THE CONFIGURATION OF CONDURITOL AND THE SYNTHESIS OF *muco*-INOSITOL AND *allo*-INOSITOL

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INTRODUCTORY NOTE. — In 1939, Gerda Dangschat and Hermann O. L. Fischer published a communication¹ on the structure of conduritol and in that paper they described the preparation of two new inositols, *muco*-inositol and *allo*-inositol. At that time, Gerda Dangschat was at the University of Berlin, while Hermann Fischer was at the Banting Institute at the University of Toronto. These two had known one another for a long time inasmuch as Mrs. Dangschat (née Gerda Anger) had worked with Emil Fischer and had married Paul Dangschat, who had also worked in Emil Fischer's laboratory. So the collaboration of Dangschat and Fischer, begun in Berlin, had continued after Fischer moved to Basel in 1932 and also after his move to Toronto in 1936. The upheaval of World War II brought an end to their joint research, and the full paper on conduritol and the new inositols did not appear as planned. However, Hermann Fischer never lost his admiration for Gerda Dangschat and the work that they had done together. A large cardboard box labelled "Condurango bark" sitting on a shelf in the lab in Toronto even in the late 1940's served as a constant reminder of this fruitful association.

In the early 1950's, Hermann Fischer showed me a German manuscript which he had, at some earlier time, received from Gerda Dangschat. This contained the experimental part of the conduction work, and Fischer was considering publishing it after a few loose ends were cleared up. At his suggestion I prepared an English translation, but the pressure of more urgent matters prevented us from undertaking further experimental work. The manuscript was again set aside, and the German version seems to have disappeared sometime after the death of Hermann Fischer in 1960. Fortunately I retained a copy of the translation.

A number of syntheses of *allo*-inositol and of *muco*-inositol have been published since the original communication appeared almost fifty years ago, but from the historical point of view the experimental details of the first preparation are of interest. This volume, commemorating the centenaries of the births of three illustrious carbohydrate chemists of the Emil Fischer school—Karl Freudenberg, Burckhardt Helferich, and Hermann O. L. Fischer—seems a most appropriate place for publication of this work.

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EDITOR'S NOTE. — The discussion section of this paper, necessary for an understanding of the experimental work, was written by D. L. MacDonald. In the Experimental section, Dangschat's original wording, as translated by MacDonald, has been used with minimal alteration. However, new formula schemes were prepared, and the subsections were rearranged to correlate with these schemes. The nomenclature was modernized, and the bibliography was supplemented with references to later workers who confirmed many of Dangschat's observations on the properties of *allo*- and *muco*-inositol and their derivatives. A number of editorial comments have been added to the text; these are enclosed in square brackets.

L.A.

^{*}Gerda Dangschat spent the post-war years in West Berlin, where she died on September 26, 1964.

DISCUSSION

The accompanying work describes the synthesis of two new inositols and at the same time establishes the configuration of conduritol (1). Evidence on the latter point was obtained by oxidative opening of the ring at the double bond, to give the *meso* hexaric acid, mucic acid. The inositols were prepared by the hydroxylation of the double bond, which for a compound of structure 1 could lead to only three products. *Cis* hydroxylation could furnish 6 (Scheme 1) or 29 (Scheme 2), whereas a *trans* hydroxylation would lead only to the previously known pL-chiro-inositol.

Conversion of conduritol into its isopropylidenc derivative followed by acetylation led to the fully blocked derivative 4 (Scheme 1). The double bond was hydroxylated using potassium permanganate, yielding 7, which was oxidized with lead tetraacetate followed by perpropionic acid to furnish derivatives of galactaric (mucic) acid (11). This result showed that conduritol must be 5-cyclohexene-1,4/2,3-tetrol (1).

The hydroxylation product 7 proved to be derived from a new inositol, which was named *allo*-inositol since acetylation followed by removal of the isopropylidenc group gave the tetraacetate 15 which on lead tetraacetate cleavage. perpropionic acid oxidation, and subsequent deacetylation yielded allaric (*allo*-mucic) acid (21).

The other inositol, *muco*-inositol, was prepared by acetylation of conduritol to give the tetraacetate **2**. The tetraacetate, on hydroxylation of the double bond (Scheme 2), gave a derivative not of *allo*-inositol, but of another previously undescribed inositol. This product was given the name *muco*-inositol because of its obvious relation to mucic acid.

