deoxygenation. At room temperature the rate of hydrogenation over the palladium catalyst used originally [7] was very low. Angyal and McHugh [7] found that when the palladium was precipitated on the surface of activated carbon, the yield of *cis*-inositol increased to 20%. Other catalysts have now been tried and the best results were obtained with freshly precipitated palladium hydroxide [10]. With this catalyst, the yield of *cis*-inositol varied between 25 and 39%. If the catalyst is filtered off and dried, its activity is greatly diminished; apparently this process reduces its surface.

When less than one equivalent of palladium is used, the hydrogenation will not proceed to completion. Since the reaction is slow, hexahydroxybenzene accumulates and crystallizes out, coating the catalyst. With 1-2 equiv of catalyst, the reaction is slow and incomplete. More than 2 equiv are required for rapid and complete hydrogenation. The large amounts of palladium required ($\sim$ 5 g for each g of *cis*-inositol obtained) makes the initial cost of this synthesis high. However, all the palladium is recoverable.

The keto–enol interconversion is catalysed by acids and bases. Hence it is not surprising that the best yield of *cis*-inositol was obtained at pH $\sim$ 7. It was the main product of the hydrogenation in the pH range 3.5–7.0.

At pH 8-9, *myo*-inositol was the main product, whereas at pH 1, much deoxygenation occurred. Hence the best conditions for the synthesis of *cis*-inositol employ the palladous hydroxide catalyst at ambient temperature and atmospheric pressure in neutral solution. Rhodizonic acid can be used instead of tetrahydroxyquinone.

One of the products of the hydrogenation is the rather inaccessible 1,2,3,4,5/-cyclohexanepentol [10] ("*cis*-quercitol") which is readily isolated from the appropriate fractions of the chromatographic separation.

An alternative attempt to synthesize *cis*-inositol proved unsuccessful. Cyclohex-5-ene-1,2,3,4/-tetrol is now available from benzene in two steps [11]. *cis*-Hydroxylation of the double bond from the unhindered side gives *allo*-inositol [12]. However, *cis*-hydroxylation from the hindered side would yield *cis*-inositol. The classical method for carrying out this reaction, the Woodward modification [13] of the Prévost reaction, however, left the tetraacetate [12] of the tetrol unchanged. Further experiments were carried out on the more readily available 1,2/3,4-isomer [12] of the tetrol. Neither its tetraacetate, nor its di-*O*-isopropylidene derivative, were attacked by silver acetate and iodine. Other recommended procedures

of *cis*-hydroxylation (iodine and iodate [14] tellurium dioxide and lithium bromide [15]) were equally unsuccessful. Apparently the presence of two adjacent oxygen atoms reduces the nucleophilicity of the double bond. A similar failure of the Woodward–Prévost reaction has recently been reported [16].

1. Experimental

Preparation of the catalyst.—Palladium metal (wire, foil, or sponge, 2.0 g) was dissolved by heating it in a mixture of concd HCl (6 mL) and concd HNO_3 (10 mL). The solution was evaporated and the brownish-red residue (or 3.34 g of $PdCl_2$) was dissolved in concd HCl (12 mL). To this solution, diluted to 1 L, was slowly added a solution of NaOH (40%, 27 mL) with stirring. The resulting milky-yellow solution (which must be strongly alkaline) was heated to boiling for 5 min, whereupon a heavy brown precipitate formed, which settles readily. The supernatant liquid was decanted, and the solid was stirred with 1 L of boiling water for 5 min; this process was repeated until the supernatant was neutral. Usually 4 washings were sufficient. The catalyst was used as soon as possible; it can be preserved, if necessary, under water.

Hydrogenation of tetrahydroxyquinone.—Tetrahydroxyquinone dihydrate (1.5 g) was added to the catalyst (from 3.34 g of $PdCl_2$) under water (150 mL) and was stirred vigorously under hydrogen gas. The catalyst gradually turned black, hydrogenation proceeded rapidly and was usually complete in 2–3 h but was continued overnight to remove the last traces of tetrahydroxyquinone. The mixture was filtered and the catalyst was washed with water. The filtrate was colourless and did not colour on exposure to air.

The palladium was dissolved in a mixture of HCl and HNO_3 and the procedure was repeated two more times.

Chromatographic separation.—A suspension of Dowex AG 50W-X2 resin (100–200 mesh, 0.076–0.152 mm) in the H^+ form in a solution of $CaCl_2$ (20%) was poured into a glass column of 2.5 cm diameter to a height of 20 cm. The column was washed with a $CaCl_2$ solution (100 mL), followed by distilled water until the effluent was free of Ca^{2+} (test with Na_2CO_3).

The filtrates from three hydrogenations were evaporated and the residue, dissolved in water (15 mL), was applied to the column. Fractions (30 mL) were collected and tested by spotting on TLC plates and detecting with H_2SO_4 and heating. Fractions 15–45 contained almost pure *cis*-inositol (1.20 g, 31%). Crystallization from water–ethanol gave lustrous flat needles, dec p 260–340°C (lit. [7] dec 377°C). A transition was observed at 206–210°C, with partial melting, which explains the mp (213–214°C) recorded by Anderson and Wallis [6]. The hexaacetate melted at 206°C (lit. [7] 208°C).

Fractions 7–10 contained *cis*-quercitol (0.48 g, 13%). To locate exactly the fractions which contain it, it is best to use TLC on a cation-exchange plate in the Ca^{2+} form [17] in which *cis*-quercitol (R_f 0.39) is widely separated from *cis*-inositol (R_f 0.07) and the other products which all have R_f values greater than 0.75.

Recrystallization of the quercitol from water–ethanol gave the quercitol as prisms which showed a transition point (with partial melting) at 155–165°C and melted with decomposition at 265–270°C (lit. [7] 235–240°C). The pentaacetate melted at 162–164°C (lit. [7] 165.5°C).

The earlier fraction contained a mixture of cyclitols including a major component comprising *myo*- and *scyllo*-inositols in the ratio of 3:1.

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