EXPERIMENTAL

Tetra-O-acetylconduritol^{*} (2). — In a mixture of 35 mL of equal parts of dry pyridine and acetic anhydride, 5 g of conduritol was dissolved by warming and shaking. After the reaction had stood overnight at room temperature, the mixture was concentrated *in vacuo*. The residue was distilled in a high vacuum, the tetra-acetate coming over almost quantitatively at 0.6 mm Hg and 165°. The substance has not been crystallized. The boiling point at 0.2 mm Hg was 152°.

Anal. Calc. for C₁₄H₁₈O₈ (314.1): C, 53.5; H, 5.8. Found: C. 53.4; H, 5.8.

Following saponification, conducted with m.p. 142–143° was recovered. No reaction occurred with iodine and silver acetate, or with perbenzoic acid, and bromine in chloroform or glacial acetic acid was not decolorized.

O-Isopropylideneconduritol* (3). - Conduritol (1; 4.5 g) was shaken on a

^{*}Systematic names: 2, (1,4/2,3)-1,2,3,4-tetra-O-acetyl-5-cyclohexene-1,2,3,4-tetrol; 3, (1,4/2,3)-2,3-()-isopropylidene-5-cyclohexene-1,2,3,4-tetrol.





machine at 37° with 300 mL of dry acetone containing 0.5% of hydrogen chloride until it was dissolved. The solution was kept at 37° for two days, then shaken with an excess of lead carbonate, the lead salts were filtered off, and the filtrate was concentrated *in vacuo* (water pump) at a bath temperature not exceeding 40°. The residue, which was partly crystalline, was digested with chloroform. The acetonated substance went into solution, and 0.8 g of undissolved conduritol was filtered off. The chloroform solution was shaken again with lead carbonate for a short while, then filtered, and concentrated *in vacuo* at a bath temperature not exceeding 40°. On cooling and rubbing the inner wall of the container, O-isopropylideneconduritol started crystallizing, and the crystallization was completed by cautious addition of petroleum ether. The yield was 3.6–3.8 g (75–80% calculated on unrecovered conduritol). For analysis the substance was recrystallized from hot ethyl acetate and petroleum ether, whereupon it melted at 100–101°.

Anal. Calc. for $C_9H_{14}O_4$ (186.1): C, 58.0; H, 7.6. Found: C, 57.9; H, 7.8. The O-isopropylideneconduritol was optically inactive, and almost indiffe-

rent toward the action of lead tetraacetate in acetic acid during several hours in the titration according to Criegee. Upon warming with dilute mineral acids, or with 50–80% acetic acid, conduritol with melting point 153° was recovered.

Di-O-acetyl-O-isopropylideneconduritol* (4). — O-Isopropylideneconduritol (3) (3.7 g) was dissolved by shaking in 10 mL of a 1:1 mixture of dry pyridine and acetic anhydride. The colorless solution was left overnight at room temperature, and then was concentrated at 45° in vacuo (water pump) to dryness. The oily residue was dissolved in hot ethanol, and water was added just to turbidity. After rubbing the inner wall of the vessel with a glass rod, crystallization of heavy plates began and was completed at 0°. The yield was 4.6 g (85%). For analysis, the substance was recrystallized from a mixture of ethyl acetate and petroleum ether. It melted at 79°.

Anal. Calc. for C₁₃H₁₈O₆ (270.1): C, 57.8; H, 6.7. Found: C, 57.7; H, 6.7.

Di-O-acetylconduritol* (5). — The di-O-acetyl-O-isopropylideneconduritol 4 was heated for 1 h on a steam bath in 50% acetic acid, and the solution was then concentrated *in vacuo* to dryness. By rubbing the residue with ether crystalline di-O-acetylconduritol was obtained. The substance was recrystallized from ethyl acetate by addition of petroleum ether. It crystallized slowly, and apparently with water of crystallization. It consumed one mole of lead tetraacetate per mole of compound. It did not melt sharply, instead turning at 101° to a viscous liquid that adhered to the wall of the tube, and melting completely on heating to 105°. For analysis, it was heated at 50° in a high vacuum.

Anal. Calc. for C₁₀H₁₄O₆ (230.1): C, 52.3; H, 6.1. Found: C, 52.2; H, 6.0.

Oxidation of di-O-acetyl-O-isopropylideneconduritol to 1,4-di-O-acetyl-5,6-Oisopropylidene-allo-inositol (7). - To 8 g of di-O-acetyl-O-isopropylideneconduritol (4) dissolved in 150 mL of ethanol was added a solution of 8 g of magnesium sulfate in 50 mL of water, followed by 12.5 mL of pyridine. Some magnesium sulfate precipitated from solution, but redissolved during the course of the oxidation. While the mixture was stirred and cooled in ice water, 125 mL of 2% potassium permanganate was added rapidly in small drops, from two separatory funnels. Then 100 mL of ethanol was added, and another 125 mL of 2% potassium permanganate was added dropwise. The oxidation mixture was concentrated in vacuo (water pump) until the colloidal manganese dioxide began to flocculate, when it was filtered through a layer of decolorizing carbon. The colorless filtrate was concentrated in vacuo until crystallization began. The aqueous solution was then extracted twice with chloroform, the combined chloroform extract was dried over anhydrous sodium sulfate, filtered, and concentrated to remove the solvent. The resulting oily residue was dissolved in a minimum amount of boiling ethanol, and on cooling, the solution deposited rectangular rod-shaped crystals. After several hours at 0°, the product was collected and weighed (0.7 g, 8%). The m.p. of this substance was 150°, and it was raised to 166–168° by recrystallization.

^{*4, (1,4/2,3)-1,4-}di-O-acetyl-2,3-O-isopropylidene-5-cyclohexene-1,2,3,4-tetrol; 5, (1,4/2,3)-1,4-di-O-acetyl-5-cyclohexene-1,2,3,4-tetrol.

The alcoholic mother liquor was concentrated to dryness at a water pump. The residue was dissolved in ether and allowed to crystallize slowly from solution. A second fraction, 5.0 g (55%) with m.p. $93-95^\circ$, was thus obtained as tapering, pointed needles.

Both oxidation products analyzed correctly for di-O-acetyl-O-isopropylideneallo-inositol. They gave by acetylation the same tetraacetate, by deacetylation with sodium methoxide the same isopropylidene inositol, and by treatment with hydrochloric acid in acetone the same di-O-acetyl-di-O-isopropylidene derivative. The lower-melting main product of the reaction proved, however, to be indifferent to lead tetraacetate, while the minor, high-melting product consumed one mole of the oxidant in acetic acid or in benzene.

The fraction with m.p. 166–168° analyzed as follows:

Anal. Calc. for C₁₃H₂₀O₈ (304.2): C, 51.3; H, 6.6. Found: C, 51.5; H, 6.7.

The fraction with m.p. $93-95^{\circ}$ was dried in a high vacuum at 50° . It had the following analysis:

Anal. Calc. for C₁₃H₂₀O₈ (304.2): C, 51.3; H, 6.6. Found: C, 51.0; H, 6.6.

If the oxidation were carried out without pyridine, the high melting fraction was obtained in still poorer yield, and could hardly be isolated when the reaction was run in more dilute solution at a lower temperature. On the other hand, the lead tetraacetate-resistant substance was converted, by distillation in a high vacuum, to the oxidizable form. [These data suggest that the product having m.p. $93-95^{\circ}$ was a regioisomer of 7, resulting from the migration of one (or both) of the *O*-acetyl groups.]

Conversion of 1,4-di-O-acetyl-5,6-O-isopropylidene-allo-inositol into tetra-Oacetylmucic acid dimethyl ester* (13). — One-half gram of the di-O-acetyl-O-isopropylidene-allo-inositol 7 (m.p. 168°) was dissolved in 10 mL of hot benzene. With the solution at 50° , 0.6 g of lead tetraacetate (1 mol. equiv.) was added, after which lead acetate soon precipitated, and in 10 min the lead tetraacetate was completely used up. After the addition of 10 mL of chloroform the mixture was heated to boiling and filtered, and the lead salt was washed with hot chloroform. The filtrate was washed with dilute sulfuric acid and water, then dried with anhydrous sodium sulfate, filtered from the salt, and the solution then concentrated to dryness in vacuo. The product was deacetonated by heating for 2 hours on a water bath in 50% acetic acid, during which time the solution turned a light vellow color. After cooling, 2 mL of a 30% solution of perpropionic acid was added, and the oxidation was allowed to proceed for 2 d at room temperature. The solution was then freed of acetic acid and propionic acid by distillation in vacuo, and the oily residue, dissolved in 3 mL of 2M sodium hydroxide, was left overnight. After acidification with sulfuric acid, the crystallization of mucic acid* (11) occurred. The yield was 0.1 g (29%) with decomposition point 219°. Acetylation with acetic anhydride and zinc chloride gave tetra-O-acetylmucic acid* (12) with decomposition point 246°, which on treatment with diazomethane was converted to tetra-O-acetylmucic acid di-

^{*}Systematic names: 11, galactaric acid: 12, 2,3,4,5-tetra-O-acetylgalactaric acid: 13. dimethyl 2.3,4,5-tetra-O-acetylgalactarie.

methyl ester* (13) with m.p. 193°, unchanged on admixture with authentic material prepared from mucic acid. [The original preparation of this compound was reported² to melt at 197°; later workers found m.p. 195.8–196.6° (ref. 3) and 196–197° (ref. 4).]

Anal. Calc. for C₁₆H₂₂O₁₂ (406.2): C, 47.3; H, 5.5; OCH₃, 15.3. Found: C, 47.5; H, 5.6; OCH₃, 15.8.

1,2,3,4-Tetra-O-acetyl-5,6-O-isopropylidene-allo-inositol (14). — In a mixture of 12 mL of equal parts pyridine and acetic anhydride was dissolved 4 g of di-O-acetyl-O-isopropylidene-allo-inositol. After one day at room temperature, the acetylation mixture was concentrated to dryness at the water pump, and then reconcentrated 2-3 times after the addition of ethanol. The resulting crystalline tetraacetate was then recrystallized from ethanol containing a little water. The yield was 4.8 g (90%) of plates. For analysis, the product was recrystallized from absolute ethanol, whereupon it melted at 125°.

Anal. Calc. for C₁₇H₂₄O₁₀ (388.2): C, 52.6; H, 6.2. Found: C, 52.7; H, 6.3.

allo-Inositol 1,2,3,4-tetraacetate (15). — 1,2,3,4-Tetra-O-acetyl-5,6-O-isopropylidene-allo-inositol (14) (5 g) was heated for 1 h on a boiling water bath with 5 parts of 80% aqueous acetic acid. The acetic acid was then removed by repeated concentration *in vacuo* with added ethanol. The resulting oily residue was dissolved in boiling ethyl acetate, an equal volume of ether was added, and then petroleum ether was added slowly just to turbidity. Crystallization was initiated by rubbing the inner wall of the vessel with a glass rod, and it was allowed to proceed slowly without sudden cooling. After several hours the product was filtered off. It weighed 3.6 g (80%). The substance crystallized from water as rods with m.p. 94°. From an ethyl acetate-ether-petroleum ether mixture it crystallized with m.p. 115°. For analysis the substance was dried in a high vacuum at 50°.

Anal. Calc. for C₁₄H₂₀O₁₀ (348.2): C, 48.3; H, 5.8. Found: C, 48.5; H, 5.9.

An attempted reaction of the tetra-O-acetyl inositol with acetone and hydrogen chloride failed to regenerate the acetonated tetraacetate.

Tetra-O-acetyl-allo-mucic dialdehyde* (17). — 1,2,3,4-Tetra-O-acetyl-alloinositol (15; 3.0 g) was partly dissolved in 60 mL of dry benzene by warming at 50°. To the warm solution was added 4.0 g (1 mol. equiv.) of lead tetraacetate, and the mixture was shaken for 20 min with the temperature being maintained at about 50°; by this time the lead tetraacetate had reacted. An equal volume of chloroform was added, the mixture was heated to boiling, and the solution was filtered from the lead salt. The salt was washed several times with hot chloroform. The combined, cooled filtrate was washed rapidly with a few mL of dilute sulfuric acid, causing the precipitation of some lead sulfate. The water layer was discarded, and the organic layer was washed with a little water, then dried with anhydrous sodium sulfate, filtered from the drying agent, and concentrated at the water pump at 40°. The residue was mostly crystalline. From ether, or a mixture of ethyl acetate and petroleum ether, 1.8 g (60%) of the crystalline tetra-O-acetyl dialdehyde was ob-

^{*}Systematic name: 2,3,4,5-tetra-O-acetyl-allo-hexodialdose.

tained. From the mother liquor additional product could be isolated as the phenylhydrazone.

For analysis the substances was recrystallized from a mixture of ethyl acetate and petroleum ether. It melted with decomposition at $163-164^{\circ}$, and reduced Fehling's solution in the cold.

Anal. Calc. for C14H18O10 (346.1): C, 48.6; H, 5.2. Found: C, 49.0; H, 5.4.

The tetra-O-acetyl dialdehyde formed the following bis(arylhydrazones) (18): bis(phenylhydrazone), recrystallized from ethanol, m.p. 163° with decomposition; bis(p-nitrophenylhydrazone), recrystallized from warm (not hot) pyridine by the addition of ethanol, discolored at 190°, sintered at 210°, and melted at 225–226°; and bis(dinitrophenylhydrazone), from pyridine by the addition of ethanol, discolored at 245°, and melted with decomposition at 250°. It also gave a dioxime, recrystallized from water, m.p. 177°. All of these compounds had satisfactory elemental analyses.

Tetra-O-acetyl-allo-mucic acid^{*} (19). — Tetra-O-acetyl-allo-mucic dialdehyde (17; 0.5 g) was partially dissolved in 3 mL of propionic acid by slight warming, and after the mixture was cooled to room temperature, 3 mL of 30% perpropionic acid was added. The mixture was shaken for a while until solution was complete and then the reaction was left for a few days at room temperature. Spontaneous precipitation of tetra-O-acetyl-allo-mucic acid as hexagonal plates occurred. The yield was 0.45 g (82.5%) with m.p. 226–228° (gas evolution). The product dissolved readily in sodium bicarbonate solution. It was recrystallized from ethyl acetate, and dried in a high vacuum at 50°.

Anal. Calc. for C₁₄H₁₈O₁₂ (378.1): C, 44.5; H, 4.8. Found: C, 44.6; H, 4.7.

Tetra-O-acetyl-allo-mucic acid dimethyl ester* (20). — When a solution of 0.10 g of tetra-O-acetyl-allo-mucic acid (19) in methanol was treated with an ethereal solution of diazomethane until a yellow color remained, crystallization of the dimethyl ester occurred in a short time. After addition of petroleum ether, crystallization was completed in the cold. The yield was 0.09 g (84%), and after recrystallization from a mixture of ethyl acetate and petroleum ether the product melted at 205° with slight yellow coloration.

Anal. Calc. for C₁₆H₂₂O₁₂ (406.2): C, 47.3; H, 5.5; OCH₃, 15.3. Found: C, 47.6; H, 5.6; OCH₃, 14.6.

allo-Mucic acid $(21)^*$, its diethyl ester $(22)^*$, and bis(phenyl)hydrazide (23). — A solution of 1.0 g tetra-O-acetyl-allo-mucic acid (19) in 8 mL of 2M sodium hydroxide was left overnight at room temperature. While vigorously stirred and cooled in ice, the solution was made acid to litmus (but not to congo red) by the dropwise addition of 8 mL of M sulfuric acid. The solution was left for 1 h at 0°, during which time the free allo-mucic acid crystallized slowly as bilateral pyramids. The yield was 0.35 g (63%) of a product melting at 196–197° with gas evolution; lit.⁵ m.p. 197–198°. It was recrystallized from water and then dried at 50° in a high vacuum.

^{*}Systematic names: 19, 2,3,4,5-tetra-O-acetylallaric acid; 20, dimethyl 2,3,4,5-tetra-O-acetylallarate; 21, allaric acid; 22, diethyl allarate.

Anal. Calc. for C₆H₁₀O₈ (210.1): C, 34.3; H, 4.8. Found: C, 34.0; H, 4.8.

When heated with acetic anhydride and zinc chloride, the acid was converted back to the tetraacetate, m.p. 226–228°. Treatment of an ethanol suspension of the acid with an ether solution of diazoethane resulted in crystallization of *allo*-mucic acid diethyl ester (22). It recrystallized from ethanol as long slender prisms with m.p. 155°; lit.⁵ m.p. 153–154°.

Anal. Calc. for $C_{10}H_{18}O_8$ (266.1): C, 45.1; H, 6.8; OC_2H_5 , 33.9. Found: C, 45.1; H, 6.8; OC_2H_5 , 33.0.

When the acid was heated with phenylhydrazine in water, the bis(phenylhydrazide) (23) crystallized from solution as rhombic plates. When filtered, washed with ethanol, and dried, the colorless product decomposed at 227° ; lit.⁵ m.p. 227-230°.

Anal. Calc. for $C_{18}H_{22}N_4O_6$ (390.2): C, 55.4; H, 5.7; N, 14.4. Found: C, 55.4; H, 5.6; N, 14.4.

5,6-O-Isopropylidene-allo-inositol (8). — One half gram of di-O-acetyl-O-isopropylidene-allo-inositol (m.p. 95°) was boiled for 5 minutes with 5 mL of 0.02M sodium methoxide in dry methanol. Then the solution was concentrated to dryness *in vacuo* at the water pump. The resulting crystalline residue was redissolved in the minimum amount of boiling ethanol and an equal volume of ether was added, followed by petroleum ether until the solution became turbid. By rubbing the inner wall of the container with a glass rod, crystallization of rhombic plates was initiated. Crystallization was completed at 0°, and the yield was 0.3 g (83%).

For analysis the product was recrystallized from an ethanol-ether mixture, when it melted at 144-145°. It was dried in a high vacuum at 50°.

Anal. Calc. for C₉H₁₆O₆ (220.1): C, 49.1; H, 7.3. Found: C, 49.1; H, 7.3.

allo-inositol (6). — 5,6-O-Isopropylidene-allo-inositol (8; 0.2 g) was heated on a boiling water bath for one hour with 1 mL of 50% aqueous acetic acid. To the warm solution was then added 2-4 volumes of ethanol. Upon cooling the solution and rubbing the inner wall of the vessel with a glass rod, the free inositol was deposited as clumped, spindle-shaped crystals in good yield. For analysis, the product was recrystallized from dilute ethanol and dried in a high vacuum at 50°. On rapid heating, the substance discolored at 235° and began to sinter at 245°; it melted completely at 270-275°. [Later workers⁶ found 290-300°.]

Anal. Calc. for C₆H₁₂O₆ (180.1): C, 40.0; H, 6.7. Found: C, 40.0; H, 6.6.

allo-Inositol hexaacetate (9). — For acetylation the inositol was warmed on a water bath for 2 h with 10 parts of acetic anhydride and a little zinc chloride. After concentration of the solution at the water pump, the hexaacetate was crystallized as rhombic plates from ethanol. It melted at $142-143^{\circ}$. [Later workers⁶⁻⁸ found $141-142^{\circ}$.]

Anal. Calc. for C₁₈H₂₄O₁₂ (432.2): C, 50.0; H, 5.6. Found: C, 50.0; H, 5.6.

allo-Inositol hexabenzoate (10). — allo-Inositol (50 mg) was warmed in a bath at 120–130° with 0.3 mL of benzoyl chloride and a small grain of zinc chloride; during the reaction hydrogen chloride gas was evolved and a clear solution resulted.

After cooling, the solution was rubbed up twice with a little 5% sodium carbonate solution, and then twice with water. When the residue was warmed with ethanol, the hexabenzoate crystallized. The yield was 0.20 g (90%), and the product melted at 188°, unchanged on recrystallization from hot acetic acid by addition of ethanol. [Later workers⁸ found m.p. 196°.]

Anal. Calc. for C₄₈H₃₆O₁₂ (804.3): C, 71.6; H, 4.5. Found: C, 71.3; H, 4.5.

1,4-Di-O-acetyl-2,3:5,6-di-O-isopropylidene-allo-inositol (16). — Di-O-acetyl-O-isopropylidene-allo-inositol (m.p. 95°; 0.5 g) was dissolved in 25 mL of dry acetone that contained 1% hydrogen chloride gas, and the solution was left overnight at 37°. The solution was then neutralized by shaking it with an excess of lead carbonate. The lead salts were filtered off, and the acetone filtrate was concentrated *in vacuo* to dryness. The residue crystallized when rubbed in ether, giving 0.25 g (44%) of product. Recrystallization from ethanol gave the pure diacetone compound as thick, rhombic plates, m.p. 218–219°. The same diacetone compound in a corresponding yield was obtained from the higher melting di-O-acetyl-O-isopropylidene-allo-inositol 7.

Anal. Calc. for C₁₆H₂₄O₈ (344.2): C, 55.8; H, 7.0. Found: C. 55.9: H, 7.0.

From the mother liquor a small amount of an isomeric di-O-acetyl-di-O-isopropylidene-*allo*-inositol, m.p. 138°, was crystallized.

Anal. Found: C, 55.9; H, 7.0.

Oxidation of tetra-O-acetylconduritol to tetra-O-acetyl-muco-inositols. - To a solution of 8.5 g of distilled tetra-O-acetylconduritol 2 in 125 mL of ethanol was added a solution of 8.5 g of magnesium sulfate in 30 mL of water. While the rapidly stirred solution was cooled in ice water, half of a solution of 4.5 g (1 mol. equiv) of potassium permanganate in 225 mL of water was added rapidly from two separatory funnels whose tips were drawn out to capillaries. Then 125 mL of ethanol was added to the reaction mixture, and after again cooling, the remainder of the potassium permanganate solution was added dropwise. The mixture was then heated slightly on a water bath to cause flocculation of the manganese dioxide, which was removed by filtration through a layer of decolorizing carbon. The slightly colored filtrate was concentrated at the water pump to a volume of about 50 mL. It was then extracted twice with chloroform, and the combined extract was dried over anhydrous sodium sulfate. The filtered solution was concentrated at atmospheric pressure in order to avoid a troublesome creeping-over of the oily residue. The oil was then distilled under high vacuum in an Anschütz distilling flask that was immersed as far as possible in a bath at 150°. Distillation up to a bath temperature of 200° gave a forerun consisting of 1.8 g of tetra-O-acetylconduritol. The remaining substance then distilled, with b.p. 218-220° at 0.3 mmHg as a viscous, slightly yellow oil that solidified. The yield was 5.6 g (60%). For analysis, the substance was fractionally distilled a second time.

Anal. Calc. for C₁₄H₂₀O₁₀ (348.2): C, 48.3; H, 5.8. Found: C, 48.4; H, 5.9.

The distilled preparation contained about 10-25% of the normal. lead tetraacetate-cleavable form of the oxidation product (1.2.3,6-tetra-O-acetyl-mucoinositol, 24), while before distillation only very little reaction with lead tetraacetate in glacial acetic acid was apparent. [These data suggest that the hydroxylation product from 2, like that from 4, is a mixture of regioisomers, here resulting from the migration of one or more acetyl groups in a portion of the initially formed tetraacetate 24.]

Conversion of tetra-O-acetyl-muco-inositol into tetra-O-acetylmucic dialdehyde* (26). — A solution of 3.5 g of the distilled tetra-O-acetyl-muco-inositol in 20 parts of hot benzene was treated at 50° with the calculated amount of lead tetraacetate (determined by titration of an aliquot of the solution with standard lead tetraacetate). An excess was to be avoided. After 20 min the mixture was diluted with an equal volume of hot chloroform and filtered, and the solid was washed with hot chloroform. The combined filtrate was washed with dilute sulfuric acid, then with water, and finally dried over anhydrous sodium sulfate. The salt was filtered off and the filtrate was concentrated at the water pump. The oily residue was taken up in ether, from which the tetra-O-acetylmucic dialdehyde slowly crystallized. The yield was about 60%, based on the oxidizable tetra-O-acetyl inositol. After recrystallization from ethyl acetate and petroleum ether the decomposition point was $172-175^\circ$. The anhydrous substance, obtained as rhombic plates from glacial acetic acid, melted at 184° with decomposition.

Anal. Calc. for C₁₄H₁₈O₁₀ (346.1): C, 48.6; H, 5.2. Found: C, 48.7; H, 5.5.

The tetra-O-acetylmucic dialdehyde formed two bis(arylhydrazones) (27): a bis(phenylhydrazone), recrystallized from ethanol, m.p. 169–170°, with decomposition; and a bis(*p*-nitrophenylhydrazone), which crystallized from the glacial acetic reaction mixture in which it was prepared and which discolored at 210° and melted with decomposition at 248°. Both of these compounds gave satisfactory elemental analyses.

Tetra-O-acetylmucic acid (12). — Oxidation of the dialdehyde 26 with perpropionic acid gave tetra-O-acetylmucic acid in good yield. It was precipitated from its solution in dilute sodium bicarbonate by the addition of sulfuric acid. The product decomposed at $245-246^{\circ}$.

Anal. Calc. for $C_{14}H_{18}O_{12} \cdot 2 H_2O$ (414.2): C, 40.6; H, 5.4. Found: C, 40.7; H, 5.2.

Saponification of the tetraacetate gave mucic acid (11) with a decomposition point of 219°. Esterification of the tetraacetate with diazomethane gave the dimethyl ester (13) with m.p. 193°. When 13 was mixed with an authentic sample prepared from commercial mucic acid, the melting point showed no depression.

1,2,3,6-Tetra-O-acetyl-4,5-O-isopropylidene-muco-inositol (28). — A solution of 5 g of the distilled tetra-O-acetyl-muco-inositol in 25 mL of dry acetone was treated with 25 mL of acetone containing 1% hydrogen chloride gas. After two days at 37°, the reaction mixture was shaken for 2 h with lead carbonate. The lead salt was removed by filtration, 1 mL of pyridine was added to the filtrate, and the solution was concentrated, bath temperature 35°, at the water pump. The residue was distilled in a high vacuum, and, at 0.6 mm Hg and a bath temperature up to

200°, 2.1 g (38%) of the acetonated compound came over. The boiling range was $175-180^{\circ}$. For analysis the product was redistilled.

Anal. Calc. for C₁₇H₂₄O₁₀ (388.2): C, 52.6; H, 6.2. Found: C, 52.2; H, 6.5.

Deacetonation of the compound by warming with aqueous acetic acid for 1 h was not quantitative. Since by longer heating with 50% acetic acid some deacetylation occurred, it was preferable to warm for 1 h with 80% acetic acid. Then, after removal of the solvent at the water pump, the unattacked compound was distilled off in a high vacuum. The tetra-O-acetyl-muco-inositol thus obtained proved to be more readily oxidized by lead tetraacetate than the material used in the acetonation reaction. The product of lead tetraacetate cleavage gave a correspondingly better yield of tetra-O-acetylmucic dialdehyde, as well as tetra-O-acetylmucic acid resulting from further oxidation with perpropionic acid. [Further evidence that "tetra-O-acetyl-muco-inositol" is a mixture of regioisomers.]

1,2-O-Isopropylidene-muco-inositol (30). — Deacetylation of 1,2,3,6-tetra-O-acetyl-4,5-O-isopropylidene-muco-inositol (28) with 0.05M sodium methoxide in methanol led to the formation of 1,2-O-isopropylidene-muco-inositol (30) that crystallized from the concentrated methanol solution. For analysis it was recrystallized from methanol by addition of ethyl acetate. The m.p. was 162°.

Anal. Calc. for C₉H₁₆O₆ (220.1): C, 49.1; H, 7.3. Found: C, 49.0; H, 7.5.

Hexa-O-acetyl-muco-inositol (25). — Tetra-O-acetylconduritol (2; 1 g) was oxidized as described above. The chloroform extract, without further purification, was heated for 2 h on the water bath with 10 parts of acetic anhydride and some zinc chloride. After removal of most of the acetic anhydride by distillation, ethanol was added and again distilled off. The hexaacetate crystallized, and after two recrystallizations from ethanol, there was obtained 0.63 g (60%) of dense prisms, m.p. 179–180°. [Later workers^{6,9} found m.p. 177–178°.]

Anal. Calc. for C₁₈H₂₄O₁₂ (432.2): C, 50.0; H, 5.6. Found: C, 50.1; H, 5.6.

muco-*Inositol* (29). — The hexaacetate (0.5 g) was heated to boiling for 5 min with 5 mL of 0.02M sodium methoxide in methanol, after which the free inositol crystallized directly in almost quantitative yield. For analysis it was recrystallized from dilute ethanol. The product became discolored at 240°, sintered at 250°, and melted completely at 285–290°. [Later workers found m.p. 280–300° (ref. 6), and m.p. 286° (ref. 10).]

Anal. Calc. for C₆H₁₂O₆ (180.1): C, 40.0; H, 6.7. Found: C, 39.8; H, 6.7.

muco-Inositol gave the Scherer test. With acetic anhydride and zinc chloride, the hexaacetate (25) with m.p. 180° was obtained.

Hexa-O-benzoyl-muco-*inositol* (31). — *muco*-Inositol (50 mg) was heated in a bath at 120–130° with 0.3 g of benzoyl chloride and a small piece of zinc chloride until evolution of hydrogen chloride gas ceased. After cooling, the melt was stirred up twice with 5% sodium carbonate solution, then with water, when the benzoate began to crystallize. The product was collected and washed with ethanol. The yield was almost quantitative, the long prisms showing m.p. 248°, unchanged on recrystallization from glacial acetic acid. [A later worker¹¹ found m.p. 254–256°.]

Anal. Calc. for C₄₈H₃₆O₁₂ (804.3): C, 71.6; H, 4.5. Found: C, 71.6; H, 4.6.

1,2:4,5-Di-O-methylene-muco-inositol (32). — One gram of muco-inositol was warmed for 30 min on a water bath with 0.33 g of trioxymethylene (about 2 mol. equiv.), and 1.5 mL of concentrated hydrochloric acid. The solution was left overnight at room temperature, and was then concentrated at the water pump at a bath temperature of 100° until nearly free of hydrogen chloride. Finally, the residue was heated in a high vacuum, when, at a bath temperature of 200–210°, a colorless oil distilled that began to solidify in the receiver. The substance, easily soluble in water but difficulty soluble in hot ethanol, was recrystallized from methanol by addition of ethyl acetate and petroleum ether. The yield was 0.33 g (29%) of a compound with m.p. 162° after prior sintering.

Anal. Calc. for C₈H₁₂O₆ (204.1): C, 47.0; H, 5.9. Found: C, 47.3; H, 5.9.

With pyridine and acetic anhydride, the compound gave a diacetate (33) with m.p. 176°.

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